CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-880

MEDICAL REVIEW(S)

Division Director Summary Review of a New Drug Application

NDA: 21-880
Drug: Revlimid® (lenalidomide) 5 and 10 mg capsules
Applicant: Celgene Corporation
Date: December 23, 2005

This new drug application was submitted on April 7, 2005 for the following proposed indication: "REVLIMID® is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities." A major amendment was received on September 23, 2005 and the user fee goal date was extended to January 7, 2006.

Clinical/Statistical Review

The Clinical Review by Maitreyee Hazarika, M.D. (efficacy), Edvardas Kaminskas, M.D., (safety), and Rajeshwari Sridhara, Ph.D. was completed on September 26, 2005. The submission and recommendations are summarized in the following sections of the review.

9.1 Conclusions.

The NDA submission consisted of two single-arm, phase 2 clinical studies relevant to the proposed indication, one very small. The patient population consisted of patients with transfusion-dependent anemia due to low or intermediate-1 risk MDS associated with del 5q cytogenetic abnormalities with or without additional cytogenetic abnormalities. The transfusion entry criterion is based on the RBC units transfused in the 8 weeks prior to start of study drug. The median number units of RBC transfused was six. The main study enrolled 148 patients using oral lenalidomide as a single agent given in 2 dose regimens, 10 mg daily or 10 mg for 21 days in a 28- day cycle.

The primary endpoint was the determination of RBC transfusion independence. A rolling 56 day (8 week) transfusion free period was used for transfusion independence response. The RBC transfusion independence response of 67% (99/148) was seen with = 1.0 g/dL increase in hemoglobin. These responses lasted for a minimum of 8 weeks with a median duration of transfusion independence in responders was 52 weeks. Major cytogenetic responses were seen in 43% (52/120) patients in whom follow-up bone marrows were present. The study was not designed or powered to prospectively compare the efficacy of the 2 lenalidomide dosing regimens.

The supportive study had 10 evaluable patients supporting the proposed indication.

FDA performed an analysis in those patients who met the major eligibility criteria. Ninety six patients had transfusion-dependent anemia due to a diagnosis of low or intermediate-1 risk MDS associated with a del 5q chromosomal abnormality with or without additional cytogenetic abnormalities. The results were consistent with the ITT population.

The demonstration of the clinical benefit of RBC transfusion independence, although substantial, is based mainly on one single-arm, multicenter trial. A randomized controlled trial is ongoing at present and the sponsor has a Phase IV commitment.

All MDS patients, those with 5q deletion (del 5q) and those without 5q deletion (non-del 5q), had adverse events during treatment with lenalidomide. In absence of a best supportive care control arm, it is not possible to assign adverse events to lenalidomide instead of MDS. The most common reported adverse events were neutropenia and thrombocytopenia. They were also the most common grade 3 or 4 adverse events, the most common serious adverse events (except for pneumonia), the most common events leading to discontinuations from studies, and the most common events leading to dose interruptions and dose reductions. Less frequently reported were rashes, infectious events, fatigue, bleeding events, gastrointestinal events, and others. A very high percentage (about 80%) of patients reported grade 3 or 4 events. There was a markedly different adverse event profile in the del 5q population from that in non- del 5q population. The del 5q patients had approximately twice as high frequencies of neutropenia and of thrombocytopenia (all grades and grades 3 – 4 in both cases), a one- third higher frequency of infections, and higher incidences of bleeding and of venous thromboembolism than non-del 5q patients.

The increased sensitivity to lenalidomide in the del 5q population may account for the much greater need for dose reductions and dose interruption of the 10 mg/ day starting dose (administered by either of the two schedules) in the del 5q population compared to non- del 5q population (80% of patients vs. 47% of patients). These data suggest that the starting dose of lenalidomide is too high for the del 5q population, and that careful monitoring is required for dose adjustment. Because neutropenia and thrombocytopenia can occur rapidly and unpredictably in some cases, and because the rate of recovery can be delayed, lenalidomide should be administered only during the period during which it maintains patients free of transfusions. In cases of patients who do not respond to lenalidomide treatment, the treatment should be discontinued once a response is unlikely to occur (about 16 weeks).

Patients with renal impairment were excluded from the studies. Because lenalidomide is mainly excreted by the kidney, renal function should be carefully monitored to avoid excess toxicity.

Until definitive toxicology studies have determined that lenalidomide, unlike thalidomide, does not pose risk as a human teratogen, the S. T. E. P. S. program should be implemented.

The benefit vs. risk profile of lenalidomide treatment in the del 5q population is substantial; the incidence of severe adverse events, some life- threatening, is high. Therefore, a balanced medical evaluation is required before prescribing lenalidomide followed by careful monitoring and dose adjustment.

A Black Box Warning should be placed in the label to include the unknown pregnancy risk and the recommendation to prevent fetal exposure and should also include weekly monitoring of neutropenias and thrombocytopenias.

9.2 Recommendation on Regulatory Action

Lenalidomide (Revlimid ®) should receive regular approval for the treatment of patients with transfusion dependent anemia due to low or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Lenalidomide was brought before the Oncology Drug Advisory Committee on Sept 14, 2005. The ODAC committee agreed that the benefit versus risk analysis warranted approval.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Due to the inadequacy of the reproductive safety assessment, FDA has a concern regarding the risk of teratogenicity and the potential fetal exposure to lenalidomide. Of concern is also the high incidence and dose modification due to neutropenias and thrombocytopenias. The sponsor should implement a risk management activity similar to the S. T. E. P. S. program until toxicology studies determine that lenalidomide is not a teratogen in species that predict human teratogenicity.

A Black Box Warning should be placed in the label to include the unknown pregnancy risk and the recommendation to prevent fetal exposure and should also include weekly monitoring of neutropenias and thrombocytopenias.

9.3.2 Required Phase 4 Commitments

Not applicable.

9.3.3 Other Phase 4 Requests

Celgene has a planned phase 3 study ongoing in Europe in MDS patients with a 5q deletion. It is a randomized, double-blind, placebo-controlled 3-arm study evaluating a lower dose of 5 mg daily versus 10 mg syncopated. The primary endpoint is RBC transfusion independence for ≥ 26 weeks. At the time of the advisory committee meeting, 20 patients had been enrolled.

The safety of lenalidomide in patients with renal impairment should be determined.

Reproductive safety assessments in this drug was inadequate as reviewed by the Pharmacology/toxicology team. Celgene is required to conduct further tests to adequately assess the risk of teratogenicity.

Medical Team Leader's Review

The Medical Team Leader's Review by Ann Farrell, M.D. was completed on October 4, 2005. Dr. Farrell's conclusions and recommendations are quoted below.

Based on the strong comments made by several ODAC members stating that hematologists and oncologist are experienced enough to appropriately dose reduce when toxicity arises and the suggested efficacy in the MDS-003 study, this reviewer recommends full approval provided the sponsor agrees to the following:

1) Strong labeling: The labeling should include Black box warnings and bolded warnings regarding the prevention of fetal exposures, 80% dose reduction and dose delay seen in the del 5 q MDS population, and the 80% grade 3 and 4 adverse event data seen in MDS- 003. The labeling should also include weekly peripheral blood counts without regard to duration.

2) Risk Management Plan: Due to lenalidomide's structural similarity to thalidomide and the inadequate developmental toxicity study, this reviewer recommends that a risk management program very similar to that for thalidomide be instituted to prevent the risk of fetal exposure until developmental toxicity issues have resolved (new studies have been performed and undergone Agency review).

3) Submission of the ongoing European study when completed. The sponsor has proposed study CC-5013-MDS-004, a randomized, double- blind, placebo-controlled, multicenter, 3-arm study of the efficiency and safety of 2 doses of lenalidomide (5 mg daily versus 10 mg days 1-21, 7 days rest (28 day cycle)) versus placebo in red blood cell (RBC) transfusion- dependent subjects with low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a del 5q cytogenetic abnormality. This study will be conducted in Europe. The primary endpoint is RBC transfusion independence for = 26 weeks (182 days).

4) Submission of adequate reproductive safety studies for the Agency to review.

Oncologic Drugs Advisory Committee

This application was presented and discussed at the September 14, 2005 meeting of the Oncologic Drugs Advisory Committee. The questions and votes are provided below.

1. Randomized controlled trials allow for direct comparisons of treatment effects and safety between treatment arms. A single arm study has been submitted using an 8- week run-in period to serve as a baseline for each patient's transfusion requirements. A comparison is subsequently made to a follow- up 8- week period on Revlimid to compare transfusion requirements. Does this study design allow adequate characterization of Revlimid's treatment effect in the population described in the proposed indication? (11 yes and 4 no)

2. In this single arm trial, 80% of patients enrolled in MDS-003 had dose reductions and/or delays and 80% of patients experienced either grade 3 or 4 adverse events. Data do not exist on the efficacy and safety of lower Revlimid doses. Approval of a drug is contingent upon being able to write adequate product labeling, requiring a recommended dose and characterization of a safety profile. Do the data provided in this single-arm trial provide a basis for a recommended dose and adequate description of a safety profile? (2 yes and 13 no).

3. Please characterize the magnitude of Revlimid's benefit and risk in the indication being sought. After this characterization, does this risk/ benefit analysis warrant approval? (10 yes and 5 no)

4. At this time, lenalidomide, a thalidomide analogue, does not have adequate nonclinical studies to assess reproductive/ developmental safety. Should a risk/ management program with a goal of no fetal exposures to Revlimid be instituted until the nonclinical reproductive/ developmental safety assessments are addressed? (There was no vote on this question.)

Despite the vote on question 2, during the discussion committee members expressed the opinion that hematologists and oncologists were experienced in monitoring for myelosuppression and lowering or holding doses when indicated.

Clinical Inspection Summary

The preliminary Clinical Inspection Summary is dated December 2, 2005. The Division of Scientific Investigations concluded the following.

The EIR from the single European site inspected is pending.

The studies that were inspected appear to have been conducted sufficiently well that the data collected can be used to base approval of an NDA. Some data is missing, but quantitatively the amount missing should not qualitatively change the overall findings. There were also some lapses outside of the data gathering/ collection efforts such as those related to informed consent documents, etc and these failures have already been brought to the attention of the clinical investigators and will be emphasized by DSI in the letter to the clinical investigators.

No evidence of withholding of serious adverse event including deaths was found.

No follow up is planned.

Although the review noted that the EIR from the German site was pending, the final classification was "probably VAI" and that "the data is acceptable."

Pharmacology Toxicology Review and Evaluation

The Pharmacology Toxicology Review and Evaluation was completed by M. Anwar Goheer, Ph.D. and Kimberly Benson, Ph.D. (reproductive and developmental toxicology) on October 9, 2005. The recommendations and summary of nonclinical findings are excerpted below.

I. Recommendations

A. Recommendation on approvability: The non-clinical studies submitted to this NDA provide sufficient information to support the use of lenalidomide (Revlimid®) in patients with transfusion-dependent anemia due to low-or intermediate--risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

B. Recommendation for nonclinical studies: Adequate reproductive toxicity assessment, specifically embryo-fetal developmental toxicity in two species, needs to be conducted.

C. Recommendations on labeling: A separate review will be conducted.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: Lenalidomide (3-(4' aminoisoindoline-1-one)-1-piperidine-2, 6- dione; CC-5013; IMiD-3 and Revlimid ®) is a thalidomide analogue. It is a racemic mixture of S (-) and R (+) forms. The *in vitro* and *in vivo* characterization of pharmacological properties of lenalidomide had demonstrated that the drug inhibits the

secretion of pro-inflammatory cytokines (TNF-α, IL-1ß, IL-6 and IL-12) and increases the secretion of anti- inflammatory cytokine (IL-10) from peripheral blood mononuclear cells (PBMC), induces T-cell proliferation (IL-2, IFN-γ), inhibits cell proliferation (MM, Burkitt's lymphoma) and inhibits angiogenesis (Knight- R, Semin Oncol 2005; 32: 24- 30 & Dredge et al., Microvasc Res. 2005; 69: 56- 63). Lenalidomide inhibits the expression of cyclooxygenase-2 (COX- 2) but did not affect COX- 1 *in vitro*. This may translate into adverse effects that need to be fully explored in clinical trials. In addition to these immune effects, there is evidence that thalidomide and its analogues may act directly on tumor cells, via inducing apoptosis or G1 growth arrest.

The oral administration of lenalidomide at dose levels of 3, 6 and 12 g/m^2 produced no effects on behavior or general activity in male rats. Intravenous administration of the drug at doses up to 400 mg/m^2 did not produce any significant effect on cardiovascular and respiratory systems of the anesthetized dog. In vitro, lenalidomide inhibited the cloned human potassium channel (hERG) current by 8% only at the highest concentration tested (787 μM).

Lenalidomide did not inhibit or induce any of the major cytochrome P450 isozymes in vitro and in vivo indicating limited potential for P450-related drug-drug interactions. Distribution of radioactivity in the fetal tissues of pregnant rat was low after oral administration but fetal brain showed more activity than maternal brain. The highest concentrations were found in the kidney (cortex and medulla), liver, spleen and the mucosa of the GI tract of rats.

During traditional toxicity assessment, lenalidomide was administered to rodents (mice, rats) and non rodents (monkeys) for 1, 7, and 28 days and 13, 26, and 52 weeks. Single dose administration of lenalidomide up to 6 g/m^2 in mice and 12 g/m^2 in rats did not cause any adverse effects. Daily oral administration of lenalidomide at 6 g/m^2 to rats for 28 days was associated with moderate to severe tubular nephropathy/ nephritis, which was attributed to precipitation of the lenalidomide in the kidney. Once daily oral administration of lenalidomide to rats at doses of 450, 900 or 1800 mg/m^2/ day for 26 weeks was mainly associated with reduced body weight gain (12%↓) for high dose males and reversible pelvic mineralization in the kidney of all treated animals.

Oral administration of lenalidomide to cynomolgus monkeys at dose levels of 12, 24, 48, or 72 mg/m^2/ day for 52 weeks was associated with hemorrhage in multiple organs, gastrointestinal tract inflammation and lymphoid and bone marrow atrophy. Dosing at 48 and 72 mg/m^2/ day was discontinued after 20 weeks of treatment due to toxicity and mortalities. A reversal of the macroscopic and microscopic findings seen in decedent and

the terminal sacrifice was noted in 7 week treatment-free recovery animals. It is clear that this species is much more sensitive to lenalidomide than rodents.

Lenalidomide did not induce mutation in the Ames test, chromosome aberrations in cultured human peripheral blood lymphocytes, or mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells. Lenalidomide did induce micronuclei in the polychromatic erythrocytes of the bone marrow of male rats.

Reproductive and developmental toxicity: Reproductive studies were conducted with lenalidomide, examining the effects on fertility and early embryo development, embryo-fetal development, and pre- and post- natal development. Only the embryo-fetal development studies are required for drugs with oncologic indications. These studies have not been adequately conducted at this time. The first study, conducted in a rat, showed very slight maternal toxicity and no fetal malformations. The rat, however, is not an adequate species for the full assessment of lenalidomide's developmental effects, given the structural similarity to thalidomide. Historical data indicates that the rat is not sensitive to the full range of thalidomide's teratogenic effects.

An additional developmental study was conducted in the rabbit, with a concurrent thalidomide dose group. This study had a confounding variable with some rabbits not eating prior to the study and all these rabbits had a negative outcome in the study. Additionally, the highest dose tested did not meet the standard criteria for sufficient drug exposure.

B. Pharmacologic activity: Both lenalidomide and thalidomide have been shown to increase the secretion of anti- inflammatory cytokine IL-10 from LPS-stimulated PBMC, stimulates T-cells proliferation and production of IL-2 and IFN-γ. Both inhibit the secretion of pro- inflammatory cytokines TNF-α, IL-1ß, and IL-6. In addition to these immune effects, there is evidence that thalidomide and its analogues may act directly on tumor cells, via inducing apoptosis or G1 growth arrest. Exact mechanisms of action however remain unknown.

C. Nonclinical safety issues relevant to clinical use: Inflammation of the gastrointestinal tract and atrophy of the bone marrow, thymus, and lymphoid tissues were observed during repeat dose toxicity studies (up to 12 months) in cynomolgus monkeys. Embryo- fetal developmental toxicity has not been adequately addressed. The structural similarity of lenalidomide to thalidomide, a known human teratogen, suggests developmental risk. Lenalidomide also inhibits expression of COX-2 in vitro but not COX-1. This finding should be fully explored in clinical trials.

The Pharmacology Toxicology Review and Evaluation of December 9, 2005 provided recommendations on labeling.

Clinical Pharmacology and Biopharmaceutics Review

The Clinical Pharmacology and Biopharmaceutics Review was completed by Gene Williams, Ph.D. on September 26, 2005. The recommendations and a summary of the clinical pharmacology and biopharmaceutics findings are provided below.

1.1. Recommendations

This NDA is acceptable from the clinical pharmacology and biopharmaceutics perspective.

1.2. Identify recommended Phase 4 study commitments if the NDA is judged approvable

Approximately 2/3 of lenalidomide is excreted as unchanged drug in urine following Revlimid dosing. In multiple myeloma patients with mild renal impairment, exposure (plasma AUC) was 56% higher than in multiple myeloma patients with normal renal function who received the same dose. Based on these data, we recommend that a study be conducted to determine the pharmacokinetics of lenalidomide in subjects with renal impairment. The study design should be consistent with the FDA Guidance, "Pharmacokinetics in Patients with Renal Impairment."

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings (1- 3 pages)

Lenalidomide is structurally similar to the teratogenic drug thalidomide.

Following oral administration, maximum lenalidomide plasma concentrations occur from 0.5 - 4 hours post- dose. Co- administration with food does not alter the extent of absorption. Half- life of lenalidomide elimination is approximately 3 hours and the pharmacokinetic disposition of lenalidomide is, at doses up to 10X the recommended clinical dose of 10 mg, linear. Approximately two- thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore entails an active component. In mutliple myeloma patients with mild renal impairment, AUCs were 56% higher than in similar patients with normal renal function.

A search for circulating lenalidomide metabolites in human biomaterials (plasma, urine or feces) was not performed.

Results from human *in vitro* metabolism studies show that lenalidomide is not metabolized through the cytochrome P450 pathway. Human *in vitro* metabolism studies also show that lenalidomide does not inhibit or induce cytochromes P450.

The pharmacokinetics of lenalidomide in patients with renal impairment or hepatic impairment have not been systematically studied. The effects of age on the pharmacokinetics of lenalidomide have not been studied. No pharmacokinetic data are available in patients below the age of 18 years. The effects of gender on the pharmacokinetics of lenalidomide have not been studied. Pharmacokinetic differences due to race have not been studied.

Lenalidomide is a BCS Class 3 (high solubility – low permeability) substance. Based on the compositional proportionality of the strengths, the dosing regimen used in clinical trials, pharamacokinetic linearity, and comparative dissolution profiles, the Applicant requests and will be granted a waiver for an in vivo bioequivalence study comparing the 5 mg capsule strength studied in efficacy and safety studies and the 10 mg strength which will be marketed, in addition to the 5 mg strength.

Chemistry Review

The Chemistry Review by Haripada Sarker, Ph.D. was completed on December 5, 2005. The recommendation and conclusion on approvability follows.

This application is recommended for APPROVAL from a chemistry, manufacturing and controls standpoint because:

The applicant addressed all the deficiencies satisfactorily. The applicant has validated the analytical methods for specified impurities and degradants. The office of compliance has provided an overall acceptable recommendation (see attached). The following comments regarding retest for the drug substance and shelf- life for the drug product should be included in the action letter:

"A retest period of or the drug substance and a shelf- life of twenty four months for the drug product will be granted based on stability data provided"

DDMAC Consultation

A DDMAC consultation on the proposed draft labeling by Joseph Grillo was completed on September 22, 2005. The comments were discussed during the labeling meetings.

DMETS Consultations

Two DMETS consultations were obtained. The consultation dated June 2, 2005, concluded the following.

> In summary, DMETS has no objection to the use of the proprietary name of Revlimid from a safety perspective. This is considered a final decision. However, if the approval of the NDA is delayed beyond 90 days from the signature date of this document, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/ or established names from the signature date of this document. In addition, DMETS recommends implementation of the label and labeling revisions outlined in this memo to minimize potential errors with the use of this product. DMETS also recommends that the division consider submitting the patient package insert to the Division of Surveillance, Research and Communication Support for review and comment. DDMAC finds the name of Revlimid acceptable from a promotional perspective.

A second DMETS consultation was completed on December 14, 2005. The consultation again concluded the following.

> In summary, DMETS has no objection to the use of the proprietary name of Revlimid from a safety perspective. In addition, DMETS recommends implementation of the label and labeling revisions outlined in this memo to minimize potential errors with the use of this product. DDMAC found the proprietary name of Revlimid acceptable from a promotional perspective in both the initial review and this re- review. This is considered a final decision...

DMETS labeling comments were conveyed to the applicant and revised labeling was submitted and reviewed.

DSRCS Medication Guide Review

The DSRCS consultation on the Medication Guide was completed on December 7, 2005. The applicant agreed to the recommended revisions to the Medication Guide.

RevAssist^{SM} Program and Office of Drug Safety Consultations

This application is being considered for approval under 21 CFR 314.520 (Subpart H). Distribution of the drug will be restricted to licensed prescribers who are registered in the RevAssist^{SM} program and understand the potential risk of teratogenicity if lenalidomide is used during pregnancy. The primary goal of the RevAssist^{SM} program is to prevent fetal exposures, pending complete and adequate preclinical characterization of the teratogenic potential of lenalidomide.

The RevAssist^{SM} program includes the following components:

1. Registration in the RevAssist^{SM} program of prescribers, pharmacies, nurses, and patients who agree to specific responsibilities and requirements in order to distribute, prescribe, dispense, and use Revlimid®.

2. Implementation of an educational program and associated materials which describe the risks and benefits of Revlimid® and the required activities for prescribers, pharmacies, nurses, and patients.
3. Implementation of a reporting and data collection system for safety surveillance including reporting of pregnancy exposures in real time, a pregnancy exposure plan, pharmacy audits, voluntary follow-up surveys of prescribers and patients, and update reports to the FDA.
4. Implementation of a plan to monitor, evaluate, and improve minimization of drug exposure during pregnancy and compliance with restrictions for safe use under the RevAssist^{SM} program.

The Office of Drug Safety Review of the RevAssist^{SM} Risk Minimization Action Plan submitted on September 30, 2005 was completed on December 15, 2005. The Executive Summary of the consultation is provided below.

> This consult follows a request from the Division of Oncologic Drug Products for the Office of Drug Safety (ODS) to review, comment, and compare the Lenalidomide Risk Minimization Action Plan (RevAssist^{SM}) to the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.®) .
>
> Lenalidomide is an immunomodulatory drug being developed for treatment of patients with transfusion- dependent anemia due to low- or intermediate- 1 risk myelodysplastic syndromes (MDS). Because of the structural similarity between thalidomide and lenalidomide, there is a concern that this product carries the same risk for teratogenicity as has been demonstrated with thalidomide. The Sponsor was informed that until such time as more definitive animal studies rule out a risk for teratogenicity, a RiskMAP similar to S.T.E.P.S will be required for approval and marketing of lenalidomide.
>
> We conclude that the RevAssist program overall looks comparable to S.T.E.P.S. based on the side-by-side comparison and therefore is acceptable to us for interim use until the questionable teratogenicity of lenalidomide is fully characterized and resolved. There are several outstanding issues that should be resolved prior to approval. The educational materials for patients and prescribers submitted to date do not adequately describe the RiskMAP components and requirements. The Sponsor should also submit a Pregnancy Exposure follow-up plan. A more complete list of comments and recommendations is included in section 7, pgs 9-10 of this document.
>
> If animal or human teratogenicity is demonstrated, we would suggest the program be modified to reflect state-of-the-art pregnancy prevention risk management standards in pregnancy testing (e.g., sensitivity to 25 mIU/mL) and contraceptive methods (e.g. removal of all references to poorly effective contraceptive techniques , as well as a clear definition of females of child- bearing potential. Currently, the standards being implemented for the iPLEDGE program represent the Agency's recommendations of the best available

standards. If adequate animal teratogenicity testing is reassuring about fetal risks such that the RevAssist program to prevent pregnancy exposures is discontinued, we recommend a pregnancy registry be established to monitor for potential human teratogenicity.

The comments and recommendations were communicated to the sponsor. On December 21, 2005 ODS provided another consultation on the RevAssist education materials submitted on December 15, 2005 and on Celgene's responses to FDA's December 12, 2005 correspondence concerning RevAssist. The comments and recommendations were communicated to the applicant. A teleconference between FDA (ODS and DDOP) was held on December 20, 2005. Agreement was reached on the RevAssist program during that telecon.

Post-Marketing Commitments

The applicant has agreed to the following post-marketing commitments:

December 15, 2005 commitment: establish a pregnancy registry to monitor for potential human teratogenicity if animal teratogenicity testing indicates that the RevAssist[SM] program for monitoring fetal exposure is unnecessary.

December 21, 2005 commitments:

1. The embryo-fetal toxicity assessment of Revlimid has not been adequately addressed. You will need to provide adequate information for this assessment in appropriate models that fully assesses the possible toxicity of Revlimid. These studies should be conducted in two different species that are appropriate to assess the full range of thalidomide embryo-fetal effects. The rat is not an acceptable model. If the study with lenalidomide in the first species shows clear evidence of teratogenesis, than a confirmatory study will not be necessary. Although not generally considered "definitive" test systems for pharmaceutical products, additional studies of an exploratory nature on the embryo-fetal effects of lenalidomide (e.g., — assay; — assay), though not required, may be useful.

Protocol Submission:	06/06
Study Start:	09/06
Final Report Submission:	12/07

2. Submission of the study report and data from the ongoing study, CC-5013-MDS-004, a randomized, double-blind, placebo-controlled, multicenter, 3-arm study of the efficacy and safety of 2 doses of lenalidomide (5 mg daily versus 10 mg day 21 days of a 28 day cycle) versus placebo in red blood cell (RBC) transfusion-dependent patients with low-or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality when completed.

Protocol Submission:	03/05
Study Start:	08/05
Final Report Submission:	12/08

3. Following Revlimid dosing, approximately 2/3 of lenalidomide is excreted as unchanged drug in urine. In multiple myeloma patients with mild renal impairment, exposure (plasma AUC) was 56% higher than in similar patients with normal renal function who received the same dose. Based on these data, you should conduct a study to determine the pharmacokinetics of lenalidomide in subjects with renal impairment. The study design should be consistent with the FDA Guidance, "Pharmacokinetics in Patients with Impaired Renal Function."

Protocol Submission:	11/04
Study Start:	03/06
Final Report Submission:	12/07

4. Regarding the Evaluation/Surveillance Plan:

   Submit a Pregnancy Exposure follow-up plan which will document your plan to follow-up pregnancy exposures to their outcome. This plan may be submitted as a post-marketing commitment.

   Plan submission 06/01/06

   Submit an Evaluation Plan of RevAssist to FDA within 3 to 6 months of approval. This should at a minimum include plans to study the Pharmacy Audit Plan, Outcomes of Pregnancy Exposures, and the Knowledge Surveys of physicians, nurses, and patients.

   Plan submission 06/01/06

5. Submit all exposed pregnancies within 15 days of receipt as 15 day expedited reports.

Conclusions

Agreement has been reached on the final labeling, the post-marketing commitments, and the RevAssist program. I concur with the recommendations for approval of this application for the proposed indication under the provisions of 21 CFR 314.520 (Subpart H).

Robert L. Justice, M.D., M.S.
Acting Director
Division of Drug Oncology Products
Office of Oncology Drug Product
Center for Drug Evaluation and Research

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/s/

Robert Justice
12/23/2005 06:54:44 PM
MEDICAL OFFICER

Division of Oncology Drug Products

Medical Team Leader's Review

NDA:	21880
Sponsor:	Celgene
Drug Product:	Revlimid, Lenalidomide, CC-5013
Projected Action Date:	October 7, 2005

Summary

On April 7, 2005, Celgene submitted this New Drug Application (NDA) for lenalidomide, a thalidomide analogue and a new molecular entity, for the treatment of patients (pts) with transfusion-dependent anemia due to low- or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q (del 5 q) cytogenetic abnormality with or without additional chromosomal abnormalities for accelerated approval.

During the application review, a number of significant issues were identified. The review team decided that the application should go to an Oncology Drugs Advisory Committee.

The key issues for consideration were:

1) Whether a single arm trial design can be used in a heterogeneous disease (myelodysplastic syndrome (MDS)),
2) Whether an "8-week transfusion-free endpoint" can be used in a single arm trial to demonstrate clinical benefit,
3) Whether the dose regimen (10 mg continuous) is excessively toxic and a reduced dose regimen should be studied,
4) Whether the teratogenic potential of lenalidomide, a thalidomide analogue, has been adequately characterized,
5) Whether additional risk management measures (e.g., STEPS program) should be implemented until completion of further studies.

On September 14, 2005, the ODAC met and discussed the application. Most members agreed that the drug had activity for this subtype of MDS (del 5 q); however, some members felt that the single arm trial design did not allow an understanding of the true benefit. In addition, most members felt the 10 mg regimens were toxic.

Reproduced below are the questions and the voting on the application.
Question #1

Randomized controlled trials allow for direct comparisons of treatment effects and safety between treatment arms. A single arm study has been submitted using an 8-week run-in period to serve as a baseline for each patient's transfusion requirements. A comparison is subsequently made to a follow-up 8-week period on Revlimid to compare transfusion requirements. Does this study design allow adequate characterization of Revlimid's treatment effect in the population described in the proposed indication?

Y = 11 ***N = 4***

Question #2

In this single arm trial, 80% of patients enrolled in MDS-003 had dose reductions and/or delays and 80% of patients experienced either grade 3 or 4 adverse events. Data do not exist on the efficacy and safety of lower Revlimid doses. Approval of a drug is contingent upon being able to write adequate product labeling, requiring a recommended dose and characterization of a safety profile. Do the data provided in this single-arm trial provide a basis for a recommended dose and adequate description of a safety profile?

Y = 2 ***N = 13***

Question #3

Please characterize the magnitude of Revlimid's benefit and risk in the indication being sought. After this characterization, does this risk/benefit analysis warrant approval?

Y = 10 ***No = 5***

Question #4

At this time, lenalidomide, a thalidomide analogue, does not have adequate nonclinical studies to assess reproductive/developmental safety. Should a risk/management program with a goal of no fetal exposures to Revlimid be instituted until the nonclinical reproductive/developmental safety assessments are addressed?

There was no vote taken on this question.

Application

This application contains 3 open-label, single arm phase studies in MDS (MDS-001, MDS-002, and MDS-003). Two of these studies have enrolled patients with

del 5q abnormality (MDS-001 and MDS-003 studies). Problems with the single arm study design include:

1) lack of information on a historical control population
2) question of whether 8 weeks (56 days) of transfusion data prior to study entry defines a population that is transfusion-dependent
3) question of whether a rolling 56 days of freedom from transfusion represents clinical benefit

Efficacy

This reviewer evaluated data from all three studies and previously submitted NDAs for the treatment of MDS. The response rates (a rolling 56 days/8 weeks of freedom from transfusion) for the del 5 MDS population in studies MDS-003 and MDS-001 are approximately 65%. The response rate (transfusion independence for 8 weeks) for the non-del 5 MDS population is 21% in MDS-002. The response rates for the placebo/supportive care arms in recently submitted NDAs are 20-30%. In MDS-003, the duration of transfusion independence for some responding patients was greater than a year, suggesting clinical benefit.

Accepting the single arm study design with all its flaws, the MDS-003 study's result suggest that 10 mg Revlimid is efficacious for the treatment of low to intermediate-1 risk del 5q MDS patients with transfusion-dependent anemia. However, the safety of this dose is a concern.

Safety/Dose Regimen Issues

The choice of 10 mg dose for the MDS-003 was based on the results from the MDS-001 study, a study that enrolled both del 5 q and non-del 5 q MDS patients. In that study 70% of patients were non-del 5 q MDS. These patients appeared better able to tolerate the 10 mg regimen as evidence by the dose reduction and safety results when studies MDS-002 and MDS-003 are compared. Approximately 80% of the del 5 q MDS patients treated with 10 mg continuous or syncopated (21days/28 days) dosing had either a dose reduction or dose delay. Thirty-four percent of patients had an additional (second) dose reduction/delay. In contrast, 47% of the non del 5 q MDS patients had a dose reduction or delay.

Few del 5 q MDS patients initiated therapy on the 5 mg dose. Only 3 del 5 q MDS patients are started initially on the 5 mg dose in the MDS-001 and MDS-003 studies. Two of those patients achieve transfusion independence for 8 weeks.

Reproductive Safety

In addition, the applicant's submission had an incomplete reproductive toxicity study. The Agency's pharmacology/toxicology review team will request at least one additional study to be performed.

<u>Recommendation</u>

Based on the strong comments made by several ODAC members stating that hematologists and oncologist are experienced enough to appropriately dose reduce/delay when toxicity arises and the suggested efficacy in the MDS-003 study, this reviewer recommends full approval provided the sponsor agrees to the following:

1) Strong labeling: The labeling should include Black box warnings and bolded warnings regarding the prevention of fetal exposures, 80% dose reduction and dose delay seen in the del 5 q MDS population, and the 80% grade 3 and 4 adverse event data seen in MDS-003. The labeling should also include weekly peripheral blood counts

2) Risk Management Plan: Due to lenalidomide's structural similarity to thalidomide and the inadequate developmental toxicity study, this reviewer recommends that a risk management program very similar to that for thalidomide be instituted to prevent the risk of fetal exposure until developmental toxicity issues have resolved (new studies have been performed and undergone Agency review).

3) Submission of the ongoing European study when completed. The sponsor has proposed study CC-5013-MDS-004, a randomized, double-blind, placebo-controlled, multicenter, 3-arm study of the efficiency and safety of 2 doses of lenalidomide (5 mg daily versus 10 mg days 1-21, 7 days rest (28 day cycle)) versus placebo in red blood cell (RBC) transfusion-dependent subjects with low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a del 5q cytogenetic abnormality. This study will be conducted in Europe. The primary endpoint is RBC transfusion independence for ≥ 26 weeks (182 days).

4) Submission of adequate reproductive safety studies for the Agency to review.

Background:

MDS

At the present time, myelodysplasia is an incurable and progressive disease with an estimated 15,000 – 20,000 new cases diagnosed each year in the US. The myelodysplastic syndromes (MDS), formerly called pre-leukemia or "smoldering" leukemia, consist of a group of heterogeneous diseases characterized by ineffective hematopoiesis leading to one or more peripheral cytopenias (neutropenia, anemia, thrombocytopenia) and progressive bone marrow failure. Although the disorder can be found in children as well as adults, the highest prevalence occurs in those over 60 years of age.

Treatment for MDS ranges from supportive care to bone marrow transplantation. Remissions do not occur without treatment. The only hope for a cure is an allogeneic bone marrow transplantation (AlloBMT). Few MDS patients are eligible for an AlloBMT because of the age limitation of this procedure (i.e., less

than 65). Recently some older patients with MDS have been undergoing nonmyeloablative therapy. Most patients receive supportive care which may include cytokine therapy (erythropoietin, granulocyte-colony stimulating factor, granulocyte-macrophage colony stimulating factor), red blood cell and platelet transfusions, and prophylactic antibiotics. The only approved therapy for MDS is Vidaza (azacitadine). Patients whose disease responded to Vidaza experienced clinical benefit such as elimination of the need for red blood cell transfusions. Vidaza responded patients also achieved other benefits such as an improvement in neutropenia and thrombocytopenia and for some patients normalization of peripheral blood counts and loss of marrow dysplasia.

Regulatory History

The IND was opened on March 31, 2000. Celgene requested Fast Track Designation on December 23, 2002. The application was denied because no efficacy data on use of Revlimid in the treatment of MDS and plan for drug development were submitted. The application was resubmitted in February 2003 and Fast Track designation was granted on April 11, 2003 based on preliminary results from the MDS-001 study and a drug development plan which included a controlled trial. The Agency has met several times with Celgene for pre-NDA meetings prior to submission of the NDA.

For additional details, please see Dr. Hazarika's review.

Chemistry:

From the ODAC briefing document

Lenalidomide and thalidomide are structurally related as they both possess piperidindione and indoline moieties. They both have an asymmetric center and both are manufactured as racematic mixtures. Lenalidomide lacks the symmetrical indolindione of thalidomide and bears an amino function on its aromatic ring system which contributes to its lower lipid solubility.

Based upon the similarity in structure, one would predict that thalidomide and lenalidomide would be metabolized and degrade in a similar manner. The asymmetric carbon on each molecule bears an acidic hydrogen and both molecules readily enolize. Imide hydrolysis and amide hydrolysis would explain the respective drug-derived moieties formed by each. Their degradative pathways, while apparently similar, have not resulted in any common degradation products in animals.

The drug-degradation products have been confirmed through [illegible] and [illegible] when studied in rat and monkey.

For further details, please see Dr. Sarker's Chemistry, Manufacturing, and Control review of this NDA.

The reviewer did not identify any phase 4 commitments.

Nonclinical Pharmacology and Toxicology Information:

Mechanism of Action

From the ODAc briefing document
Lenalidomide and the parent compound, thalidomide, possesses both immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines, increased the secretion of anti-inflammatory cytokine from peripheral blood mononuclear cells, and induced T-cell proliferation. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide but not thalidomide, was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Thalidomide is considered less potent relative to lenalidomide, depending upon the assay used. The mechanisms of action responsible for anticancer activity for either compound remains to be fully explored.

Developmental toxicology studies were conducted in rats and rabbits to examine possible teratogenic effects of lenalidomide. The rabbit study contained a thalidomide arm as a positive control, as the New Zealand White rabbit is known to be sensitive to thalidomide's teratogenic effects. Teratogenic effects were not seen in either study with lenalidomide. However, the rat is not sensitive to thalidomide and thus is not considered a useful model for evaluating thalidomide-like effects. The highest dose used in the pivotal rabbit teratogenicity study did not meet the level of being sufficiently maternally toxic, a standard endpoint in teratogenicity studies to assess appropriate dosing. Maternal toxicity was observed in rabbits at higher doses in the dose-range finding study.

Thalidomide is a well-known teratogen, but the mechanism of teratogenicity is not established. It is not known whether thalidomide itself, degradation product(s), or both are responsible for teratogenicity. Thalidomide derived products have been identified in animals and humans; lenalidomide derived products have been identified in animals but not searched for in humans. It is likely that both compounds share similar metabolic or degradative pathways. Modeling suggests that the intermediates and final products would be structurally similar, but chemically unique, for each drug.

The pharmacology toxicology team finds the submitted developmental toxicity/reproductive safety studies to be inadequate and recommends that additional studies be performed as phase 4 commitments.

For further details, please see the Pharmacology and Toxicology reviews of this NDA.

Human Pharmacology:

From the ODAC Briefing Document

Lenalidomide pharmacokinetics in patients with renal impairment or hepatic impairment have not been studied. The effects of age on lenalidomide pharmacokinetics have not been evaluated. No pharmacokinetic data are available in patients <18 years. The effects of gender on lenalidomide pharmacokinetics have not been studied. Pharmacokinetic differences due to race have not been studied. A search for circulating lenalidomide metabolites in human biomaterials (plasma, urine or feces) was not performed.

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) identified the lack of a renal impairment study for Revlimid, which is renally excreted, to be a concern.

The Office of Clinical Pharmacology and Biopharmaceutics phase 4 commitment is that the sponsor conduct a renal impairment study.

Reviewer's Comment: Enrolled patients in the clinical studies submitted were required to have a serum creatinine < 2.5 mg/dl.

Clinical Studies Summary:

Three single arm, open-label studies are submitted for review. MDS-002 and MDS-003 are multicenter, whereas MDS-001 is single center. For all studies the crucial inclusion criteria were:

1) diagnosis of low- or intermediate-1- risk IPSS MDS
2) RBC transfusion- dependent anemia defined as having received ≥ 2 units of RBCs within 8 weeks of study treatment
3) Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days of starting study drug. In addition, sexually active WCBP must agree to use adequate contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) while on study drug. WCBP must agree to have pregnancy tests every 4 weeks while on study drug

The crucial exclusion criteria were:

1) Pregnant or lactating females
2) Proliferative (WBC ≥ 12,000/µL) chronic myelomonocytic leukemia (CMML)
3) Use of hematopoietic growth factors within 7 days of the first day of study drug treatment
4) Chronic use (> 2 weeks) of greater than physiologic doses of a corticosteroid agent (dose equivalent to > 10 mg/ day of prednisone) within 28 days of the first day of study CC- 5013 treatment
5) Use of experimental or standard drugs (i.e. chemotherapeutic, immunosuppressive, and cytoprotective agents) for the treatment of MDS within 28 days of the first day of study CC- 5013 treatment.
6) Use of any other experimental therapy within 28 days of the first day of study CC- 5013 treatment.
7) Renal insufficiency (patients with a serum creatinine ≥2.5 mg/dl)

MDS-001 inclusion and exclusion criteria differed slightly in that patients with hemoglobin less than 10 mg/dl were included in the study even if they did not require transfusions.

Table of Revlimid Studies

Study Identifier	Study Design	Patient Population	Dose escalation range and regimen (number of pts)	Response criteria used for response rate (RR) determination*
MDS-001	Pilot, dose ranging study	45 MDS pts with either transfusion dependence or hemoglobin less than 10	25 mg continuous (13 pts); 10 mg continuous (12 pts); 10 mg syncopated (20 pts)	Major and minor response
MDS-002	Dose regimen study	215 MDS pts without del 5 q with transfusion dependence	10 mg continuous (100 pts); 10 mg syncopated (115 pts)	Transfusion free for rolling 56 weeks
MDS-003	Dose regimen study	148 MDS pts with del 5 q with transfusion dependence	10 mg continuous (103); 10 mg syncopated (45)	Transfusion free for rolling 56 weeks

*Modified from IWG criteria
Reviewer's Table

The primary endpoint for the MDS-003 study was RBC transfusion independence defined as the absence of the intravenous infusion of any RBC transfusion during any consecutive "rolling" 56 days during the treatment period, i.e., days 1 to 56, days 2 to 57, days 3 to 58 etc. and at least a 1 gm/dl increase in hemoglobin over baseline.

Reviewer's Comment: The transfusion independence criteria in the MDS-003 study are modified from the Independent Working Group criteria. The IWG criteria are more stringent in that those criteria require at least a 2 gm/dl hemoglobin increase and that the responder be not receiving cytotoxic therapy at the time of response.

This review focuses on the del 5 q MDS population as this is the indicated population for Revlimid. These patients were enrolled in MDS-001 and MDS-003.

Relevant Concomitant Medication Use and Prior Medical History
Although a number of medications were used by patients on studies, this reviewer was impressed by the use of medications to treat MDS or complications of MDS. For MDS-003, 31.8% of patients used iron chelating agents. For the MDS-003 study, approximately 90/148 (61%) of patients had hemachromatosis as a diagnosis with an additional 4/148 (2.7%) of patients had hemosiderosis. For MDS-003, 17/148 (11.5%) had used injectable forms of erythropoietin.

Prior Transfusion History
Prior transfusion history is limited by baseline data collection. For some patients, the only baseline data is that collected from the 8 weeks prior to study entry. Per the medical efficacy reviewer the median number of transfused units is 6 for the MDS-003 study.

For the MDS-003 study, the median time from diagnosis of MDS is 3.4 years (0.1-20.7).

For other details on enrollment criteria and demographics for these studies as well as analysis populations, please see Dr. Hazarika's review.

Results
Trial results for MDS patients (using sponsor's data)

Study Identifier	RR 25mg	RR 10 mg continuous	RR 10 mg syncopated	RR del 5 q MDS	RR non-del 5 q MDS population
MDS-001 (N=43)*	3/13 (23%)	5/12 (42%)	2/18* (10%)	9/13 (70)%	8/30 (27%)
MDS-002 (N=211)**	Not applicable	18/98 (18%)	28/113 (25%)	Not applicable	46/211 (22%)
MDS-003 (N=148)***	Not applicable	67/101 (66%)	25/44 (57%)	92/145 (63%)	Not applicable

*Two patients excluded from this table had CML.
**For Study MDS-002: Four patients did not have MDS. Two patients in each dose regimen did not have MDS. Two patients started on 5 mg continuous and one had a major response.
***For Study MDS-003: Three patients did not have MDS. One patient was started on 5 mg and had a major response.
Reviewer's Table

Comment Regarding Transfusion Independence Response Rates: Similar analyses of transfusion-independence in MDS applications submitted for review have suggested that 20%-30% of transfusion-dependent MDS patients on the supportive care/placebo arm can achieve a transfusion-free period of 8 weeks or more.

In MDS-003, in general patients with more than one genetic abnormality did not do as well as those with the isolated del 5 q MDS.

Below is this reviewer's table of RR by cytogenetic abnormality. Although it is difficult to ascribe categories with this type of data, this reviewer reviewed the dataset CYTO and categorized patients as having isolated del 5 or not. To have an isolated del 5, the deletion had to involve some part of q31-33.

Reviewer's Table: RR in MDS by cytogenetic abnormality

Study Identifier	RR isolated del 5 MDS	RR del 5 MDS plus other abnormality
MDS-001 (N=43)*	9/13 (70%)	1/1 (100%)
MDS-003 (N=145)	62/89 (70%)	32/56 (57%)

Reviewer's Comment: These results agree with the sponsor's analyses.

The sponsor performed additional sensitivity analyses of the hemoglobin (Hgb) change from baseline Hgb level by different computations. In sensitivity analysis #1 (pre mean-post mean): the mean baseline Hgb value in the 56-day period preceding first dose of study drug is subtracted from the mean Hgb value during the response period (excluding the 30 days after the last transfusion prior to the response period). In sensitivity analysis 2 (pre min-post mean): the minimum baseline Hgb in the 56-day period preceding first dose of study drug is subtracted from the mean Hgb value during the response period (excluding the 30 days after last transfusion prior to the response period).

The table below shows the hemoglobin change based on the different sensitivity analyses.

Sponsor's Table: Sensitivity Analyses of Change from Baseline Hemoglobin

Analysis	Hemoglobin (g/dL)							
	ITT				**MITT**			
	N	Median at baseline	Median during Response	Median Change	N	Median at baseline	Median during Response	Median Change
Original NDA	95	7.8	13.3	**5.2**	57	7.7	13.6	**5.5**

Sensitivity 1	91	8.7	12.3	**3.2**	56	8.6	12.5	**3.6**
Sensitivity 2	95	7.8	12.2	**4.2**	57	7.7	12.4	**4.6**

Response to FDA request for information, August 24, 2005.
N=number of transfusion independence responders

Reviewer's Comment: Due to the confounding transfusions in the pre-study period, an accurate assessment of hemoglobin benefit is extremely difficult and subject to bias. The above analysis highlights one of the main problems with determining the effectiveness of this agent with the single arm trial design.

In MDS-003, major cytogenetic responses defined as no detectable cytogenetic abnormality if present at baseline were observed in approximately 41% of patients.

Reviewer's Comment: The development of a new clone would not effect the major cytogenetic response rate.

For additional details regarding response criteria, definitions, and secondary endpoint results, please see the Medical Officer's review of this NDA.

Overall Safety Assessment

Two major safety concerns exist with this dose and the continuous and syncopated regimens. The first is the concern for tetratogenicity because of the inadequacy of the rat and rabbit study for maternal and fetal toxicity. The second is the high number of del 5 q MDS patients who had to have either a dose reduction/delay with either the 10 mg continuous or syncopated dosing regimens due to toxicity.

Adverse events (AEs) seen in greater than 5% of patients included: gastrointestinal (diarrhea, constipation, nausea, vomiting, abdominal pain, and dry mouth), skin and subcutaneous tissue disorders (pruritis, rash, dry skin, night sweats), general (fatigue, edema, pyrexia, asthenia, edema, pain including chest pain), hematologic (neutropenia, thrombocytopenia and anemia), respiratory (cough, dyspnea, nasopharyngitis, epistaxis), musculoskeletal (muscle cramp, arthralgia, back pain, pain in limb, myalgia, swelling), nervous system (headache, dizziness, and dysgeusia), infection, metabolism and nutrition (anorexia and decresed appetite), eye disorder (blurred vision), and psychiatric disorder (insomnia). The 2 most frequent AEs were hematologic followed by gastrointestinal.

The most common serious adverse events (SAEs) seen in greater than 1% of the patients were gastrointestinal (diarrhea), hematologic (anemia, neutropenia, thrombocytopenia, pancytopenia) general (pyrexia, asthenia), respiratory (pleural effusion, dyspnea), infection, metabolism and nutrition (dehydration), cardiac

disorder (failure, atrial fibrillation) and vascular disorder (deep vein thrombosis). The 2 most common SAEs appeared to be infections and hematolgic.

Interestingly, there appeared to be a difference in serious adverse event rates between the 2 MDS populations when MDS-002 and MDS-003 are compared. The Agency safety reviewer's table below illustrates the differences in some adverse event rates between the 2 studies for the 10mg dosing regimens combined (continuous and syncopated).

Key Differences in the Frequency of Serious Adverse Events between MDS-003 and MDS-002 (Reviewer's Table)

Serious Adverse Event	MDS-003, N = 148	MDS-002, N = 215
Percentage of patients with SAE	41.2%	35.8%
Blood -Neutropenia and febrile neutropenia -Thrombocytopenia -Anemia -Pancytopenia	 9.5% 3.4% 2.7% 2.0%	 2.8% 0.9% 3.7% 0.9%
Infections -Pneumonia, pneumonitis, sepsis, infection	13.6%	5.1%
Vascular -Pulmonary embolism -Deep venous thrombosis	 2% 2%	 0% 0%

Data source: Table 33 (MDS-003 Study Report) and Table 34 (MDS-002 Study Report)

Reviewer's Comment: The efficacy data and the serious adverse event data above seem to suggest that the del 5 q MDS population appear more sensitive as well as responsive to the drug.

In MDS-003, 80% of patients had any dose reduction/delay, while another 34% had an additional dose reduction/delay. The majority of patients had both a dose reduction and a delay. Lower percentages of patients in the MDS-002 study had any dose reduction/delay (47%) and a second dose reduction/delay (23%).

In MDS-003, the most common adverse events and serious adverse events reported in the studies were hematologic (neutropenia and thrombocytopenia) and infections. Eighty percent of patients had grade 3 or 4 adverse events.

Reviewer's Comment: Due to the single arm study design it is difficult to determine whether the need for dose reductions is due to the underlying MDS or lenalidomide or both.

The sponsor performed subgroup analyses. Patients older than 65 years of age had more SAEs than subjects 65 years of age and younger (42.1%, 120/285 vs. 28.2%, 31/110). There was no significant difference between males and females in the frequencies of SAEs (38.0% vs. 38.5%). More DVTs occurred among females (2.1%) than in males (0%). Ethnicity analyses were not performed as 94% of the population was white. In general the Agency safety reviewer agreed with the sponsor. The Agency safety reviewer stated in his review that "All of the above categories (hematological, infectious, respiratory, gastrointestinal, vascular, and general disorders) were all about twice as frequent in the over 65 year old patients. "

Deaths

Although the Agency and sponsor agreed that the on study death rate was approximately 7%, some differences between the safety reviewer and the study report exist in attribution of death. Attribution of death in a single arm trial can be difficult. Also, noted in some cases, patients died either during study or of ongoing complications following their termination from study. Twenty-eight on-study deaths (either during the study or within 30 days after the last visit date) occurred in 408 subjects. The 120-Day Safety Update contains narratives of a total of 42 deaths.

Reviewer's Comment: In a single arm study, it is difficult to establish causality. In the absence of certain data, this reviewer would attribute the possibility that lenalidomide contributed at least in part to some of the deaths.

For further details, please see the Medical Officers' review of this NDA.

Ongoing Study

The sponsor also has an ongoing study, CC-5013-MDS-004, a randomized, double-blind, placebo-controlled, multicenter, 3-arm study of the efficiency and safety of 2 doses of lenalidomide (5 mg daily versus 10 mg days 1-21, 7 days rest (28 day cycle)) versus placebo in red blood cell (RBC) transfusion-dependent subjects with low-or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a del 5q cytogenetic abnormality. This study is ongoing in Europe. The primary endpoint is RBC transfusion independence for ≥ 26 weeks (182 days).

Division of Scientific Investigations

For additional details, please see the Division of Scientific Investigations report.

Discussion

This reviewer remains concerned about the potential for fetal exposure and the high rate of dose reduction/delay in the MDS-003 study in the indicated population. Once a drug is approved and marketed, the adverse events usually increase as the drug is no longer being monitored and administered under the well controlled conditions of an investigational trial.

Conclusions and Recommendations

Based on the strong comments made by several ODAC members stating that hematologists and oncologist are experienced enough to appropriately dose reduce when toxicity arises and the suggested efficacy in the MDS-003 study, this reviewer recommends full approval provided the sponsor agrees to the following:

1) Strong labeling: The labeling should include Black box warnings and bolded warnings regarding the prevention of fetal exposures, 80% dose reduction and dose delay seen in the del 5 q MDS population, and the 80% grade 3 and 4 adverse event data seen in MDS-003. The labeling should also include weekly peripheral blood counts

2) Risk Management Plan: Due to lenalidomide's structural similarity to thalidomide and the inadequate developmental toxicity study, this reviewer recommends that a risk management program very similar to that for thalidomide be instituted to prevent the risk of fetal exposure until developmental toxicity issues have resolved (new studies have been performed and undergone Agency review).

3) Submission of the ongoing European study when completed. The sponsor has proposed study CC-5013-MDS-004, a randomized, double-blind, placebo-controlled, multicenter, 3-arm study of the efficiency and safety of 2 doses of lenalidomide (5 mg daily versus 10 mg days 1-21, 7 days rest (28 day cycle)) versus placebo in red blood cell (RBC) transfusion-dependent subjects with low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a del 5q cytogenetic abnormality. This study will be conducted in Europe. The primary endpoint is RBC transfusion independence for ≥ 26 weeks (182 days).

4) Submission of adequate reproductive safety studies for the Agency to review.

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/s/

Ann Farrell
10/4/2005 04:05:50 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-880
Submission Code	N 000
Letter Date	April 7, 2005
Stamp Date	April 7, 2005
PDUFA Goal Date	October 7, 2005
Efficacy Reviewer	Maitreyee Hazarika, MD
Safety Reviewer	Edvardas Kaminskas, MD
Medical Team Leader	Ann Farrell, MD
Statistical Reviewer	Yuan Li Shen, DrPh
Statistical Team Leader	Raji Sridhara, PhD
Review Completion Date	September 26, 2005
Established Name	Lenalidomide
(Proposed) Trade Name	Revlimid®
Therapeutic Class	Immunomodulatory Drug
Applicant	Celgene Corporation
Priority Designation	P
Formulation	Oral
Dosing Regimen	10 mg daily or 10 mg x 21 days/28 day cycle

Indication Treatment of patients with transfusion dependent anemia due to low or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities

Intended Population Patients with transfusion dependent anemia due to low or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based on this review of NDA 21-880, Lenalidomide (Revlimid®) should receive regular approval for the treatment of patients with transfusion-dependent anemia due to low or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Lenalidomide was brought before the Oncology Drug Advisory Committee on Sept 14, 2005. The ODAC committee agreed that the benefit versus risk analysis warranted approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Due to the inadequacy of the reproductive safety assessment, FDA has a concern regarding the risk of teratogenicity and the potential fetal exposure to lenalidomide. The sponsor should implement a risk management plan (S.T.E.P.S. program) until the reproductive safety tests have been completed satisfactorily.

Of concern is also the high incidence of neutropenias and thrombocytopenias requiring dose modifications. The risk management plan should include close monitoring of cytopenias.

A Black Box Warning should be placed in the label to include the unknown pregnancy risk and the recommendation to prevent fetal exposure and should also include weekly monitoring of neutropenias and thrombocytopenias.

1.2.2 Required Phase 4 Commitments

Not applicable.

1.2.3 Other Phase 4 Requests

Celgene has a phase 3 study (CC-5013-MDS-004) ongoing in Europe. It is a randomized, double-blind, multicenter, placebo-controlled 3-arm study evaluating a lower dose of 5 mg daily versus 10 mg for 21 days in a 28 day cycle, administered to red blood cell (RBC) transfusion-dependent adult patients with low or intermediate-1 risk myelodysplastic syndrome (MDS) associated with a 5q [31] deletion (del 5q) cytogenetic abnormality. Patients with MDS clones that have a del 5q cytogenetic abnormality plus other additional cytogenetic abnormalities are eligible. The primary endpoint is RBC transfusion independence for ≥26 weeks.

Reproductive safety assessment in this drug was inadequate as reviewed by the pharmacology/toxicology team. Celgene is required to conduct further tests to adequately assess the risk of teratogenicity.

A renal impairment study should be conducted.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Celgene Corporation has submitted a New Drug Application (NDA) for lenalidomide for regular approval based primarily on the results from a single-arm study in patients with transfusion dependent anemia due to low or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5 (q 31-33) (del 5q) cytogenetic abnormality with or without additional cytogenetic abnormalities.

The sponsor submitted three single-arm, open-label studies in the application's clinical section. CC-5013-MDS-003 was a single-arm, phase 2, multicenter study in transfusion-dependent MDS patients with an International Prognostic Scoring System (IPSS) of low or intermediate-1 risk with an associated del 5q. CC-501-MDS-001 was a pilot, phase 1/2 , single-center, dose-finding study in patients with MDS. CC-5013-MDS-002 was a phase 2, multicenter study in transfusion-dependent MDS patients with an IPSS of low or intermediate-1 risk without an associated del 5q.

Patients enrolled in study CC-5013-MDS-002 and CC-5013-MDS-003 were transfusion-dependent as defined by a requirement of 2 or more units of packed red blood cell (RBC) units 8 weeks prior to start of study drug. Patients enrolled in study CC-501-MDS-001 required to be transfusion-dependent as defined by a requirement of $\geq$ 4 RBC units 8 weeks before enrollment, or have less than a certain hemoglobin level.

CC-5013-MDS-003 is the main study for consideration of this application with CC-501-MDS-001 containing supportive data. CC-5013-MDS-002 serves as a reference for the response rate in a population that may not be sensitive to lenalidomide.

1.3.2 Efficacy

The NDA submission consisted of two single-arm, phase 2 clinical studies relevant to the proposed indication, one very small. The patient population consisted of patients with transfusion-dependent anemia due to low or intermediate-1 risk MDS associated with del 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. The transfusion entry criterion is based on the RBC units transfused in the 8 weeks prior to start of study drug. The median number of RBC units transfused was 6. The main study enrolled 148 patients using oral lenalidomide as a single agent given in 2 dose regimens, 10 mg daily or 10 mg for 21 days in a 28-day cycle.

The primary endpoint was the determination of RBC transfusion independence. A rolling 56 day (8 week) transfusion free period was used for transfusion independence response. The RBC transfusion independence response of 67% (99/148) was seen with ≥1.0 g/dL increase in hemoglobin. These responses lasted for a minimum of 8 weeks with a median duration of transfusion independence in responders of 52 weeks. Major cytogenetic responses were seen in 43% (52/120) patients in whom follow-up bone marrows were present. The study was not designed or powered to prospectively compare the efficacy of the 2 lenalidomide dosing regimens.

The supportive study had 10 evaluable patients supporting the proposed indication.

FDA performed an analysis in those patients who met the major eligibility criteria. Ninety-six patients had transfusion-dependent anemia due to a diagnosis of low or intermediate-1 risk MDS associated with a del 5q chromosomal abnormality with or without additional cytogenetic abnormalities. The results were consistent with the intent-to-treat population.

The demonstration of the clinical benefit of RBC transfusion independence with median duration of responses lasting for a year, although substantial, is based mainly on one single-arm, multicenter trial. A randomized controlled trial is ongoing at present and the sponsor has a Phase IV commitment.

1.3.3 Safety

All MDS patients, those with 5q deletion (*del 5q*) and those without 5q deletion (*non-del 5q*), had adverse events during treatment with lenalidomide. In absence of a best supportive care control arm, it is not possible to assign adverse events to lenalidomide instead of MDS. The most common reported adverse events were neutropenia and thrombocytopenia. They were also the most common grades 3 or 4 adverse events, the most common serious adverse events (except for pneumonia), the most common events leading to discontinuations from studies, and the most common events leading to dose interruptions and dose reductions. Less frequently reported were rashes, infectious events, fatigue, bleeding events, gastrointestinal events, and others. A very high percentage (about 80%) of patients reported grades 3 or 4 events. There was a markedly different adverse event profile in the *del 5q* population from that in *non-del 5q* population. The *del 5q* patients had approximately twice as high frequencies of neutropenia and of thrombocytopenia (all grades and grades 3 – 4 in both cases), a one-third higher frequency of infections, and higher incidences of bleeding and of venous thromboembolism than *non-del 5q* patients.

The increased sensitivity to lenalidomide in the *del 5q* population may account for the much greater need for dose reductions and dose interruption of the 10 mg/day starting dose (administered by either of the two schedules) in the *del 5q* population compared to *non-del 5q* population (80% of patients vs. 47% of patients). <u>These data suggest that the starting dose of lenalidomide is too high for the *del 5q* population, and that careful monitoring is required for dose adjustment.</u> Because neutropenia and thrombocytopenia can occur rapidly and unpredictably in some cases, and because the rate of recovery can be delayed, lenalidomide should be administered only during the period during which it maintains patients free of

transfusions. In cases of patients who do not respond to lenalidomide treatment, the treatment should be discontinued once a response is unlikely to occur (about 16 weeks).

Patients older than 65 years of age had a higher incidence of serious adverse events than younger patients, and a greater proportion of them discontinued from the studies because of adverse events. There were no differences in the overall frequencies of serious adverse events between genders, and approximately proportions discontinued from the studies because of adverse events. Patients with renal impairment were excluded from the studies. Because lenalidomide is mainly excreted by the kidney, renal function should be carefully monitored to avoid excess toxicity during periods of decreased renal function.

Until definitive toxicology studies have determined that lenalidomide, unlike thalidomide, does not pose risk as a human teratogen, the S.T.E.P.S.program should be implemented.

The benefit of lenalidomide treatment in the del 5q population is substantial; the incidence of severe adverse events, some life-threatening, is high. Therefore, a balanced medical evaluation is required before prescribing lenalidomide followed by careful monitoring and dose adjustment.

A Black Box Warning should be placed in the label to include the unknown pregnancy risk and the recommendation to prevent fetal exposure and should also include weekly monitoring of neutropenias and thrombocytopenias.

1.3.4 Dosing Regimen and Administration

The recommended dose is 10 mg daily or 10 mg for 21 days in a 28-day cycle. Dosing issues are addressed in detail in the Safety Section. In the submitted studies, dose delays or reductions were seen in 80% of patients on the proposed dose regimens. Thus, the recommended dose is too high for most patients.

1.3.5 Drug-Drug Interactions

A clinical drug interaction study was performed to evaluate the effect of lenalidomide on the pharmacokinetics and activity of warfarin. Neither activities nor pharmacokinetics of either drug were altered by co-administration.

1.3.6 Special Populations

In the main study, the median age of patients overall was 70 years. The majority of the patients were female (66%) and Caucasian (97%). Sixty eight percent of the patients were aged 65 years and older.

The transfusion-independent responses were similar between age and gender subgroups.

The frequency of serious adverse events(SAEs) was higher in subjects >65 years of age than in younger subjects (42% vs. 28%). A greater proportion of subjects >65 years of age discontinued from the studies because of adverse events than the proportion of younger subjects (26% vs.

16%). There were no differences between genders in the overall frequencies of SAEs and in percentages of patients who discontinued from studies.

Lenalidomide has an orphan drug status, and pediatric studies are not required.

Patients with serum creatinine ≥2.5 mg/dL were excluded. No renal impairment study was performed. Patients with renal or hepatic impairment were excluded. The study excluded patients with a serum creatinine >2.5 mg/dL. No renal impairment study was performed. Because lenalidomide is mainly excreted by the kidney, renal function should be carefully monitored to avoid excess toxicity.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Established name and proposed trade name:	Lenalidomide (Revlimid ®)
Chemical class:	3-(4'- amino- 1,3- dihydro- 1- oxo- 2H- isoindol- 2- yl)- 2,6- piperidinedione
Pharmacological class:	Immunomodulatory Drug

Proposed indication: Treatment of patients with transfusion-dependent anemia due to low or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Dosing regimen: 10 mg daily.

2.2 Currently Available Treatment for Indications

Recent FDA Approved Drugs for the Treatment of MDS

Azacitidine (Vidaza®) for injectable suspension received regular approval by the FDA in 2004 for the treatment of patients with the following myelodysplastic syndrome subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia and requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.

Effectiveness was demonstrated in one randomized, controlled trial of comparing azacitidine administered subcutaneously with best supportive care (observation group) and in two supportive single-arm studies, one in which azacitidine was administered subcutaneously and the other in which it was administered intravenously. The primary efficacy endpoint was the overall response rate, consisting of complete or partial normalization of blood cell counts and of bone marrow morphology. Response rate in the azacitidine arm was about 16% with no responses in the observation arm. Approval was based on a favorable safety profile and a clinical benefit of eliminating transfusion dependence and complete or partial normalization of blood counts and bone marrow blast percentages in responding patients.

Non-approved Drugs in Current Usage

Erythropoietin injection (Procrit®) is indicated for the treatment of anemia in cancer patients on chemotherapy to decrease the need for transfusion in patients who will be receiving concomitant

chemotherapy for a minimum of 2 months. Procrit may decrease transfusion requirements in 15-25% of patients with MDS, usually those with low plasma levels of erythropoietin. The addition of G-CSF may increase the response rate, mostly in patients with low transfusion requirements.

Darbepoetin alfa (Aranesp®) was used to treat 37 anemic patients with low- to intermediate-1 risk MDS for 12 weeks. An erythroid response (13 major, 2 minor, according to the IWG criteria) was seen in 15 (40.5%) patients. These were maintained for 7-22 months in 13 of the responders (1).

Antithymocyte globulin (Atgam, ATG) has been associated with transfusion independence in 11 (44%) of patients out of 25 transfusion-dependent MDS patients (with <20% blasts) treated, with a median duration of 10 months (range 3-38 months). Overall survival was 84% at 38 months (2).

5-Aza-2-deoxycytidine (decitabine) was used to treat 66 patients in a phase 2 study with RAEB or RAEB-t (3). The overall response rate was 49%. The actuarial median response duration was 31 weeks and median survival was 22 months. In addition, 31% of patients with cytogenetic abnormalities presented before treatment achieved a cytogenetic response which conferred a survival advantage to these patients. At present, decitabine is not marketed.

2.3 Availability of Proposed Active Ingredient in the United States

This drug is not currently marketed in this country.

2.4 Important Issues With Pharmacologically Related Products

Lenalidomide is a member of a class of pharmaceutical compounds known as immunomodulatory drugs with a spectrum of activity that is not fully characterized.

Thalidomide (Thalomid®, Celgene Corporation), an immunomodulatory drug, was approved by the FDA in July 1998 (NDA 020785) for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum. It is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of erythema nodosum leprosum recurrence.

The most serious toxicity associated with thalidomide is its documented human teratogenicity. The risk of severe birth defects, primarily phocomelia or fetal death, is extremely high during the critical period of pregnancy. Somnolence, dizziness, and rash are the most commonly observed adverse events associated with the use of thalidomide. Thalidomide is also associated with drowsiness/somnolence, peripheral neuropathy, orthostatic hypotension, deep venous thrombosis, neutropenia, and HIV viral load increase. Hypersensitivity to thalidomide and bradycardia in patients treated with thalidomide have been reported.

Thalidomide is under investigation for use in MDS and in multiple myeloma (MM).

Of major concern to the FDA is whether the structural similarity between thalidomide and lenalidomide may predict for the reproductive toxicity with this class of drugs. The embryo-fetal development in lenalidomide has not been adequately addressed. Please refer to the Pharmacology/Toxicology review for further details.

2.5 Presubmission Regulatory Activity

April 27, 2000: Investigational New Drug (IND) # 60100 allowed to proceed

May 1, 2002:

May 1, 2002:

July 25, 2002:

December 23, 2002: The Fast Track Designation was denied due to lack of a drug development plan that included a randomized, controlled trial.

January 23, 2003:

April 11, 2003: Fast Track Designation granted to treat patients with transfusion-dependent MDS based on preliminary results from study 001 and a drug development plan which included MDS-002 (Phase 2 open-label study) and MDS-00X, a Phase 3 multicenter, randomized, controlled study.

June 6, 2003: End-of-Phase 1 Myelodysplastic Syndrome
FDA agreed that transfusion independence with an appropriate trial design could be an acceptable endpoint to demonstrate clinical benefit. However, the short time-frame to establish a baseline for the required transfusion-dependence entry criteria was discussed and the short time-frame to establish efficacy (i.e., 8 weeks) in a patient population that will survive for years and potentially use this drug for years was discussed. RBC transfusion independence as an endpoint may not be acceptable if there is an increased need for platelet transfusions. The duration of response of 8 weeks may not be acceptable where the median survival is measured in years. FDA recommended randomized, controlled trials using an endpoint with a longer duration of response.

January 29, 2004: Granted orphan drug status for the treatment of MDS on Designation Request # 03-1803. Celgene expects to be granted 7 years marketing exclusivity from the date of approval for the use lenalidomide in MDS, under Section 527(a)(3) of the Food Drug and Administration Act.

August 24, 2004: Pre-NDA meeting for MDS
FDA pointed out that despite the discussions in the End-of-Phase 1 meeting, Celgene has pursued a registration strategy based on a single arm study with relatively short duration of response. Results of a single arm trial would only be interpretable if results were outstanding in

duration and number of patients clearly offering irrefutable evidence of a direct drug effect on transfusion requirements.

December 14, 2004: Rolling Review granted for MDS

April 7, 2005: NDA # 21880 Clinical Review submitted

April 20, 2005: —

June 28, 2005: —

July 21, 2005: Sponsor Presentation of MDS NDA # 21880

August 4, 2005: —

August 23, 2005: Risk Management Plan meeting

2.6 Other Relevant Background Information

This drug is not marketed in other countries.

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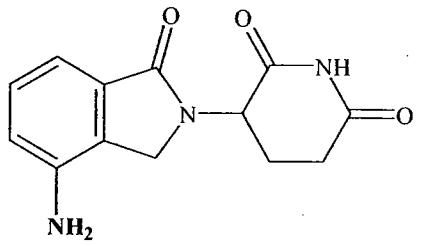
3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

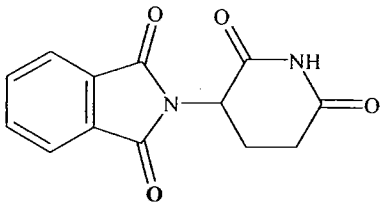
Please see detailed reviews by Drs Hari Sarker, primary reviewer, and Nallaperumal Chidambaram, team leader.

Lenalidomide and thalidomide have similarities in structure. Lenalidomide is an amide and bears an amino group in the aromatic ring whereas thalidomide is an imide. Both possess piperidindione and indoline moieties. Both have an asymmetric center and both are manufactured as racemic mixtures.

Lenalidomide



Thalidomide



3.2 Animal Pharmacology/Toxicology and Reproductive Safety Assessment

Please see detailed reviews by Drs Anwar Goheer, primary reviewer for pharmacology/toxicology, Kimberly Benson, primary reviewer for reproductive safety assessment, and John Leighton, team leader.

Lenalidomide and the parent compound, thalidomide, possesses both immunomodulatory and antiangiogenic properties. The mechanisms of action responsible for anticancer activity remain to be fully explored.

The embryo-fetal development in lenalidomide has not been adequately addressed. Please consult the Pharamacology/Toxicology review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source for this NDA review consisted of datasets and study reports submitted on the two studies: CC-5013-MDS-003 and CC-501-MDS-001. Additional information was submitted in the study CC-5013-MDS-002. Information from IND # 60100 was used. Relevant published literature was reviewed.

The Division of Scientific Investigations (DSI) was consulted. Sites and investigators were identified for DSI to investigate.

Study CC-5013-MDS-003 enrolled 148 patients in 32 centers in the United States and 1 center in Germany.

Study CC-501-MDS-001 enrolled 45 patients at one site in the United States.

Information was also obtained from the Oncology Drugs Advisory Committee held on September 14, 2005. A summary of the questions is in Section 8.5 and a detailed description can be found on the FDA website.

4.2 Tables of Clinical Studies

The following is a list of the clinical studies submitted with the NDA.

1. Study CC-5013-MDS-003
2. Study CC-501-MDS-001
3. Study CC-5013-MDS-002
4. Study 5013-CRPS-001
5. Study CDC-501-MEL-001
6. Study CDC-501-MEL-002

The studies listed are summarized in the table below. All the studies are relevant to safety.

Table 1 Safety Studies Submitted

Study ID	Evaluable Patients	Study Design	Dosing Regimens
CC-5013-MDS-003	94/148	Single arm, open-label, multicenter Phase 2 in low or intermediate-1 risk MDS with 5 (q31-33) deletion	2 dosing regimens: Oral 10 mg daily, 10 mg x 21d/q 28d
CC-501-MDS-001	10/45	Single arm, open-label, single center Phase 1/2 in MDS	3 dosing regimens: Oral 25 mg daily, 10 mg daily, 10 mg x 21d/q 28d
CC-5013-MDS-002	215	Single arm open-label Phase 2 in	2 dosing regimens:

		low or intermediate-1 risk MDS without 5q deletion	Oral 10 mg daily, 10 mg x 21d/q 28d
5013-CRPS-001	40	Open-label Phase 2 in Complex Regional Pain Syndrome	Oral 10 mg daily
CDC-501-MEL-001	295	Randomized, double-blind Phase 2/3 in metastatic malignant melanoma	Oral 5 and 25 mg daily
CDC-501-MEL-002	305	Randomized, double-blind, placebo-controlled Phase 2/3 in metastatic malignant melanoma	Oral 25 mg daily

Derived from Source from CC-5013 5.2 Listing of Clinical Studies

The studies relevant to the efficacy submitted in the application are summarized in the table below.

Table 2 Description of Clinical Efficacy Studies

Clinical Study	Study Design	Dose and Regimen	Primary Endpoint(s)	Evaluable Patients/N
CC-5013-MDS-003	Single arm, open-label, multicenter Phase 2	10 mg daily 10 mg 21d/7 d rest	Transfusion Independence	94/148[a]
CC-501-MDS-001	Single arm, open-label, single center Phase 1/2	25 mg 10 mg daily 10 mg 21d/7 d rest	Major and minor Erythroid Response	10/45[b]

[a] Number of patients evaluated by the sponsor for efficacy in transfusion- dependent anemia due to low- or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5 q cytogenetic abnormality with or without additional cytogenetic abnormalities
[b] Number of patients evaluated by the sponsor for efficacy in transfusion- dependent anemia due to low- or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5 q cytogenetic abnormality with or without additional cytogenetic abnormalities

4.3 Review Strategy

For efficacy, this review focused on the NDA data submitted by Celgene Corporation on Study CC-5013-MDS-003 and CC-501-MDS-001 including datasets, case report forms, study reports and other information submitted. The evaluable population most relevant to lenalidomide's proposed indication, treatment of patients with transfusion-dependent anemia due to low or intermediate-1 risk myelodysplastic syndromes associated with a del 5q cytogenetic abnormality with or without additional cytogenetic abnormalities, is a subgroup of patients in study CC-5013-MDS-003 (96/148 [65%] of enrollment). The study CC-501-MDS-001 had 10/45 (22%) patients relevant to the proposed indication. Study CC-5013-MDS-002 was conducted in MDS patients without the 5q deletion cytogenetic abnormality and is not relevant to the proposed indication. It serves as a reference for MDS patients without the 5q deletion. For details of study CC-5013-MDS-002, please refer to Section 10.1. under Appendices.

Materials consulted in the review included the regulatory history of the application, IND # 60,100, rolling submission NDA #21-880, relevant published literature and sponsor presentation of NDA on July 21, 2005.

There were different reviewers to assess efficacy, safety, clinical pharmacology and statistics. This review incorporates the reviews with overall conclusions for efficacy and safety including statistics. The clinical pharmacology review has been documented separately.

4.4 Data Quality and Integrity

The primary data and responses were analyzed for consistency with the study reports, with the datasets submitted and with selected case report forms (CRFs). The Division of Scientific Investigation (DSI) was consulted to inspect study sites and follow up on various anonymous complaints received regarding under-reporting of deaths to the FDA. Study sites for the DSI inspections were selected based on the sites with the most accrual and the sites with the most responses in the pivotal study, CC-5013-MDS-003. DSI investigated 3 out of the 4 sites identified.

The DSI report is pending at the time of this review.

4.5 Compliance with Good Clinical Practices

The sponsor states that the study has been performed in accordance with the ICH E6 Guideline: "Good Clinical Practice: Consolidated Guidance" and applicable regulatory requirements.

4.6 Financial Disclosures

Study MDS-003 enrolled 148 patients in 32 centers in the United States and 1 center in Germany. There were 33 investigators.

Study MDS-001 enrolled 45 patients in 2 centers in the Unites States, Tucson, AZ and Tampa, FL. There were two investigators.

The sponsor certified that except in the case of the 3 investigators noted below, no financial arrangements were made with the other investigators involved in the Study MDS-003 and Study MDS-001 and they did not have any financial interests to disclose where study outcome could affect compensation.

The sponsor provided the following information regarding the 3 named investigators who participated in financial arrangements or hold proprietary interest in Celgene.

1. — MD: was paid 18,000 dollars in consulting fees for time/travel to meetings and awarded 25,000 dollars for a — Award.
2. — MD: owns 3200 shares of Celgene stock.
3. — MD: was issued Celgene stock options (5000 shares) for consulting. The options were exercised in 2004.

The sponsor certified that they have acted with due diligence to obtain from the 3 clinical investigators listed below and it was not possible to do so. The reason why this information could not be obtained is attached.

Table 3 Investigators Without Financial Certification/Disclosure

Investigator	Study(s)	Reason Certification/Disclosure Could not be Obtained
	CC-5013-MDS-002 and CC-5013-MDS-003	Investigator is on sabbatical
	CC-5013-MDS-002 and CC-5013-MDS-003	Investigator has left the institution
	CC-5013-MDS-002 and CC-5013-MDS-003	Investigator has left the institution

NDA 21880, financial.pdf

APPEARS THIS WAY
ON ORIGINAL

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Maximum plasma concentrations were typically obtained within a few hours of dosing. Volume of distribution is moderate and clearance is fairly rapid resulting in a half-life approximating 3 hours. The primary route of elimination is renal excretion of parent drug.

Following single doses, $AUC_{0-\infty}$ and Cmax increased in a dose-proportional manner over a dose-range of 5 to 50 mg.

As would be predicted from the single dose pharmacokinetics, there was no observable accumulation of the drug in plasma upon multiple daily dosing of doses up to 50 mg.

Pharmacokinetic changes due to patient characteristics were not studied. The presence and identity of circulating metabolites was not studied in humans.

5.2 Pharmacodynamics

The clinical program did not assess pharmacodynamic endpoints (biomarkers) associated with effectiveness or safety for MDS.

5.3 Exposure-Response Relationships

With the exception of limited data on the regimen using 10 mg x 21 days in a 28 day cycle (syncopated) regimen and the 25 mg daily dose, clinical studies assessing the relationship between exposure and efficacy were not performed.

Patients were not sampled for pharmacokinetics in Studies MDS-001 and MDS-003. Thus, the relationship between concentration and clinical outcome cannot be explored.

APPEARS THIS WAY
ON ORIGINAL

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

This NDA application seeks to market lenalidomide at a starting dose of 10 mg for the following indication. The wording of the proposed indication is:

> "Treatment of patients with transfusion-dependent anemia due to low or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional chromosomal abnormalities".

6.1.1 Methods

The efficacy review is based primarily on 2 single-arm, non-randomized trials of lenalidomide. This review focused on the NDA submitted by Celgene Corporation.

The study CC-5013-MDS-003 was the main study reviewed including datasets, case report forms (CRFs), study reports and other information on patients with transfusion dependent anemia due to low- or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional chromosomal abnormalities. This was a single-arm, open-label, multi-center study in 148 patients in which the sponsor examined 2 dose regimens of 10 mg: 10 mg every 21 days of a 28 day cycle (syncopated regimen); and 10 mg daily (continuous regimen).

Study CC-501-MDS-001 was the supportive study reviewed with the focus on the subset of MDS patients with transfusion dependent anemia due to low or intermediate-1 risk MDS. This was a pilot, phase 1/2, dose-finding study which started with 25 mg daily and was later reduced to 10 mg in 2 dose regimens.

The two trials are entitled:
Study Protocol CC-5013-MDS-003: A multi-center, single-arm, open-label study of the efficacy and safety of CC-5013 monotherapy in red blood cell transfusion-dependent subjects with myelodysplastic syndromes associated with a del (5q) cytogenetic abnormality.

Study Protocol CC-501-MDS-001: A Phase II open label study of the safety and efficacy of CC-5013 (Revimid ™) treatment for patients with myelodysplastic syndrome.

6.1.2 General Discussion of Endpoints

Study CC-5013-MDS-003

Primary endpoint

- RBC transfusion independence defined as the absence of the intravenous infusion of any RBC transfusion during any consecutive "rolling" 56 days during the treatment period, i.e., days 1 to 56, days 2 to 57, days 3 to 58 etc.

Secondary endpoints

- Cytogenetic response
- ≥ 50% decrease in RBC transfusion requirements
- Change of hemoglobin concentration from baseline
- Safety (type, frequency, severity, and relationship of adverse events to CC- 5013)
- Platelet response
- Neutrophil response
- Bone marrow response
- Duration of response

The main objective was to evaluate the efficacy of lenalidomide treatment to achieve hematologic improvement in patients with low- or intermediate-1 risk IPSS MDS associated with a del (5q31-33) cytogenetic abnormality.

The bone marrow biopsy and aspirate samples, peripheral blood smear slides and pathology reports for each subject were reviewed centrally by an independent hematologic reviewer, John M Bennett, MD, University of Rochester Cancer Center, Rochester, NY. The cytogenetic reports and chromosome prints for each subject were centrally reviewed by an independent cytogenetic reviewer, Gordon W. Dewald, MD, The Mayo Clinic, Rochester, MN.

Study CC-501-MDS-001

Primary Objective
To estimate the percent of patients with myelodysplastic syndrome (MDS) who experienced erythroid response and the interval to response after treatment.

Secondary Objectives
• To evaluate the effect of treatment with lenalidomide on neutrophil and platelet count response and on bone marrow and cytogenetic response.
• To evaluate the relationship between any hematologic response to lenalidomide and changes in biological endpoints, including bone marrow apoptotic index, microvessel density (MVD), plasma tumor necrosis factor alpha (TNF-α) and vascular endothelial growth factor (VEGF) concentrations, and progenitor colony- forming capacity.
• To evaluate the safety of lenalidomide in patients with MDS.

Reviewer's Comments:

1. *Transfusion independence which are durable may be considered to be evidence of clinical benefit. Previously azacitidine was approved based on the primary efficacy endpoint of overall response rate, defined as complete or partial response of bone marrow and peripheral blood, and a response rate in the azacitidine arm of about 16% with no responses in the observation arm.*

2. *At the end-of-phase 1 meeting (June 6, 2003), FDA had informed the sponsor of the use of a 56-day rolling duration as problematic in an unblinded single-arm study. The duration of response of 8 weeks in a population where the median survival is measured in years may not be adequate.*

6.1.3 Study Design

Study CC-5013-MDS-003

Patients received CC-5013 in 28-day cycles for up to 24 cycles, or until bone marrow disease progression, or progression/relapse following erythroid hematologic improvement or until CC-5013 became commercially available. Study visits occurred every cycle (every 28 days) for the first 12 cycles and then every other cycle thereafter starting with cycle 13 (pregnancy tests were done every 28 days for women of child bearing potential (WCBP). Laboratory monitoring to assess hematological parameters occurred every 14 days during the first 6 cycles and then every 28 days (Day One of every cycle) thereafter. Treatment continued until unacceptable AEs occurred, bone marrow disease progression was documented, progression or relapse following erythroid improvement was documented, or for a maximum of 24 cycles, whichever occurred first. Safety and efficacy assessments were performed during the study. The number of patients planned was 90 but 148 were enrolled.

Study Population:
Inclusion Criteria:

1. Must understand and voluntarily sign an informed consent form
2. Age ≥ 18 years at the time of signing the informed consent form
3. Must be able to adhere to the study visit schedule and other protocol requirements
4. Diagnosis of low or intermediate-1 risk IPSS MDS associated with a del (5q) cytogenetic abnormality. The cytogenetic abnormality of chromosome 5 must involve a deletion between bands q31 and q33. The del (5q) cytogenetic abnormality may be an isolated cytogenetic finding or may be associated with other cytogenetic abnormalities.
5. RBC transfusion- dependent anemia defined as having received ≥2 units of RBCs within 8 weeks of study treatment
6. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2
7. Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days of starting study drug. In addition, sexually active WCBP must agree to use adequate contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra- uterine device; barrier contraceptive with spermicide; or vasectomized partner) while on study drug. WCBP must agree to have pregnancy tests every 4 weeks while on study drug

Exclusion Criteria:

1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form or that will place the subject at unacceptable risk if he/ she were to participate in the study or confounds the ability to interpret the data
2. Pregnant or lactating females

3. Prior therapy with CC- 5013
4. Inability to aspirate bone marrow (dry tap)
5. Proliferative (WBC ≥12,000/μL) chronic myelomonocytic leukemia (CMML)
6. Any of the following lab abnormalities:
   •Absolute neutrophil count (ANC) <500 cells/mm3 (0.5 x 10^9/L)
   • Platelet count <50,000/mm^3 (50 x 10^9/L)
   • Serum creatinine >2.5 mg/dL (221μmol/L)
   • Serum SGOT/AST or SGPT/ALT >3.0 x upper limit of normal (ULN)
   • Serum direct bilirubin >2.0 mg/dL (34 μmol/L)
7. Prior ≥grade 3 (National Cancer Institute [NCI] Common Toxicity Criteria [CTC]) allergic reaction/hypersensitivity to thalidomide
8. Prior ≥grade 3 (NCI CTC) rash or any desquamation (blistering) while taking thalidomide
9. Clinically significant anemia due to factors such as iron, B_{12} or folate deficiencies, autoimmune or hereditary hemolysis or gastrointestinal bleeding (if a marrow aspirate is not evaluable for storage iron, transferrin saturation must be ≥20 % and serum ferritin not less than 50 ng/mL)
10. Use of hematopoietic growth factors within 7 days of the first day of study drug treatment
11. Chronic use (>2 weeks) of greater than physiologic doses of a corticosteroid agent (dose equivalent to >10 mg/ day of prednisone) within 28 days of the first day of study CC-5013 treatment
12. Use of experimental or standard drugs (i.e. chemotherapeutic, immunosuppressive, and cytoprotective agents) for the treatment of MDS within 28 days of the first day of study CC- 5013 treatment.
13. Prior history of malignancy other than MDS (except basal cell or squamous cell carcinoma or carcinoma in situ of the cervix or breast) unless the subject has been free of disease for ≥3 years.
14. Use of any other experimental therapy within 28 days of the first day of study CC- 5013 treatment.

Study Sites: United States and Germany

Treatment Plan:
Oral CC-5013 10 mg (two 5 mg capsules) daily on days 1-21 every 28 days was the syncopated dosing regimen used initially which was changed to a continuous dosing regimen of 10 mg daily every 28 days.

Safety Analysis:
The safety population included all subjects who received at least 1 dose of study drug. Adverse events, vital sign measurements, clinical laboratory information, concomitant medications, and ECG interpretations, will be tabulated and summarized. All toxicities will be summarized by frequency, severity grade based on the NCI CTC and relationship to study drug. Serious adverse events and events leading to discontinuation will be listed separately.

Response Criteria:
The efficacy endpoints in this study were modified from the recommendations of the International Working Group (IWG) to Standardize Response Criteria for Myelodysplastic Syndromes (4). RBC transfusion independence was defined to be RBC transfusion independence (the absence of the intravenous infusion of any RBC transfusion) during any consecutive "rolling" 56 days during the treatment period, i.e. days 1 to 56, days 2 to 57, days 3 to 58, etc. RBC transfusion independence required patients to be completely transfusion free and this was considered a major response. All responses required that patients remained transfusion independent for a minimum of 8 consecutive weeks. Included in the study report was the addition of ≥1 g/dL increase in the hemoglobin level to the definition of transfusion independence.

Efficacy Analysis:
Primary efficacy analyses were performed by the sponsor on the modified intent-to-treat (MITT) population that included all subjects who met all of the following conditions: had a diagnosis of low or intermediate-1 risk MDS with a del (5q31-33) cytogenetic abnormality based on confirmation by the central hematologic and cytogenetic reviewers; received at least two transfusions in each of the eight week periods during the 16 week pre-treatment period and subjects must not have been transfusion-free for any 56 consecutive days during the 16 week pre-treatment period; took at least one dose of study drug. Subjects who dropped out without having a response were considered to be non-responders.

An analysis was performed by the sponsor for the efficacy evaluable (EE) subset of the MITT population, i.e., those subjects who met all the requirements given above in the MITT section for whom response could be fairly assessed (subjects who withdrew from the study before completing 6 cycles for non-treatment related reasons without responding were not included in the denominator used in the response estimates). Subjects who withdrew for treatment related reasons were categorized as non-responders in this analysis.

Amendments:
The original protocol was submitted on May 2, 2003.

Amendment # 1 (dated August 27, 2003): increased the number of planned subjects from 36 to 90; changed the dosing regimen from a syncopated regimen (administration of 10 mg daily on Days 1-21 of a 28-day cycle) to a continuous regimen (administration of 10 mg on Days 1- 28 of a 28-day cycle); increased the duration of treatment from 6 cycles to until bone marrow disease progression or progression/ relapse following erythroid hematologic improvement or for a total of 24 cycles, whichever occurs first; and provided additional clarifications on dose modifications for thrombocytopenia (including changing the platelet count requirement for re-starting study drug after an interruption due to thrombocytopenia from ≥50,000/μL to ≥30,000/μL), hyperthyroidism, and other toxicities. Amendment #1 also changed the exclusion criteria to exclude subjects from whom a bone marrow aspirate could not be obtained at screening/baseline (dry tap) and those who have proliferative CMML (WBC of ≥12,000/μL); modified the exclusion criterion for bilirubin to stipulate that direct, rather than total bilirubin would be measured; clarified that local laboratory results are used to determine a subject's eligibility for the study and to determine dose modifications during treatment; clarified that local review of

hematologic and cytogenetic data are used to determine a subject's eligibility for the study; and modified the statistical analysis plan and statistical methods to increase the sample size and to change the definition of the MITT population to include the stipulation " that the subjects must have received at least 2 transfusions in each of the 8-week periods during the 16-week pretreatment period and must not have been transfusion free for any 56 consecutive days during the 16-week pretreatment period. "

Amendment #2 (dated September 12, 2003): provided additional clarification of the dose reduction schedule in subjects who remained on the syncopated regimen, provided additional clarification on dose modifications for constipation and hepatic and other nonhematologic grades 3 and 4 AEs, and clarified that local laboratory results for Hgb could be used in the analysis of the secondary efficacy endpoints if values from the central laboratory were missing or invalid.

Amendment #3 (dated January 13, 2004): added the requirement to perform a complete blood cell count weekly during the first 8 weeks of therapy to monitor for early hematologic AEs; provided additional dose modification guidelines for neutropenia and thrombocytopenia that occur during the first 4 weeks of therapy; expanded the secondary efficacy measures; and clarified the procedures for the central cytogenetic reviewer.

Reviewer's Comments:

1. *This is a single-arm, open-label study which was designed for a Phase 2 study in which initial efficacy and safety were to be evaluated. This study was not intended to be a registration trial. At the end-of-phase 1 meeting (June 6, 2003), FDA had recommended a randomized controlled trial.*
2. *Initially, the sponsor had planned to provide an application for all patients with low- to intermediate-1 risk MDS for which they were granted a Fast Track Designation provided that they conducted a randomized trial. However, based on the findings from the phase 1/2 pilot study CC-501-MDS-001, they proposed to submit the NDA for the patients with 5q deletion low- or intermediate-1 MDS based on this single-arm Phase 2 study. The protocol for the randomized trial in this population was submitted to the FDA in March 2005 and the trial will be conducted in Europe in patients with del 5q. The planned phase 3 study is a randomized, double-blind, placebo-controlled 3-arm trial evaluating a lower dose: 5 mg vs. 10 mg x21d/28 d cycle vs. placebo. The primary endpoint is RBC transfusion independence for ≥26 weeks.*
3. *Based on the preliminary data from the pilot study, Study CC-503-MDS-001, the first 45 patients enrolled were treated with the 10 mg syncopated dosing regimen (10 mg x21 days of a 28 day cycle). Subsequently, when additional information from the pilot study suggested that the onset of response was more rapid with the 10 mg continuous dosing (10 mg daily) regimen, this was adopted and 103 patients were enrolled and treated with the continuous regimen. Patients who were started on the syncopated regimen and had not experienced dose-limiting toxicity were allowed to be switched to the daily dose of 10 mg.*
4. *Monitoring of complete blood cell count was increased from every 14 days to weekly during the first 8 weeks of therapy to monitor for early hematologic adverse events.*
5. *The definition of the MITT population was changed to include the stipulation that the subjects must have received at least 2 transfusions in each of the 8- week periods during*

the 16- week pretreatment period and must not have been transfusion free for any 56 consecutive days during the 16-week pretreatment period.

6. *Although an increase in ≥ 1 gm hemoglobin was included in the definition of the primary endpoint in the clinical study report, this criterion was not included in the protocol (or amendments) or in the statistical analysis plan.*
7. *There was no protocol amendment submitted to the FDA when the number of patients in the study was increased from 90 to 148. There was no modified statistical analysis plan and statistical methods for the increase in the sample size.*

Study CC-501-MDS-001

This was a pilot, phase 1/2 , dose-ranging study of CC- 5013 in patients with MDS. Patients received 25 mg oral CC- 5013 daily. Response rate was assessed in cohorts stratified by the likelihood of an MDS subtype to transform to leukemia according to the International Prognostic Scoring System (IPSS)-defined risk groups (i.e., IPSS low and intermediate-1; versus IPSS intermediate-2 and high). Patients who failed to experience any hematologic response and dose limiting toxicity after 16 weeks of therapy were eligible for dose escalation to 50 mg daily for 8 additional weeks of treatment. In the first stage 15 patients were to be enrolled and the number of patients experiencing erythroid response (major or minor response) by week 16 would be evaluated. If no responses were observed the study would be terminated due to lack of efficacy, while if 4 or more responses were observed the study would be continued due to promising clinical activity. In the intermediate case (1, 2 or 3 responses), a second stage of an additional ten (10) patients would be entered. If after the completion of this second stage, four (4) or more responses were observed in the 25 patients treated, then it would be concluded that the drug shows promising clinical activity.

Patients who demonstrated a hematologic response at week 16 (erythroid, platelet, or neutrophil response) or who, in the judgment of the investigator, experienced clinical benefit were eligible to continue therapy at the same dose of study drug for up to 8 additional months (12 months total).

Objectives:
Primary objective: To estimate the percent of patients with MDS who experienced erythroid response and the interval to response.

Secondary objectives:

- to evaluate the effect of treatment with CC- 5013 on neutrophil and platelet count response, and bone marrow and cytogenetic response,
- to estimate the tolerance of dose escalation to 50 mg CC- 5013 daily,
- to estimate the frequency of response in patients whose doses of CC- 5013 are escalated to 50 mg,
- to evaluate the relationship between any hematologic response to CC- 5013 and changes in biological endpoints: including bone marrow apoptotic index and MVD, plasma TNF a and VEGF concentration, and progenitor colony forming capacity,
- to evaluate the safety of CC- 5013 in patients with MDS.

Study Population:
Inclusion criteria:

- Diagnosis of *de novo* myelodysplastic syndrome of at least 12 weeks duration, with one of the following subtypes: Refractory anemia (RA); Refractory anemia with ring sideroblasts (RARS); Refractory anemia with excess (5%- 20%) blasts (RAEB); RAEB in transformation (RAEB-t) (21%- 30% blasts); Non-proliferative (WBC < 12,000/μL) Chronic myelomonocytic leukemia (CMML),
- Baseline mean hemoglobin <10.0 g/ dL (un-transfused) or transfusion-dependent, defined as requiring at least 4 units of RBC in the 8 weeks prior to baseline.
- More than 30 days must have elapsed since any previous treatment for MDS, other than transfusion.
- Performance status of 0, 1 or 2 (ECOG Scale).
- Adequate renal (creatinine ≤1.5 x ULN) and hepatic function: bilirubin <2.5 mg/dL; AST/ALT <2 x ULN.
- Men and Women >18 years of age.
- Women of reproductive potential must be using adequate birth control measures (abstinence, oral contraceptives, intrauterine device, barrier method with spermicide or surgical sterilization) during treatment with study drug. Women of reproductive potential must have a negative serum pregnancy test within 7 days of baseline.
- Are able to adhere to the study visit schedule, understand and comply with other protocol requirements.
- Understand and sign written informed consent.

Exclusion criteria:

- Myelosclerosis (or myelofibrosis) occupying more than 30% of marrow space or assessed as grade 3+ or greater.
- Any grade 4 (as per NCI CTC) thrombocytopenia or neutropenia.
- Any clinically significant pulmonary, cardiovascular, endocrine, neurologic, gastrointestinal or genitourinary disease unrelated to underlying hematologic disorder.
- Any life-threatening or active infection requiring parenteral antibiotic therapy.
- Pregnant or lactating females.
- Have a history of active tuberculosis requiring treatment within the previous 3 years or opportunistic infections, including but not limited to evidence of active cytomegalovirus, active Pneumocystis carinii, or atypical mycobacterium infection, etc., or documented HIV infection, within the previous 6 months (also excluded are patients with evidence of an old tuberculosis infection without documented adequate therapy).
- Requirement for ongoing treatment with corticosteroids.
- Patients with chromosome abnormalities common to *de novo* AML, i.e., t(8: 21), t(15; 17), and inv (16).
- Known hepatitis-B surface antigenemia.
- Use of other experimental study drug within 30 days of baseline.
- Bone marrow blasts >30 %.

- History of active non-hematopoietic malignancy, or a similar diagnosis within 3 years (except basal cell or squamous cell carcinoma of the skin or cervical carcinoma in situ).
- Clinically significant anemia due to factors such as iron, B_{12} or folate deficiencies, autoimmune or hereditary hemolysis or gastrointestinal bleeding (if a marrow aspirate is not evaluable for storage iron transferrin saturation must be ≥ 20 % and serum ferritin not less than 50 ng/mL).
- Life expectancy of <4 months.

Study Site: Tampa, FL

Study drug, dosage, and mode of administration:
CC- 5013 was supplied in strengths of 5 mg and 25 mg for once daily oral use.

Efficacy evaluation:
Patients were assessed for hematologic response (including evaluation of erythroid, platelet, and neutrophil response), cytogenetic response, and bone marrow response. These endpoints were determined by monitoring of hematologic laboratory values, RBC and platelet transfusion requirements, and by review of bone marrow biopsies and aspirates.

Safety:
All patients were assessed for safety by monitoring adverse events, clinical laboratory tests, and physical examinations.

Statistical Methods:
Sample Size: The Fleming two-stage design was used in this study to yield a power of 76.6% to test the null hypothesis that the rate was not more than 5%, versus the alternative that the response rate was at least 20% with a significance level of 3.4%.

Efficacy analyses:

Response Criteria
The efficacy endpoints in this study were modified from the recommendations of the International Working Group (IWG) to Standardize Response Criteria for Myelodysplastic Syndromes (4). All responses required that patients maintain major or minor response for a minimum of 8 consecutive weeks. As a secondary endpoint, response rates were assessed according to IPSS Prognostic Scoring System.

Erythroid Response
Major response: Transfusion-independence for patients who were RBC transfusion-dependent at baseline; for patients with a mean pretreatment hemoglobin (mean 8 week hemoglobin) <11 g/dL, a >2 g/dL rise in hemoglobin without transfusion.

Minor response: For patients with a mean pretreatment hemoglobin (mean 8 week hemoglobin) <11 g/dL, hemoglobin is sustained 1.0 to 2.0 g/dL above the baseline value without transfusion;

for transfusion-dependent patients a 50% or greater decrease in 8-week RBC transfusion requirements compared to baseline.

Platelet Response
Platelet response will be evaluated in patients with pretreatment thrombocytopenia as defined by a mean 8-week platelet count <50,000/ μL or platelet transfusion-dependence defined as any platelet transfusion within 8 weeks prior to baseline.

Major response: For platelet transfusion-independent patients, a >50% increase in platelet count with a minimum net increase >30,000/μL without platelet transfusion; for platelet transfusion-dependent patients, a sustained platelet count at or above the mean baseline value with elimination of platelet transfusion requirements.

Minor response: For platelet transfusion-independent patients a >50% increase in platelet count with net increase <30,000/μL without platelet transfusion.

The primary endpoint in this study was the percentage of patients who experienced a major or minor erythroid response. Decisions about clinical efficacy during the two-stage design was based upon the number of patients at each stage who demonstrated a response using these criteria. At week 16, the proportion of responders in each of the IPSS-defined risk groups and for the entire sample was determined together with exact 95% confidence intervals. Similar analyses were performed for the secondary variables: platelet, neutrophil, bone marrow and cytogenetic response. The relationship between hematologic response and changes in biomarkers was explored by both parametric and non-parametric correlational analyses. Methods similar to those described in the above was used to analyze the response data obtained from patients who continued to receive CC- 5013 after the initial 16 weeks.

Safety Analyses:
Data from all patients who received one or more doses of drug were incorporated into the final safety analyses. To assess clinical safety, adverse events, vital sign measurements and clinical laboratory information were summarized by visit. Adverse events and laboratory results were also summarized by severity grade (NCI CTC). Descriptive statistics were generated and shift tables as appropriate. No formal statistical analyses were planned.

Amendments:
The original protocol was submitted on 19 July 2001.

Amendment #1 (dated January 17, 2003): allowed for new dose levels (10 mg/day, 10 mg 21days/7days rest); increased the number of patients planned; removed references to dose escalations to 50 mg; modified inclusion and exclusion criteria; added a second extension period of 12 months to increase the total study duration to 24 months; and clarified erythroid and platelet response criteria.

Amendment #2 (dated April 20, 2003): added bone marrow biopsy/aspirate at 8 weeks to the schedule of study procedures.

Amendment #3 (dated January 13, 2004): permitted patients to remain in the study until they developed progressive disease, unacceptable toxicity, or withdrew consent; permitted patients that have not achieved a major erythroid response to switch to 10 mg daily; and updated the statistical plan to allow for the possible dose changes.

Reviewer's Comments:

1. *This was a pilot, phase 1/2, dose-finding study in which initial efficacy and safety was evaluated. The initial starting dose was 25 mg daily based on the findings of a Phase 1 study in myeloma, and the first 13 patients were enrolled at this dose. A high incidence of neutropenia and thrombocytopenia was observed within the first 4 to 8 weeks of treatment, as a result of which the protocol was amended to study 2 lower-dose levels of 10 mg.*
2. *The definition of transfusion-dependence anemia differs from study CC-5013-MDS-003. Study CC-5013-MDS-003 defined transfusion dependence as requiring ≥2 units of RBC in the 56 day period prior to start of study drug. In study CC-501-MDS-001, transfusion dependent was defined by requiring at least 4 units of RBC in the 8 weeks prior to baseline.*
3. *The primary endpoint was a major or minor erythroid response which was modified from the IWG MDS Response Criteria.*

6.1.4 Efficacy Findings

Datasets Analyzed

Study CC-5013-MDS-003

The sponsor has submitted the MITT population as the primary population for the efficacy analyses which includes 94 of the 148 subjects who were enrolled in the study. Efficacy data were also reported by the sponsor for the intent-to-treat (ITT) and per-protocol (PP) populations, which included 148 and 115 subjects, respectively.

Efficacy Populations:
Modified Intent-to-treat (MITT) Population: includes all subjects who 1) received ≥ 2 units of pRBCs in each of the 8- week periods (56 days) during the 16 weeks prior to administration of study drug (screening Weeks -1 to - 8 and Weeks - 9 to - 16) and who did not have a 56-day, RBC-transfusion-free period during the 16 weeks prior to administration of study drug, 2) have a diagnosis of low or intermediate-1 risk MDS that was confirmed by central hematologic review of an evaluable bone marrow aspirate/ biopsy, 3) have a confirmed 5q deletion based on central cytogenetic review, and 4) took at least 1 dose of study drug.

Intent-to-treat (ITT) Population: includes all subjects who received at least 1 dose of study medication.

Per-protocol (PP) Population: The per-protocol (PP) population includes all subjects who 1) received ≥ 2 units of PRBCs during the immediate 56 days (8 weeks) prior to administration of study drug, 2) have a diagnosis of low or intermediate-1 risk MDS that was confirmed by central

hematologic review of an evaluable bone marrow aspirate/ biopsy, 3) have a confirmed 5q del based on central cytogenetic review, and 4) took at least 1 dose of study drug.

The table below summarizes the number of patients who were included in the efficacy analyses submitted by the sponsor.

Table 4 Number of Subjects included in Efficacy Analysis (Applicant's Table)

Analysis Populations	10mg Cont. n (%)	10mg Sync. n (%)	Overall n (%)
Intent-to-treat (ITT)[a]	103 (100.0)	45 (100.0)	148 (100.0)
Safety [b]	103 (100.0)	45 (100.0)	148 (100.0)
Per Protocol (PP)[c]	79 (75.7)	37 (82.2)	115 (77.7)
Modified intent-to-treat (MITT)[d]	63 (61.2)	31 (68.9)	94 (63.5)

Data Source: Table 14.1.1
[a] The ITT population includes all enrolled subjects.
[b] The safety population includes all subjects who took at least one dose of study drug.
[c] The PP population includes all safety subjects who were confirmed by central reviewers to have a diagnosis of low- or intermediate-1 risk MDS associated with a del (5q31-33) cytogenetic abnormality and who received at least 2 units of PRBC transfusion during the 56 days prior to starting study medication.
[d] The MITT population includes all PP subjects who received at least two transfusions in each of the eight week periods during the 16 week pre-treatment period and were not transfusion-free for any 56 consecutive days during the 16 week pre-treatment period.

Source: CC-5013-MDS, Table 13

The FDA reviewed the data for the ITT population which consisted of 148 patients who were enrolled in the study. Those that met the population of interest were considered evaluable and also reviewed. These included all RBC transfusion dependent patients as defined in the protocol who had low or intermediate-1 risk MDS that was confirmed by central hematologic review and were associated with a 5q deletion cytogenetic abnormality with or without other deletions when analyzed in at least 20 metaphases. Additional analyses were done by the FDA on the subgroup of patients with an isolated 5q deletion only. The table below shows a summary of the sponsor's and FDA's patient populations.

Table 5 Summary of Patient Populations (Reviewer's Table)

Patient Population	Number of Patients	
	Sponsor N (%)	FDA N (%)
All enrolled	148 (100.0)	148 (100.0)
Per Protocol	115 (77.7)	115 (77.7)
Transfusion dependent anemia (≥ 2 units RBC transfusion in two 8-week periods) low or intermediate-1 risk MDS with 5q deletion or additional abnormalities	94 (63.5)	Not done
Transfusion dependent anemia (≥ 2 units RBC transfusion 8-weeks prior to start of study drug) low or intermediate-1 risk MDS with 5q deletion or additional abnormalities	Not done	96 (64.9)
Isolated 5q deletion MDS	Not done	72 (48.6)

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5q del + other abnormalities	Not done	24 (16.2)

Study CC-501-MDS-001

There were 45 patients enrolled in the study which made up the ITT population. The sponsor has submitted the efficacy analysis in the modified intent-to-treat (MITT) population (i.e., had a diagnosis of MDS and received at least 1 dose of study medication) in which 43/45 enrolled patients met the criteria. The efficacy evaluable (EE) population (had a diagnosis of MDS and completed at least 1 cycle of therapy) had 38 patients in that category. The table below summarizes the number of patients who were included in the efficacy analyses submitted by the sponsor.

Table 6 Number of Patients Included in Efficacy Analyses (Applicant's Table)

Analysis Populations	25mg n (%)	10mg n (%)	10mg Sync. n (%)	Overall n (%)
ITT Population [a]	13 (100.0)	12 (100.0)	20 (100.0)	45 (100.0)
Modified Intent-to-treat (MITT) [b]	13 (100.0)	12 (100.0)	18 (90.0)	43 (95.6)
Efficacy evaluable [c]	10 (76.9)	12 (100.0)	16 (80.0)	38 (84.4)

Data Source: Table 14.1.1
[a] The ITT population includes all patients who took at least one dose of study drug.
[b] The MITT population includes all patients who took one dose of study drug but excludes patients 138 and 139 who had a diagnosis of chronic myeloid leukemia (CML).
[c] The efficacy evaluable population includes all patients who completed at least one cycle of study medication. Patients 138 and 139 were excluded from this group since they are diagnosed with CML.

Source: CC-501-MDS-001, Table 7.

The FDA reviewed the data for the ITT population which consisted of 45 patients who were enrolled in the study. Those that met the population of interest were then analyzed in detail. These included 10 patients with RBC transfusion dependent low- or intermediate-1 risk MDS associated with a 5q deletion cytogenetic abnormality with or without other deletions. FDA agreed with the sponsor's analysis.

Dosing Regimens

Study CC-5013-MDS-003 and Study CC-501-MDS-001

Study CC-501-MDS-001 was a Phase 1/2, open- label, single-arm, 2-stage, dose-finding study of the safety and efficacy of lenalidomide for the treatment of patients with MDS. Based on the findings of a Phase 1 study of lenalidomide in subjects with multiple myeloma (Study CDC-501- 001), the initial starting dose of lenalidomide in this study was 25 mg daily, and the first 13 patients who were enrolled in the study were treated with this dose. A high incidence of neutropenia and thrombocytopenia was observed within the first 4 to 8 weeks of treatment, as a result of which, the protocol was amended to study 2 lower-dose regimens in sequential order: 1) a " continuous " regimen in which 10 mg of lenalidomide was administered daily without a planned rest, and 2) a " syncopated " regimen in which 10 mg of lenalidomide was administered on Days 1 through 21 of repeated 28- day cycles. Twelve subjects were treated with the 10-mg

continuous regimen, and, although erythroid responses were observed, the median time to dose-limiting neutropenia or thrombocytopenia was found to be 13 weeks. Based on these safety findings, enrollment into the 10-mg syncopated regimen was initiated. After 3 erythroid responses were observed among the first 5 subjects who were treated with the 10-mg syncopated dosing regimen, an additional 15 subjects were enrolled in that group to gain further clinical experience with the syncopated regimen.

A total of 45 subjects were enrolled in Study CC-501-MDS-001 of whom 43 had the protocol-specified diagnosis of MDS with or without an associated del 5 (q31- 33) cytogenetic abnormality (2 of the subjects had a diagnosis of Philadelphia chromosome- negative chronic myeloid leukemia and, therefore, were excluded from the analyses). The major erythroid response rate was 44.2% (19/ 43) and the minor erythroid response rate was 7.0% (3/ 43) across the 3 lenalidomide regimens; all of the responses were observed in subjects who had low- or intermediate-1 risk MDS. Subjects with a del 5 (q31- 33) cytogenetic abnormality appeared to be particularly responsive to lenalidomide: the major erythroid response rate was 69.2% (9/ 13) in this population and was associated with a median increase of 5.3 g/ dL in Hgb and with major cytogenetic responses in 84.6% (11/13) of the subjects. Overall, the results of this study suggested that lenalidomide, administered at a dose of 10 mg/day, was an effective treatment for subjects with low or intermediate-1 risk MDS and an associated del 5 (q31-33) cytogenetic abnormality. As a result of the findings in this study, Study CC-5013-MDS-003 was initiated in subjects with low or intermediate- 1 risk MDS associated with a del 5 (q31-33) cytogenetic abnormality to confirm the efficacy and safety of lenalidomide at a dose of 10 mg/day in this subject population.

Study CC-5013-MDS-003 was a Phase 2, multicenter, open-label, single-arm study of the efficacy and safety of lenalidomide when administered at a dose of 10 mg daily either as a " syncopated " (i.e., administration of 10 mg/ day of lenalidomide on Days 1-21 of repeated 28-day cycles) or " continuous " (administration of 10 mg/day of lenalidomide without a planned rest) regimen to patients with an IPSS diagnosis of low or intermediate-1 risk MDS and an associated del 5 (q31-33) cytogenetic abnormality with or without other cytogenetic abnormalities and RBC transfusion-dependent anemia. Based on preliminary data from the pilot study (Study CC-501-MDS-001), the first 45 enrolled subjects were treated with the 10-mg syncopated dosing regimen. However, after additional information from the pilot study suggested that the onset of response was more rapid with the 10-mg continuous dosing regimen than with the 10-mg syncopated regimen, without additional safety concerns, the 10-mg continuous dosing regimen was adopted, and 103 subjects were enrolled in the study and treated with the continuous dosing regimen. Patients who initially began therapy on the syncopated regimen and who did not experience dose-limiting AEs were allowed to switch to the continuous regimen.

The table below shows the number of patients who received the 2 or 3 doses in both studies.

Table 7 Dosing Regimens in ITT Population (Reviewer's Table)

Study	25 mg daily	10 mg syncopated	10 mg continuous
CC-501-MDS-001	13	20	12
CC-5013-MDS-003	0	45	103

Baseline Demographic and Disease Characteristics

Study CC-5013-MDS-003

Sponsor's Analysis

The sponsor submitted the table below summarizes the baseline demographic and disease-related characteristics for the 148 patients in the ITT population.

Table 8 Baseline Demographic and Disease-Related Characteristics (ITT Population) (Applicant's Table)

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	10mg Cont. (N=103)	10mg Sync. (N=45)	Overall (N=148)
Age (years)			
n	103	45	148
Mean	69.3	71.5	70.0
SD	10.91	9.45	10.50
Median	71.0	72.0	71.0
Min, Max	37.0, 95.0	51.0, 91.0	37.0, 95.0
Age distribution	n (%)	n (%)	n (%)
<=65	35 (34.0)	13 (28.9)	48 (32.4)
>65	68 (66.0)	32 (71.1)	100 (67.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Sex	n (%)	n (%)	n (%)
Male	34 (33.0)	17 (37.8)	51 (34.5)
Female	69 (67.0)	28 (62.2)	97 (65.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Race [1]	n (%)	n (%)	n (%)
White	100 (97.1)	43 (95.6)	143 (96.6)
Black	0 (0.0)	0 (0.0)	0 (0.0)
Hispanic	2 (1.9)	1 (2.2)	3 (2.0)
Asian/Pacific Islander	1 (1.0)	1 (2.2)	2 (1.4)
American Indian/Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Height (inches)			
n	95	38	133
Mean	65.9	65.8	65.9
SD	3.73	3.60	3.68
Median	66.0	65.0	65.7
Min, Max	57.3, 75.0	60.0, 75.2	57.3, 75.2

[1] Percents may add up to more than 100% since subjects were allowed to select more than one Race.
[2] IPSS Score = Sum of Marrow blast + Karyotype + Cytopenia Score
[3] Eastern Cooperative Oncology Group Performance Status: 0=Fully active, no restrictions (Karnofsky 90-100); 1=Restricted but ambulatory and capable of light work (Karnofsky 70-80); 2=Ambulatory and capable of self-care but unable to work (Karnofsky 50-60).
[4] French-American-British (FAB) classification of MDS. See Appendix II of the protocol for the classification criteria.
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	10mg Cont. (N=103)	10mg Sync. (N=45)	Overall (N=148)
Weight (lbs)			
n	102	43	145
Mean	170.1	171.0	170.4
SD	46.03	35.31	43.01
Median	162.2	168.0	165.3
Min, Max	89.0, 300.9	110.0, 262.0	89.0, 300.9
Duration of MDS (years)			
n	103	45	148
Mean	3.4	3.4	3.4
SD	3.36	3.13	3.29
Median	2.5	2.5	2.5
Min, Max	0.1, 20.7	0.2, 14.4	0.1, 20.7
5q(-) (31-33) Chromosomal Abnormality	n (%)	n (%)	n (%)
Yes	103 (100.0)	45 (100.0)	148 (100.0)
No	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
IPSS Score(based on Central Review)[2]	n (%)	n (%)	n (%)
Low (0)	42 (40.8)	13 (28.9)	55 (37.2)
Intermediate-1 (0.5-1.0)	40 (38.8)	25 (55.6)	65 (43.9)
Intermediate-2 (1.5-2.0)	4 (3.9)	2 (4.4)	6 (4.1)
High (>=2.5)	1 (1.0)	1 (2.2)	2 (1.4)
Missing	16 (15.5)	4 (8.9)	20 (13.5)
ECOG Performance Status[3]	n (%)	n (%)	n (%)
0	43 (41.7)	16 (35.6)	59 (39.9)
1	50 (48.5)	25 (55.6)	75 (50.7)
2	10 (9.7)	4 (8.9)	14 (9.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)

[1] Percents may add up to more than 100% since subjects were allowed to select more than one Race.
[2] IPSS Score = Sum of Marrow blast + Karyotype + Cytopenia Score
[3] Eastern Cooperative Oncology Group Performance Status: 0=Fully active, no restrictions (Karnofsky 90-100); 1=Restricted but ambulatory and capable of light work (Karnofsky 70-80); 2=Ambulatory and capable of self-care but unable to work (Karnofsky 50-60).
[4] French-American-British (FAB) classification of MDS. See Appendix II of the protocol for the classification criteria.
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Source: CC-5013-MDS-003, Table 14.1.4.1.

Medical History and Prior/Concomitant Medications

In the ITT population, hemochromatosis was present in 30.4% (45/148) patients and an additional 2.7% (4/148) had hemosiderosis. Iron chelating agents were used by 33.8% (50/148) patients, 8.8% (13/148) used various forms of erythropoietin and colony stimulating factors were used in 15.5% (23/148) patients.

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FDA Analysis of Demographics and Baseline Disease Characteristics: Study CC-5013-MDS-003

Demographics

The reviewer did an analysis of the demographics and baseline disease characteristics in the ITT population of 148 patients enrolled. The mean age of patients overall was 70 years with a range of 37 to 95 years. The majority of the patients were female (66%) and Caucasian (97%). Seventy one percent (71%) patients were ≥ 65 years of age. Baseline ECOG performance status score was ≤2 in all the patients. The demographics for the ITT population are shown in the table below. Analyses were also done on the populations that received 10 mg syncopated dose and 10 mg continuous dose. This table is consistent with the sponsor's analysis.

Table 9 Demographics in the ITT Population (Reviewer's Table)

Demographics	10 mg sync N=45	10 mg cont N=103	ITT N=148 (%)
Age (years)			
Mean	71.5	69.3	70
Median	72	71	71
SD	9.4	10.9	10.5
Range	51-91	37-95	37-95
Age Distribution			
Age < 65	13 (28.9)	30 (29.1)	43 (29.1)
Age ≥ 65	32 (71.1)	73 (70.9)	105 (70.9)
Gender			
Female	28 (37.8)	69 (67.0)	97 (65.5)
Male	17 (62.2)	34 (33.0)	51 (34.5)
Race			
White	43 (95.6)	100 (97.1)	143 (96.6)
Hispanic	1 (2.2)	2 (1.9)	3 (2.0)
Asian/Pacific Islander	1 (2.2)	1 (1.0)	2 (1.3)
ECOG performance status			
0	16 (35.6)	43 (41.7)	59 (39.9)
1	25 (55.6)	50 (48.5)	75 (50.7)
2	4 (8.9)	10 (9.7)	14 (9.4)

Baseline Disease Characteristics

Myelodysplasia Classification

The bone marrow biopsy and aspirate samples, peripheral blood smear slides and pathology reports for each subject were reviewed centrally by an independent hematologic reviewer, John M Bennett, MD, University of Rochester Cancer Center, Rochester, NY).

The FAB classification considered by the FDA was adjudicated by the independent hematologic reviewer. Seventy seven (52%) patients had refractory anemia (RA), 16 (10.8%) patients had refractory anemia with ringed sideroblasts (RARS), 2 patients had RA/RARS and 30 (20%) patients had refractory anemia with excess blasts (RAEB). The others were diagnosed with CMML (3), acute leukemia (1), not MDS (2) and unable to classify (17). Thus, 84.4% patients had a diagnosis of MDS. The table below shows the results of the central hematologic review. This table is consistent with the sponsor's analysis.

Table 10 MDS Subtypes by FAB Classification ITT Population (Reviewer's Table)

MDS Subtypes	10 mg Sync N=45	10 mg Cont N=103	N=148 (%)
RA	24 (53.3)	53 (51.5)	77 (52.0)
RARS	3 (6.7)	13 (12.6)	16 (10.8)
RA/RARS	1 (2.2)	1 (1.0)	2 (1.2)
RAEB	12 (26.7)	18 (17.5)	30 (20.3)
CMML	1 (2.2)	2 (1.9)	3 (2.0)
Acute Leukemia	1 (2.2)	0 (0.0)	1 (0.7)
Not MDS	0 (0.0)	2 (1.9)	2 (1.3)
Unable to classify	3 (2.9)	14 (13.6)	17 (11.5)

Reviewer's Comment:
One hundred and twenty eight (85.9 %) patients had a classification of MDS.

IPSS Scores and Risk Category

The cytogenetic reports and chromosome prints for each subject were centrally reviewed by an independent cytogenetic reviewer, Gordon W. Dewald, MD, The Mayo Clinic, Rochester, MN, and submitted in the central cytogenetic review.

The FDA considered the cytopenias, percent myeloblasts and karyotype assigned for a combined IPSS score and subsequent classification of the risk category that were adjudicated by the independent cytogenetic reviewer. The karyotype analysis was based on the central cytogenetic review.

The 5q deletion was present in all 148 patients enrolled. The 5q deletion was an isolated abnormality in 110 (74.3%) patients and was present with other cytogenetic abnormalities in 38 (25.7%) patients diagnosed. At least 20 banded metaphase spreads were analyzed in 119 (80.4%) patients and < 20 metaphases were analyzed in 29 (19.6%) patients for diagnosis of the cytogenetic abnormality. The sponsor was queried on the minimum number of analyzable metaphase spreads used as a requirement for diagnosis. They stated (Response to FDA request for information, August 9, 2005): "while not all patients had at least 20 analyzable metaphases at baseline, all had evidence of a deletion 5q abnormality in at least 2 (two) metaphases, or by FISH (in one case) upon central review".

There were at least 2 karyotype analyses (baseline and follow-up) done in 111 (75%) patients. In these patients, 92 (82.9%) had at least 20 metaphases spreads analyzed in the first visit and 84 (75.7%) patients had at least 20 metaphases analyzed in the second visit.

A good prognosis karyotype was present in 112 (75.7%), an intermediate prognosis karyotype in 25 (16.9%) and a poor prognosis karyotype in 11 (7.4%) patients. The marrow blast percentage was < 5 in 99 (66.9%), 5-10 in 25 (16.9%), 11-20 in 4 (2.7%), 20-30 in 1 (0.7%) and >30 in (0.7%) patients. Bone marrow blasts were missing in 19 (12.8%) patients. The missing blast scores were due to inadequate bone marrow aspirate sample at baseline. The sponsor was queried and they explained that (Response to FDA request for information, June 14, 2005) if the quality of the baseline bone marrow biopsy was such that the Central Reviewer was able to assess the FAB classification as RA, then <5% myeloblasts were assumed when calculating the IPSS. Cytopenias seen in the platelet, hemoglobin and absolute neutrophil counts were missing in the central laboratory values in 5 patients. The missing cytopenias were explained by the sponsor (Response to FDA request for information, June 14, 2005) to be due to unavailability of the values by central laboratory in which case the local laboratory values were used. The sponsor submitted the missing values. Based on the above, the risk category was assigned as low risk in 55 (37.1%) patients, intermediate-1 risk in 65 (43.2%) patients, intermediate-2 risk in 6 (4.0%) patients and high risk in 2 (1.3%) patients. There was no category assigned in the 20 (13.5%) patients with missing values. The table below shows the results of marrow blasts, karyotype and cytopenias leading to the combined score and final classification of the risk category.

Table 11 IPSS Scores and Risk Category at Baseline ITT Population (Reviewer's Table)

IPSS	10 mg Sync N=45	10 mg Cont N=103	ITT N=148
Cytogenetics			
5q deletion present	45 (100.0)	103 (100.0)	148 (100.0)
5q deletion as isolated abnormality	31 (68.9)	79 (76.7)	110 (74.3)
5q deletion with other cytogenetic abnormalities	14 (31.1)	24 (23.3)	38 (25.7)
≥ 20 metaphases analyzed at baseline	34 (75.6)	85 (82.5)	119 (80.4)
< 20 metaphases analyzed at baseline	11 (24.4)	18 (17.5)	29 (19.6)
Good karyotype	31 (68.9)	81 (78.6)	112 (75.7)
Intermediate karyotype	9 (20.0)	17 (16.5)	26 (17.6)
Poor karyotype	5 (11.1)	5 (4.9)	10 (6.8)
Marrow Blasts (%)			
<5	29 (64.4)	70 (68.0)	99 (66.9)
5-10	9 (20.0)	14 (13.6)	23 (15.5)
11-20	2 (4.4)	2 (1.9)	4 (2.7)
21-30	0 (0.0)	0 (0.0)	0 (0.0)
>30	1 (2.2)	0 (0.0)	1 (0.7)
Missing	4 (8.9)	17 (16.5)	21 (14.2)

Cytopenias			
0 or 1	23 (51.1)	68 (66.1)	91 (61.5)
2 or 3	22 (48.8)	35 (34.0)	57 (38.5)
Risk Category			
Low	13 (28.9)	42 (40.8)	55 (37.1)
Intermediate-1	25 (55.6)	40 (38.8)	65 (43.2)
Intermediate-2	2 (4.4)	4 (3.9)	6 (4.0)
High	1 (2.2)	1 (1.0)	2 (1.3)
Missing	4 (8.9)	16 (15.5)	20 (13.5)

Reviewer's Comments:

1. *Typically, the analysis of a minimum of 20 banded metaphase spreads is recommended for diagnosis for normal and abnormal karyotypes. The analysis of 25 or more metaphases can further improve the sensitivity of karyotype analysis and leads to the identification of additional clinically relevant abnormal clones or subclones in a substantial proportion of patients with MDS (5). For the evaluable population analyses, FDA included the patients with a diagnosis of MDS with low or intermediate-1 risk IPSS score associated with a 5q deletion diagnosed on analysis of at least 20 metaphases by conventional cytogenetics technique.*
2. *One hundred and twenty (80.3%) patients had a risk category of low or intermediate-1 risk MDS which is the population in the indication.*

RBC Transfusion-Dependent Anemia at Baseline

As per the protocol, RBC transfusion-dependent anemia was defined as requiring ≥ 2 units of RBCs within 8 weeks of study treatment. The sponsor in the MITT population defined patients as transfusion dependent at baseline when they had received at least two transfusions in each of the eight week periods during the 16 week pre-treatment period and the patients were not transfusion-free for any 56 consecutive days during the 16 week pre-treatment period.

FDA analyses found discrepancies in the number of units transfused within 56 days from baseline prior to start of study drug in 4 patients 0203001, 0303003, 0373024 and 0393003. In the case of patient 0373024, based on Listing 16.2.6.2 the FDA calculated 5 units transfused prior to start of study drug, while the sponsor calculated 8 units. On querying the sponsor, they stated (Response to FDA request for information, June 14, 2005) that they have included the 3 PRBC transfusions on day 1 although the patient received the first dose of the drug on that day. The sponsor was re-queried to explain the rationale used to include PRBC transfusions on day 1 for patient 0373024 when the patient also received the first dose of the drug on that day. The sponsor gave the following explanation (Response to FDA request for information, dated July 8, 2005): "PRBC transfusions given on day 1, the day that the first dose of study drug was given, were included in the baseline count because the decision to transfuse the patient on that day was based on information obtained prior to the first dose of study medication. For patient 0373024, the hemoglobin from the local lab was 6.9 g/dL the day before the transfusion was given and before the start of study drug". Copies of the original documents showing the date and times of transfusion and start of study drug were requested from the sponsor and submitted on August 31, 2005.

One hundred and forty one (95.3%) patients received ≥ 2 RBC units within 8 weeks prior to start of study drug, of which 110 (74.3%) received at least 3 units within 8 weeks. Seven (4.7%) patients received < 2 units within 8 weeks. The median was 6 units and the range 0-18 units in the 8 weeks prior to start of study drug. The table below shows the patients with transfusion dependence at baseline.

Table 12 Transfusion Dependence at Baseline ITT Population (Reviewer's table)

Transfusion Dependence	N=148	%
≥ 2 RBC units within 8 weeks of start of study drug	141	95.3
≥ 3 RBC units within 8 weeks of start of study drug	110	74.3
0-2 units within 8 weeks	42	28.4
0-1 unit within 8 weeks	7	4.7
Median number of units Min, Max	6 0-18	

Reviewer's Comment:

1. *Ninety-five percent of patients received at least 2 units within 8 weeks prior to start of study drug. 72% received more than 3 units. The median was 6 units and the range 0-18 units. There is no definition of what is a truly transfusion dependent population.*

Study CC-501-MDS-001

The table below summarizes the baseline demographic and disease-related characteristics for the MITT population as submitted by the sponsor.

Table 13 Baseline Demographic and Disease-Related Characteristics (MITT Population) (Applicant's Table)

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	25mg (N=13)	10mg (N=12)	10mg Sync. (N=18)	Overall (N=43)
Age (years)				
n	13	12	18	43
Mean	73.1	70.9	66.7	69.8
SD	8.88	9.93	13.82	11.55
Median	74.0	69.5	71.0	72.0
Min, Max	51.0, 85.0	56.0, 85.0	27.0, 82.0	27.0, 85.0
Age distribution				
≤65	2 (15.4)	4 (33.3)	7 (38.9)	13 (30.2)
>65	11 (84.6)	8 (66.7)	11 (61.1)	30 (69.8)
Sex				
Male	7 (53.8)	9 (75.0)	10 (55.6)	26 (60.5)
Female	6 (46.2)	3 (25.0)	8 (44.4)	17 (39.5)
Race [a]				
White	11 (84.6)	12 (100.0)	15 (83.3)	38 (88.4)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hispanic	2 (15.4)	0 (0.0)	2 (11.1)	4 (9.3)
Asian/Pacific Islander	0 (0.0)	0 (0.0)	1 (5.6)	1 (2.3)
American Indian/Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Duration of MDS (years)				
n	13	12	18	43
Mean	4.6	3.2	2.6	3.4
SD	4.51	2.53	2.89	3.40
Median	2.5	3.1	1.0	2.5
Min, Max	0.5, 14.1	0.4, 8.8	0.1, 11.1	0.1, 14.1
5q(-) (31-33) Chromosomal Abnormality				
Yes	5 (38.5)	3 (25.0)	5 (27.8)	13 (30.2)
No	8 (61.5)	9 (75.0)	13 (72.2)	30 (69.8)
IPSS Score [b]				
Low (0)	4 (30.8)	5 (41.7)	6 (33.3)	15 (34.9)
Intermediate-1 (0.5-1.0)	5 (38.5)	6 (50.0)	12 (66.7)	23 (53.5)
Intermediate-2 (1.5-2.0)	3 (23.1)	1 (8.3)	0 (0.0)	4 (9.3)
High (>=2.5)	1 (7.7)	0 (0.0)	0 (0.0)	1 (2.3)
ECOG Performance Status[c]				
0	6 (46.2)	6 (50.0)	7 (38.9)	19 (44.2)
1	6 (46.2)	6 (50.0)	10 (55.6)	22 (51.2)
2	1 (7.7)	0 (0.0)	1 (5.6)	2 (4.7)
FAB Classification				
RA	4 (30.8)	5 (41.7)	11 (61.1)	20 (46.5)
RARS	3 (23.1)	6 (50.0)	4 (22.2)	13 (30.2)
RAEB	5 (38.5)	1 (8.3)	2 (11.1)	8 (18.6)
CMML	0 (0.0)	0 (0.0)	1 (5.6)	1 (2.3)
RAEB-T	1 (7.7)	0 (0.0)	0 (0.0)	1 (2.3)

Data Source: Table 14.1.2.1

[a] Percents may add up to more than 100% since patients were allowed to select more than one Race.

[b] IPSS Score = Sum of Marrow blast + Karyotype + Cytopenia Score. Note: Patients 125 and 144 were missing % blasts at the screening/baseline visit. For purposes of IPSS categorization, blasts were assumed to be < 5% for these two patients because they had been assessed as having RARS and RA, respectively.

[c] Eastern Cooperative Oncology Group Performance Status: 0=Fully active, no restrictions (Karnofsky 90-100); 1=Restricted but ambulatory and capable of light work (Karnofsky 70-80); 2=Ambulatory and capable of self-care but unable to work (Karnofsky 50-60); 3=Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40); 4=Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20).

Source: CC-501-MDS-001, Table 9

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FDA Analysis of Baseline Disease Characteristics: Study CC-501-MDS-001

The reviewer did an analysis of the baseline disease characteristics in the ITT population of the 45 patients enrolled. Twenty patients (44.4%) had RA, 13 (28.9%) had RARS and 8 (17.8%) patients had RAEB. The others were diagnosed with RAEB-t (1), CMML (1) and 2 patients were not MDS. Thus 91% patients were diagnosed with MDS. The 5q deletion was present in 13 (28.9%) patients and absent in the rest. Fifteen (33.3%) patients were classified in the low risk category, 25 (55.5%) patients were in the intermediate-1 risk category, 4 (8.9%) patients were in the intermediate-2 risk category and 1 patient was in the high-risk category.

Table 14 Disease Characteristics at baseline ITT Population (Reviewer's Table)

Characteristics	N=45	%
MDS Subtypes		
RA	20	44.4
RARS	13	28.9
RAEB	8	17.8
RAEB-t	1	2.2
CMML	1	2.2
Not MDS	2	4.4
Cytogenetics		
5q deletion present 5q deletion absent	13 32	28.9 71.1
Risk Category		
Low	15	33.3
Intermediate-1	25	55.5
Intermediate-2	4	8.9
High	1	2.2

Disposition of Subjects

Study CC-5013-MDS-003

Sponsor's Analysis

The sponsor used September 15, 2004 as the data cutoff date. As of the 15 September 2004 data cutoff date, 42 (28.4%) of the 148 subjects had discontinued from the study: 34 (23.0%) of the 148 subjects discontinued before completing 24 weeks of the study, and 8 (5.4%) discontinued treatment after completing 24 weeks of the study. The primary reasons for discontinuation were AEs (10.8%; 16/148) and lack of therapeutic effect (8.8%; 13/148). Of the 106 subjects who remained in the study as of the data cutoff date, 103 had completed at least 24 weeks of the study, and 3 had not yet completed 24 weeks of the study. Overall, 111 (75.0%) of the 148 subjects had completed at least 24 weeks of the study as of 15 September 2004. The table below summarizes the disposition of patients as submitted by the sponsor.

Table 15 Disposition of Patients (Applicant's Table)

	10mg Cont. n (%)	10mg Sync. n (%)	Overall n (%)
No. of Subjects in ITT Population	103	45	148
Subjects active in study	77 (74.8)	29 (64.4)	106 (71.6)
Did not complete 24 weeks of study but still active	3 (2.9)	0 (0.0)	3 (2.0)
Completed 24 weeks of study and still active	74 (71.8)	29 (64.4)	103 (69.6)
Subjects withdrawn from study	26 (25.2)	16 (35.6)	42 (28.4)
Withdrew prior to 24 weeks of study	20 (19.4)	14 (31.1)	34 (23.0)
Withdrew after 24 weeks of study	6 (5.8)	2 (4.4)	8 (5.4)
Primary reason for discontinuation			
Adverse event	7 (6.8)	9 (20.0)	16 (10.8)
Lack of therapeutic effect	9 (8.7)	4 (8.9)	13 (8.8)
Subject withdrew consent	1 (1.0)	1 (2.2)	2 (1.4)
Subject lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Death	6 (5.8)	2 (4.4)	8 (5.4)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
Other	3 (2.9)	0 (0.0)	3 (2.0)
Total number of subjects who completed 24 weeks of study	80 (77.7)	31 (68.9)	111 (75.0)

Data Source: Table 14.1.1
[a] Percents are based on the ITT (safety) population.

Source: CC-5013-MDS-003, Table 10

FDA Analysis

The reviewer analyzed the primary reasons for discontinuation in the 148 patients enrolled. The primary reasons for discontinuation were adverse events in 16 patients (10.8%) and lack of therapeutic effect in 13 patients (8.8%). The main reasons for the adverse events were rash (7), thrombocytopenia (5), pneumonia (5), neutropenia (4), pruritis (4), fever (3), anemia (3), diarrhea (2), dyspnea, edema, neuropathy, pancytopenia, colon cancer and cerebrovascular accident. Patients withdrew consent after neutropenic sepsis, pneumonia and pruritis. Deaths were due to neutropenia (5) with sepsis in 3 patients and thrombocytopenia (3) with subdural hematoma in one patient and transfusion reaction in another. The FDA analysis of patient disposition in the ITT population is shown in the table below.

Table 16 Patient Disposition ITT Population (Reviewer's Table)

Patient Disposition	N=148	%
ITT population	148	100.0
Completion of protocol specified treatment	106	71.6
Reasons for Treatment Discontinuation		
Adverse events	16	10.8
Lack of therapeutic effect	13	8.8
Death	8	5.4
Withdrew consent	2	1.3
Transformed into AML	1	0.7
Progression	1	0.7
Non-compliance	1	0.7

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Study CC-501-MDS-001

Forty- five patients were enrolled in the study. As of the 05 February 2004 data cutoff date, 14 (31.1%) of the 45 patients had discontinued from the study before completing the first 16 weeks (core phase) of therapy. The primary reasons for discontinuation from the study during the first 16 weeks were adverse events (15.6%; 7/ 45) and treatment failure (8.9%; 4/ 45). The frequency of early discontinuation due to adverse events was higher (30.8%; 4/ 13) in the 25-mg dosing group than in either the 10-mg continuous (8.3%; 1/ 12) or 10-mg syncopated (10.0%; 2/ 18) dosing group. Two (4.4%) of the 45 patients died during the core phase of the study of causes that the investigator judged to be unrelated to lenalidomide (multiorgan failure due to sepsis in Patient 112 [25-mg dosing group] and splenic infarction in Patient 134 [10-mg syncopated dosing group]). The table below summarizes the disposition of patients for the core phase (Weeks 1-16) of the study as submitted by the sponsor.

Table 17 Disposition of Patients in Core Phase (Weeks 1-16) (Applicant's Table)

	25mg		10mg		10mg Sync.		Overall	
	n	(%)	n	(%)	n	(%)	n	(%)
ITT Population[a]	13	(100.0)	12	(100.0)	20	(100.0)	45	(100.0)
MITT [b]	13	(100.0)	12	(100.0)	18	(90.0)	43	(95.6)
Entered Core Phase[c]	13	(100.0)	12	(100.0)	18	(90.0)	43	(95.6)
Completed 16 weeks of study medication	8	(61.5)	7	(58.3)	16	(80.0)	31	(68.9)
Discontinued study med. prior to Week 16	5	(38.5)	5	(41.7)	4	(20.0)	14	(31.1)
Primary reason for discontinuation								
Adverse event	4	(30.8)	1	(8.3)	2	(10.0)	7	(15.6)
Protocol violation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Investigator withdrew Patient	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Study discontinued by sponsor	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Death	1	(7.7)	0	(0.0)	1	(5.0)	2	(4.4)
Patient withdrew consent	0	(0.0)	1	(8.3)	0	(0.0)	1	(2.2)
Treatment failure	0	(0.0)	3	(25.0)	1	(5.0)	4	(8.9)
Patient lost to follow-up	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Data Source: Table 14.1.1
[a] The ITT population includes all patients who took at least one dose of study drug.
[b] The MITT population includes all patients who took one dose of study drug but excludes patients 138 and 139 who had a diagnosis of chronic myeloid leukemia (CML).
[c] Percents for the Core Phase are based on the overall ITT population.

Source: CC-501-MDS-001, Table 4

As of the 05 February 2004 data cutoff date, 29 (64.4%) of the 45 enrolled patients had entered the extension phase (Weeks 17- 52) of the study. Thirteen (44.8%) of these 29 patients had discontinued from the study before completing the planned 52 weeks of the extension period as of the 05 February 2004 data cutoff date. The primary reason for discontinuation from the study in the extension phase was adverse events (27.6%; 8/29). Two (6.9%) of the 29 patients discontinued from the study due to treatment failure, 2 (6.9%) were lost to follow- up, and 1 (3.4%) died of multiorgan failure that developed secondary to pneumonia (Patient 108); the death was judged by the investigator to be unrelated to lenalidomide. The table below summarizes the disposition of patients during the extension phase as submitted by the sponsor.

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Table 18 Disposition of Patients in Extension Phase (Weeks 17-52) (Applicant's Table)

	25mg n (%)	10mg n (%)	10mg Sync. n (%)	Overall n (%)
ITT Population [a]	13 (100.0)	12 (100.0)	20 (100.0)	45 (100.0)
Entered Extension Phase[b]	7 (53.8)	7 (58.3)	15 (75.0)	29 (64.4)
Completed 52 Weeks of study medication	4 (57.1)	4 (57.1)	0 (0.0)	8 (27.6)
Discontinued study med.prior to Week52	3 (42.9)	3 (42.9)	7 (46.7)	13 (44.8)
Primary reason for discontinuation				
Adverse event	1 (14.3)	3 (42.9)	4 (26.7)	8 (27.6)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigator withdrew Patient	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study discontinued by sponsor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	1 (14.3)	0 (0.0)	0 (0.0)	1 (3.4)
Patient withdrew consent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment failure	0 (0.0)	0 (0.0)	2 (13.3)	2 (6.9)
Patient lost to follow-up	1 (14.3)	0 (0.0)	1 (6.7)	2 (6.9)

Data Source: Table 14.1.1
[a] The ITT population includes all patients who took at least one dose of study drug.
[b] Percents for the Extension Phases are based on the number of ITT patients who entered that phase

Source: CC-501-MDS-001, Table 5

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Protocol Deviations

Study CC-5013-MDS-003

Sponsor's Analysis
According to the sponsor, the most common protocol deviations were errors in the study medication regimens (e. g., missed dose).

The 16 occurrences of deviations from the inclusion criteria in 15 subjects and the 9 occurrences of deviations from exclusion criteria in 9 subjects represent bone marrow biopsies that were not done on time, thereby preventing the timely determination of the FAB classification and IPSS score. Use of erythropoietin was reported in 4 subjects during the study (Subjects 0243016, 0293010, 0333005, and 0443002). Three of these subjects (Subjects 0293010, 0333005, and 0443002) received erythropoietin after administration of their last dose of study medication but before they had discontinued from the study; the fourth subject (Subject 0243016) received erythropoietin both before entry into and during the study (this subject was still participating in the study as of the 15 September 2004 data cutoff date). None of these subjects had responded (i.e., became RBC- transfusion independent) to lenalidomide by the time they had discontinued treatment (Subjects 0293010, 0333005, and 0443002) or as of the 15 September 2004 data cutoff date for the analysis (Subject 0243016).

Three subjects received prednisone concomitantly with lenalidomide during the study (Subjects 013003, 0223003, and 0373031). Two of these subjects were taking prednisone at entry into the study (violation of entry criterion 12) for conditions that included chronic polymyalgias (Subject 0223003) and joint pain (Subject 0373031); these subjects continued to receive prednisone concomitantly with lenalidomide during the study. Prednisone was initiated in the third subject (Subject 0013003) during the study as treatment for arthritis.

The table below summarizes protocol deviations for the total study population submitted by the sponsor.

Table 19 Protocol Deviations in the Total Study Population (Applicant's Table)

Deviation	No. of Occurrences	No. of Subjects N=148
Deviation From Inclusion Criteria	16	15
Deviation From Exclusion Criteria	9	9
Investigational Drug Noncompliance	120	63
Concomitant Medication Noncompliance	13	10

Data Source: Listing 16.2.2

Source; CC-5013-MDS-003, Table 12

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FDA Analysis of Protocol Deviations: Study CC-5013-MDS-003

FDA assessed the protocol deviations in the study protocol. Laboratory tests that were required for exclusion were either not done or were abnormal yet included in 42 (28.4%) patients. Direct bilirubin was not done 22/23 patients in one center in Germany. An IPSS score could not be assigned due to missing myeloblast percentage or due to missing laboratory values in 20 (13.5%) patients. The central reviewer was unable to classify MDS in 17 patients, could not diagnose MDS in 2 patients and reviewed 1 patient with acute leukemia for a total of 20 (13.5%) patients who did not have a classification of MDS. The risk category was intermediate-2 or high in 8 (5.4%) patients. Seven (4.7%) patients did not receive ≥ 2 units of RBC transfusion within 8 weeks prior to start of study drug and were thus not transfusion dependent at baseline. Current informed consent form was not signed by 1 (0.7%) patient. A 28-day wash-out period was not followed in 1 (0.7%) patient. Touch prep used to determine eligibility in 1 (0.7%) patient. One (0.7%) patient had a dry tap.

The table below summarizes the protocol deviations based on the inclusion and exclusion criteria for Study MDS-003 as assessed by the FDA. Those marked with stars were considered major protocol deviations. These patients could not be adjudicated by the independent hematologic or cytogenetic reviewer and were excluded from the evaluable population analyzed by the FDA.

Table 20 Inclusion and Exclusion Criteria Protocol Deviations (Reviewer's table)

Protocol Deviations	**Number of patients (n=148)**	**%**
Laboratory tests required for exclusion not done or included if abnormal	42	28.4
Direct bilirubin not done	23	15.5
Iron stain not done	11	7.4
SGPT/ALT > 3 x ULN or not done	3	2.0
Creatinine not done	1	0.7
Unable to assign IPSS score due to missing myeloblasts or	**20**	**13.5**

laboratory values*		
Unable to classify MDS/FAB subtype or Not MDS or acute leukemia*	**20**	**13.5**
Risk category intermediate-2 or high*	**8**	**5.4**
Patient not transfusion dependent at baseline i.e., did not receive ≥ 2 units RBC within 8 weeks *	**7**	**4.7**
Use of growth factors	2	1.4
Current informed consent form not signed by patient	1	0.7
28-day wash-out period not followed	1	0.7
Touch prep used to determine eligibility	1	0.7
Patient had a dry tap	1	0.7

* major protocol deviations

Other deviations not in the inclusion and exclusion criteria but considered significant by the FDA are shown in the table below. These were study conduct issues.
FDA found that data in Listing 16.2.2 (Protocol Deviations) was contradicted by data in Listing 16.2.6.3 (Cytogenetics Central Review). The sponsor was queried and responded (Response to FDA request for Information, dated July 12, 2005):
"Listing 16.2.2 is a comprehensive listing of deviations as captured by the study monitor. Some of these reported deviations were subsequently clarified or corrected, but that information does not appear in this listing. The data provided in final study tables and listings are the final "cleaned" data, after questions and issues noted on monitoring of the study were resolved to the extent possible".

The sponsor was queried on the patients who received growth factors while on study. They stated (Response to FDA request for information, dated August 9, 2005) that the doses were not captured on the CRFs but provided the reasons for use and duration of use. Patient 0203001 was mistakenly noted and did not receive Procrit. Patient 0293010 received darbepoietin alfa (Aranesp) for 1 day only. Patient 0243016 received darbepoietin alfa (Aranesp) for anemia for 216 days. This patient did not have a transfusion independent response or a major cytogenetic response.

The sponsor was queried on the patients who received corticosteroids while on study. They stated (Response to FDA request for information, dated August 9, 2005) that the doses were not captured in the CRFs but provided the reasons for use and duration of use. Patient 0013003 received medrol/prednisone for 6 days. Patient 0373009 received decortin H 5 times during the study for reactions to plaletet transfusion. Patient 0373022 received prednisone for 10 days for bronchitis and 28 days for itching. Patient 0373031 received decortin H for joint pain.

There were 8 patients who did not have a baseline iron stain done (0053002, 0143003, 0303001, 0373001, 0373014, 0373018, 0373021, 0373024). Five of them were excluded for other reasons shown in the next section. Three of the patients did not have a transfusion independent or major cytogenetic response.

Except for the patients who did not have at least 20 metaphases analyzed at baseline during cytogenetic review, the rest were included in the efficacy analyses in the evaluable population. The table below summarizes protocol deviations apart from the inclusion and exclusion criteria for this protocol.

Table 21 Other Protocol Deviations (Reviewer's Table)

Protocol Deviations	Number of patients (n=148)	%
< 20 metaphases analyzed at baseline*	**29**	**19.6**
Date of cytogenetic aspirate at screening not within 28 days before first dose of study drug	21	14.2
Date of bone marrow aspirate at screening not within 28 days before first dose of study drug	21	14.2
CBC/peripheral blood smear at screening not within 28 days before first dose of study drug	18	12.2
BMBx or Peripheral blood smear slides not sent to central review	10	6.8
ECG not done at baseline or done >28 days prior to start of study drug	12	8.1
Corticosteroids while on study	5	3.4
Procrit or Aranesp while on study	4	2.7
Labs > 28 days prior	1	0.7

* considered for eligibility in evaluable population

Study CC-501-MDS-001

As per the sponsor, the most common protocol deviations were missed visits or assessments (54 occurrences in 24 patients), visits or assessments that were outside of the pre-specified window (23 occurrences in 16 patients), and noncompliance (e.g., not starting the next cycle on schedule) to the study medication regimen (34 occurrences in 16 patients). In addition, 2 patients, both in the 10-mg syncopated dosing group, were found to have a diagnosis other than MDS after enrollment into the study; the diagnosis of both these patients (Patients 138 and 139) was revised to Philadelphia chromosome-negative CML. The table below summarizes protocol deviations for the overall study population. FDA agrees with the analysis.

Table 22 Protocol Deviations (Applicant's Table)

Deviation	No. of Occurrences	No. of Patients N=45
Deviation From Inclusion Criteria	2	2
Deviation From Exclusion Criteria	0	0
Investigational Drug Noncompliance	34	16
Concomitant Medication Noncompliance	0	0
Missing Visits or Assessments	54	24
Out-of-window Visits or Assessments	23	16
Other	0	0

Data Source: Listing 16.2.2

Source: CC-501-MDS-001, Table 6

Eligibility

Study CC-5013-MDS-003

The results of local laboratory and/or central analyses of laboratory data were used to determine a subject's eligibility for the study. The results of local review of bone marrow biopsy/aspirate, peripheral blood smear slides, pathology reports and cytogenetic reports and chromosome prints were used to determine a subject's eligibility for the study.

Reasons for Exclusions

Sponsor's Analysis
The sponsor excluded 54 patients from the ITT population for the following reasons: 1) inability to obtain documentation that the subject received ≥2 units of pRBCs in the 8- to 16- week period before the first dose of lenalidomide (n= 19); 2) a diagnosis of low-or intermediate- 1- risk MDS was not documented by central review of the baseline bone marrow aspirate and biopsy slides (n= 28); and 3) the subject was found to have been RBC-transfusion-free for ≥ 56 days during the immediate 16 weeks prior to the start of study treatment (n= 7). They did an efficacy analysis on the population after exclusion called the modified ITT population (MITT).

FDA Analysis
The FDA performed analyses in the patients that were evaluable and excluded 29 (19.6%) patients whose diagnosis of the 5q deletion or other cytogenetic abnormalities was based on <20 metaphase spreads analyzed; 28 (18.2%) patients who did not have a diagnosis of low or intermediate-1 MDS and 7 (4.7%) patients who were not transfusion dependent at baseline i.e., did not receive ≥2 units within 8 weeks.

Table 23 Reasons for Exclusion/Ineligibility from FDA Efficacy Analysis (Reviewer's Table)

Reason	(n=148) N (%)	Patient ID
Less than 20 metaphases used to diagnose 5q deletion	29 (19.6)	0073001, 0073004, 0083001, 0083003, 0093003, 0143002, 0223002, 0223004, 0233002, 0233003, 0233005, 0233009, 0233010, 0243003, 0243006, 0243013, 0273001, 0293002, 0293004, 0293011, 0303001, 0303003, 0373012, 0373016, 0373019, 0373021, 0373026, 0393001, 0393002
Unable to classify MDS/FAB subtype or Not MDS or acute leukemia	20 (13.5)	0053002, 0093003, 0103002, 0233005, 0233006, 0233009, 0243010, 0273001, 0273002, 0293002, 0293011, 0313002, 0323004, 0333004, 0373014, 0373018, 0373021, 0373028, 0393001, 0393002
Unable to assign IPSS score due to missing myeloblasts or laboratory values	20 (13.5)	0053002, 0093003, 0103002, 0233005, 0233006, 0233009, 0243010, 0273001, 0273002, 0293002, 0293011, 0313002, 0323004, 0333004, 0373014, 0373018, 0373021, 0373028, 0393001, 0393002
Risk category intermediate-2 or high risk	8 (4.7)	0053001, 0163001, 0223002, 0263001, 0373015,0373020, 0383001, 0383002

Patient not transfusion dependent at baseline i.e., did not receive ≥ 2 units within 8 weeks	7 (4.7)	0073002, 0243012, 0293007, 0293010, 0323003, 0373015, 0393001

Unable to Assign IPSS Scores

FDA analyses found patients 0083002, 0113002, 0333003, 0373020, 0373026 and 0383002 to have been assigned a higher cytopenia based on the listings. The sponsor was queried on these patients and they stated (Response to FDA request for information, June 14, 2005): "The minimum hemoglobin level (central or local lab) during the 56-day period prior to the first study drug dose was used in the calculation of the cytopenia score". The correct values were submitted to the FDA. These patients were included in the FDA analyses.

FDA analyses found that some central labs for patients 0113001, 0263001, 0303002, 0373005 and 0373006 were missing the baseline cytopenias and were unable to assign an IPSS score. The sponsor was queried on these patients and they stated (Response to FDA request for information, June 14, 2005): "If central lab information was missing for abs. neutrophil count or platelet coune then local lab values were used". The sponsor submitted the values as shown below. These patients were included in the FDA analyses.

FDA analyses revealed that patients 0123001, 0233008, 0293004 and 0303004 did not have percent marrow myeloblasts due to inadequate bone marrow aspirate sample at baseline thus were unable to assign an IPSS score. The sponsor stated (Response to FDA request for information, June 14, 2005): "If percent marrow myeloblasts were missing due to inadequate bone marrow aspirate at baseline, but the quality of the baseline bone marrow biopsy was such that the Central Reviewer was able to assess the FAB classification as RA, then <5% myeloblasts were assumed when calculating the IPSS". These patients were included in the FDA analyses.

Patient 0293009 has percent myeloblasts in bone marrow aspirate out of range under Listing 16.2.2 but is recorded as 8% in dataset and listings. Page 9000 of the Case Report Form confirmed 8% myeloblasts in the bone marrow aspirate but the protocol deviation log recorded an exemption granted for an IPSS score of > 1.0. FDA calculated an IPSS score of 1.0 which confirmed the sponsor's recorded score. The sponsor was queried on patient 0293009 and stated (Response to FDA request for information, dated July 12, 2005) : "CRF page 6 has percent myeloblasts recorded as 12%, which is out of range, and a query was issued and response noted on Listing 16.2.2. The Central Reviewer percent myeloblasts were recorded as 8%, which is what appears in the dataset".

Karyotype Analyses

FDA requested Case Report Forms for the following patients (0053004, 0053005, 0073001, 0293009) due to discrepancies found in the FDA analyses as explained below:

Listing 16.2.6.3 reported karyotype analysis for Patients 0053004 and 0053005 and described them as having a 5q deletion, but Listing 16.2.2 states that chromosomal analysis not performed due to lack of dividing cells. Page 8000 of the Case Report Form for patient 0053004 revealed that the screening bone marrow biopsy on February 4, 2004 did show a 5q deletion although the protocol deviations page recorded as chromosomal analysis was not performed by — due to lack of dividing cells. The Case Report Form for patient 0053004 revealed that the screening bone marrow biopsy on February 4, 2004 showed a 5q deletion on Page 8000 but the protocol deviations page has a record that chromosomal analysis was not performed by Impath due to lack of dividing cells.

Page 8000 of the Case Report Form for patient 0053005 revealed that the screening bone marrow biopsy on July 1, 2004 did show a 5q deletion although the protocol deviations page recorded as chromosomal analysis was not performed by — due to lack of dividing cells as shown in the excerpt below. The Case Report Form for patient 0053005 revealed that the screening bone marrow biopsy on July 1, 2004 showed a 5q deletion on Page 8000 but the protocol deviations page has a record that chromosomal analysis was not performed by — due to lack of dividing cells.

The sponsor was queried on the patients 0053004 and 0053005 above and stated (Response to FDA question, dated July 12, 2005): "Both subjects referenced (0053004 and 0053005) have "not performed by — optional central laboratory) due to lack of dividing cells" noted on Listing 16.2.2, however, data is present on Page 7 and on Central Reviewer forms from the sites local laboratory evaluation. Thus, although it was reported that — was unable to perform the analysis, it was indeed performed by the local laboratory".

Transfusion Entry Requirement

Patient 0073001 under Listing 16.2.2 reportedly deviated from the inclusion criteria but Listing 16.2.6.2 showed 4 units in last 56 days. Page 8 of the Case Report Form confirmed 4 units in the 56 days prior to start of study drug. There were no comments regarding transfusions in the protocol deviation log.

There were differences in the calculation of the number of RBC units transfused within 56 days from baseline in the analyses between that of the FDA and the sponsor in the following patients (the units recorded by the sponsor and FDA are given in parenthesis): 0203001 (4;5), 0303003 (4;5), 0373024 (8;5) and 0393003 (6;8). The sponsor was queried and explained (Response to FDA request for information, dated June 14, 2005) the discrepancies. In patient 0373024, the sponsor included RBC transfusions on day 1, the same day that the patient received the first dose of the drug. The sponsor was queried again and responded as follows (Response to FDA request for information, dated July 8, 2005): "PRBC transfusions given on day 1, the day that the first dose of study drug was given, were included in the baseline count because the decision to transfuse the patient on that day was based on information obtained prior to the first dose of study medication".

There were discrepancies in the reason that patients were excluded in the MITT population in Listing 16.2.3 and the data listing 16.2.2 which showed the dates patients were transfused in the 21 patients shown in the table below. The sponsor was queried on these differences. Explanations were submitted in their response to FDA request for information dated August 5, 2005. The sponsor's response was very confusing and they were again queried on their responses above (FDA query dated August 11, 2005) with the following question for further clarification: "isn't day -17 within the first 8 weeks?" The sponsor's response (dated August 22, 2005) stated: "Please note that we counted the days during the baseline period chronologically, rather than backwards from start of drug. Hence, the first 8 weeks of the 16 weeks preceding start of drug includes days -55 to -110 inclusive. The referenced patient (ID 0013003) only received one transfusion and that was at study day -17 so failed to meet the criteria for MITT. The same reasoning applies to the other patients on the list."

Table 24 Transfusion Discrepancy (Reviewer's Table)

Patient ID	Reason Patient Excluded Listing 16.2.3	Discrepancy Listing 16.2.6.2
0013003	Did not receive at least 2 units PRBC in 8-16 weeks prior to first dose; is transfusion free for a 56-day period prior to first dose	2 units transfused in the 56 day period prior to first dose
0023001	Did not receive at least 2 units PRBC in 8-16 weeks prior to first dose	2 units transfused in the 56 day period prior to first dose
0053003	Is transfusion free for a 56-day period prior to first dose	2 units transfused in the 56 day period prior to first dose
0053004	Did not receive at least 2 units PRBC in 8-16 weeks prior to first dose	4 units transfused in the 56 day period prior to first dose
0053005	Did not receive at least 2 units PRBC in 8-16 weeks prior to first dose	2 units transfused in the 56 day period prior to first dose
0103003	Did not receive at least 2 units PRBC in 8-16 weeks prior to first dose; is transfusion free for a 56-day period prior to first dose	2 units transfused in the 56 day period prior to first dose
0113007	Did not receive at least 2 units PRBC in 8-16 weeks prior to first dose; is transfusion free for a 56-day period prior to first dose	2 units transfused in the 56 day period prior to first dose
0193001	Did not receive at least 2 units PRBC in 8-16 weeks prior to first dose; is transfusion free for a 56-day period prior to first dose	2 units transfused in the 56 day period prior to first dose
0223004	Did not receive at least 2 units PRBC in 8-16 weeks prior to first dose; is transfusion free for a 56-day period prior to first dose	4 units transfused in the 56 day period prior to first dose
0243002	Is transfusion free for a 56-day period prior to first dose	2 units transfused in the 56 day period prior to first dose
0243005	Did not receive at least 2 units PRBC in 8-16 weeks prior to first dose; is transfusion free for a 56-day period prior to first dose	4 units transfused in the 56 day period prior to first dose
0243009	Is transfusion free for a 56-day period prior to first dose	3 units transfused in the 56 day period prior to first dose
0243017	Is transfusion free for a 56-day period prior to first dose	2 units transfused in the 56 day period prior to first dose

0313001	Did not receive at least 2 units PRBC in 8-16 weeks prior to first dose; is transfusion free for a 56-day period prior to first dose	2 units transfused in the 56 day period prior to first dose
0313005	Is transfusion free for a 56-day period prior to first dose	3 units transfused in the 56 day period prior to first dose
0333001	Did not receive at least 2 units PRBC in 8-16 weeks prior to first dose	12 units transfused in the 56 day period prior to first dose
0373007	Is transfusion free for a 56-day period prior to first dose	2 units transfused in the 56 day period prior to first dose
0373025	Did not receive at least 2 units PRBC in 8-16 weeks prior to first dose; is transfusion free for a 56-day period prior to first dose	2 units transfused in the 56 day period prior to first dose
0373034	Did not receive at least 2 units PRBC in 8-16 weeks prior to first dose; is transfusion free for a 56-day period prior to first dose	6 units transfused in the 56 day period prior to first dose
0383004	Did not receive at least 2 units PRBC in 8-16 weeks prior to first dose; is transfusion free for a 56-day period prior to first dose	5 units transfused in the 56 day period prior to first dose
0413001	Is transfusion free for a 56-day period prior to first dose	2 units transfused in the 56 day period prior to first dose

FDA considered the transfusion dependent population based on the definition of transfusion dependent anemia in the inclusion criteria in the protocol (RBC transfusion- dependent anemia defined as having received ≥2 units of RBCs within 8 weeks of study treatment).

FDA excluded patients from the ITT population based on the criteria as discussed in detail above to identify patients in the evaluable population. The table below gives a patient-by-patient reason for exclusion.

Table 25 List of Patients and Reasons for Exclusion (Reviewer's Table)

No.	Patient ID	Reason for Exclusion
1.	0053001	risk category intermediate-2
2.	0053002	unable to classify MDS subtype; unable to assign IPSS score as myeloblasts n/a
3.	0073001	15 metaphases analyzed for diagnosis
4.	0373002	patient not transfusion dependent at baseline; received zero units in 8 weeks
5.	0073004	6 metaphases analyzed for diagnosis
6.	0083001	9 metaphases analyzed for diagnosis
7.	0083003	7 metaphases analyzed for diagnosis
8.	0093003	unable to classify MDS subtype; unable to assign IPSS score as baseline myeloblasts n/a; 3 metaphases analyzed for diagnosis
9.	0103002	unable to classify MDS subtype; unable to assign IPSS score as baseline myeloblasts n/a
10.	0143002	16 metaphases analyzed for diagnosis
11.	0163001	risk category high-risk
12.	0223002	risk category intermediate-2; 9 metaphases analyzed for diagnosis
13.	0223004	11 metaphases analyzed for diagnosis
14.	0233002	15 metaphases analyzed for diagnosis
15.	0233003	11 metaphases analyzed for diagnosis
16.	0233005	unable to classify MDS subtype; unable to assign IPSS score as baseline myeloblasts n/a ; 5 metaphases analyzed for diagnosis

17.	0233006	diagnosis not MDS; cannot assign IPSS score
18.	0233009	unable to classify MDS subtype; unable to assign IPSS score as baseline myeloblasts n/a; 6 metaphases analyzed for diagnosis
19.	0233010	16 metaphases analyzed for diagnosis
20.	0243003	5 metaphases analyzed for diagnosis
21.	0243006	7 metaphases analyzed for diagnosis
22.	0243010	diagnosis acute leukemia; cannot assign IPSS score
23.	0243012	patient not transfusion dependent at baseline; received zero units in 8 weeks
24.	0243013	19 metaphases analyzed for diagnosis
25.	0263001	risk category intermediate-2
26.	0273001	unable to classify MDS subtype; unable to assign IPSS score as baseline myeloblasts n/a; 4 metaphases analyzed for diagnosis
27.	0273002	unable to classify MDS subtype; unable to assign IPSS score as baseline myeloblasts n/a
28.	0293002	unable to classify MDS subtype; unable to assign IPSS score as baseline myeloblasts n/a; 8 metaphases analyzed for diagnosis
29.	0293004	19 metaphases analyzed for diagnosis
30.	0293007	patient not transfusion dependent at baseline; received one unit in 8 weeks
31.	0293010	patient not transfusion dependent at baseline; received zero units in 8 weeks
32.	0293011	unable to classify MDS subtype; unable to assign IPSS score as baseline myeloblasts n/a; 9 metaphases analyzed for diagnosis
33.	0303001	15 metaphases analyzed for diagnosis
34.	0303003	11 metaphases analyzed for diagnosis
35.	0313002	diagnosis not MDS; unable to assign IPSS score
36.	0323003	patient not transfusion dependent at baseline; received zero units in 8 weeks
37.	0323004	unable to classify MDS subtype; unable to assign IPSS score as baseline myeloblasts n/a
38.	0333004	unable to classify MDS subtype; unable to assign IPSS score as baseline myeloblasts n/a
39.	0373012	6 metaphases analyzed for diagnosis
40.	0373014	unable to classify MDS subtype; unable to assign IPSS score as baseline myeloblasts n/a
41.	0373015	patient not transfusion dependent at baseline; received zero units in 8 weeks; risk category intermediate-2
42.	0373016	16 metaphases analyzed for diagnosis
43.	0373018	unable to classify MDS subtype; unable to assign IPSS score as baseline myeloblasts n/a
44.	0373019	10 metaphases analyzed for diagnosis
45.	0373020	risk category intermediate-2
46.	0373021	unable to classify MDS subtype; unable to assign IPSS score as baseline myeloblasts n/a; 4 metaphases analyzed for diagnosis
47.	0373026	13 metaphases analyzed for diagnosis
48.	0373028	unable to classify MDS subtype; unable to assign IPSS score as baseline myeloblasts n/a
49.	0383001	risk category intermediate-2
50.	0383002	risk category high
51.	0393001	unable to classify MDS subtype; unable to assign IPSS score as baseline myeloblasts n/a ; patient not transfusion dependent at baseline; received zero units in 8 weeks; 17 metaphases analyzed for diagnosis
52.	0393002	unable to classify MDS subtype; unable to assign IPSS score as baseline myeloblasts n/a; 6 metaphases analyzed for diagnosis

Reviewer's Comments:

1. *For regulatory purposes, the primary analysis of interest is based on those patients who meet the major eligibility criteria. FDA performed an analysis in those patients in the evaluable population who had a diagnosis of an MDS subtype with a 5q deletion chromosomal abnormality without or with other cytogenetic abnormalities; who had baseline cytopenias, bone marrow myeloblasts and central karyotype analysis which were necessary to give a combined IPSS score; whose karyotype analysis was based on at least 20 banded metaphase spreads; who were either low or intermediate-1 risk category and who had received ≥ 2 units of RBC transfusion in the 8 weeks (56 days) prior to start of study drug. Excluded were 52 (35.1%) patients. Thus, 96 (64.9%) patients were considered in the FDA evaluable population analyses.*
2. *FDA also performed additional analyses in the subgroup of patients with isolated 5q deletion only and in the subgroup of patients with deletion 5q + other abnormalities..*

Study CC-501-MDS-001

Reasons For Exclusions

Sponsor Analysis

The sponsor excluded two patients who initially were treated with the 10-mg syncopated regimen from the MITT and EE efficacy analyses because they were found to have a diagnosis other than MDS (at histologic bone marrow review both were found to have Philadelphia chromosome- negative CML). Five additional patients (3 in the 25 mg group and 2 in the 10 mg syncopated dosing group) were excluded from the EE analyses because they failed to complete at least 1 cycle of therapy. The table below summarizes the patients who were excluded from the efficacy analyses as submitted by the sponsor.

Table 26 Patients Excluded from Efficacy Analyses (Applicant's Table)

Patient Number	Lenalidomide Treatment Group	Reason for Exclusion
Excluded From MITT and EE Populations		
138	10 mg Sync.	Diagnosis of Philadelphia chromosome-negative chronic myeloid leukemia (CML).
139	10 mg sync.	Diagnosis of Philadelphia chromosome-negative chronic myeloid leukemia (CML).
Excluded From EE Population Only		
101	25 mg	Did not complete at least 1 cycle of lenalidomide.
109	25 mg	Did not complete at least 1 cycle of lenalidomide.
112	25 mg	Did not complete at least 1 cycle of lenalidomide.
134	10 mg Sync.	Did not complete at least 1 cycle of lenalidomide.
145	10 mg sync.	Did not complete at least 1 cycle of lenalidomide.

Data Source: Listing 16.2.1 and Listing 16.2.4

Source: CC-501-MDS-001, Table 8

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FDA Analysis

The FDA excluded all patients who did not have a diagnosis of low or intermediate-1 MDS, who did not have a 5q deletion and who were not transfusion dependent at baseline i.e., did not receive ≥ 2 units within 8 weeks.

Table 27 FDA Reasons for Exclusions (Reviewer's Table)

Reason	(n=45) N (%)	Patient ID
Does not have a 5q deletion [q31-33]chromosomal abnormality	32	102, 104, 106, 108, 109, 110, 111, 112, 114, 115, 116, 117, 118, 120, 122, 124, 125, 126, 127, 129, 130, 131, 135, 137, 138, 139, 140, 141, 142, 143, 144, 145
MDS/FAB subtype RAEB-t or not MDS	3	111, 138, 139
Patient not transfusion dependent at baseline i.e., did not receive ≥ 2 units within 8 weeks	4	102, 106, 113, 136
Risk category intermediate-2 or high risk	5	101, 104, 106, 111, 114

FDA excluded 35 (77.8%) patients from the ITT population due to the differences shown below from the population of interest. Thus 10 (22.2%) patients were the population analyzed for efficacy in this supportive study.

Table 28 List of Patients and Reasons for Exclusion (Reviewer's Table)

Patient ID	Reason for Exclusion
101	Risk category intermediate-2
102	Does not have a 5q deletion chromosomal abnormality; not transfusion dependent at baseline i.e., did not receive ≥ 2 units within 8 weeks
104	Risk category intermediate-2
106	Does not have a 5q deletion chromosomal abnormality; risk category intermediate-2; not transfusion dependent at baseline i.e., did not receive ≥ 2 units within 8 weeks
108	Does not have a 5q deletion chromosomal abnormality
109	Does not have a 5q deletion chromosomal abnormality
110	Does not have a 5q deletion chromosomal abnormality
111	MDS subtype RAEB-t; does not have a 5q deletion chromosomal abnormality; risk category high risk
112	Does not have a 5q deletion chromosomal abnormality
113	Not transfusion dependent at baseline i.e., did not receive ≥ 2 units within 8 weeks
114	Does not have a 5q deletion chromosomal abnormality; risk category intermediate-2 risk
115	Does not have a 5q deletion chromosomal abnormality
116	Does not have a 5q deletion chromosomal abnormality
117	Does not have a 5q deletion chromosomal abnormality

118	Does not have a 5q deletion chromosomal abnormality
120	Does not have a 5q deletion chromosomal abnormality
122	Does not have a 5q deletion chromosomal abnormality
124	Does not have a 5q deletion chromosomal abnormality
125	Does not have a 5q deletion chromosomal abnormality
126	Does not have a 5q deletion chromosomal abnormality
127	Does not have a 5q deletion chromosomal abnormality
129	Does not have a 5q deletion chromosomal abnormality
130	Does not have a 5q deletion chromosomal abnormality
131	Does not have a 5q deletion chromosomal abnormality
135	Does not have a 5q deletion chromosomal abnormality
136	Not transfusion dependent at baseline i.e., did not receive ≥ 2 units within 8 weeks
137	Does not have a 5q deletion chromosomal abnormality
138	Does not have a 5q deletion chromosomal abnormality
139	Does not have a 5q deletion chromosomal abnormality
140	Does not have a 5q deletion chromosomal abnormality
141	Does not have a 5q deletion chromosomal abnormality
142	Does not have a 5q deletion chromosomal abnormality
143	Does not have a 5q deletion chromosomal abnormality
144	Does not have a 5q deletion chromosomal abnormality
145	Does not have a 5q deletion chromosomal abnormality

Reviewer's Comment:
1. For regulatory purposes, the primary analysis of interest is based on those patients who meet the major eligibility criteria. FDA included patients who had a diagnosis of an MDS subtype with a 5q deletion chromosomal abnormality with an IPSS score who were either low or intermediate-1 risk category and who had received ≥ 2 units of RBC transfusion in the 8 weeks (56 days) prior to start of study drug. Excluded were 35 (77.8%) patients. Thus 10 (22.2%) patients were considered evaluable for efficacy in this supportive study.

Primary Efficacy Endpoint
Study CC-5013-MDS-003

Primary Efficacy Endpoint: RBC Transfusion Independence

The International Working Group (IWG) Response criteria for MDS includes the major erythroid response which for RBC transfusion-dependent patients is transfusion independence and for patients with pretreatment hemoglobin <11 g/dL, a greater than 2 g/dL increase in hemoglobin. The minor erythroid response is a 50% decrease in transfusion requirements and 1-2 g/dL increase in hemoglobin.The IWG also states that improvements must last at least 2 months in the absence of ongoing cytotoxic therapy.

In the protocol, RBC transfusion independence was defined to be RBC transfusion independence (the absence of the intravenous infusion of any RBC transfusion) during any consecutive "rolling" 56 days during the treatment period, i.e. days 1 to 56, days 2 to 57, days 3 to 58, etc. Hematologic improvements must last ≥ 2 months. RBC transfusion independence required

patients to be completely transfusion-free and this was considered a major response. A minor response required ≥ 50% decrease in RBC transfusions from pre-treatment requirements.

Sponsor's Analysis

In the ITT population, 95 (64.2%) patients had achieved RBC- transfusion independence. Responses were observed both in patients with low- risk (70.9%; 39/148) and in patients with intermediate-1 risk (63.1%; 41/148) MDS and with both the 10-mg continuous (68.0%; 70/103) and the 10- mg syncopated (55.6%;25/45) dosing regimens. The table below shows the sponsor's assessment of the frequency of transfusion independence in the ITT population.

Table 29 RBC Transfusion Independence ITT Population (Applicant's Table)

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IPSS Risk Category[2] at Baseline	Statistic	10mg Cont.	10mg Sync.	Overall
Overall	Number of Subjects	103	45	148
	Number Transfusion Independent	70	25	95
	% Transfusion Independent	(68.0)	(55.6)	(64.2)
	Exact 95% CI	[58.0, 76.8]	[40.0, 70.4]	[55.9, 71.9]
Low+Int-1	Number of Subjects	82	38	120
	Number Transfusion Independent	57	23	80
	% Transfusion Independent	(69.5)	(60.5)	(66.7)
	Exact 95% CI	[58.4, 79.2]	[43.4, 76.0]	[57.5, 75.0]
Low	Number of Subjects	42	13	55
	Number Transfusion Independent	28	11	39
	% Transfusion Independent	(66.7)	(84.6)	(70.9)
	Exact 95% CI	[50.5, 80.4]	[54.6, 98.1]	[57.1, 82.4]
Int-1	Number of Subjects	40	25	65
	Number Transfusion Independent	29	12	41
	% Transfusion Independent	(72.5)	(48.0)	(63.1)
	Exact 95% CI	[56.1, 85.4]	[27.8, 68.7]	[50.2, 74.7]
Int-2+High	Number of Subjects	5	3	8
	Number Transfusion Independent	3	0	3
	% Transfusion Independent	(60.0)	(0.0)	(37.5)
	Exact 95% CI	[14.7, 94.7]	[0.0, 70.8]	[8.5, 75.5]
Int-2	Number of Subjects	4	2	6
	Number Transfusion Independent	2	0	2
	% Transfusion Independent	(50.0)	(0.0)	(33.3)
	Exact 95% CI	[6.8, 93.2]	[0.0, 84.2]	[4.3, 77.7]
High	Number of Subjects	1	1	2
	Number Transfusion Independent	1	0	1
	% Transfusion Independent	(100.0)	(0.0)	(50.0)
	Exact 95% CI	[2.5,100.0]	[0.0, 97.5]	[1.3, 98.7]

[1] The absence of the intravenous infusion of any RBC transfusion during any consecutive rolling 56 days during the treatment period and an increase in hemoglobin of at least 1 g/dL from the minimum during the screening/baseline period to the maximum during the transfusion-independent period, excluding the first 30 days after the last transfusion before the transfusion-free period

[2] IPSS Risk Category: Low (combined score = 0), Intermediate-1 (combined score = 0.5 to 1.0), Intermediate-2 (combined score = 1.5 to 2.0), High (combined score >= 2.5); Combined score = (Marrow blast score + Karyotype score + Cytopenia score)

Source: CC-5013-MDS-003, Table 14.2.1.1

FDA Analysis

FDA analyzed the primary endpoint of transfusion independence in the ITT population as well as the evaluable population of 96 patients as defined in the previous sections. FDA also did an analysis on the low-risk and intermediate-1 transfusion dependent MDS patients with an isolated

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deletion of 5q cytogenetic abnormality. FDA agreed with the sponsor's analysis of the responses in the ITT population. In the evaluable MDS population with 5q and other deletions consisting of 96 patients, 61 (63.5%) patients achieved transfusion independence. In the subset of patients with an isolated 5q deletion consisting of 72 patients, 46 (63.9%) of patients achieved transfusion independence. The table below summarizes and compares the frequency of RBC transfusion independence in the various populations analyzed.

Table 30 RBC Transfusion Independence Various Populations (Reviewer's Table)

Population	Number transfusion independent	% transfusion independent	95% CI (%)
Sponsor/FDA ITT			
Overall (N=148)	95	64.2	56, 72
10 mg cont (N=103)	70	68.0	58, 77
10 mg sync (N=45)	25	55.6	40, 70
FDA evaluable			
Overall (N=96)	61	63.5	53, 73
10 mg cont (N=67)	44	65.7	53, 77
10 mg sync (N=29)	17	58.6	39, 76
Isolated 5q deletion MDS			
Overall (N=72)	46	63.9	52, 75
10 mg cont (N=53)	35	60.0	52, 78
10 mg sync (N=19)	11	57.9	34, 80

Updated Efficacy Data (August 15, 2005)

The sponsor submitted updated efficacy data from study CC-5013-MDS-003 in an amendment on August 15, 2005. The cut-off date was March 31, 2005. The amendment consisted of seven datasets and associated tables and listings.

In the ITT population, patients 0203001, 0233006, 0243015 and 0393003 continued to be responders. Patient 0273003 was recorded as a responder; however, this patient was never in the original dataset and was not one of the 148 patients enrolled. It is not clear from where this patient came from (Cleveland, Ohio). Patient 0243017 was a responder in the original dataset and is no longer a responder in the updated dataset. The sponsor was queried and sent their response (dated August 26, 2005) which stated: "Patient 0243017 transferred to a different investigational site between the NDS submission cutoff (original dataset) and the 31 Mar 05 cutoff (updated dataset). Consequently, the patient was assigned a new patient number (0273003) at the new site. Therefore, all instances of patient number 0243017 in the original datasets were replaced with patient number 0273003 in the updated datasets".

In the updated dataset, FDA agreed with the sponsor's analysis of the responses in the ITT population. In the FDA evaluable population with 5q and other deletions consisting of 96

patients, 64 (66.7%) patients achieved transfusion independence. In the subset of patients with an isolated 5q deletion consisting of 72 patients, 47 (65.3%) of patients achieved transfusion independence. In the subset of patients with 5q deletion plus other abnormalities consisting of 24 patients, 16 (66.7%) of patients achieved transfusion independence.The table below summarizes and compares the frequency of RBC transfusion independence in the various populations analyzed.

Table 31 RBC Transfusion Independence Various Populations Updated Data (Reviewer's Table)

Population	Number transfusion independent	% transfusion independent	95% CI (%)
Sponsor/FDA **ITT**			
Overall (N=148)	99	66.9	59, 74
10 mg cont (N=103)	72	69.9	60, 79
10 mg sync (N=45)	27	60.0	44, 74
FDA evaluable			
Overall (N=96)	64	66.7	56, 76
10 mg cont (N=67)	45	67.2	55, 78
10 mg sync (N=29)	19	65.5	46, 82
Isolated 5q deletion MDS			
Overall (N=72)	47	65.3	53, 76
10 mg cont (N=53)	36	67.9	54, 80
10 mg sync (N=19)	11	57.9	34, 80
5q + other deletions			
Overall (N=24)	16	66.7	45, 84
10 mg cont (N=14)	9	64.3	35, 87
10 mg sync (N=10)	7	70.0	35, 93

Reviewer's Comments:

1. *In MDS, which is a heterogenous disease, single arm studies using patients as their own controls are generally not acceptable. The sponsor definition of transfusion independence with a rolling duration as defined here is problematic in an unblinded study. In an end-of-phase 1 meeting with the sponsor (dated June 6, 2003), FDA recommended a randomized, controlled trial using an endpoint with a longer duration of response.*
2. *The transfusion independence response was consistent in the various populations.*
3. *The statistical reviewer noted that there was a correlation in the number of pre-treatment RBC transfusion and the transfusion response. It is more likely for those patients with less than or equal to 5 pre-treatment transfusions to develop a transfusion independent response.*
4. *The 2 dosing regimens were explored by the FDA but the study was not designed or powered to prospectively compare the efficacy of the two lenalidomide regimens.*

Study CC-501-MDS-001

Primary Efficacy Endpoint: Response Rate

Sponsor's Analysis

The sponsor did an analysis of response rate in patients who were transfusion dependent at baseline. The primary efficacy endpoint was the percentage of patients who had a major or minor erythroid response, as determined by the criteria in the protocol modified from the IWG response criteria for MDS. The sponsor identified 10 patients with the following characteristics: 1) a diagnosis of low or intermediate-1 risk MDS 2) a del 5 (q31-33) cytogenetic abnormality of their MDS clone at baseline and 3) transfusion-dependent anemia at baseline. Of these 10 patients, 7 (70.0%) experienced a major erythroid response (RBC- transfusion independence associated with an increase in blood Hgb concentration) to lenalidomide treatment. Nine (90%) of these 10 patients had an isolated del 5 (q31- 33) cytogenetic abnormality, and one patient (Patient 121) had a trisomy 21 abnormality in addition to the del 5 (q31- 33) cytogenetic abnormality. Patient 121 was one of the patients who achieved a durable major erythroid response. The table below summarizes erythroid responses in the patients with a del 5 (q31- 33) cytogenetic abnormality as submitted by the sponsor.

Table 32 Erythroid Response (Applicant's Table)

IPSS Risk Category[a] at Baseline CI]	Erythroid Response [b] [c]	25mg n (%) N [Ex. 95% CI]	10mg n (%) N [Ex. 95% CI]	10mg Sync. n (%) N [Ex. 95% CI]	Overall n (%) N [Ex. 95%
Low+Int-1		3	3	4	10
	Major	2	3	2	7
		(66.7)	(100.0)	(50.0)	(70.0)
		[9.4, 99.2]	[29.2,100.0]	[6.8, 93.2]	[34.8, 93.3]
	Minor	0	0	0	0
		(0.0)	(0.0)	(0.0)	(0.0)
		[0.0, 70.8]	[0.0, 70.8]	[0.0, 60.2]	[0.0, 30.8]

Source: Table 14.2.1.3.3

[a] IPSS Risk Category: Low (combined score = 0), Intermediate-1 (combined score = 0.5 to 1.0), Intermediate-2 (combined score = 1.5 to 2.0), High (combined score >= 2.5); Combined score = (Marrow blast score + Karyotype score + Cytopenia score)

[b] Major Response: Transfusion-independence for 8 consecutive weeks for patients who were RBC transfusion-dependent at baseline; for patients with a mean pretreatment hemoglobin (mean 8-week hemoglobin) < 11 g/dL, a > 2 g/dL rise in hemoglobin without transfusion.

[c] Minor Response: For transfusion dependent patients, a 50% or greater decrease in 8-week hemoglobin; For patients with a mean pretreatment hemoglobin (mean 8-week hemoglobin) < 11 g/dL, hemoglobin is sustained 1.0 to 2.0 g/dL above the baseline value without transfusion. The minor response counts in this table do not include major responders.

Source: CC-501-MDS-001, Table 14.

FDA Analysis

The table below shows the FDA and sponsor responses in the 10 patients that the FDA found evaluable for efficacy. This confirmed the sponsor's response rate of 70.0% (7/10) patients in the evaluable population as shown above. The response rate in the 9 patients with isolated 5 q deletion was 77.8% (7/9).

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Table 33 FDA and Sponsor Responses in the Evaluable Population (Reviewer's Table)

Pt ID	Sponsor assessed Response	FDA assessed Response
103	none	none
105	major	major
107	major	major
119	major	major
121	major	major
123	major	major
128	major	major
132	major	major
133	none	none
134	none	none

Reviewer's Comments:

1. *The FDA assessment confirmed the sponsor's assessment that out of the 10 patients evaluable for efficacy, 7 (70.0%) patients had a major response. In the 9 patients with isolated 5 q deletion, response rate was 77.8%. The number of patients in the subgroup of the population of interest is too small to make any comments or comparisons in this single-arm trial. The definitions of transfusion-dependent anemia at baseline were different in the 2 studies. In CC-501-MDS-001, transfusion dependent anemia was defined by requiring at least 4 units of RBC in the 8 weeks prior to baseline or a baseline mean hemoglobin < 10.0 g/dL (untransfused). The response criteria were erythroid response (major or minor) modified from the IWG criteria. The response rate shown was in the patients who required at least 2 units RBC at baseline.*
2. *The 3 dosing regimens cannot be compared as the study was not designed or powered to prospectively compare the efficacy of the lenalidomide regimens and the numbers are too small.*

<u>Secondary Efficacy Endpoints: Duration of Response</u>

Study CC-5013-MDS-003

Sponsor's Analysis

Duration of response according to the IWG criteria is time to disease progression as per bone marrow response or progression/relapse following hematologic improvement as per hematologic improvement as per the IWG response criteria. The response duration was measured by the sponsor from the last of the consecutive 56 days during which the subject was free of RBC transfusions to the date of the first RBC transfusion. If the patient who responded had not received an RBC transfusion at the time of analysis, then duration of response was censored at the time of last follow-up or September 15, 2004, whichever was earlier.

Of the 95 subjects in the ITT population who achieved RBC transfusion independence, 82 (86.3%) remained transfusion independent, and 13 (13.7%) had relapsed (i. e., required a transfusion after a response) as of the 15 September 2004 data cutoff date. The duration of RBC

transfusion independence was at least 24 weeks in 70 (73.7%) of the 95 responders in the ITT population. Three patients (Patients 0233010, 0243005, and 0373035) achieved RBC transfusion independence, relapsed, and then once again achieved RBC transfusion independence with continued therapy.

Table 34 Duration of Transfusion Independence Response ITT Population (Applicant's Table)

Duration of transfusion independence response (weeks)	10mg Cont. (N=103)	10mg Sync. (N=45)	Overall (N=148)
Kaplan-Meier estimates			
Subjects with Transfusion Independence Response	70	25	95
Subjects who progressed (had a transfusion after response)	10 (14.3)	3 (12.0)	13 (13.7)
Subjects who maintained transfusion independence (censored[2])	60 (85.7)	22 (88.0)	82 (86.3)
Median	NE	NE	NE
95% confidence interval	(37.9, NE)	NE	NE
Summary statistics			
Mean	27.5	34.1	29.2
SD	8.16	13.23	10.11
Median	27.5	40.7	30.0
Min, Max	8.1, 44.0+	8.1, 48.1+	8.1, 48.1+
Duration of response at least 4 weeks	70 (100.0)	25 (100.0)	95 (100.0)
Duration of response at least 8 weeks	70 (100.0)	25 (100.0)	95 (100.0)
Duration of response at least 12 weeks	65 (92.9)	22 (88.0)	87 (91.6)
Duration of response at least 16 weeks	64 (91.4)	20 (80.0)	84 (88.4)
Duration of response at least 20 weeks	61 (87.1)	20 (80.0)	81 (85.3)
Duration of response at least 24 weeks	50 (71.4)	20 (80.0)	70 (73.7)

[1] Measured from the first of the consecutive 56 days during which the subject was free of RBC transfusions to the date of the first RBC transfusion after this period.
[2] Duration of response was censored at the date of last visit for subjects who maintained transfusion independence.
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Source: CC-5013-MDS-003, Table 14.2.3.1.

Reviewer's Comment:
1. The statistical reviewer notes that in the sponsor's table above, since the baseline time point is not well defined, the FDA does not consider the Kaplan-Meier estimates as a valid method for analysis of duration of response.

FDA Analysis of Duration of Transfusion Independence

The sponsor was queried on the method used to calculate the duration of transfusion independence and whether it was required to have a hemoglobin value drawn on the date selected. The sponsor stated (Response to FDA request for information, July 8, 2005): "To calculate the duration of transfusion independence the start date was defined as the first date in the beginning of the transfusion-free period, i.e., the first day after the day the last transfusion was given. The end date was defined as the day before the next transfusion (that represented the end of the transfusion-free period) was given. It was not required to have

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a hemoglobin value drawn on the date used as the start date of the transfusion-free period. At least one hemoglobin value during the transfusion-free period, excluding the first 30 days following the last pRBC transfusion, was needed to meet the hemoglobin increase criteria for transfusion independence response".

FDA also did an analysis in the 96 patients who were the evaluable population based on summary statistics. Out of 61 patients who achieved RBC transfusion independence, 54 (88.5%) remained transfusion independent and 7 (11.5%) had relapsed (i.e., required a transfusion after a response). The median survival time can not be computed based on current data (i.e. not enough relapse cases). These computations are based on the assumption that we agree with the sponsor defined response. The statistical reviewer's summary of duration of transfusion independence response for the FDA evaluable population is based on the FDA assessment. The table below shows the data in the ITT and the FDA evaluable population.

Table 35 Duration of Transfusion Independence Response in Weeks (Reviewer's Table)

Duration of transfusion independence in weeks	**Overall**	**10 mg Cont**	**10 mg Sync**
ITT	**N=95**	**N= 70**	**N=25**
Patients progressed	13 (13.7%)	10 (14.3%)	3 (12.0%)
Patients censored	82 (86.3%)	60 (85.7%)	22 (88.0%)
Summary statistic			
Mean	29.2	27.5	34.1
SD	10.1	8.2	13.2
Median	30.0	27.5	40.7
Min, Max	8.1, 48.1	8.1, 44.0	8.1, 48.1
FDA Evaluable	**N=61**	**N=44**	**N=17**
Patients progressed	7 (11.5%)	5 (11.4%)	2 (11.8%)
Patients censored	54 (88.5%)	39 (88.6%)	15 (88.2%)
Summary statistic			
Mean	29.4	27.8	33.4
SD	10.3	8.1	14.1
Median	30.0	28.5	40.7
Min, Max	8.1, 48.1	8.1, 44.0	8.1, 48.1
5q deletion MDS	**N=46**	**N=35**	**N=11**
Patients progressed	4 (8.7%)	4 (11.4%)	0 (0.0%)
Patients censored	42 (91.3%)	31 (88.6%)	11 (100.0%)
Summary statistic			
Mean	29.1	27.2	35.3
SD	9.9	7.7	13.6
Median	30.0	29.0	40.7
Min, Max	8.1, 48.1	8.1, 43.4	9.0, 48.1

Updated Efficacy Data (August 15, 2005)

The sponsor submitted updated efficacy data from study CC-5013-MDS-003 in an amendment on August 15, 2005. The cut-off date was March 31, 2005. The amendment consisted of seven datasets and associated tables and listings.

In the updated data, the median duration of response increased from 30 weeks to 52 weeks in all the populations analyzed. Relapses from transfusion independent to transfusion dependent occurred in 32 out of the 99 responders, of which 13 occurred within the treatment period (based on a window of 14 days post last dosing).

Table 36 Duration of Transfusion Independence Response in Weeks Updated Data (Reviewer's Table)

Duration of transfusion independence in weeks	**Overall**	**10 mg Cont**	**10 mg Sync**
ITT	**N=99**	**N= 72**	**N=27**
Patients progressed	32 (32.3%)	25 (34.7%)	7 (25.9%)
Patients censored	67 (67.7%)	47 (65.3%)	20 (74.1%)
Summary statistic			
Mean	45.7	45.1	47.3
SD	18.5	16.4	23.5
Median	52.3	50.9	58.0
Min, Max	8.1, 74.6	8.1, 74.6	8.1, 72.7
FDA Evaluable	**N=64**	**N=45**	**N=19**
Patients progressed	18 (28.1%)	13 (28.9%)	5 (26.3%)
Patients censored	46 (71.9%)	32 (71.1%)	14 (73.7%)
Summary statistic			
Mean	46.2	47.1	44.1
SD	18.9	16.2	24.6
Median	52.3	52.1	53.9
Min, Max	8.1, 74.6	8.1, 74.6	8.1, 72.7
5q deletion MDS	**N=47**	**N=36**	**N=11**
Patients progressed	10 (21.3%)	9 (25.0%)	1 (9.1%)
Patients censored	37 (78.7%)	27 (75.0%)	10 (90.9%)
Summary statistic			
Mean	46.7	46.1	48.9
SD	18.5	16.3	25.1
Median	52.3	52.2	60.0
Min, Max	8.1, 72.7	8.1, 71.4	9.0, 72.7

Sensitivity Analyses

The sponsor was requested to perform a sensitivity analysis based on a longer duration of transfusion independence which they submitted in their response to FDA request for information (dated August 24, 2005). The table below shows the different sensitivity analyses.

Table 37 Sensitivity Analyses based on Duration of Transfusion Independence (Applicant's Table)

Population	Transfusion Independence n (%)		
	≥ 56 days	≥ 3 months	≥ 6 months
ITT	95 (64)	89 (60)	70 (47)
MITT	57 (61)	53 (56)	39 (42)

Source: response to FDA request for information (dated August 24, 2005)

Reviewer's Comments:

1. *The median duration of transfusion independence was for one year which suggests that it may be considered to be evidence of clinical benefit.*
2. *The sensitivity analyses show that on increasing the requirement of the duration of transfusion independence from 56 days to 3 months to 6 months decreases the transfusion independence from 64% to 60% to 47%.*
3. *The statistical reviewer noted that in the sponsor's analysis, the duration of response has been estimated using the Kaplan-Meier procedure. Patients who had not received an RBC transfusion at the time of analysis were censored at the time of last follow-up or cut-off time (9/15/2004) whichever was earlier. Since this is a single-arm non-comparative study, the clinical significance of the observed duration of transfusion independence is in question. At the time of cut-off, progression occurred in 18/64 patients, giving a median duration of 52 weeks with a range of 8 to 75 weeks for the responders. The median duration of transfusion independent response is 35 (range, 0-75) based on the ITT population (assuming zero duration for the non-responders).*
4. *The updated data submitted increased the median duration from 30 to 52 weeks but also increased the relapses from 13 to 32 patients.*

Study CC-501-MDS-001

All responses required that values be sustained above the response threshold for a minimum of 8 consecutive weeks. As of the 05 February 2004 data cutoff date, 2 (22.2%) of the 9 patients with low- or intermediate-1 risk MDS and an isolated 5q deletion cytogenetic abnormality who had achieved a response were still responding to therapy, and 7 (77.8%) had progressed (i.e., required a transfusion after a response). Based on Kaplan-Meier estimates of data available as of the 05 February 2004 data cutoff date, the median duration of major erythroid response in these 9 patients was 47.4 weeks (95% CI: 38.6, 88.1), (range, 61.1- 88.1 weeks). The table below summarizes the Kaplan- Meier estimates of the duration of major erythroid response for this patient subgroup submitted by the sponsor.

Table 38 Kaplan-Meier Estimates of Duration (Weeks) of Major Erythroid Response MITT Population (Applicant's Table)

	25mg	10mg	10mg Sync.	Overall
Patients with a major erythroid Response [a]	3	3	3	9
Patients who progressed (did not maintain a major response)	3 (100.0)	2 (66.7)	2 (66.7)	7 (77.8)
Patients who maintained a major response (censored[b])	0 (0.0)	1 (33.3)	1 (33.3)	2 (22.2)
Median	48.7	40.0	38.6	47.4
95% confidence interval	[47.4, 88.1]	[31.7, NA]	[16.1, NA]	[38.6, 88.1]
Mean	61.4	46.2	32.0	46.6
SD	23.14	18.45	13.85	20.71
Min, Max	47.4, 88.1	31.7, 67.0	16.1, 41.4	16.1, 88.1

NA, not available
Data Source: Table 14.2.4.2.1
[a] Major Response: Transfusion-independence for 8 consecutive weeks for patients who were RBC transfusion-dependent at baseline; for patients who were not RBC transfusion dependent at baseline but had a mean pretreatment hemoglobin level(mean 8-week hemoglobin) < 11 g/dL, a > 2 g/dL rise in hemoglobin without transfusion sustained for 2 months.
[b] Duration of response was censored at the date of last visit for patients who maintained transfusion independence.

Source: CC-501-MDS-001, Table 15.

Reviewer's Comment:
The statistical reviewer notes that in the table above, since the baseline time point is not well-defined, FDA does not consider the Kaplan-Meier analysis as a valid method for duration of response.

FDA Analysis
The median duration of transfusion independence response in the 7 responders was 41.4 weeks with a range of 31 to 88 weeks.

Secondary Efficacy Endpoints: Change of Hemoglobin Concentration from Baseline

Study CC-5013-MDS-003

In the IWG response criteria for MDS, a major erythroid response included for patients with pretreatment hemoglobin <11 g/dL, greater than 2 g/dL increase in hemoglobin and minor erythroid response included for patients with pretreatment hemoglobin <11 g/dL, a 1-2 g/dL increase in hemoglobin.

Sponsor's Analysis
The sponsor defined a change in hemoglobin based on the minimum hemoglobin value in the 8 week period preceding first dose of study drug for baseline and the maximum hgb value during the response period, excluding the 30 days after the last transfusion prior to the response period.

The median increase in blood hemoglobin level from baseline to maximum hemoglobin level during RBC transfusion independence was 5.2 g/dL (range, 1.1-11.4 g/dL) for the 95 responders in the ITT population. The table below summarizes the change from baseline in hemoglobin for the patients in the ITT population who became RBC transfusion independent submitted by the sponsor.

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Table 39 Change in Hemoglobin (g/dL) From Baseline to Maximum Value in Transfusion-independent Responders ITT Population (Applicant's Table)

		10mg Cont. (N=70)			10mg Sync. (N=25)			Overall (N=95)		
	Stat	BL	Max	Change	BL	Max	Change	BL	Max	Change
Hemoglobin (g/dL)	N	70	70	70	25	25	25	95	95	95
	Mean	7.8	13.1	5.3	8.0	13.4	5.3	7.8	13.2	5.3
	SD	1.01	1.99	1.97	0.73	1.98	2.03	0.95	1.98	1.98
	Median	7.7	13.2	5.1	8.0	13.3	5.3	7.8	13.3	5.2
	Min	5.3	9.2	2.2	7.0	9.3	1.1	5.3	9.2	1.1
	Max	10.4	18.6	11.4	10.3	16.9	9.1	10.4	18.6	11.4

Source: CC-5031-MDS-003, Table 14.2.4.1.

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FDA Analysis of Change of Hemoglobin Concentration

FDA found that in 68 (45.9%) patients, the baseline hemoglobin values used by the sponsor to calculate the change in hemoglobin values did not correspond to the values submitted in Listing 16.2.6.2 leading to lesser changes in blood hemoglobin level from baseline to the maximum hemoglobin level achieved than that reported by the sponsor. The sponsor was queried on this discrepancy and replied (Response to FDA request for Information, July 8, 2005): " To determine the increase in hemoglobin, the baseline value was chosen to be the minimum value (using both local and central lab data) within the 56-days prior to the first dose date and including the date of first dose, i.e., study days -54 to 1, inclusive". The sponsor also submitted a by-patient listing identifying the hemoglobin values used to determine response. FDA used the listing to correlate hemoglobin values with the sponsor's and also requested the sponsor to submit the database of the local laboratory values to be able to validate the data and perform an audit. In their response to FDA request for information dated July 27, 2005, the sponsor submitted a table compiling the hemoglobin data and again stated that "for hemoglobin the minimum among central labs and local labs during the 56-days prior to first study drug dosing was used". FDA requested the sponsor to submit the database containing the local laboratory values on which they have claimed to base their baseline hemoglobin values. Their response noted that the local hemoglobin data were in 3 different datasets. It is confusing why they have the local data in different places.

FDA found the median increase in blood hemoglobin level from baseline to maximum hemoglobin level during RBC transfusion independence was 3.3 g/dL (range, 3.1-9.3 g/dL in the responders in the ITT population and 5.2 g/dL (range, 1.1-11.4 g/dL) for the responders in the FDA evaluable population. The table below summarizes the change from baseline in hemoglobin for the patients in the ITT population who became RBC transfusion independent submitted by the sponsor. The tables below show the percentage of patients with greater than 1

g/dL change of hemoglobin concentration from baseline in the transfusion independent responders and the summary statistics.

Table 40 Change of Hemoglobin Concentration from Baseline in Transfusion-Independent Responders Various Populations (Reviewer's Table)

Category	ITT N=148 (%)	FDA Evaluable Population N=96 (%)	5 q deletion MDS N=72 (%)
Change of mean hemoglobin concentration from mean baseline of ≥ 1 unit 95% C.I.	n=142 101 (71.1%) (62.9%, 78.4%)	n = 93 68 (73.1%) (62.9%, 81.8%)	n =71 52 (73.2%) (61.4%, 83.1%)

Table 41 Summary Statistics for Hemoglobin Based on Responders in the Various Populations (Reviewer's Table)

Hgb	ITT			FDA evaluable			5q deletion MDS		
Stats	BL	MAX	Change	BL	MAX	Change	BL	MAX	Change
N	92	95	92	61	61	61	46	46	46
Mean	8.1	13.2	5.1	8.1	13.4	5.3	8.2	13.3	5.1
Sd	1.2	1.8	2.1	1.3	1.7	2.1	1.4	1.6	1.9
Median	8.0	13.2	5.0	8.0	13.5	5.4	8.1	13.4	5.3
Min	5.3	9.5	-0.8	5.3	10.0	-0.8	5.3	10.0	-0.8
Max	13.0	17.7	10.9	13.0	17.5	10.9	13.0	16.9	9.3

BL-baseline

Sensitivity Analyses

FDA requested the sponsor to perform a sensitivity analysis of the change from baseline in Hgb level by different computations. They responded (dated August 24, 2005) and performed 2 sensitivity analyses and compared to the original dataset as shown in the table below. The definitions used are given below.

Sensitivity Analysis 1 (pre mean-post mean): uses the mean Hgb value in the 56-day period preceding first dose of study drug for baseline and the mean Hgb value during the response period (excluding the 30 days after the last transfusion prior to the response period).

Sensitivity Analysis 2 (pre min-post mean): uses the minimum Hgb in the 56-day period preceding first dose of study drug for baseline and the mean Hgb value during the response period (excluding the 30 days after last transfusion prior to the response period).

The table below shows the hemoglobin change based on the different sensitivity analyses.

Table 42 Sensitivity Analyses of Change from Baseline Hemoglobin Levels in Transfusion Independent Responders (Applicant's Table)

Analysis	Hemoglobin (g/dL)							
	ITT				MITT			
	N	Median at baseline	Median during Response	Median Change	N	Median at baseline	Median during Response	Median Change
Original NDA	95	7.8	13.3	**5.2**	57	7.7	13.6	**5.5**
Sensitivity 1	91	8.7	12.3	**3.2**	56	8.6	12.5	**3.6**
Sensitivity 2	95	7.8	12.2	**4.2**	57	7.7	12.4	**4.6**

N=number of transfusion independence responders
Source: Response to FDA request for information, August 24, 2005.

Reviewer's Comments:

1. *The lowest hemoglobin value in the 56 days prior to start of study drug was used as the baseline value and if the value from the central laboratory was missing or invalid, then the local lab value was used in the analysis by the sponsor, potentially leading to bias.*
2. *The sensitivity analyses show that the sponsor's analysis based on maximum change from baseline hemoglobin level (minimum in baseline) may be highly biased. The median change from baseline based on the other criteria (pre mean-post mean or pre min-post mean) results in smaller changes.*
3. *Due to the concern that the transfusion independent response is a subjective measure and the correlation with the hemoglobin level is unclear, the statistical reviewer performed an analyses to evaluate the correlation of the transfusion independent response and the last hemoglobin level prior to the transfusion independent date. The results show that the closest post-treatment hemoglobin level (prior to transfusion independent date) the closest post-treatment hemoglobin level (prior to transfusion independent date) correlates well with the transfusion independent response. It is more likely for patients with higher post-treatment hemoglobin level (close to the transfusion independent event) to develop transfusion independence response.*
4. *An increase in hemoglobin of at least 1 g/dL was included in the definition of the primary endpoint in the clinical study report by the sponsor but was not in the protocol or in the statistical analysis plan. All responding patients had ≥ 1 g/dL increase in hemoglobin by sensitivity analysis.*

Study CC-501-MDS-001

The sponsor submitted the table below for all responders with an isolated 5 q deletion cytogenetic abnormality which summarizes the change from baseline in Hgb concentration.

Table 43 Change in Hemoglobin from Baseline to Maximum Value During Response Period (Applicant's Table)

		25mg (N=3)			10mg (N=3)			10mg Sync. (N=3)			Overall (N=9)		
	Stat	BL	Max	Change	BL	Max	Change	BL	Max	Change	BL	Max	Change
Hemoglobin (g/dL)	N	3	3	3	3	3	3	3	3	3	9	9	9
	Mean	8.6	13.2	4.6	7.6	14.3	6.7	8.1	13.3	5.3	8.1	13.6	5.5
	SD	0.17	0.52	0.62	0.95	1.45	2.29	0.32	1.32	1.55	0.67	1.14	1.70
	Median	8.5	12.9	4.4	7.1	14.3	7.2	8.2	13.6	5.3	8.3	13.6	5.3
	Min	8.5	12.9	4.1	7.0	12.9	4.2	7.7	11.9	3.7	7.0	11.9	3.7
	Max	8.8	13.8	5.3	8.7	15.8	8.7	8.3	14.5	6.9	8.8	15.8	8.7

[1] Response period is defined as 30 days from the time of last transfusion prior to being transfusion independent to the next transfusion or last assessment.

Source: CC-501-MDS-001, Table 14.2.5.2.2.

Secondary Efficacy Endpoints: Decrease of ≥ 50% in RBC Transfusion Requirements

Study CC-5013-MDS-003

The sponsor modified the IWG Response criteria for MDS for a minor response. The sponsor's definition of 50% reduction of RBC transfusion requirement overlapped with the transfusion free definition (i.e. all transfusions-independent responders had greater than 50% requirement of RBC transfusion).

Sponsor's Analysis

In the sponsor's submission, of the subjects in the ITT population 74.3% (110/148) achieved a ≥ 50% decrease in their pretreatment RBC- transfusion requirements (transfusion- reduction response) during lenalidomide therapy, including 76.4% (42/55) of the patients with low-risk MDS and 76.9 % (50/65) of the patients with intermediate-1 risk MDS. The table below summarizes the frequency of patients in the ITT population who achieved a ≥ 50% decrease in RBC transfusions as submitted by the sponsor.

Table 44 Frequency of Patients With 50% or Greater Decrease in RBC Transfusion Requirements ITT Population (Applicant's Table)

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IPSS Risk Category[2] at Baseline	Statistic	10mg Cont.	10mg Sync.	Overall
Overall	Number of Subjects	103	45	148
	Number of Responders[1]	79	31	110
	% Responders	(76.7)	(68.9)	(74.3)
	Exact 95% CI	[67.3, 84.5]	[53.4, 81.9]	[66.5, 81.1]
Low+Int-1	Number of Subjects	82	38	120
	Number of Responders[1]	63	29	92
	% Responders	(76.8)	(76.3)	(76.7)
	Exact 95% CI	[66.2, 85.4]	[59.8, 88.6]	[68.1, 83.9]
Low	Number of Subjects	42	13	55
	Number of Responders[1]	30	12	42
	% Responders	(71.4)	(92.3)	(76.4)
	Exact 95% CI	[55.4, 84.3]	[64.0, 99.8]	[63.0, 86.8]
Int-1	Number of Subjects	40	25	65
	Number of Responders[1]	33	17	50
	% Responders	(82.5)	(68.0)	(76.9)
	Exact 95% CI	[67.2, 92.7]	[46.5, 85.1]	[64.8, 86.5]
Int-2+High	Number of Subjects	5	3	8
	Number of Responders[1]	4	0	4
	% Responders	(80.0)	(0.0)	(50.0)
	Exact 95% CI	[28.4, 99.5]	[0.0, 70.8]	[15.7, 84.3]
Int-2	Number of Subjects	4	2	6
	Number of Responders[1]	3	0	3
	% Responders	(75.0)	(0.0)	(50.0)
	Exact 95% CI	[19.4, 99.4]	[0.0, 84.2]	[11.8, 88.2]
High	Number of Subjects	1	1	2
	Number of Responders[1]	1	0	1
	% Responders	(100.0)	(0.0)	(50.0)
	Exact 95% CI	[2.5,100.0]	[0.0, 97.5]	[1.3, 98.7]

[1] At least a 50% reduction in the number of transfusions reflected over any 56-day rolling period during the study as compared to the 56-day period prior to start of study medication.

[2] IPSS Risk Category: Low (combined score = 0), Intermediate-1 (combined score = 0.5 to 1.0), Intermediate-2 (combined score = 1.5 to 2.0), High (combined score >= 2.5); Combined score = (Marrow blast score + Karyotype score + Cytopenia score)

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Source: CC-5013-MDS-003, Table 14.2.1.4.

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FDA Analysis

In the FDA analysis, in the patients in the ITT population, 74.3% (110/148) achieved a ≥50% decrease in their pretreatment RBC transfusion requirements (transfusion reduction response) during lenalidomide therapy. In the FDA evaluable population, 71 (74%) patients and in the isolated 5q deletion patients 55 (76.4%) patients achieved a ≥50% decrease in their pretreatment RBC transfusion requirements. In both populations, the responses overlapped with the patients who achieved a transfusion independent response. The table below summarizes the frequency of patients in the ITT and evaluable population who achieved a ≥50% decrease in RBC transfusions.

Table 45 Frequency of Patients with Decrease of ≥ 50% in RBC Transfusion Requirements in Different Populations (Reviewer's Table)

Population	≥ 50% decrease in RBC Transfusion Requirements	%	95% CI (%)
Sponsor/FDA ITT			
Overall (N=148)	110	74.3	67, 81
10 mg cont (N=103)	79	76.7	67, 84
10 mg sync (N=45)	31	68.9	53, 82
FDA evaluable			
Overall (N=96)	71	74.0	64, 82
10 mg cont (N=67)	50	74.6	63, 84
10 mg sync (N=29)	21	72.4	53, 87
Isolated 5q deletion MDS			
Overall (N=72)	55	76.4	65, 86
10 mg cont (N=53)	41	77.4	64, 88
10 mg sync (N=19)	14	73.7	49, 91

Updated Efficacy Data (August 15, 2005)

The sponsor submitted updated efficacy data from study CC-5013-MDS-003 in an amendment on August 15, 2005. The cut-off date was March 31, 2005. The amendment consisted of seven datasets and associated tables and listings.

Based on the updated datasets, FDA updated the table below which summarizes and compares the frequency of patients with decrease of ≥50% in RBC transfusion requirements in various populations analyzed.

Table 46 Frequency of Patients with Decrease of ≥ 50% in RBC Transfusion Requirements in Various Populations Updated Data (Reviewer's Table)

Population	≥ 50% decrease in RBC Transfusion Requirements	%	95% CI (%)
Sponsor/FDA ITT			
Overall (N=148)	112	75.7	68, 82
10 mg cont (N=103)	80	77.7	68, 85
10 mg sync (N=45)	32	71.1	56, 84
FDA evaluable			
Overall (N=96)	73	76.0	66, 84
10 mg cont (N=67)	51	76.1	64, 86
10 mg sync (N=29)	22	75.9	56, 90
Isolated 5q deletion MDS			
Overall (N=72)	56	77.8	66, 87
10 mg cont (N=53)	42	79.3	66, 89
10 mg sync (N=19)	14	73.7	49, 91

Reviewer's Comments:

1. *The sponsor's definition of 50% reduction of RBC transfusion requirement overlapped with the transfusion-free definition (i.e. all transfusions independent responders had greater than 50% requirement of RBC transfusion).*
2. *There were no minor erythroid responses in the study CC-501-MDS-001.*

Secondary Efficacy Endpoints: Platelet Response, Neutrophil Response, Cytogenetic Response, Bone Marrow Effects, and Changes in Biological Endpoints

Study CC-5013-MDS-003

Sponsor's Analysis

No major or minor platelet responses were observed among the 16 subjects in the MITT population who were evaluable for platelet response. The major platelet response rate was 4.0% (1/25) among the evaluable subjects in the ITT population; none of the evaluable subjects achieved a minor platelet response. No major or minor platelet responses were observed among the 17 evaluable subjects in the PP population.

One major neutrophil response was observed among the 6 subjects in the MITT population who were evaluable for neutrophil response; no minor neutrophil responses were observed.

As of the 15 September 2004 data cutoff date, 22 (32.4%) major cytogenetic responses and 22 (32.4%) minor cytogenetic responses had been observed among the 68 subjects in the MITT population who were evaluable for cytogenetic response. In the ITT population, major cytogenetic responses were observed in 41.4% (46/111) and minor cytogenetic responses were observed in 26.1% (29/111) of the subjects who were evaluable for cytogenetic response. The

major cytogenetic response rate was 40.9% (26/ 88 evaluable subjects) and the minor cytogenetic response rate was 27.3% (28/88 evaluable subjects) in the PP population.

The table below summarizes the platelet, neutrophil and cytogenetic responses in the ITT population.

Table 47 Secondary Efficacy Endpoint Responses ITT Population (Applicant's Table)

Secondary Efficacy Endpoint	Response Category [1]	10mg Cont. N [2]	n	(%)	[Ex. 95% CI]	10mg Sync. N [2]	n	(%)	[Ex. 95% CI]	Overall N [2]	n	(%)	[Ex. 95% CI]
Platelet Response	Major	14	1	(7.1)	[0.2, 33.9]	11	0	(0.0)	[0.0, 28.5]	25	1	(4.0)	[0.1, 20.4]
	Minor		0	(0.0)	[0.0, 23.2]		0	(0.0)	[0.0, 28.5]		0	(0.0)	[0.0, 13.7]
	None		13	(92.9)			11	(100.0)			24	(96.0)	
Neutrophil Response	Major	9	1	(11.1)	[0.3, 48.2]	4	0	(0.0)	[0.0, 60.2]	13	1	(7.7)	[0.2, 36.0]
	Minor		0	(0.0)	[0.0, 33.6]		0	(0.0)	[0.0, 60.2]		0	(0.0)	[0.0, 24.7]
	None		8	(88.9)			4	(100.0)			12	(92.3)	
Cytogenetic Response	Major	78	32	(41.0)	[30.0, 52.7]	33	14	(42.4)	[25.5, 60.8]	111	46	(41.4)	[32.2, 51.2]
	Minor		21	(26.9)	[17.5, 38.2]		8	(24.2)	[11.1, 42.3]		29	(26.1)	[18.2, 35.3]
	None		25	(32.1)	[21.9, 43.6]		11	(33.3)	[18.0, 51.8]		36	(32.4)	[23.9, 42.0]

[1] See Appendix I of the protocol for the definitions of the response criteria.
[2] Number of subjects evaluable for response. For platelet response, the patient must have a baseline platelet count <100 x10^9/L to be included in the analysis. For neutrophil response, the patient is required to have a baseline ANC <1 x10^9/L. For cytogenetic response, only subjects with both a baseline and post-baseline evaluation of abnormal metaphases are included in the analysis.
Program path: \\sasdbvm\data\prd\Projects\CC-5013\CC-5013-MDS-003\programs\tables\secresp.sas

Protocol CC-5013-MDS-003, Table 14.2.6.1.

FDA Analyses of Secondary Endpoints

Platelet and Neutrophil Response

There were 14 patients eligible for a platelet response in the FDA evaluable population and 82 patients were not eligible for a response. The one patient counted by the sponsor to have a platelet response (0053002) is not considered evaluable for efficacy by the FDA. Thus there were no platelet responses, major or minor, in the FDA analysis.

There were 6 patients eligible for a neutrophil response in the FDA evaluable population; 90 patients were not eligible. One patient had a major response while 5 patients had no response.

The table below shows the FDA analyses results of the platelet response and neutrophil response in the evaluable population.

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Table 48 Platelet and Neutrophil Responses in Evaluable Population (Reviewer's Table)

Category	FDA Evaluable N=96 (%)	95 % CI
Platelet response	0 (0.0)	[0, 3.8]
major	0 (0.0)	[0, 3.8]
minor	0 (0.0)	[0, 3.8]
Neutrophil response	1 (1.0)	[0, 5.7]
major	1 (1.0)	[0, 5.7]
minor	0 (0.0)	[0, 3.8]

Cytogenetic Response

Cytogenetic response was evaluated using IWG criteria which specified at least 20 metaphases be analyzed for cytogenetic response. The table below summarizes the criteria for cytogenetic response in patients with MDS.

Table 49 Criteria for Cytogenic Response in Patients With Myelodysplastic Syndrome (Applicant's Table)

Outcome	Criteria
Major Response	• No detectable cytogenetic abnormality if preexisting abnormality was present
Minor Response	• ≥50% reduction in percent of abnormal metaphases at 1 or more evaluations

Note: The assessment of cytogenetic response requires 20 analyzable metaphases if conventional cytogenetic techniques are used: fluorescent in situ hybridization (FISH) may be used as a supplement to follow a specifically defined cytogenetic abnormality.

Protocol CC-5013-MDS-003 Table 9.

In their initial application, the sponsor analyzed patients who had less than 20 metaphases analysed. The sponsor was queried and they stated (response to FDA request for information, August 9, 2005) that: "the cytogenetic analysis submitted did consider all patients for whom follow-up cytogenetic data were available, including data from karyotype analyses in which fewer than 20 metaphases were analyzed". Based on the FDA query, the sponsor analyzed patients who had at least 20 analyzable metaphases at baseline and at least 1 post-baseline visit and found 72 patients in the ITT population were evaluable for major and minor cytogenetic response and submitted the following responses:

- 32/72 (44%) major response
- 21/72 (29%) minor response

In the FDA review, out of 148 patients, 26 patients did not have at least 20 metaphases analyzed for the diagnosis and 22 patients did not have 20 analyzable metaphases for follow-up of cytogenetic responses. All 148 patients had at least one karyotypic analysis done for cytogenetics and 111 patients had 2 karyotypic analyses done in 2 visits. An MDS clone with the 5q deletion associated with additional cytogenetic abnormalities.was seen in 110 (74.3 %) patients and 38 (25.7 %) patients had isolated 5 q deletion cytogenetic abnormality only. The

additional cytogenetic abnormalities included abnormalities of chromosome 7 in 4 patients, intermediate prognostic cytogenetic abnormalities in 32 and –Y chromosomal abnormalities in 2 patients. Complex chromosomes were seen in 5 (5.1%) patients. The table below shows the patients without at least 20 analyzable metaphases at diagnosis and follow-up.

Table 50 Patients with Analyzable Metaphases (Reviewer's Table)

Metaphases Analyzed	Patient ID
< 20 metaphases analyzed at diagnosis	0073001, 0073004, 0083001, 0083003, 0093003, 0143002, 0223002, 0233002, 0233003, 0233005, 0233009, 0233010, 0243006, 0243013, 0273001, 0293002, 0293004, 0293011, 0303001, 0303003, 0373012, 0373016, 0373019, 0373021, 0373026, 0393001
< 20 metaphases analyzed at follow-up	0023002, 0083001, 0083003, 0113004, 0113009, 0163001, 0223004, 0233001, 0233006, 0243006, 0243007, 0243009, 0243012, 0313004, 0313005, 0333005, 0373008, 0373015, 0373016, 0373020, 0373025, 0373029

FDA conducted the cytogenetic response analysis in those patients who had at least 20 metaphases analyzed at diagnosis as well as during follow-up. The karyotypic abnormalities were defined by the presence of at least two abnormal cells in metaphase. There were 58 patients in the FDA evaluable population who had karyotypic analysis done on 2 visits. There were 26 (44.8%) major and 17 (29.3%) minor cytogenetic responses observed among the 58 patients in the FDA evaluable population who were evaluable for cytogenetic response. The major cytogenetic response rate was 40/46 (43.5%) in the population with MDS with isolated 5q deletion and 6/12 (50%) in the population with 5q deletion + additional abnormalities.

Updated Cytogenetic Response (August 15, 2005)

The table below shows the updated cytogenetic responses in the various populations. A major cytogenetic response was seen in 43% patients.

Table 51 Comparison of Cytogenetic Response in Different Populations Updated data (Reviewer's Table)

Population Evaluable Number Cytogenetic Response	Major Response (%)	95% CI	Minor Response (%)	95% CI
ITT (N=120)	52 (43.3)	[34.3, 52.7]	30 (25.0)	[17.6, 33.7]
FDA evaluable (N=58)	26 (44.8)	[31.7, 58.5]	17 (29.3)	[18.1, 42.7]
Isolated 5q deletion MDS (N=46)	20 (43.5)	[28.9, 58.9]	14 (30.4)	[17.7, 45.8]
5q + other deletions (N=12)	6 (50.0)	[21.1, 78.9]	3 (25.0)	[5.5, 57.2]

The sponsor was requested to perform analyses in both the ITT and MITT population showing the transfusion independence response at 8 weeks by cytogenetic category (isolated del 5q vs. del 5q plus other abnormalities) and responded on September 15, 2005 as shown below. The ITT population, N=144, excluded 4 patients whose diagnosis upon study entry was not MDS according to central review.

Table 52 Transfusion Independence by Cytogenetic Category (Applicant's Table)

Cytogenetic Complexity	n/N	%
ITT (N=144)		
Isolated 5q-	76/108	70.4
5q- + i abn	13/24	54.2
Complex	7/11	63.6
Unknown (FISH)	0/1	0
MITT (N=94)		
Isolated 5q-	48/74	64.9
5q- + i abn	8/15	53.3
Complex	4/5	80.0

Source: Response to FDA request for information, September 15, 2005.

Reviewer's Comment:

1. *In the protocol the IWG criteria specified that 20 metaphases were required for a cytogenetic response. Interphase FISH without conventional cytogenetics was used for response. Interphase FISH may be insufficient for the diagnosis of 5q deletion; although deletion of 5q may be confirmed, other abnormalities would not have been ruled out. The FDA analyses of cytogenetic response was done in those patients who had at least 20 metaphases analyzed on diagnosis and on follow-up.*
2. *Cytogenetic responses were consistent in the various populations.*

RBC-Transfusion Independence by Baseline Cytogenetic Findings

Sponsor's Analysis

The sponsor reported that 74 (67.3%) of the 110 subjects with an isolated del 5q abnormality and 21 (56.8%) of the 37 subjects with a del 5q abnormality and an additional cytogenetic abnormality achieved RBC transfusion independence. The sponsor also reported that among the 75 patients with a cytogenetic response and the 3 cytogenetic non-responders who achieved a complete resolution of the del 5q abnormality (n=78), 74 (94.9%) also achieved RBC-transfusion independence. Eleven (33.3%) of 33 patients who did not experience either a cytogenetic response or a resolution of the del 5q abnormality in the absence of a cytogenetic response achieved RBC transfusion independence. The rates of RBC transfusion independence were similar between major cytogenetic responders (95.7%; 44/46) and minor cytogenetic responders (93.1%; 27/29).

FDA Analysis

In the evaluable patients, FDA found that 23 (95.8 %) of the 24 patients with a 5q deletion abnormality with additional cytogenetic abnormalities (and who also had major cytogenetic

response) achieved RBC-transfusion independence. The rates of RBC-transfusion independence in the major cytogenetic responders was 23/24 (95.8 %) and in the minor cytogenetic responders was 18/19 (94.7 %).

Reviewer's Comment:
This was to evaluate the association of cytogenetic response with RBC transfusion independence

Bone Marrow Effects

Sponsor's Analysis
At least 1 bone marrow specimen was sent to central review for 147 (99.3%) of the 148 patients who were enrolled in the study (ITT population). Among the 81 subjects with available follow-up bone marrow aspirate specimens, the follow-up bone marrow aspirates from 27 (33.3%) subjects were assessed by the central reviewer to have no evidence of MDS (morphologic and pathologic complete remission).

Reviewer's Comment:
This data was not well documented in the submission. The definition of a CR as per the IWG criteria included normalization of the bone marrow as well as the peripheral blood counts.

Study CC-501-MDS-001

The secondary endpoints were platelet response, neutrophil response, cytogenetic response, and bone marrow response, as assessed by the MDS IWG criteria, and changes in biological endpoints, including bone marrow apoptotic index, microvessel density, plasma TNF-α and VEGF concentrations and progenitor colony-forming capacity.

Ten patients in the ITT population were RBC- transfusion dependent and had a diagnosis of low or intermediate-1 risk MDS with a del (5q31-33) cytogenetic abnormality at baseline. One patient was evaluable for platelet response; this patient achieved a major platelet response during lenalidomide therapy. Two patients were evaluable for neutrophil response; 1 of the 2 patients achieved a major neutrophil response. Major cytogenetic responses were observed in 9 (90%) of 10 patients who were evaluable for cytogenetic response. Two of the 9 patients with major cytogenetic responses did not achieve an erythroid response (Patients 103 and 133). Complete histologic remission was observed in 2 (33.3%) of the 6 patients who were evaluable for bone marrow response. The sponsor submitted the table shown below which summarizes the results of the secondary endpoints. FDA agrees with the sponsor's analysis.

Table 53 Secondary Efficacy Endpoint Responses (Applicant's Table)

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Secondary Efficacy Endpoint	N[a] / Response Category	25mg (N=3) n (%) [Ex.95% CI]	10mg (N=3) n (%) [Ex.95% CI]	10mg Sync. (N=4) n (%) [Ex.95% CI]	Overall (N=10) n (%) [Ex.95% CI]
Platelet Response	N[a]	0	1	0	1
	Major	0	1	0	1
			(100.0)		(100.0)
			[2.5,100.0]		[2.5,100.0]
	Minor	0	0	0	0
			(0.0)		(0.0)
			[0.0, 97.5]		[0.0, 97.5]
Neutrophil Response	N[a]	0	2	0	2
	Major	0	1	0	1
			(50.0)		(50.0)
			[1.3, 98.7]		[1.3, 98.7]
	Minor	0	0	0	0
			(0.0)		(0.0)
			[0.0, 84.2]		[0.0, 84.2]
Bone Marrow Response	N[a]	2	1	3	6
	Complete	2	0	0	2
		(100.0)	(0.0)	(0.0)	(33.3)
		[15.8,100.0]	[0.0, 97.5]	[0.0, 70.8]	[4.3, 77.7]
	Partial	0	0	0	0
		(0.0)	(0.0)	(0.0)	(0.0)
		[0.0, 84.2]	[0.0, 97.5]	[0.0, 70.8]	[0.0, 45.9]
	Dis. Prog.	0	1	0	1
		(0.0)	(100.0)	(0.0)	(16.7)
		[0.0, 84.2]	[2.5,100.0]	[0.0, 70.8]	[0.4, 64.1]
	AML Trans.	0	0	0	0
		(0.0)	(0.0)	(0.0)	(0.0)
		[0.0, 84.2]	[0.0, 97.5]	[0.0, 70.8]	[0.0, 45.9]
Cytogenetic Response	N[a]	3	3	4	10
	Major	3	3	3	9
		(100.0)	(100.0)	(75.0)	(90.0)
		[29.2,100.0]	[29.2,100.0]	[19.4, 99.4]	[55.5, 99.7]
	Minor	0	0	0	0
		(0.0)	(0.0)	(0.0)	(0.0)
		[0.0, 70.8]	[0.0, 70.8]	[0.0, 60.2]	[0.0, 30.8]

Source: Table 14.2.6.3.1
[a] Number of evaluable patients for the efficacy endpoint.

Source: CC-501-MDS-00, Table 20.

Bone Marrow Effects
Complete histologic remission was observed in 2 (33.3%) of the 6 patients who were evaluable for bone marrow response bases on the listings submitted.

Changes in Biological Endpoints
Plasma and serum biomarkers evaluations were performed at the screening/baseline visit; at study Weeks 8, 16, 40, and 52; every 6 months after Week 52; and at treatment discontinuation. Plasma and serum biomarkers were evaluated using monoclonal IgG2a antibodies (provided by — that recognize either the CD3 (PSI clone) or CD20 (L26 clone) antigens, and the data were analyzed by Dr. Alan List's laboratory at the Arizona Cancer Center.

As per the study report, the analysis of these data showed that lenalidomide treatment had no effect on peripheral blood plasma or serum biomarkers. However, decreases in VEGF and FGF levels in the bone marrow plasma of major erythroid responders were noted. In addition, normalization of in vitro colony growth of bone marrow erythroid and myeloid progenitor cells was observed in patients who achieved lenalidomide-induced major erythroid responses.

These serum and plasma biomarker data were not captured on Celgene CRFs, are not in the Celgene database, and were not summarized in this report.

Reviewer's Comments:

1. *The bone marrow effects could not be validated in the datasets submitted. Moreover, the definition of a CR as per the IWG criteria included normalization of the bone marrow as well as the peripheral blood counts.*
2. *A secondary objective of this study was an evaluation of the relationship between a hematologic response to lenalidomide and changes in biological endpoints, including bone marrow apoptotic index, microvessel density, plasma TNF-α and VEGF concentrations, and progenitor colony-forming capacity. However, these serum and plasma biomarker data were not captured on the CRFs, are not in the database, and were not summarized in this report.*

Time to Response

Study CC-5013-MDS-003

Time to response was not an endpoint in the study. FDA did not review the findings. In the sponsor's analysis, the median time to RBC transfusion independence in the ITT population was 4.1 weeks (95% CI: 3.4, 5.3; range, 0.3-19.1 weeks).

Table 54 Time (Weeks) to RBC Transfusion Independence ITT Population (Applicant's Table)

	10mg Cont. (N=103)	10mg Sync. (N=45)	Overall (N=148)
Time to transfusion independence (weeks)			
Number of subjects	70	25	95
Median	4.5	3.6	4.1
95% Confidence Interval	[3.6, 5.3]	[2.3, 6.1]	[3.4, 5.3]
Mean	5.0	5.1	5.0
SD	4.08	5.04	4.33
Min, Max	0.3, 19.1	0.3, 18.9	0.3, 19.1

Source: CC-5013-MDS-003, Table 14.2.2.1

Study CC-501-MDS-001

The median time to major erythroid response in the 9 responders who had a diagnosis of low or intermediate-1 risk MDS with an isolated 5q deletion cytogenetic abnormality (both transfusion dependent and independent at baseline) was 8.3 weeks (95% CI: 5.6, 11.1), (range, 2.3- 40 weeks) (see Table 14.2.3.2).

Reviewer's Comment:
The time to RBC transfusion independence is based on responders only, therefore no censoring is involved. The FDA does not agree with the "time to event" analysis based on the responders only.

6.1.5 Clinical Microbiology

Not Applicable

6.1.6 Efficacy Conclusions

The efficacy database consisted of two single-arm, open label, Phase 2 clinical studies, CC-5013-MDS-003 and CC-501-MDS-001.

In study CC-5013-MDS-003, there were 148 patients enrolled. The primary efficacy endpoint was transfusion independence, defined as the absence of any RBC transfusion during any consecutive "rolling" 56 days during the treatment period, i.e., days 1 to 56, days 2 to 57, days 3 to 58 etc. FDA analyses of data were done on patients with low or intermediate-1 risk MDS associated with 5q (q31-33) deletion with or without additional cytogenetic abnormalities who had transfusion-dependent anemia at baseline. The critical eligibility criteria were met by 96 patients for response evaluation for transfusion independence. Transfusion independence, which included at least a 1g/dL increase in hemoglobin values, was seen in 67% patients with 95% CI of 56% to 76%. These responses lasted for a minimum of 8 weeks. The median duration was 52 weeks. These responses were accompanied by cytogenetic responses in 43% patients. These responses were not accompanied by any platelet or neutrophil response.

Study CC-5013-MDS-001 had 45 patients enrolled, of which 10 evaluable patients had a low or intermediate-1 risk MDS with transfusion dependence and 5q 31-33 deletion. Transfusion independence was seen in 70% with 95% CI of 35% and 93%. The median duration of erythroid response was 47 weeks with 95% CI of 33 to 88 weeks.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In this review, adverse event data will be presented for the MDS-003 trial, they key trial for the intended population (5q deletion syndrome), for the MDS-002 trial, the trial in the MDS population for which lenalidomide is not intended (5q deletion patients were excluded), and the composite data for all three trials. Any substantive differences in the adverse event data between the MDS-003 trial and the MDS-002 trial will be described.

7.1.1 Deaths

According to the submission, the frequency of on-study deaths was 6.9% in the three MDS studies. The sponsor states that this frequency is typical for the low and INT-1 risk MDS population, according to Greenberg et al. publication defining IPSS (1997). There were 28 on-study deaths (either during the study or within 30 days after the last visit date) in 408 subjects. In addition, four deaths were reported more than 30 days after the subject completed the last study visit. The 120-Day Safety Update contains narratives of a total of 42 deaths.

Sponsor's Table 8 (Summary of Clinical Safety), shown below, summarizes the 32 deaths in the three MDS studies. Reviewer's evaluations, based on case narratives in the original submission and in the 120-Day Safety Update, follow.

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Table 8. Deaths in MDS Studies (MDS-001, MDS-002, and MDS-003)

Subject No.	Age/Gender IPSS Score	Initial Regimen	Date of Last Dose	Date of Death	Cause	Related
Study MDS-001						
108	69/F Low	25 mg	10 Sep 02		Multiorgan failure	No
112	82/M Low	25 mg	17 May 02		Multiorgan failure	No
134	72/F Int-1	10 Sync.	20 Apr 03		Splenic infarction	No
Study MDS-002						
0022001[a]	73/M Low	10 Sync	24 Feb 04		Unknown	-
0042003	82/F Unknown[b]	10 Sync.	24 Dec 03		Myelodysplasia	No
0062001	80/F Int-1	10 Cont.	29 Dec 03		Septic shock due to a perforated colon	No
0092001	76/F Low	10 Sync.			Cardiogenic shock Cardiomyopathy Congestive heart failure	No No No
0112004	71/M Int-1	10 Cont.	04 Jan 04		Cardiopulmonary arrest Acute myeloid leukemia	No No
0112005	87/M Unknown[b]	10 Cont.	06 Jan 04		Disease progression due to acute myeloid leukemia	No
0122003	77/M Unknown[b]	10 Cont.	12 Feb 04		Pneumonia	No
0122005	79/M Low	10 Cont.	27 Apr 04		End-stage myelodysplasia with secondary GI bleeding related to end-stage myelodysplasia	No
0152002	81/M Unknown[b]	10 Sync.	10 Sep 03		Disease progression	No
0152003	92/M Unknown[b]	10 Sync.	23 Feb 04		Cardiac arrest	No
0152005	72/F Unknownb	10 Cont.	17 Feb 04		End-stage liver disease with probable alcoholic hepatitis, alcoholic versus other cardio-myopathy causing CHF, thrombocytopenia, coagulopathy, paroxysmal atrial fibrillation, hemochromatosis, and MDS	No

Table 8. Deaths in MDS Studies (MDS-001, MDS-002, and MDS-003) (continued)

Subject No.	Age/Gender IPSS Score	Initial Regimen	Date of Last Dose	Date of Death	Cause	Related
Study MDS-002 (continued)						
0262008	80/F Low	10 Cont.	—		Urosepsis/septic shock Pancytopenia	Yes Yes
0292004	85/M Int-1	10 Sync.	13 Oct 03		Renal failure secondary to disease progression	No
0312004	65/M Unknownb	10 Sync.	—		Respiratory failure	Yes
0322001	75/M Int-1	10 Cont	02 Feb 04		Pneumonia	No
0342002[a]	77/F Low	10 Sync.	01 Dec 03		Unknown	-
0362005[a]	46/F Low	10 Cont	29 Apr 04		Cardiac failure secondary to cardiomyopathy	No
Study MDS-003						
0023001	68/F Low	10 Sync.	01 Dec 03		Metastatic lung cancer	No
0113003	85/M Int-1	10 Sync.	16 Mar 04		Congestive heart failure Pneumonitis Myelodysplastic syndrome	No No No
0163001[a]	68/F High	10 Sync.	27 Oct 03		Myelodysplastic syndrome	No
0233009	65/M Low	10 Cont.	—		Respiratory distress Sepsis Pancytopenia (secondary)	Yes No Yes
0243010	60/F Unknown[b]	10 Sync.	11 Dec 03		Multisystem organ failure due to thrombocytopenia-induced hemorrhage	No
0293011	88/F Unknown[b]	10 Cont.	—		Cardiac failure	No
0323002	79/F Low	10 Cont.	—		Pneumonia Pancytopenia (secondary)	Yes Yes
0323004	69/F Unknown[b]	10 Cont.	—		Sudden death	No
0333001	61/F Int-1	10 Sync.	19 Nov 03		Subdural/subarachnoid hemorrhage	No
0373011	83/F Low	10 Cont.	02 Feb 04		Respiratory failure secondary to pneumonia	No
0373024	72/M Int-1	10 Cont.	20 Jun 04		Unknown	-
0373031	79/F Low	10 Cont.	—	—	Sepsis secondary to a bowel perforation	No

CHF, congestive heart failure; GI, gastrointestinal; Int-1, intermediate-1; MDS, myelodysplastic syndrome

Data Source: *Study MDS-001, Listing 16.2.6.1, Listing 16.2.7.4, Section 14.3.3; Study MDS-002, Listing 16.2.6.1, Listing 16.2.7.4, Section 14.3.3; Study MDS-003, Listing 16.2.6.1, Listing 16.2.7.4, Section 14.3.3*

[a]Death occurred >30 days after the last visit date.

[b]Unable to classify

The Reviewer's assessments and comments on the above cases, following reviews of the patient's narratives, are shown in Reviewer's Tables below.

Table 55 Review Assessments and Comments on Deaths in MDS-001 (Reviewer's Table)

Subject Number	Comments	Relationship to Drug
001108	Received 25 mg for 51 days, when drug was stopped because of neutropenia and thrombocytopenia. Two weeks later, when still leukopenic, had a strep throat. Upon recovery patient was restarted at 10 mg. After 7 weeks hospitalized with pneumonia. WBC not stated. Drug discontinued one week later and patient died 16 days later from "multiorgan failure."	Sponsor: None. Reviewer: Probable. Most likely the patient died from pneumonia in the setting of drug-induced neutropenia.
001113	Received 25 mg for 9 days. Pancytopenia, consumption coagulopathy, renal and respiratory failure. ANC, platelet count not stated. Sepsis and "multiorgan failure."	Sponsor: None. Reviewer: Probable, as a result of drug-induced pancytopenia and sepsis.
001134	Received 10 mg for 6 days. Had splenomegaly before start of therapy. CT - Splenic infarction and subcapsular bleeding. Platelets decreased from 65,000 to 10,000 despite transfusions. Died 6 days later. Investigator: progression of splenomegaly with splenic infarction.	Sponsor: None. Reviewer: Yes. Drug-induced thrombocytopenia and splenic bleed.

Table 56 Reviewer's Assessments and Comments on Deaths in MDS-002 (Reviewer's Table)

Subject Number	Comments	Relationship to Drug
0022001	Narrative does not state that the patient died (54 days after the last dose of lenalidomide). Developed grade 4 neutropenia 45 days after start of Rx, drug dose reduced twice, and after 156 days of treatment lenalidomide was discontinued because of continuing neutropenia. Improvement of anemia not described. Patients other medical problems were arthritis, fatigue and renal failure. Cause of death unknown.	Yes, drug-related neutropenia. Relationship to death – unknown.
0042003	MDS and angiodysplasia with GI bleeding. On drug 15 days; bleeding started on Day 3.	Sponsor & Reviewer: None.
0052001	MDS with thrombocytopenia before lenalidomide. On drug 27 days. Perforated bowel and septic shock.	Sponsor & Reviewer: None.
0092001	On drug 51 days. Dose reduced once. Cardiogenic shock.	Sponsor & Reviewer: None.
0102005	Not listed in sponsor's table. Hospitalized for extreme weakness. No improvement in anemia. Hgb 5.0 g/dL. Drug discontinued after treatment for 108 days. Not transfused, because of difficulties in finding matching blood. Transferred to hospice care, date of death unknown. Other medical problems CVA, insomnia, hypertension.	Reviewer: Probably untreated anemia due to MDS.
0112004	After 54 days of treatment, Gr.1 rash and Gr. 3 thrombocytopenia. Drug d/c'd. AML diagnosed 72 days later. Cardio-pulmonary arrest.	Sponsor & Reviewer: None.
0112005	After 12 days of treatment grade 4 thrombocytopenia; drug d/c'd 8 days later. Hyperbilirubinemia (cause unknown). AML dx'd 20 days after discontinuance of drug. Thrombocytopenia continued until death 22 days after drug d/c'd.	Sponsor & Reviewer: None.

0122003	Drug (10 mg, then 5 mg) for 45 days. Post-obstructive pneumonia (probable tumor).	Sponsor & Reviewer: None.
0122005	Total treatment 69 days with 2 dose reductions because of grade 3 thrombocytopenia. Thrombocytopenia (grade 3) first diagnosed 14 days after drug was started. Drug dc'd because of diarrhea and nausea. One month after the drug was dc'd patient was hospitalized with grade 4 refractory thrombocytopenia, grade 4 anemia, grade 4 neutropenia (neutropenia not listed), subarachnoid & subdural hemorrhage, GI bleeding, and consumptive coagulopathy.	Sponsor: MDS and 2ry GI bleeding. Reviewer: Probable, drug probably contributed to pancytopenia, 2ry bleeding, sepsis, and consumptive coagulopathy.
0152002	One 21-day course of 10 mg. Twelve days after start noted neutropenia (not listed). Died 2 months after the last dose. Disease progression not listed in the narrative. Death not described, cause unknown.	Sponsor: Unknown.
0152008	Not listed in sponsor's table. Developed grade 4 neutropenia after 10 days of 10 mg lenalidomide. Neutropenia was ongoing >3.5 months after discontinuation of the drug, when patient died. Cause of death unknown.	Sponsor: Unknown.
0152009	End-stage liver disease possibly due to alcoholic hepatitis, etc.	Sponsor & Reviewer: None.
0252002	Not listed in sponsor's table. 10 mg on 21/28 day schedule reduced to 5 mg qd for 131 days. Ongoing diverticulitis throughout the course of treatment. Cause of death (not stated in the narrative) 2 months after the last dose. Pancytopenic when drug discontinued	Sponsor & Reviewer: Possible.
0252003	Not listed in sponsor's table. Death not described in the narrative. 10 mg for 21 days. Coombs-pos. hemolytic anemia. Drug d/c'd because of elevated ALT. Date or cause of death not stated.	Sponsor & Reviewer: Unknown.
0252014	Not listed in sponsor's table. Drug dose reduced once. Developed AML and died 77 days after the last dose.	Sponsor & Reviewer: None.
0262008	Received 10 mg daily for 111 days. Benefit not described. Grade 4 pancytopenia and uroseptic shock 20 days after last dose.	Sponsor and Reviewer: Yes
0292004	Received 10 mg daily for 14 days. Platelets decreased from 62,000 to 19,000 after 8 days and to 9,000 after 14 days of therapy, together with a decrease in WBC from 4,700 to 2,000. Generalized rash. Pancytopenia continued; WBC 500, platelets 7,000, Hgb. 8.5. Subdural hematoma after fall. Renal and hepatic failure. Died 17 days after last dose.	Sponsor: None. Reviewer: Yes, drug most likely contributed to pancytopenia and bleed.
0312004	Received 10 mg, then 5 mg for 129 days. Died of atypical pneumonia and respiratory failure in the setting of COPD. No counts. No evidence of benefit.	Sponsor: Yes. Reviewer: Possible, insufficient information.
0322001	Received drug for 42 days with one dose reduction. Grade 2 rash after 5 days, grade 3 thrombocytopenia after 13 days. Continuing anemia and grade 4 thrombocytopenia. Died of pneumonia, plural effusion, CHF.	Sponsor: None. Reviewer: Yes, aggravation of MDS by the drug.
0342002	Received drug for 49 days. Thrombocytopenia and neutropenia 20 days after start of medication and continuing until death 6.5 months after start of medication. Cause of death unknown.	Sponsor: Yes. Reviewer: Possible, insufficient information.
0362005	Received drug for 84 days with one dose reduction. Pancytopenic 39 days after start of the drug, subsequent values not described. Fatigue, cardiomyopathy, cardiac insufficiency, renal insufficiency, CHF, hypotension. Died 46 days after drug stopped. No evidence of benefit from the drug.	Sponsor & Reviewer: None.

Table 57 Reviewer's Assessments and Comments on Deaths in MDS-003 (including 120-day Safety Update) (Reviewer's Table)

Subject Number	Comments	Relationship to Drug
0023001	Treatment for 15 days with 10 mg, when grade 3 full body rash, fever, urticarial edema. Full transfusion independence response. Died 14 weeks after drug d/c'd from metastatic lung CA.	Sponsor & Reviewer: None.
0073001	Safety Update: Treated for 289 days with two dose reductions for grade 4 neutropenia. From transfusion-dependency became independent after 3 months of treatment. Treatment dc'd due to grade 3 thrombocytopenia, which did not recover after stopping treatment. Became anemic. Six weeks after stopping treatment was diagnosed with AML and died 11 days later.	Sponsor: Yes, AML related to drug. Reviewer: None.
0113003	Treated for 147 days with two dose reductions and 2 dose delays. No neutropenia. Died of pneumonia, CHF.	Sponsor & Reviewer: None.
0163001	Treated for 43 days with one dose reduction and one dose delay. Grade 4 thrombocytopenia and grade 1 neutropenia after 8 days of therapy (platelets 86,000 at baseline to 5,000, neutrophils from 1,600 to 1,150). Febrile neutropenia due to pneumonia and sepsis led to d/c of the drug. Drug restarted for 10 days, then dc'd because of continuing grade 4 thrombocytopenia. Neutropenia improved, but thrombocytopenia never resolved. Died 43 days later (> 30 days after drug dc'd) with AML and pneumonia.	Sponsor: None. Reviewer: None.
0233008	Treated for 79 days. Grade 4 neutropenia (not listed), sepsis, pneumonia, pancytopenia.	Sponsor & Reviewer: Yes
0243010	Treated for 21 days. Reason for drug discontinuation not given, but grade 3 thrombocytopenia was found some time later. Eleven weeks after drug discontinuation hospitalized with sepsis, thrombocytopenia induced hemorrhage, coagulopathy. Death due to multiorgan failure due to thrombocytopenia-induced hemorrhage. Suspected progression of MDS, but not proven.	Sponsor: None. Reviewer: Probable. Sepsis (probably due to unstated neutropenia), consumption coagulopathy, and bleeding 2ry to thrombocytopenia.
0293002	Safety Update: Treatment for 14 days. Grade 4 pancytopenia 11 days after start of treatment. Splenomegaly without infarct or bleed. Pneumonias 7 months and 8 months after drug dc'd. Sepsis 10 months after drug dc'd. Abdominal pain due to splenomegaly 10.5 months and 11.5 months after drug dc'd. Disease progression suspected. Died after the first week of chemotherapy (reason for and type unknown) 10 days later.	Sponsor & Reviewer: None. (probably had lymphoma in addition to MDS)
0293011	Treated for 75 days with one dose reduction and one dose delay. 14 days after start of treatment developed pneumonia and grade 4 neutropenia. Died of hepatitis B and CHF.	Sponsor & Reviewer: None.
0303003	Treated for 324 days (21/28 regimen). Developed ischemic colitis, then cardiac and respiratory failure and death. Hgb 7.4, normal WBC and platelets.	Sponsor & Reviewer: None.
0323002	Treatment for 20 days, discontinued because of grade 4 neutropenia and platelets of 16,000; grade 3 sepsis, pneumonia, pancytopenia (WBC 300, platelets 10,000). CBC prior to drug Rx not stated.	Sponsor & Reviewer: Yes
0323004	Treatment for 64 days, one dose reduction and one drug delay. 12 days after start had grade 4 neutropenia and peri-rectal abscess. Recovered from neutropenia and abscess. Treatment restarted at lower dose; CBC at	Sponsor & Reviewer: None.

	acceptable levels. Sudden death while on treatment.	
0333001	Treated for 73 days (21/28 regimen). 19 days after last dose, fell, struck her head and had a grade 4 subarachnoid hemorrhage and temporal lobe hemorrhage. Platelets 23,000 (grade 3 thrombocytopenia), down from 76,000 6 days earlier. Died 21 days after the fall and 40 days after last dose of lenalidomide. Subdural/subarachnoid hemorrhage primary cause. Thrombocytopenia not listed.	Sponsor: None. Reviewer: Yes (intracranial bleeding aggravated by thrombocytopenia).
0373009	Treated for 137 days. 5 months after last dose diagnosed with AML. Died one month later.	Sponsor & Reviewer: None.
0373011	Treatment for 28 days. After 26 days of treatment experienced grade 4 neutropenia and pneumonia. Treated with antibiotics, refused ventilatory support and died from respiratory failure due to pneumonia. In reviewer's opinion neutropenia contributed to occurrence of pneumonia and failure to recover from it.	Sponsor: None. Reviewer: Yes.
0373019	Treatment for 110 days. Five months after stopping lenalidomide was found to have AML and died 3 months later.	Sponsor & Reviewer: None.
0373024	Two treatment periods of 4 weeks. Developed AML and died.	Sponsor & Reviewer: None.
0373031	Treatment for 95 days until the day of death, one dose reduction. Major response. Perforated bowel during colonoscopy and 2ry sepsis with leukopenia (WBC from 3470 to 1080 the next day), renal failure, cardiac arrest. Cause of death sepsis from bowel perforation.	Sponsor: No. Reviewer: Yes (Neutropenia contributed to sepsis.)
0373033	Treated for 250 days. Fell, broke left hip, was operated, developed thrombocytopenia and neutropenia, then sepsis and multiorgan failure. Thrombocytopenia (grade 3) ongoing at time of death. Died of cardiac failure.	Sponsor: No Reviewer: Possible because of sepsis, neutropenia and thrombocytopenia.

Reviewer's Comments:

1. *It is not possible to assess lenalidomide safety without a comparator of best supportive care study arm.*
2. *Review of the above cases suggests that some of the deaths may be related to treatment with lenalidomide.*
3. *Lenalidomide may be contributory factor in causing death by aggravating pancytopenia of MDS, or by causing neutropenia and/or thrombocytopenia.*
4. *Thrombocytopenia and/or neutropenia appear after days, weeks or months of exposure to lenalidomide.*
5. *Thrombocytopenia and neutropenia may last for weeks or months after lenalidomide exposure. It is difficult to be certain whether prolonged thrombocytopenia and neutropenia are due to the drug, progression of MDS or incipient development of AML.*
6. *Thirty days after last dose may be inadequate length of time for assessment of lenalidomide toxicity, as SAEs and drug-related deaths may continue for long periods after drug discontinuation.*
7. *Lenalidomide appears to be administered until adverse event(s) force its discontinuation, without regard of benefit. There appear to be no stopping rule for discontinuation if there is no evidence of achievement of transfusion independence.*

Relationship to lenalidomide therapy. Of the 28 on-study deaths, 24 were assessed by the investigators as unrelated to lenalidomide therapy, 4 were suspected by the investigators to have a relationship to therapy. The details of these four patients were as follows:

- Subject 0262008, who had a history of long-standing cytopenia, had urosepsis and septic shock in the setting of pancytopenia 28 days after discontinuation of lenalidomide.
- Subject 0312004, who had a history of COPD with frequent hospitalizations, died of respiratory failure 25 days after discontinuation of lenalidomide.
- Subject 0233008, who had drug-related pancytopenia during the study, died of respiratory distress and sepsis 4 days after discontinuation of lenalidomide.
- Subject 0323002, who had drug-related pancytopenia during the study, died of pneumonia 16 days after discontinuation of lenalidomide.

Reviewer's Comments:
As noted above, it is difficult to establish causality in MDS, in which pancytopenia is the usual pathophysiology and which is treated with a drug that causes pancytopenia, especially in a study without a supportive care only arm. Furthermore, narratives provided insufficient information in some cases. Assignment of "multiorgan failure" in cases with neutropenia, sepsis and pneumonia appears inappropriate to this reviewer.

In the reviewer's opinion the following additional nine deaths may have been drug-related. Patients are identified by the following numbers:

- *001108*
- *001113*
- *001134*
- *0292004*
- *0322001*
- *0333001*
- *0373011*
- *0373031*
- *0373033*

In the reviewer's opinion, the following deaths in MDS-003 may have been drug drug-related, five during the study period and the 30-day follow up period (two identified by the sponsor's investigators) and two at later times.

- *0233008 (identified by sponsor)*
- *0323002 (identified by sponsor)*
- *0373011*
- *0373031*
- *0373033*
- *0243010 (>30 days post-study follow-up)*
- *0333001 (>30 days post-study follow-up)*

Relationship to lenalidomide dose and schedule. According to the Sponsor, there were 2 deaths (15.4%) among 13 patients whose initial dose was 25 mg/day, and 30 deaths (7.6%) among the 395 subjects who received the 10 mg starting dose. There were 16 deaths (7.4%) among 215 patients who were treated with 10 mg/day on a continuous basis, and 14 deaths (7.8%) among 180 patients who were treated with 10 mg on a syncopated schedule.

Reviewer's Comment:
The above Sponsor's analysis above does not take into account length of treatment and dose reductions, nor the possible differences between the del 5q population and the non-del 5q population. According to the Reviewer's analysis, there were no significant differences in death rates in MDS-003 (11/148=7.4%) compared to MDS-002 (17/215=7.9%).

The higher incidence of deaths in the 25 mg dose group suggests a dose-dependent relationship, but the small number of patients renders this conclusion tentative.

Categories of causes of deaths, simplified by the reviewer, are shown in Reviewer's table below.

Table 58 Causes of Death (Reviewer's Table)

Causes of deaths	Number of cases
Infections, including sepsis and pneumonia	9
AML	9
Bleeding	5
Cardiac	5
End-stage liver disease	2
Perforated colon and sepsis	2
Multiorgan failure with pancytopenia	1
Carcinoma of the lung	1
Angiodysplasia and bleeding	1
Cause unknown	7
TOTAL	**42**

Reviewer's Comment:
Twenty-four of the 42 deaths were probably related to MDS (infections, AML, bleeding, and multiorgan failure); about 11 of the deaths were probably not directly related to MDS (cardiac causes, perforated colon, end-stage liver disease (due to alcoholic cirrhosis and to hepatitis B), angiodysplasia, and carcinoma of the lung); cause was unknown in 7. These mortality statistics are typical of MDS, a chronic condition in which about 30% of patients die of causes other than MDS.

7.1.2 Other Serious Adverse Events

At least one SAE was reported in 151 (38.2%) of the 395 subjects who received the 10 mg/day starting dose of lenolidomide. Most SAEs were hematological (anemia, neutropenia, febrile neutropenia, thrombocytopenia and pancytopenia) and infectious (pneumonia, UTI, sepsis). Sponsor's Table 9 summarizes the SAEs.

Table 9. Frequency of Serious Adverse Events Reported in 1% or More of Subjects Treated With the 10-mg Lenalidomide Starting Dose in the MDS Studies (MDS-001, MDS-002, and MDS-003)

	Over All MDS Studies			
System organ class/ Preferred term [a]	25mg (N=13)	10mg Cont. (N=215)	10mg Sync. (N=180)	10mg Overall (N=395)
SUBJECTS REPORTING AT LEAST ONE SERIOUS ADVERSE EVENT	5 (38.5)	83 (38.6)	68 (37.8)	151 (38.2)
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
ANEMIA NOS	0 (0.0)	8 (3.7)	8 (4.4)	16 (4.1)
NEUTROPENIA	0 (0.0)	9 (4.2)	3 (1.7)	12 (3.0)
THROMBOCYTOPENIA	0 (0.0)	4 (1.9)	5 (2.8)	9 (2.3)
FEBRILE NEUTROPENIA	1 (7.7)	4 (1.9)	4 (2.2)	8 (2.0)
PANCYTOPENIA	0 (0.0)	4 (1.9)	1 (0.6)	5 (1.3)
INFECTIONS AND INFESTATIONS				
PNEUMONIA NOS	2 (15.4)	14 (6.5)	8 (4.4)	22 (5.6)
URINARY TRACT INFECTION NOS	0 (0.0)	3 (1.4)	2 (1.1)	5 (1.3)
SEPSIS NOS	0 (0.0)	2 (0.9)	2 (1.1)	4 (1.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
PYREXIA	2 (15.4)	6 (2.8)	5 (2.8)	11 (2.8)
ASTHENIA	0 (0.0)	2 (0.9)	2 (1.1)	4 (1.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
PLEURAL EFFUSION	0 (0.0)	4 (1.9)	2 (1.1)	6 (1.5)
DYSPNEA NOS	0 (0.0)	3 (1.4)	1 (0.6)	4 (1.0)
GASTROINTESTINAL DISORDERS				
DIARRHEA NOS	0 (0.0)	4 (1.9)	2 (1.1)	6 (1.5)
CARDIAC DISORDERS				
CARDIAC FAILURE CONGESTIVE	0 (0.0)	3 (1.4)	4 (2.2)	7 (1.8)
ATRIAL FIBRILLATION	0 (0.0)	3 (1.4)	3 (1.7)	6 (1.5)
METABOLISM AND NUTRITION DISORDERS				
DEHYDRATION	0 (0.0)	5 (2.3)	1 (0.6)	6 (1.5)
VASCULAR DISORDERS				
DEEP VEIN THROMBOSIS	0 (0.0)	1 (0.5)	3 (1.7)	4 (1.0)

Data Source: ISS, Table 1.6.1
NOS, not otherwise specified
[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A subject with multiple occurrences of an AE is counted only once in the AE category.

The following analysis by the Reviewer of the differences in SAEs between MDS-003 study and MDS-002 are shown in the table below. Only key differences between the two studies are shown. For the sake of clarity, the dosing regimens (10 mg/day continuous vs. 10 mg/day syncopated) and the numbers of patients reporting SAEs are omitted, only percentages of patients are shown.

Table 59 Key Differences in the Frequency of Serious Adverse Events between MDS-003 and MDS-002 (Reviewer's Table)

Serious Adverse Event	MDS-003, N = 148	MDS-002, N = 215
Percentage of patients with SAE	41.2%	35.8%
Blood		
-Neutropenia and febrile neutropenia	9.5%	2.8%
-Thrombocytopenia	3.4%	0.9%
-Anemia	2.7%	3.7%
-Pancytopenia	2.0%	0.9%
Infections		

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-Pneumonia, pneumonitis, sepsis, infection	13.6%	5.1%
Vascular -Pulmonary embolism -Deep venous thrombosis	 2% 2%	 0% 0%

Data source: Table 33 (MDS-003 Study Report) and Table 34 (MDS-002 Study Report)

Reviewer's Comments:

1. *There is some evidence of a relationship between dose and toxicity in the Sponsor's combined data table. Neutropenia, pneumonia and diarrhea were more frequent in the 10 mg continuous dose group (who received 280 mg per 28 days) than in the 10 mg syncopated group (who received 210 mg per 28 days). On the other hand, anemia, thrombocytopenia, febrile neutropenia, pancytopenia sepsis, and pyrexia were not increased in the continuous group.*
2. *On the other hand, the differences in SAE frequency between MDS-003 (del 5q population) and MDS-002 (non-del 5q population) are striking. There is a 3-fold higher incidence of neutropenia- and thrombocytopenia-related SAEs, a 2-fold higher incidence of pancytopenia-related SAEs, a 2.7-fold higher incidence of infectious diseases-related SAEs, and cases of venous thromboembolism and pulmonary embolism in MDS-003 but not in MDS-002.*

Sponsor's sub-group analyses of SAEs (all three MDS studies):
Subgoup analyses by the sponsor showed that

a. Subjects older than 65 years of age had more SAEs than subjects 65 years of age and younger (42.1%, 120/285 vs. 28.2%, 31/110). The only SAE that was more frequent in subjects less than 65 years of age than in older subjects was neutropenia (4.2%, 12/285 vs. 0%, 0/110).
b. There was no significant difference between males and females in the frequencies of SAEs (38.0% vs. 38.5%). There more DVTs among females (2.1%) than in males (0%).
c. Effects of race and ethnicity could not be evaluated because more than 94% of subjects were white.

Reviewer's sub-group analysis of SAEs in MDS-003 is shown in Reviewer's table below.

Table 60 Serious Adverse Events by Age in MDS-003* (Reviewer's Table)

SAE	≤65 years of age N = 48	>65 years of age N = 100
Patients with at least one SAE (%)	29.2%	47.0%
Blood disorders --Neutropenia --Febrile neutropenia --Thrombocytopenia	6.3% 0% 2.1% 0%	17.0% 9.0% 4.0% 5.0%
Infections and infestations	8.3%	19.0%
General disorders (pyrexia, fatigue, multi-organ failure, asthenia, chest pain, fall, etc.)	6.3%	11.0%

Respiratory --Pulmonary embolism (3 cases)	4.2% 2.1%	11.0% 2.0%
Gastrointestinal	4.2%	8.0%
Vascular --Deep vein thrombosis	2.1% 2.1%	5.0% 1.0%

*Data from Tables 14.3.2.2.1 in MDS-003 and MDS-002.

SAEs were 61% higher in patients over 65 years of age than in younger patients in the del 5q population. All of the above categories (hematological, infectious, respiratory, gastrointestinal, vascular, and general disorders) were all about twice as frequent in the over 65 year old patients.

Reviewer's sub-group analysis of SAEs by gender in MDS-003 is shown in the table below.

Table 61 Serious Adverse Events by Gender in MDS-003* (Reviewer's Table)

SAE	Male N = 51	Female N = 97
Patients with at least one SAE (%)	45.1%	39.2%
Blood disorders --Neutropenia --Febrile neutropenia --Thrombocytopenia	17.6% 7.8% 2.0% 2.0%	11.3% 5.2% 4.1% 4.1%
Infections and infestations	11.8%	17.5%
General disorders (pyrexia, fatigue, multi-organ failure, asthenia, chest pain, fall, etc.)	11.8%	8.2%
Respiratory --Pulmonary embolism (3 cases)	13.7% 2.0%	6.2% 2.1%
Gastrointestinal	0%	10.3%
Vascular --Deep vein thrombosis	2.0% 0%	5.2% 3.1%

*Data from Tables 14.3.2.13.2 in MDS-003 and MDS-002

The overall frequencies of SAEs were not markedly different between males and females. Some categories of SAEs were more frequent in females (infections, gastrointestinal events, thrombocytopenia and vascular events including DVTs), other categories were more frequent in males (blood disorders including neutropenia and respiratory system events).

Reviewer's Additional Comments on Hematological SAEs

While reviewing the narratives of deaths and SAEs, this reviewer noted:

- rapidity of onset of grade 3-4 neutropenias and thrombocytopenias in some cases (i.e. within 1-2 weeks in 13 instances), and
- unpredictability of resolution of grade 3-4 neutropenias and thrombocytopenias after discontinuation of lenalidomide. While in some patients they resolved within days or weeks, in others they continued for months and remained unresolved at the time of the original narrative or safety update. It is difficult to estimate the extent of this problem from the data in the submission. The sponsor was requested to provide all the data available.

In a response dated September 30, 2005, the sponsor provided the following data, which included data from the safety update:

- Median time to onset of neutropenia in 70 out of 147 patients (47.6%) after starting treatment with lenalidomide was 42 days (range, 14 - 411 days)
- Median time to recovery of neutropenia to grades 1, 2 or 3 in 64 of these 70 patients was 17 days (range, 2 – 170 days),
- Median time to grade 3 or 4 leucopenia was 29 days (range, 14 – 428 days) and median time to recovery grades 1 or 2 was 22.5 days (range, 7 – 354 days),
- Median time to onset of grade 3 or 4 thrombocytopenia in 70 out of 147 patients (47.6%) was 28 days (range, 8 – 290 days),
- Median time to recovery of thrombocytopenia to grades 1 or 2 in 60 of these 70 patients was 22 days (range, 5 – 224 days).

7.1.3 Dropouts and Other Significant Adverse Events

The primary reason for discontinuation from the studies in all treatment groups was adverse events. According to Sponsor's Table 2 in the Integrated Summary of Safety (shown below), of the 395 subjects who received the 10 mg/day starting dose, 75 (19%) discontinued from the studies because of adverse events. Sponsor's Table 2 shows the reasons for discontinuations from the studies.

Table 2. Frequency of Reasons for Discontinuation From MDS Studies (MDS-001, MDS-002, and MDS-003)

	Over All MDS Studies			
	25mg (N=13)	10mg Cont. (N=215)	10mg Sync. (N=180)	10mg Overall (N=395)
Patients enrolled	13	215	180	395
Discontinued study medication [a]	11 (84.6)	83 (38.6)	96 (53.3)	179 (45.3)
Primary reason for discontinuation				
Adverse event	6 (46.2)	31 (14.4)	44 (24.4)	75 (19.0)
Lack of therapeutic effect	1 (7.7)	27 (12.6)	32 (17.8)	59 (14.9)
Subject withdrew consent	1 (7.7)	11 (5.1)	7 (3.9)	18 (4.6)
Subject lost to follow-up	1 (7.7)	0 (0.0)	2 (1.1)	2 (0.5)
Death	2 (15.4)	9 (4.2)	6 (3.3)	15 (3.8)
Protocol violation	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
Other	0 (0.0)	5 (2.3)	4 (2.2)	9 (2.3)

Data Source: ISS, Table 1.2.1
[a] Discontinued either during core treatment period or during follow-up period

Sponsor's Table 37 in the Integrated Summary of Safety (and Table 10 in Summary of Clinical Safety) presents the types of adverse events that led to withdrawal from the studies. According to sponsor's Tables 10 and 37, of the 395 subjects who received the 10 mg/day starting dose, 93 (23.5%) discontinued treatment due to adverse events. *(Reviewer's Note: There are discrepancies between source documents Tables 1.2.1 and 1.7.1 in the number of patients who discontinued from MDS studies because of adverse events – 75 vs. 93).*

Thrombocytopenia (6.1%; 24/395) and neutropenia (3.5%; 14/395) were the most frequently reported adverse events in this category, followed by rash, nausea, diarrhea, fatigue, and pneumonia. Other events that led to withdrawal from the studies were less frequent. It is apparent

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from sponsor's Tables 10 and 37 that a large number of types of events led to discontinuation from the MDS studies.

The relationship of dose and adverse events leading to discontinuation from the studies are apparent. Of the patients who were started on 25 mg, 69% discontinued compared to 23.5% of patients who were started on 10 mg daily dose.

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Table 10. Frequency of Adverse Events Leading to Discontinuation in the MDS Studies (MDS-001, MDS-002, and MDS-003)

	Over All MDS Studies			
System organ class/ Preferred term [a]	25mg (N=13)	10mg Cont. (N=215)	10mg Sync. (N=180)	10mg Overall (N=395)
SUBJECTS REPORTING AT LEAST ONE ADVERSE EVENT LEADING TO DISCONTINUATION OF STUDY DRUG	9 (69.2)	43 (20.0)	50 (27.8)	93 (23.5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
THROMBOCYTOPENIA	2 (15.4)	9 (4.2)	15 (8.3)	24 (6.1)
NEUTROPENIA	5 (38.5)	8 (3.7)	6 (3.3)	14 (3.5)
ANEMIA NOS	0 (0.0)	3 (1.4)	1 (0.6)	4 (1.0)
HEMOLYTIC ANEMIA NOS	1 (7.7)	1 (0.5)	1 (0.6)	2 (0.5)
WARM TYPE HEMOLYTIC ANEMIA	0 (0.0)	1 (0.5)	1 (0.6)	2 (0.5)
FEBRILE NEUTROPENIA	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
LEUKOPENIA NOS	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
PANCYTOPENIA	1 (7.7)	1 (0.5)	0 (0.0)	1 (0.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
RASH NOS	0 (0.0)	3 (1.4)	5 (2.8)	8 (2.0)
DERMATITIS BULLOUS	0 (0.0)	1 (0.5)	1 (0.6)	2 (0.5)
FACE EDEMA	0 (0.0)	1 (0.5)	1 (0.6)	2 (0.5)
PRURITUS	0 (0.0)	1 (0.5)	1 (0.6)	2 (0.5)
NIGHT SWEATS	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
RASH PRURITIC	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
SKIN LESION NOS	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
URTICARIA NOS	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
GASTROINTESTINAL DISORDERS				
NAUSEA	0 (0.0)	4 (1.9)	2 (1.1)	6 (1.5)
DIARRHEA NOS	0 (0.0)	3 (1.4)	2 (1.1)	5 (1.3)
ABDOMINAL DISTENSION	0 (0.0)	1 (0.5)	3 (1.7)	4 (1.0)
ABDOMINAL PAIN NOS	0 (0.0)	1 (0.5)	1 (0.6)	2 (0.5)
CONSTIPATION	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
DIVERTICULITIS NOS	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
FLATULENCE	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
GASTROINTESTINAL HEMORRHAGE NOS	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
SMALL INTESTINAL OBSTRUCTION NOS	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
FATIGUE	0 (0.0)	2 (0.9)	2 (1.1)	4 (1.0)
PYREXIA	0 (0.0)	2 (0.9)	1 (0.6)	3 (0.8)
FALL	0 (0.0)	1 (0.5)	1 (0.6)	2 (0.5)
GAIT ABNORMAL	0 (0.0)	1 (0.5)	1 (0.6)	2 (0.5)
DISEASE PROGRESSION NOS	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
INFLUENZA LIKE ILLNESS	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
EDEMA NOS	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
SUDDEN DEATH	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
ASTHENIA	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
MALAISE	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)
MULTI-ORGAN FAILURE	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)
CARDIAC DISORDERS				
CARDIAC FAILURE CONGESTIVE	0 (0.0)	2 (0.9)	1 (0.6)	3 (0.8)
ATRIAL FIBRILLATION	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
BRADYCARDIA NOS	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
CARDIAC ARREST	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
CARDIOGENIC SHOCK	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
MYOCARDIAL INFARCTION	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
MYOCARDIAL ISCHEMIA	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
DYSPNEA NOS	0 (0.0)	3 (1.4)	0 (0.0)	3 (0.8)
COUGH	0 (0.0)	1 (0.5)	1 (0.6)	2 (0.5)
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
DYSPNEA EXERTIONAL	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
INTERSTITIAL LUNG DISEASE	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
PLEURAL EFFUSION	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
RESPIRATORY FAILURE	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)

Table 10. Frequency of Adverse Events Leading to Discontinuation in the MDS Studies (MDS-001, MDS-002, and MDS-003) (continued)

System organ class/ Preferred term [a]	Over All MDS Studies			
	25mg (N=13)	10mg Cont. (N=215)	10mg Sync. (N=180)	10mg Overall (N=395)
NERVOUS SYSTEM DISORDERS				
CEREBELLAR INFARCTION	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
CEREBROVASCULAR ACCIDENT	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
DIZZINESS	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
DIZZINESS POSTURAL	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
HEADACHE	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
NEUROPATHY NOS	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
INFECTIONS AND INFESTATIONS				
PNEUMONIA NOS	0 (0.0)	3 (1.4)	1 (0.6)	4 (1.0)
KLEBSIELLA SEPSIS	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
ARTHRALGIA	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.5)
GOUTY ARTHRITIS	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
MYALGIA	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
PAIN IN LIMB	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
METABOLISM AND NUTRITION DISORDERS				
ANOREXIA	0 (0.0)	3 (1.4)	0 (0.0)	3 (0.8)
DEHYDRATION	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
INVESTIGATIONS				
ALANINE AMINOTRANSFERASE INCREASED	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
BLOOD CREATININE INCREASED	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
WEIGHT DECREASED	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
HEPATOBILIARY DISORDERS				
HEPATOMEGALY	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
PORTAL HYPERTENSION	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)				
ACUTE MYELOID LEUKEMIA NOS	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
COLON CANCER NOS	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
PSYCHIATRIC DISORDERS				
ABNORMAL DREAMS	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
CONFUSIONAL STATE	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
HALLUCINATION NOS	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
EAR AND LABYRINTH DISORDERS				
VERTIGO	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
RENAL AND URINARY DISORDERS				
RENAL FAILURE NOS	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.3)
VASCULAR DISORDERS				
HYPOTENSION NOS	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.3)
HEMORRHAGE NOS	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)

Data Source: ISS, Table 1.7.1
NOS, not otherwise specified
[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A subject with multiple occurrences of an AE is counted only once in the AE category.

Subgroup analyses by the Sponsor:

- More subjects who discontinued from the studies due to adverse events were >65 years of age (26.3%; 75/285) than those 65 years of age and younger (16.4%; 18/110).
- There was no difference in the percentages of men and women who discontinued from studies due to adverse events (24.0% vs. 23.0%).
- No racial/ethnic analyses could be carried out for the reason stated above.

Differences between some broad categories of adverse events between MDS-003 and MDS-002 were assembled by the Reviewer and are shown in the Reviewer's Table below.

Table 62 Analysis of Adverse Events between MDS-003 and MDS-002* (Reviewer's Table)

Adverse Event Category	MDS-003, N = 148	MDS-002, N = 215
Subjects with at least one grade 3 or 4 event	88.5%	72.1%
Subjects with at least one SAE	41.2%	35.8%
Subjects with at least one AE leading to discontinuation of study drug	14.2%	27.0%
Subjects with an AE leading to a dose reduction/interruption	82.4%	55.8%

*Data from MDS-003 Clinical Study Report Table 29 and from MDS-002 Clinical Study Report Table 30.

Reviewer's Comments:

1. *The frequency of discontinuation of study drug because of adverse event was lower in study MDS-003 (14.2%) than in MDS-002 (27.0%). In MDS-003, discontinuation rate was higher in the syncopated regimen than in continuous regimen. IN MDS-002, the discontinuation rate was the same in both regimens.*
2. *The frequency of dose reductions/interruption due to an adverse event was far higher in MDS-003 than in MDS-002 (see below).*
3. *The frequency of patients with a grade 3-4 adverse event in MDS-003 (88.5%) was greater than in MDS-002 (72.1%). Toxicity was greater in the continuous regimen than in syncopated regimen in study MDS-003 (92.2% frequency of grade 3-4events vs. 80.0%), but not in study MDS-002 (69.0% in continuous vs. 74.8% in syncopated).*
4. *The frequency of subjects with SAEs in MDS-003 (41.2%) was slightly greater than in MDS-002 (35.8%).*

7.1.4 Other Search Strategies

Not performed.

7.1.5 Common Adverse Events

All adverse events (AEs) that were reported by the subjects or observed by the investigators were reported in the subject's CRF. An adverse event was defined as any sign, symptom, illness, or diagnosis that appeared or worsened during the course of the study. The severity of AEs and laboratory abnormalities was graded by NCI CTC v. 2.0. Treatment-emergent AEs were coded using the MedDRA classification system. The frequencies of adverse events were tabulated by body system, MedDRA term, and treatment regimen, with subjects reporting the same event more than once counted only once in the tabulations.

At least one adverse event was reported in 407 (99.8%) of the 408 subjects who were treated with lenalidomide in the 3 MDS studies. These are adverse events of all grades (1 – 4) and not categorized as drug-related or not. Sponsor's Table 4 shows the frequency of these events reported in 5% or more subjects.

Table 4. Frequency of Adverse Events Reported in 5% or More of Subjects in the MDS Studies (MDS-001, MDS-002, and MDS-003)

	Over All MDS Studies			
System organ class/ Preferred term [a]	25mg (N=13)	10mg Cont. (N=215)	10mg Sync. (N=180)	10mg Overall (N=395)
SUBJECTS WITH AT LEAST ONE ADVERSE EVENT	13 (100.0)	215 (100.0)	179 (99.4)	394 (99.7)
GASTROINTESTINAL DISORDERS				
DIARRHEA NOS	6 (46.2)	81 (37.7)	61 (33.9)	142 (35.9)
CONSTIPATION	3 (23.1)	53 (24.7)	42 (23.3)	95 (24.1)
NAUSEA	4 (30.8)	41 (19.1)	34 (18.9)	75 (19.0)
VOMITING NOS	1 (7.7)	17 (7.9)	18 (10.0)	35 (8.9)
ABDOMINAL PAIN NOS	3 (23.1)	20 (9.3)	11 (6.1)	31 (7.8)
DRY MOUTH	0 (0.0)	14 (6.5)	15 (8.3)	29 (7.3)
ABDOMINAL PAIN UPPER	1 (7.7)	16 (7.4)	9 (5.0)	25 (6.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
PRURITUS	8 (61.5)	72 (33.5)	53 (29.4)	124 (31.4)
RASH NOS	5 (38.5)	69 (32.1)	48 (26.7)	117 (29.6)
DRY SKIN	1 (7.7)	21 (9.8)	15 (8.3)	36 (9.1)
NIGHT SWEATS	1 (7.7)	12 (5.6)	14 (7.8)	26 (6.6)
RASH PRURITIC	0 (0.0)	10 (4.7)	10 (5.6)	20 (5.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
FATIGUE	9 (69.2)	64 (29.8)	67 (37.2)	131 (33.2)
EDEMA PERIPHERAL	4 (30.8)	29 (13.5)	45 (25.0)	74 (18.7)
PYREXIA	3 (23.1)	37 (17.2)	24 (13.3)	61 (15.4)
ASTHENIA	3 (23.1)	23 (10.7)	11 (6.1)	34 (8.6)
EDEMA NOS	0 (0.0)	12 (5.6)	16 (8.9)	28 (7.1)
PAIN NOS	2 (15.4)	13 (6.0)	12 (6.7)	25 (6.3)
CHEST PAIN	1 (7.7)	14 (6.5)	6 (3.3)	20 (5.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
NEUTROPENIA	9 (69.2)	112 (52.1)	52 (28.9)	164 (41.5)
THROMBOCYTOPENIA	7 (53.8)	101 (47.0)	63 (35.0)	164 (41.5)
ANEMIA NOS	1 (7.7)	20 (9.3)	15 (8.3)	35 (8.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
COUGH	6 (46.2)	31 (14.4)	37 (20.6)	68 (17.2)
DYSPNEA NOS	5 (38.5)	32 (14.9)	32 (17.8)	64 (16.2)
NASOPHARYNGITIS	1 (7.7)	31 (14.4)	17 (9.4)	48 (12.2)
EPISTAXIS	1 (7.7)	20 (9.3)	22 (12.2)	42 (10.6)
PHARYNGITIS	0 (0.0)	24 (11.2)	18 (10.0)	42 (10.6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
MUSCLE CRAMP	1 (7.7)	39 (18.1)	33 (18.3)	72 (18.2)
ARTHRALGIA	3 (23.1)	41 (19.1)	29 (16.1)	70 (17.7)
BACK PAIN	1 (7.7)	32 (14.9)	29 (16.1)	61 (15.4)
PAIN IN LIMB	2 (15.4)	19 (8.8)	21 (11.7)	40 (10.1)
MYALGIA	2 (15.4)	12 (5.6)	13 (7.2)	25 (6.3)
PERIPHERAL SWELLING	0 (0.0)	11 (5.1)	9 (5.0)	20 (5.1)

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Table 4. Frequency of Adverse Events Reported in 5% or More of Subjects in the MDS Studies (MDS-001, MDS-002, and MDS-003) (continued)

System organ class/ Preferred term [a]	Over All MDS Studies			
	25mg (N=13)	10mg Cont. (N=215)	10mg Sync. (N=180)	10mg Overall (N=395)
		Over All MDS Studies		
NERVOUS SYSTEM DISORDERS				
HEADACHE	3 (23.1)	35 (16.3)	33 (18.3)	68 (17.2)
DIZZINESS	1 (7.7)	32 (14.9)	32 (17.8)	64 (16.2)
DYSGEUSIA	0 (0.0)	15 (7.0)	7 (3.9)	22 (5.6)
INFECTIONS AND INFESTATIONS				
UPPER RESPIRATORY TRACT INFECTION NOS	4 (30.8)	24 (11.2)	20 (11.1)	44 (11.1)
URINARY TRACT INFECTION NOS	3 (23.1)	18 (8.4)	19 (10.6)	37 (9.4)
PNEUMONIA NOS	2 (15.4)	19 (8.8)	12 (6.7)	31 (7.8)
SINUSITIS NOS	1 (7.7)	12 (5.6)	10 (5.6)	22 (5.6)
METABOLISM AND NUTRITION DISORDERS				
ANOREXIA	1 (7.7)	23 (10.7)	14 (7.8)	37 (9.4)
APPETITE DECREASED NOS	1 (7.7)	12 (5.6)	13 (7.2)	25 (6.3)
EYE DISORDERS				
VISION BLURRED	0 (0.0)	6 (2.8)	17 (9.4)	23 (5.8)
PSYCHIATRIC DISORDERS				
INSOMNIA	0 (0.0)	14 (6.5)	17 (9.4)	31 (7.8)

Data Source: ISS, Table 1.4.1
NOS, not otherwise specified
[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A subject with multiple occurrences of an AE is counted only once in the AE category.

The most commonly reported AEs were neutropenia and thrombocytopenia (each in 41.5% of patients). Febrile neutropenia occurred in 3.3% of patients.

Bleeding events: Epistaxis was reported in 10.7% of subjects, ecchymoses in 3.3%, patechiae in 1.8%, hematuria in 1.5%, gingival bleeding in 1.1%, and hematomas in 1.0%. Hemoptysis, hemorrhage, and vaginal bleeding were reported in one or two subjects. Most of the above bleeding events were grade 1; however, epistaxis was grade 3 in 2 subjects, grade 2 in 3 subjects, and grade 1 in 34 subjects.

Of greater importance were single cases of subdural hematoma (grade 4), subarachnoid hemorrhage (grade 4), intracranial hemorrhage (grade 3), and grade 4 hematuria (penile bleeding) (grade 4). One patient, who suffered subdural/subarachnoid hemorrhage died, and one patient who had a gastrointestinal hemorrhage discontinued treatment.

Infections: Most of the infections were typical in this age group, such as upper respiratory infections (33.9%), urinary tract infections (9.4%), pneumonia (7.8%), and influenza.

Rashes and Itching: Pruritus in 31.4%, rash in 29.6%, pruritic rash in 5.1%.

Fatigue and Asthenia: Fatigue was reported by 33.2% of patients, peripheral edema by 18.7%, fever by 15.4%, asthenia by 8.6%.

Gastrointestinal: Diarrhea was reported by 35.9%, constipation by 24.1%, nausea by 19.0%, anorexia by 9.4%, vomiting by 9.4%.

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Other commonly reported AEs: Respiratory symptoms, musculoskeletal symptoms, headache, and dizziness.

Adverse events in study MDS-003 are summarized in Sponsor's Table 30 below.

Table 30. Frequency of Adverse Events Reported in 10% or More of Lenalidomide-treated Subjects by Initial Lenalidomide Regimen and Overall (Safety Population)

System organ class/ Preferred term [a]	10mg Cont. (N=103) n	(%)	10mg Sync. (N=45) n	(%)	Overall (N=148) n	(%)
Subjects with at least one adverse event	103	(100.0)	45	(100.0)	148	(100.0)
Blood and lymphatic system disorders						
Thrombocytopenia	63	(61.2)	26	(57.8)	89	(60.1)
Neutropenia	69	(67.0)	15	(33.3)	84	(56.8)
Gastrointestinal disorders						
Diarrhea NOS	45	(43.7)	19	(42.2)	64	(43.2)
Constipation	27	(26.2)	7	(15.6)	34	(23.0)
Nausea	21	(20.4)	10	(22.2)	31	(20.9)
Skin and subcutaneous tissue disorders						
Pruritus	40	(38.8)	19	(42.2)	59	(39.9)
Rash NOS	37	(35.9)	14	(31.1)	51	(34.5)
Dry skin	15	(14.6)	4	(8.9)	19	(12.8)
General disorders and administration site conditions						
Fatigue	28	(27.2)	15	(33.3)	43	(29.1)
Edema peripheral	13	(12.6)	15	(33.3)	28	(18.9)
Pyrexia	18	(17.5)	8	(17.8)	26	(17.6)
Asthenia	17	(16.5)	3	(6.7)	20	(13.5)
Respiratory, thoracic and mediastinal disorders						
Cough	14	(13.6)	13	(28.9)	27	(18.2)
Dyspnea NOS	13	(12.6)	12	(26.7)	25	(16.9)
Nasopharyngitis	22	(21.4)	3	(6.7)	25	(16.9)
Pharyngitis	17	(16.5)	5	(11.1)	22	(14.9)
Epistaxis	13	(12.6)	7	(15.6)	20	(13.5)
Musculoskeletal and connective tissue disorders						
Back pain	17	(16.5)	11	(24.4)	28	(18.9)
Muscle cramp	19	(18.4)	7	(15.6)	26	(17.6)
Arthralgia	19	(18.4)	6	(13.3)	25	(16.9)
Nervous system disorders						
Dizziness	18	(17.5)	8	(17.8)	26	(17.6)
Headache	15	(14.6)	11	(24.4)	26	(17.6)
Infections and infestations						
Pneumonia NOS	10	(9.7)	6	(13.3)	16	(10.8)
Upper respiratory tract infection NOS	13	(12.6)	3	(6.7)	16	(10.8)

Data Source: Table 14.3.2.2

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A subject with multiple occurrences of an AE is counted only once in the AE category.

The key differences between the adverse event profiles in MDS-003 and MDS-002 are shown in Reviewer's Table below.

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Table 63 Key Differences in the Frequencies of Adverse Events Reported in Lenalidomide-treated Subjects in Studies MDS-003 and MDS-002 (Reviewer's Table)

System organ class/Preferred term AE	MDS-003 N = 148	MDS-002 N = 215
Neutropenia	56.8%	29.8%
Thrombocytopenia	60.1%	27.0%
Infections, all categories	50.0%	40.9%
Diarrhea	43.2%	28.8%
Pruritus	39.9%	25.1%
Rash	34.5%	27.0%
Fatigue	29.1%	29.3%
Pyrexia	17.6%	11.6%
Bleeding events, all categories	32.4%	18.1%

*Data from MDS-003 Table 14.3.2.2 and MDS-002 Table 14.3.2.2.

Reviewer's Comments on the differences in the frequencies of AEs between study MDS-003 and study MDS-002:
There are very significant differences between the AEs in del 5q population in MDS-003 and the non-del 5q population in MDS-002. Especially noteworthy are

- *Neutropenia, almost twice as high in MDS-003*
- *Thrombocytopenia, more than twice as high in MDS-003*
- *Infections, higher in MDS-003 (especially serious infections, as described below)*
- *Higher bleeding rate in MDS-003*
- *Higher rates of diarrhea, fever, rash and pruritus*
- *There were no significant AEs that were more frequent in the MDS-002 study than in the MDS-003 study.*

The Sponsor presents some interesting analyses of neutropenia and of thrombocytopenia in study MDS-003. The neutropenia analysis is shown in Sponsor's Table 35 below.

Table 35. Summary of Neutropenia by Initial Lenalidomide Regimen and Overall

Parameter	10 mg Cont N=103	10 mg Sync N=45	Overall N=148
Neutropenia			
Any Grade Neutropenia	69 (67.0)	15 (33.3%)	84 (56.8%)
Grade 3/4 Neutropenia	65 (63.1%)	14(31.1%)	79 (53.4%)
Serious Neutropenia	7 (6.8%)	2 (4.4%)	9 (6.1%)
Discontinuations Due to Neutropenia	3 (2.9%)	0 (0.0%)	3 (2.0%)
Dose Reduction/Interruption Due to Neutropenia	45 (43.7%)	11 (24.4%)	56 (37.8%)
Febrile Neutropenia			
Febrile Neutropenia	3 (2.9%)	3 (6.7%)	6 (4.1%)
Grade 3/4 Febrile Neutropenia	3 (2.9%)	3 (6.7%)	6 (4.1%)
Serious Febrile Neutropenia	3 (2.9%)	2 (4.4%)	5 (3.4%)
Discontinuations Due to Febrile Neutropenia	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dose Reduction/Interruption Due to Febrile Neutropenia	1 (1.0%)	2 (4.4%)	3 (2.0%)

Data Source: Table 14.3.2.2, Table 14.3.2.8, Table 14.3.2.13, Table 14.3.2.15, Table 14.3.2.16

Reviewer's comments:

1. *A clear dose-toxicity relationship is evident in any grade neutropenia (67% in continuous vs. 33.3% syncopated), in grade 3 and 4 neutropenia (63.1% vs. 31.1%), and in dose reduction/interruption due to neutropenia (43.7% vs. 24.4%).*
2. *Other categories are also more frequent in the continuous dose group than in syncopated dose group, but the number of events is too small to form conclusions.*
3. *Noteworthy is the role of neutropenia in dose reductions/interruptions (37.8% of cases).*
4. *A similar analysis of thrombocytopenia (Sponsor's Table 36, not shown) did not show a dose-toxicity relationship in any grade thrombocytopenia, grade 3 a d 4 thrombocytopenia, or in dose reduction/interruption due to thrombocytopenia.*
5. *Thrombocytopenia accounted for 43.2% of dose reductions/interruptions.*

Bleeding events: Twenty-seven of 148 subjects received platelet transfusions; 7 because of bleeding episodes, 20 for prevention of possible bleeding events.

Drug-related adverse events

Reviewer's Note:
Sponsor presents this section, even though in the absence of a control group (e.g. best supportive care only), it is difficult to attribute adverse events to lenalidomide in the setting of MDS.

At least one drug-related adverse event was reported in 352 (89.1%) of the 395 subjects who were treated with the 10 mg/day starting dose of lenalidomide. Sponsor's Table 5 summarizes the drug-related adverse events that were reported in ≥ 5% of the subjects.

Neutropenia and thrombocytopenia may be due to MDS, to lenalidomide, or to both.

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Table 5. Frequency of Drug-related Adverse Events Reported in 5% or More of Subjects Treated With 10-mg/day Dose by Initial Lenalidomide Regimen (MDS-001, MDS-002, and MDS-003)

Preferred Term	25 mg (N=13)	10 mg Cont. (N=215)	10 mg Sync. (N=180)	10 mg Overall N=395)
At Least 1 Drug-related Event	**13 (100)**	**198 (92.1)**	**154 (85.6)**	**352 (89.1)**
Neutropenia	9 (69.2)	99 (46.0)	47 (26.1)	146 (37.0)
Thrombocytopenia	7 (53.8)	88 (40.9)	55 (30.6)	143 (36.2)
Pruritus	7 (53.8)	56 (26.0)	46 (25.6)	102 (25.8)
Rash NOS	2 (15.4)	55 (25.6)	39 (21.7)	94 (23.8)
Diarrhea NOS	3 (23.1)	42 (19.5)	28 (15.6)	70 (17.7)
Fatigue	7 (53.8)	26 (12.1)	28 (15.6)	54 (13.7)
Constipation	2 (15.4)	26 (12.1)	21 (11.7)	47 (11.9)
Muscle Cramp	1 (7.7)	17 (7.9)	16 (8.9)	33 (8.4)
Nausea	0 (0.0)	17 (7.9)	14 (7.8)	31 (7.8)
Edema Peripheral	1 (7.7)	5 (2.3)	25 (13.9)	30 (7.6)
Dry Skin	1 (7.7)	12 (5.6)	9 (5.0)	21 (5.3)

Data Source: ISS, Table 1.4.3
Note: Drug-related adverse events are those that the investigator suspected to be related to the study medication.

Sponsor's investigators suspected these AEs as being drug-related. Of interest is the increased toxicity with increased dose (i.e. greater with continuous than with syncopated) listed for both neutropenia and thrombocytopenia.

7.1.6 Less Common Adverse Events (CTC Grades 3 and 4 events will be described)

Grades 3 and 4 adverse events were reported in 314 (79.5%) of the 395 subjects who were treated with the 10 mg/day starting dose of lenalidomide. Sponsor's Table 6 lists these adverse events and the number of subjects who experienced them.

Reviewer's Comment:
The high frequency of grade 3 and 4 adverse events cannot fail but impress, especially the 38.5% incidence of grades 4 and 3 neutropenia (<500/cu.mm and <1000 – 500/cu.mm, respectively) and the 34.4% incidence of grades 4 and 3 thrombocytopenia (<10,000/cu.mm and <50,000 – 10,000/cu.mm, respectively). These values predispose to infection and to bleeding.

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Table 6. Frequency of Grade 3/4 Adverse Events Reported in 1% or More of Subjects Treated With 10-mg Lenalidomide Starting Dose in the MDS Studies (MDS-001, MDS-002, and MDS-003)

	Over All MDS Studies			
System organ class/ Preferred term [a]	25mg (N=13)	10mg Cont. (N=215)	10mg Sync. (N=180)	10mg Overall (N=395)
SUBJECTS WITH AT LEAST ONE NCI CTC GRADE 3 OR 4 ADVERSE EVENT [b]	13 (100.0)	176 (81.9)	138 (76.7)	314 (79.5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
NEUTROPENIA	9 (69.2)	103 (47.9)	49 (27.2)	152 (38.5)
THROMBOCYTOPENIA	7 (53.8)	79 (36.7)	57 (31.7)	136 (34.4)
ANEMIA NOS	0 (0.0)	16 (7.4)	11 (6.1)	27 (6.8)
FEBRILE NEUTROPENIA	0 (0.0)	4 (1.9)	7 (3.9)	11 (2.8)
LEUKOPENIA NOS	0 (0.0)	9 (4.2)	1 (0.6)	10 (2.5)
PANCYTOPENIA	1 (7.7)	4 (1.9)	2 (1.1)	6 (1.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
FATIGUE	4 (30.8)	15 (7.0)	9 (5.0)	24 (6.1)
PYREXIA	0 (0.0)	4 (1.9)	3 (1.7)	7 (1.8)
CHEST PAIN	1 (7.7)	5 (2.3)	0 (0.0)	5 (1.3)
PAIN NOS	1 (7.7)	2 (0.9)	3 (1.7)	5 (1.3)
EDEMA PERIPHERAL	0 (0.0)	2 (0.9)	2 (1.1)	4 (1.0)
INFECTIONS AND INFESTATIONS				
PNEUMONIA NOS	0 (0.0)	12 (5.6)	9 (5.0)	21 (5.3)
CELLULITIS	0 (0.0)	1 (0.5)	4 (2.2)	5 (1.3)
INFECTION NOS	0 (0.0)	1 (0.5)	4 (2.2)	5 (1.3)
SEPSIS NOS	1 (7.7)	3 (1.4)	2 (1.1)	5 (1.3)
GASTROINTESTINAL DISORDERS				
DIARRHEA NOS	1 (7.7)	9 (4.2)	7 (3.9)	16 (4.1)
NAUSEA	0 (0.0)	8 (3.7)	1 (0.6)	9 (2.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
DYSPNEA NOS	2 (15.4)	11 (5.1)	4 (2.2)	15 (3.8)
PLEURAL EFFUSION	0 (0.0)	3 (1.4)	3 (1.7)	6 (1.5)
HYPOXIA	0 (0.0)	2 (0.9)	3 (1.7)	5 (1.3)
EPISTAXIS	0 (0.0)	3 (1.4)	1 (0.6)	4 (1.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
BACK PAIN	0 (0.0)	8 (3.7)	4 (2.2)	12 (3.0)
ARTHRALGIA	1 (7.7)	4 (1.9)	4 (2.2)	8 (2.0)
PAIN IN LIMB	0 (0.0)	3 (1.4)	3 (1.7)	6 (1.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
RASH NOS	0 (0.0)	7 (3.3)	12 (6.7)	19 (4.8)
PRURITUS	0 (0.0)	3 (1.4)	1 (0.6)	4 (1.0)
CARDIAC DISORDERS				
CARDIAC FAILURE CONGESTIVE	0 (0.0)	4 (1.9)	6 (3.3)	10 (2.5)
ATRIAL FIBRILLATION	0 (0.0)	5 (2.3)	4 (2.2)	9 (2.3)
SINUS TACHYCARDIA	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.5)
NERVOUS SYSTEM DISORDERS				
DIZZINESS	0 (0.0)	5 (2.3)	1 (0.6)	6 (1.5)
METABOLISM AND NUTRITION DISORDERS				
ANOREXIA	0 (0.0)	3 (1.4)	1 (0.6)	4 (1.0)
HYPOKALEMIA	1 (7.7)	3 (1.4)	1 (0.6)	4 (1.0)
VASCULAR DISORDERS				
DEEP VEIN THROMBOSIS	0 (0.0)	5 (2.3)	4 (2.2)	9 (2.3)
HYPERTENSION NOS	0 (0.0)	4 (1.9)	2 (1.1)	6 (1.5)
INVESTIGATIONS				
ALANINE AMINOTRANSFERASE INCREASED	0 (0.0)	3 (1.4)	2 (1.1)	5 (1.3)
RENAL AND URINARY DISORDERS				
RENAL FAILURE NOS	0 (0.0)	3 (1.4)	1 (0.6)	4 (1.0)
HEPATOBILIARY DISORDERS				
HYPERBILIRUBINEMIA	1 (7.7)	2 (0.9)	3 (1.7)	5 (1.3)

Data Source: ISS, Table 1.5.1
NOS, not otherwise specified
[a] System Organ Class and Preferred Terms are coded using the MedDRA dictionary. A subject with multiple occurrences of an AE is counted only once in the Preferred term category.
[b] NCI CTC=National Cancer Institute Common Toxicity Criteria version 2.

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Toxicity dose-dependence. Sponsor's Table 7 analyzes the dose-dependence of hematological adverse events in the combined data sets of the three MDS studies. Even though the number of

patients who received 25 mg/day dosing was small, grade 4 neutropenia and grade 3 thrombocytopenia occurred in a greater percentage of patients than in patients treated with 10 mg/day doses.

Continuous dosing with 10 mg/day lenalidomide resulted in a higher percentage of patients with grade 3 and 4 neutropenia (47.9%) than syncopated dosing (27.2%), which delivered a 25% lower 28-day dose. Grade 3 and 4 thrombocytopenia did not show this dose-dependence. It occurred in 36.7% of patients on continuous dosing and in 31.6% of patients on syncopated dosing.

Anemia, febrile neutropenia, leucopenia, pancytopenia, pneumonia and other infections, gastrointestinal disorders, fatigue and most other grade 3/4 AEs also did not show dose-dependence, at least with this number of events and within this dose-range.

Table 7. Frequency of Grade 3 and Grade 4 Hematologic Events by Initial Lenalidomide Dosing Regimen

Preferred Term [a]	25 mg (N=13)		10 mg Cont. (N=215)		10 mg Sync. (N=180)		10 mg Overall (N=395)	
	Grade		Grade		Grade		Grade	
	3	4	3	4	3	4	3	4
Neutropenia	0 (0.0)	9 (69.2)	25 (11.6)	78 (36.3)	17 (9.4)	32 (17.8)	42 (10.6)	110 (27.8)
Thrombocytopenia	6 (46.2)	1 (7.7)	67 (31.2)	12 (5.6)	42 (23.3)	15 (8.3)	109 (27.6)	27 (6.8)
Anemia NOS	0 (0.0)	0 (0.0)	9 (4.2)	7 (3.3)	8 (4.4)	3 (1.7)	17 (4.3)	10 (2.5)
Febrile Neutropenia	0 (0.0)	0 (0.0)	4 (1.9)	0 (0.0)	5 (2.8)	2 (1.1)	9 (2.3)	2 (0.5)
Leukopenia	0 (0.0)	0 (0.0)	5 (2.3)	4 (1.9)	1 (0.6)	0 (0.0)	6 (1.5)	4 (1.0)
Pancytopenia	0 (0.0)	1 (7.7)	1 (0.5)	3 (1.4)	0 (0.0)	2 (1.1)	1 (0.3)	5 (1.3)

Data Source: ISS, Table 1.5.1.4 and Table 1.5.1.5.
[a] Events that were reported as grade 3/4 in 2l% of subjects treated with the 10-mg/day dose (as shown in Table 6)

Grade 3 and 4 AEs in the **MDS-003** study are shown in Sponsor's Table 31 (below).

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Table 31. Frequency of Grade 3/4 Adverse Events Reported in 10% or More of Lenalidomide-treated Subjects in a System Organ Class by Initial Lenalidomide Regimen and Overall (Safety Population)

System organ class/ Preferred term [a]	10mg Cont. (N=103) n	(%)	10mg Sync. (N=45) n	(%)	Overall (N=148) n	(%)
Subjects with at least one Grade 3 or 4 AE	**95**	**(92.2)**	**36**	**(80.0)**	**131**	**(88.5)**
Blood and lymphatic system disorders	**80**	**(77.7)**	**30**	**(66.7)**	**110**	**(74.3)**
Neutropenia	65	(63.1)	14	(31.1)	79	(53.4)
Thrombocytopenia	51	(49.5)	23	(51.1)	74	(50.0)
Anemia NOS	6	(5.8)	3	(6.7)	9	(6.1)
Leukopenia NOS	7	(6.8)	1	(2.2)	8	(5.4)
Febrile neutropenia	3	(2.9)	3	(6.7)	6	(4.1)
Granulocytopenia	2	(1.9)	1	(2.2)	3	(2.0)
Pancytopenia	2	(1.9)	1	(2.2)	3	(2.0)
Coagulopathy	0	(0.0)	1	(2.2)	1	(0.7)
Myelosuppression	1	(1.0)	0	(0.0)	1	(0.7)
Infections and infestations	**14**	**(13.6)**	**10**	**(22.2)**	**24**	**(16.2)**
Pneumonia NOS	5	(4.9)	6	(13.3)	11	(7.4)
Sepsis NOS	3	(2.9)	1	(2.2)	4	(2.7)
Infection NOS	0	(0.0)	2	(4.4)	2	(1.4)
Respiratory tract infection NOS	2	(1.9)	0	(0.0)	2	(1.4)
Upper respiratory tract infection NOS	2	(1.9)	0	(0.0)	2	(1.4)
Bacteriemia	0	(0.0)	1	(2.2)	1	(0.7)
Cellulitis	1	(1.0)	0	(0.0)	1	(0.7)
Central line infection	1	(1.0)	0	(0.0)	1	(0.7)
Clostridial infection NOS	1	(1.0)	0	(0.0)	1	(0.7)
Encephalitis herpes	0	(0.0)	1	(2.2)	1	(0.7)
Enterobacter sepsis	0	(0.0)	1	(2.2)	1	(0.7)
Eye infection NOS	0	(0.0)	1	(2.2)	1	(0.7)
Fungal infection NOS	0	(0.0)	1	(2.2)	1	(0.7)
Influenza	1	(1.0)	0	(0.0)	1	(0.7)
Infusion site infection	0	(0.0)	1	(2.2)	1	(0.7)
Klebsiella sepsis	1	(1.0)	0	(0.0)	1	(0.7)
Lobar pneumonia NOS	1	(1.0)	0	(0.0)	1	(0.7)
Sinusitis NOS	0	(0.0)	1	(2.2)	1	(0.7)
Sinusitis acute NOS	1	(1.0)	0	(0.0)	1	(0.7)
Skin fungal infection NOS	0	(0.0)	1	(2.2)	1	(0.7)
General disorders and administration site Conditions	**16**	**(15.5)**	**5**	**(11.1)**	**21**	**(14.2)**
Fatigue	6	(5.8)	1	(2.2)	7	(4.7)
Pyrexia	4	(3.9)	1	(2.2)	5	(3.4)
Chest pain	3	(2.9)	0	(0.0)	3	(2.0)
Asthenia	2	(1.9)	0	(0.0)	2	(1.4)
Multi-organ failure	0	(0.0)	2	(4.4)	2	(1.4)
Lethargy	1	(1.0)	0	(0.0)	1	(0.7)
Edema peripheral	1	(1.0)	0	(0.0)	1	(0.7)
Pain NOS	0	(0.0)	1	(2.2)	1	(0.7)
Sudden death	1	(1.0)	0	(0.0)	1	(0.7)
Respiratory, thoracic and mediastinal disorders	**13**	**(12.6)**	**8**	**(17.8)**	**21**	**(14.2)**
Dyspnea NOS	4	(3.9)	3	(6.7)	7	(4.7)
Pulmonary embolism	1	(1.0)	2	(4.4)	3	(2.0)
Respiratory distress	2	(1.9)	1	(2.2)	3	(2.0)
Epistaxis	2	(1.9)	0	(0.0)	2	(1.4)
Hypoxia	1	(1.0)	1	(2.2)	2	(1.4)
Pleural effusion	0	(0.0)	2	(4.4)	2	(1.4)
Pneumonitis NOS	1	(1.0)	1	(2.2)	2	(1.4)
Pulmonary hypertension NOS	0	(0.0)	2	(4.4)	2	(1.4)
Chronic obstructive airways disease exacerbated	0	(0.0)	1	(2.2)	1	(0.7)
Dyspnea exertional	1	(1.0)	0	(0.0)	1	(0.7)
Dyspnea paroxysmal nocturnal	0	(0.0)	1	(2.2)	1	(0.7)
Respiratory failure	1	(1.0)	0	(0.0)	1	(0.7)
Rhinitis NOS	1	(1.0)	0	(0.0)	1	(0.7)

Table 31. Frequency of Grade 3/4 Adverse Events Reported in 10% or More of Lenalidomide-treated Subjects in a System Organ Class by Initial Lenalidomide Regimen and Overall (Safety Population) (continued)

System organ class/ Preferred term [a]	10mg Cont. (N=103) n	(%)	10mg Sync. (N=45) n	(%)	Overall (N=148) n	(%)
Skin and subcutaneous tissue disorders	**13**	**(12.6)**	**5**	**(11.1)**	**18**	**(12.2)**
Rash NOS	5	(4.9)	5	(11.1)	10	(6.8)
Pruritus	2	(1.9)	1	(2.2)	3	(2.0)
Sweating increased	2	(1.9)	0	(0.0)	2	(1.4)
Night sweats	1	(1.0)	0	(0.0)	1	(0.7)
Pruritus generalized	1	(1.0)	0	(0.0)	1	(0.7)
Rash macular	1	(1.0)	0	(0.0)	1	(0.7)
Rash pruritic	1	(1.0)	0	(0.0)	1	(0.7)
Skin lesion NOS	1	(1.0)	0	(0.0)	1	(0.7)
Gastrointestinal disorders	**12**	**(11.7)**	**4**	**(8.9)**	**16**	**(10.8)**
Nausea	5	(4.9)	1	(2.2)	6	(4.1)
Diarrhea NOS	3	(2.9)	2	(4.4)	5	(3.4)
Vomiting NOS	1	(1.0)	1	(2.2)	2	(1.4)
Abdominal pain lower	1	(1.0)	0	(0.0)	1	(0.7)
Abdominal pain upper	1	(1.0)	0	(0.0)	1	(0.7)
Gastroenteritis NOS	1	(1.0)	0	(0.0)	1	(0.7)
Intestinal perforation NOS	1	(1.0)	0	(0.0)	1	(0.7)
Perirectal abscess	1	(1.0)	0	(0.0)	1	(0.7)
Musculoskeletal and connective tissue disorders	**13**	**(12.6)**	**3**	**(6.7)**	**16**	**(10.8)**
Back pain	6	(5.8)	1	(2.2)	7	(4.7)
Muscle cramp	3	(2.9)	0	(0.0)	3	(2.0)
Arthralgia	2	(1.9)	0	(0.0)	2	(1.4)
Pain in limb	1	(1.0)	1	(2.2)	2	(1.4)
Bursitis	1	(1.0)	0	(0.0)	1	(0.7)
Intervertebral disc degeneration NOS	0	(0.0)	1	(2.2)	1	(0.7)
Joint swelling	1	(1.0)	0	(0.0)	1	(0.7)
Osteoarthritis NOS	1	(1.0)	0	(0.0)	1	(0.7)
Periarthritis	1	(1.0)	0	(0.0)	1	(0.7)
Peripheral swelling	1	(1.0)	0	(0.0)	1	(0.7)
Nervous system disorders	**13**	**(12.6)**	**3**	**(6.7)**	**16**	**(10.8)**
Dizziness	4	(3.9)	0	(0.0)	4	(2.7)
Headache	2	(1.9)	0	(0.0)	2	(1.4)
Syncope	2	(1.9)	0	(0.0)	2	(1.4)
Ageusia	1	(1.0)	0	(0.0)	1	(0.7)
Cerebrovascular accident	1	(1.0)	0	(0.0)	1	(0.7)
Cervical radiculopathy	1	(1.0)	0	(0.0)	1	(0.7)
Depressed level of consciousness	0	(0.0)	1	(2.2)	1	(0.7)
Intracranial hemorrhage NOS	0	(0.0)	1	(2.2)	1	(0.7)
Memory impairment	1	(1.0)	0	(0.0)	1	(0.7)
Migraine NOS	0	(0.0)	1	(2.2)	1	(0.7)
Paresthesia	1	(1.0)	0	(0.0)	1	(0.7)
Polyneuropathy NOS	1	(1.0)	0	(0.0)	1	(0.7)
Speech disorder	1	(1.0)	0	(0.0)	1	(0.7)
Subarachnoid hemorrhage NOS	0	(0.0)	1	(2.2)	1	(0.7)
Torticollis	1	(1.0)	0	(0.0)	1	(0.7)
Transient ischemic attack	1	(1.0)	0	(0.0)	1	(0.7)
Visual field defect NOS	1	(1.0)	0	(0.0)	1	(0.7)

Data Source: Table 14.3.2.8

[a] Preferred terms and system organ classes are coded using the MedDRA dictionary. They are listed in descending order of preferred term frequency. A subject with multiple occurrences of an AE is counted only once in the Preferred term category.

The same data for study **MDS-002** is presented below:

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Table 32. Frequency of Grade 3/4 Adverse Events Reported in 10% or More of Lenalidomide-treated Subjects in a System Organ Class by Initial Lenalidomide Regimen and Overall (Safety Population)

System organ class/ Preferred term [a]	10mg Cont. (N=100) n	(%)	10mg Sync. (N=115) n	(%)	Overall (N=215) n	(%)
Subjects with at least one grade 3 or 4 AE	69	(69.0)	86	(74.8)	155	(72.1)
Blood and lymphatic system disorders						
Neutropenia	30	(30.0)	27	(23.5)	57	(26.5)
Thrombocytopenia	24	(24.0)	22	(19.1)	46	(21.4)
Anemia NOS	7	(7.0)	7	(6.1)	14	(6.5)
Febrile neutropenia	1	(1.0)	4	(3.5)	5	(2.3)
Pancytopenia	2	(2.0)	1	(0.9)	3	(1.4)
Warm type hemolytic anemia	1	(1.0)	2	(1.7)	3	(1.4)
Autoimmune hemolytic anemia NOS	2	(2.0)	0	(0.0)	2	(0.9)
Leukopenia NOS	2	(2.0)	0	(0.0)	2	(0.9)
Bone marrow depression NOS	1	(1.0)	0	(0.0)	1	(0.5)
Hemolysis NOS	1	(1.0)	0	(0.0)	1	(0.5)
Hemolytic anemia NOS	1	(1.0)	0	(0.0)	1	(0.5)
Splenic infarction	0	(0.0)	1	(0.9)	1	(0.5)
Cardiac disorders						
Atrial fibrillation	5	(5.0)	3	(2.6)	8	(3.7)
Cardiac failure congestive	3	(3.0)	3	(2.6)	6	(2.8)
Myocardial ischaemia	0	(0.0)	2	(1.7)	2	(0.9)
Sinus tachycardia	0	(0.0)	2	(1.7)	2	(0.9)
Angina pectoris	0	(0.0)	1	(0.9)	1	(0.5)
Atrial fibrillation aggravated	0	(0.0)	1	(0.9)	1	(0.5)
Bradycardia NOS	1	(1.0)	0	(0.0)	1	(0.5)
Cardiac arrest	0	(0.0)	1	(0.9)	1	(0.5)
Cardio-respiratory arrest	1	(1.0)	0	(0.0)	1	(0.5)
Cardiogenic shock	0	(0.0)	1	(0.9)	1	(0.5)
Cardiomyopathy NOS	1	(1.0)	0	(0.0)	1	(0.5)
Myocardial infarction	1	(1.0)	0	(0.0)	1	(0.5)
Pulmonary edema NOS	0	(0.0)	1	(0.9)	1	(0.5)
Supraventricular arrhythmia NOS	1	(1.0)	0	(0.0)	1	(0.5)
Ventricular dysfunction	0	(0.0)	1	(0.9)	1	(0.5)
Gastrointestinal disorders						
Diarrhea NOS	3	(3.0)	4	(3.5)	7	(3.3)
Gastrointestinal hemorrhage NOS	0	(0.0)	3	(2.6)	3	(1.4)
Nausea	3	(3.0)	0	(0.0)	3	(1.4)
Abdominal distension	0	(0.0)	2	(1.7)	2	(0.9)
Abdominal pain NOS	1	(1.0)	1	(0.9)	2	(0.9)
Flatulence	0	(0.0)	2	(1.7)	2	(0.9)
Ascites	1	(1.0)	0	(0.0)	1	(0.5)
Diverticulitis NOS	0	(0.0)	1	(0.9)	1	(0.5)
Inguinal hernia, obstructive	1	(1.0)	0	(0.0)	1	(0.5)
Intestinal perforation NOS	1	(1.0)	0	(0.0)	1	(0.5)
Melena	0	(0.0)	1	(0.9)	1	(0.5)
Pancreatitis NOS	0	(0.0)	1	(0.9)	1	(0.5)
Pancreatitis due to biliary obstruction	0	(0.0)	1	(0.9)	1	(0.5)
Periodontal disorder NOS	0	(0.0)	1	(0.9)	1	(0.5)
Infections and infestations						
Pneumonia NOS	5	(5.0)	3	(2.6)	8	(3.7)
Cellulitis	0	(0.0)	3	(2.6)	3	(1.4)
Infection NOS	1	(1.0)	2	(1.7)	3	(1.4)
Urinary tract infection NOS	1	(1.0)	1	(0.9)	2	(0.9)
Bronchial infection	0	(0.0)	1	(0.9)	1	(0.5)
Central line infection	0	(0.0)	1	(0.9)	1	(0.5)
Ear infection NOS	1	(1.0)	0	(0.0)	1	(0.5)
Gastroenteritis salmonella	0	(0.0)	1	(0.9)	1	(0.5)
Gastroenteritis viral NOS	1	(1.0)	0	(0.0)	1	(0.5)
Localized infection	0	(0.0)	1	(0.9)	1	(0.5)

Table 32. Frequency of Grade 3/4 Adverse Events Reported in 10% or More of Lenalidomide-treated Subjects in a System Organ Class by Initial Lenalidomide Regimen and Overall (Safety Population) (continued)

System organ class/ Preferred term [a]	10mg Cont. (N=100) n	(%)	10mg Sync. (N=115) n	(%)	Overall (N=215) n	(%)
Infections and infestations (cont)						
Lung infection NOS	0	(0.0)	1	(0.9)	1	(0.5)
Oral infection	1	(1.0)	0	(0.0)	1	(0.5)
Sepsis NOS	0	(0.0)	1	(0.9)	1	(0.5)
Septic shock	1	(1.0)	0	(0.0)	1	(0.5)
Staphylococcal bacteriemia	0	(0.0)	1	(0.9)	1	(0.5)
Urosepsis	1	(1.0)	0	(0.0)	1	(0.5)

Data Source: Table 14.2.2.8

[a] Preferred terms and system organ classes are coded using the MedDRA dictionary. They are listed in descending order of preferred term frequency. A subject with multiple occurrences of an AE is counted only once in the Preferred term category.

The key differences in the frequencies of grades 3 and 4 adverse events between MDS-003 and MDS-002 are depicted in Reviewer's Table below.

Table 64 Key Differences in the Frequencies of Grades 3 and 4 Adverse Events Reported in Lenalidomide-treated Subjects in Studies MDS-003 and MDS-002* (Reviewer's Table)

System organ class/Preferred term AE	MDS-003 N = 148	MDS-002 N = 215
Neutropenia	53.4%	26.5%
Thrombocytopenia	50.0%	21.4%
Infections (all) --Pneumonia	16.2% --8.9%	12.1%% --3.7%
Rash	6.8%	4.2%
Fatigue	4.7%	3.3%
Pyrexia	3.4%	0.9%
Bleeding events, all types	2.7%	2.8%
Pulmonary embolism Deep venous thrombosis	2.0% 3.5%	0% 0.9%

*Data from MDS-003 Table 14.3.2.7 and MDS-002 Table 14.3.2.7.

Reviewer's Comments:
The frequency of patients with Grades 3 and 4 AEs in the MDS-003 trial is strikingly different from that in MDS-002 trial in the following categories:

- *Neutropenia (53.4% in MDS-003 vs. 26.5% in MDS-002)*
- *Thrombocytopenia (50.0% in MDS-003 vs. 21.4% in MDS-002)*
- *Pneumonia (including pneumonitis and lobar pneumonia) (8.9% vs. 3.7%)*
- *Pulmonary embolism (2% in MDS-003 vs.0% in MDS-002)*
- *DVT (3.5% in MDS-003 vs. 0.9% in MDS-002)*

7.1.7 Laboratory Findings

The key laboratory data in MDS are hematological parameters. Patients were followed according to protocol as described above under Efficacy. Sponsor's Table 11 (below) shows the shifts from baseline in hematology parameters. Again, these are difficult to interpret in single-arm trials, as there are no control groups.

The overall shifts from baseline values of grade 0, 1, 2, or 3 was low among the 389 of 395 subjects in the 3 MDS studies who received 10 mg/day starting dose. The most extreme values during treatment are shown in Sponsor's Table 11 for blood counts.

Table 11. Shifts From Baseline in Hematology Parameters Based on the Most-extreme Value Obtained During Treatment (10-mg Starting Dose Overall) in the MDS Studies (MDS-001, MDS-002, and MDS-003)

	Lenalidomide 10mg Overall (N=395) Most Extreme Values					
Baseline Grade [b]	Normal n (%)	Gr 1 n (%)	Gr 2 n (%)	Gr 3 n (%)	Gr 4 n (%)	Total n (%)
ABS NEUTROPHILS	N=389 [a]					
Normal	40 (10.3)	17 (4.4)	48 (12.3)	73 (18.8)	56 (14.4)	234 (60.2)
Grade 1	1 (0.3)	1 (0.3)	11 (2.8)	25 (6.4)	11 (2.8)	49 (12.6)
Grade 2	0 (0.0)	2 (0.5)	1 (0.3)	26 (6.7)	22 (5.7)	51 (13.1)
Grade 3	1 (0.3)	0 (0.0)	0 (0.0)	13 (3.3)	30 (7.7)	44 (11.3)
Grade 4	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.3)	8 (2.1)	11 (2.8)
Total	42 (10.8)	21 (5.4)	61 (15.7)	138 (35.5)	127 (32.6)	
ABS LYMPHOCYTES	N=31 [a]					
Normal	8 (25.8)	7 (22.6)	1 (3.2)	0 (0.0)	0 (0.0)	16 (51.6)
Grade 1	1 (3.2)	1 (3.2)	7 (22.6)	2 (6.5)	0 (0.0)	11 (35.5)
Grade 2	0 (0.0)	0 (0.0)	2 (6.5)	1 (3.2)	0 (0.0)	3 (9.7)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)	1 (3.2)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (29.0)	8 (25.8)	10 (32.3)	4 (12.9)	0 (0.0)	
WBC	N=389 [a]					
Normal	60 (15.4)	24 (6.2)	72 (18.5)	80 (20.6)	8 (2.1)	244 (62.7)
Grade 1	2 (0.5)	2 (0.5)	20 (5.1)	27 (6.9)	2 (0.5)	53 (13.6)
Grade 2	0 (0.0)	2 (0.5)	13 (3.3)	38 (9.8)	5 (1.3)	58 (14.9)
Grade 3	0 (0.0)	0 (0.0)	1 (0.3)	24 (6.2)	8 (2.1)	33 (8.5)
Grade 4	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Total	62 (15.9)	29 (7.5)	106 (27.2)	169 (43.4)	23 (5.9)	
HGB	N=389 [a]					
Normal	0 (0.0)	3 (0.8)	6 (1.5)	4 (1.0)	0 (0.0)	13 (3.3)
Grade 1	0 (0.0)	16 (4.1)	64 (16.5)	34 (8.7)	1 (0.3)	115 (29.6)
Grade 2	1 (0.3)	8 (2.1)	97 (24.9)	93 (23.9)	18 (4.6)	217 (55.8)
Grade 3	0 (0.0)	1 (0.3)	10 (2.6)	19 (4.9)	10 (2.6)	40 (10.3)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.8)	4 (1.0)
Total	1 (0.3)	28 (7.2)	177 (45.5)	151 (38.8)	32 (8.2)	
PLATELETS	N=389 [a]					
Normal	67 (17.2)	100 (25.7)	46 (11.8)	66 (17.0)	2 (0.5)	280 (72.0)
Grade 1	3 (0.8)	6 (1.5)	15 (3.9)	49 (12.6)	4 (1.0)	77 (19.8)
Grade 2	3 (0.8)	2 (0.5)	3 (0.8)	12 (3.1)	0 (0.0)	20 (5.1)
Grade 3	1 (0.3)	0 (0.0)	0 (0.0)	10 (2.6)	1 (0.3)	12 (3.1)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	74 (19.0)	108 (27.8)	63 (16.2)	137 (35.2)	7 (1.8)	

Data Source: ISS, Table 1.5.4
[a] Number of subjects with baseline and post-baseline measurements. This number is used as the denominator for calculation of percents.
[b] Baseline = last value before start of treatment.

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Most subjects had normal values for serum chemistries at baseline and most extreme values during treatment were grade 0, 1, or 2. Among all adverse events in MDS-003, the following were laboratory abnormalities (recorded in 25.0%). Among them were the following renal and hepatic function tests:

- ALT increased in 7.4%,
- AST increased in 4.1%,
- Alkaline phosphatase increased in 2%,
- Bilirubin increased in 0.7%,
- BUN and creatinine increased in 0.7%.

In MDS-003 the following grade 3 abnormalities were the most extreme. Only one case had a grade 4 abnormality (uric acid). Numbers in parentheses indicate numbers of subjects:

- LFTs: AST (1), ALT (3), alkaline phosphatase (0), total bilirubin (1), albumin (0).
- Renal/electrolytes: Creatinine (0), uric acid (1), Na (4), CO_2 (0), K (2), Ca (0), Mg (0), PO_4 (4).
- Glucose (5).

Reviewer's Notes: There were five cases of cholecystitis with LFT abnormalities, and four cases of acute renal failure and azotemia with renal function abnormalities, as well as cardiac failure cases, accounting for the laboratory abnormalities noted above.

7.1.8 Vital Signs

Vital signs were not analyzed, as MDS does not affect vital signs except during intercurrent illnesses.

7.1.9 Electrocardiograms (ECGs)

At the time of the submission, most subjects had not had yet a follow-up ECG. Of the 17 subjects in MDS-003 who had follow-up analyses available, only one subject was reported to have a prolonged QT interval. This subject had taken levofloxacin and ondansetron, both of which are known to prolong the QTc interval. The subject subsequently died of progression of MDS.

Reviewer's Comment:
Since many of the patients in the study probably have greater or lesser degrees of transfusion hemosiderosis, it would not be surprising to find cardiomyopathies, pump failures and conduction defects. These would result from MDS and not from the drug.

7.1.10 Immunogenicity

Lenalidomide has not been tested for immunogenicity.

7.1.11 Human Carcinogenicity

Carcinogenicity has not been tested, as lenalidomide has been designated as Orphan Drug, and is used to treat neoplastic disorders. It is not listed among known human carcinogens.

7.1.12 Special Safety Studies

A study testing the interaction of lenalidomide with warfarin has been carried out. It failed to detect an interaction. No other studies have been carried out with respect to other drugs, QT prolongation, or populations with renal or hepatic impairment.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

None.

7.1.14 Human Reproduction and Pregnancy Data

None (verbal communication from the sponsor, 2005). Please see Pharmacology/Toxicology review for an assessment of teratogenic potential.

7.1.15 Assessment of Effect on Growth

None known.

7.1.16 Overdose Experience

None known.

7.1.17 Postmarketing Experience

Lenalidomide has not been marketed in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

Reviewer's Note:
Emphasis in this review will be placed on MDS patients with 5q deletion. These patients are the population for which the drug is intended. Furthermore, these patients appear to have different efficacy and safety profiles from patients without 5q deletion.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Pooled data from three studies, MDS-001, MDS-002 and MDS-003, in 408 subjects with MDS provide the primary safety data. Of these 408 subjects, 395 received treatment with the recommended starting dose of 10 mg/day either as a continuous regimen of daily doses (215 subjects) or as a "syncopated" regimen (21 days of treatment in 28-day cycles) (180 subjects). The mean duration of exposure was 22.7 weeks; the median duration was 22.4 weeks; about one-half (189 or 47.8% of 395) of the subjects received treatment with 10 mg/day lenalidomide for at least 24 weeks. Thirteen patients received a daily 25 mg dose. Reviewer's Table below

summarizes the duration of exposure to lenalidomide in the three MDS studies (data from Sponsor's Table 1, Summary of Clinical Safety).

Table 65 Duration of Exposure to Lenalidomide in MDS-001, MDS-002 and MDS-003 (Reviewer's Table)

Treatment Duration (weeks)	No. patients 25 mg/day	No. of patients 10 mg Continuous	No. of patients 10 mg Syncopated	No. of patients 10 mg total
Study entry (received at least one dose)	13	215	180	395
At least 4 weeks	10	199	158	357 (90.4%)
At least 8 weeks	9	175	143	318 (80.5%)
At least 16 weeks	8	142	121	263 (66.6%)
At least 24 weeks	6	102	87	189 (47.8%)
At least 32 weeks	6	50	47	97 (24.6%)
At least 48 weeks	4	7	11	18 (4.6%)
Mean	35.0	22.5	23.1	22.7
Median (Min.Max.)	20.6 (1.3, 87.0)	21.7 (0.4, 71.1)	23.0 (0.7, 59.1)	22.4 (0.4, 71.1)

Duration of exposure in MDS-003 trial is shown in Sponsor's Table 27 (below). The exposure in MDS-003 is longer than in all three MDS studies combined. Over 50% of patients were treated for at least 32 weeks, almost 70% for at least 24 weeks, and over 80% for at least 16 weeks.

Table 27. Duration of Exposure to Lenalidomide as of 15 September 2004 Data Cutoff Date by Initial Lenalidomide Regimen and Overall (Safety Population)

Treatment Duration Duration (weeks) [a]	10mg Cont. (N=103)		10mg Sync. (N=45)		Overall (N=148)	
n	103		45		148	
Mean	29.4		30.9		29.8	
SD	12.34		19.24		14.73	
Median	32.4		33.0		32.9	
Min, Max	0.4, 56.1		2.0, 61.9		0.4, 61.9	
Distribution of Treatment Duration	n	(%)	n	(%)	n	(%)
At least 4 weeks	98	(95.1)	39	(86.7)	137	(92.6)
At least 8 weeks	95	(92.2)	35	(77.8)	130	(87.8)
At least 16 weeks	85	(83.5)	33	(73.3)	119	(80.4)
At least 24 weeks	73	(70.9)	29	(64.4)	102	(68.9)
At least 32 weeks	62	(60.2)	25	(55.6)	87	(58.8)

Data Source: Table 14.3.1.1
[a] Duration (weeks) = (date of last dose - date of first dose + 1) / 7

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A substantial percentage of patients in all three studies had reductions of the initial dose or interruption of dosing because of adverse events. Reviewer's table below shows the dose reductions and dosing interruptions by study. These data were not integrated by the sponsor into a composite of three studies. Generally, the differences between the continuous and syncopated 10 mg dosing regimens were not noteworthy; therefore the data from the two regimens are condensed for ease of presentation.

Table 66 Dose Reductions Due to Adverse Events in MDS-001, MDS-002 and MDS-003 (ITT Populations)* (Reviewer's Table)

Dose Reduction/ Interruption**	**MDS-001, 25 mg No. patients (%) N = 13**	**MDS-001, 10 mg No. patients (%) N = 32**	**MDS-002, 10 mg No. patients (%) N = 215**	**MDS-003, 10 mg No. patients (%) N = 148**
Had at least 1 dose reduction/interruption	8 (62%)	12 (38%)	102 (47%)	**118 (80%)**
Time to 1st dose reduction/interruption Median (range), days	50 days	85– 96 (44 – 184) days	42 (3 – 148) days	**21 (2 – 253) days**
Duration of 1st dose interruption Median (range), days	Not stated	Not stated	16 (2 – 65) days	**22 (2 – 265) days**
Had 2nd dose reduction/interruption	7 (54%)	0	49 (23%)	**50 (34%)**
Interval between 1st and 2nd reduction/interruption Median (range), days	128 (36 – 169) days	0	36 (2 – 159) days	**51 (15 – 205) days**
Duration of 2nd dose interruption Median (range), days	Not stated	N/A	12 (2 – 60) days	**21 (2 – 148) days**

*Data from Table 24 (MDS-001), Table 29 (MDS-002), and Table 28 (MDS-003).
**Definitions: Time to dose reduction/interruption: the time from the first dose of lenalidomide to the start of first reduction/interruption. Duration of dose interruption: The time from last dose of one dosing regimen to first dose of the next dosing regimen. A dosing change is considered an interruption if the start of the new dosing record is >1 day after the end of the previous dosing record. Interval between 1st and 2nd reduction/interruption: time from the start of the first dose reduction/interruption to the start of the second dose reduction/interruption.

Reviewers Comments:
*A substantial proportion of patients treated with all doses and all schedules had to have dose reductions and dose interruptions because of drug toxicity. Especially noteworthy were dose reduction and dose interruptions in the MDS-003 study, in which the MDS patients with del 5q were treated (in **bold type** above). Eighty percent of patients had to have the initial 10 mg/day reduced and/or delayed at least once or twice. Typically, an adverse event forces discontinuation of treatment. The drug is restarted at 5 mg/day dose once the adverse event subsided (median delay of 21 days with a wide range of delays). Another adverse event that forces discontinuation of treatment is followed by another delay (median delay of 51 days, with a wide range of delays) before treatment is re-instituted with a 5 mg q.o.d. dose.*

Greater detail of dose reductions and interruptions in the **MDS-003** trial are shown in Sponsor's Table 28 (below).

Table 28. Dose Reductions by Initial Dosing Regimen and Overall (Safety Population)

Dose Reduction	10mg Cont. (N=103)	10mg Sync. (N=45)	Overall (N=148)
Had at least one dose reduction/interruption			
Due to AE			
Yes	89 (86.4)	29 (64.4)	118 (79.7)
No	14 (13.6)	16 (35.6)	30 (20.3)
Time to first dose reduction/ interruption(days) due to AE [a]			
n	89	29	118
Mean	35.9	32.7	35.1
SD	35.41	47.17	38.44
Median	22.0	21.0	21.0
Min, Max	2.0, 198.0	3.0, 253.0	2.0, 253.0
Duration of first dose interruption(days) [b]			
n	59	29	118
Mean	23.1	45.2	28.5
SD	19.76	56.13	33.74
Median	15.0	26.0	22.0
Min, Max	2.0, 119.0	10.0, 265.0	2.0, 265.0
Had second dose reduction/interruption due to AE			
Yes	39 (37.9)	11 (24.4)	50 (33.8)
No	64 (62.1)	34 (75.6)	98 (66.2)
Interval between first and second reduction/ interruption(days) [c] due to AE			
n	39	11	50
Mean	59.9	59.0	59.7
SD	42.78	16.94	35.45
Median	50.0	58.0	51.0
Min, Max	15.0, 205.0	39.0, 85.0	15.0, 205.0
Duration of second dose interruption(days) [b]			
n	39	11	50
Mean	23.6	33.5	25.8
SD	24.79	39.23	28.42
Median	15.0	21.0	21.0
Min, Max	2.0, 147.0	3.0, 148.0	2.0, 148.0

Data Source: Table 14.3.1.6

[a] Time to dose reduction/interruption is the time from first dose of study medication to the start of first reduction/interruption.

[b] Duration of dose interruption is the time from last dose of one dosing regimen to first dose of the next dosing regimen. A dosing change is considered an interruption if the start of the new dosing record is greater than 1 day after the end of the previous dosing record.

[c] Time from the start of the first dose reduction/interruption to the start of the second dose reduction/interruption.

The median number of days on treatment until the first dose reduction was 21.
The median duration of treatment interruption after drug is held the first time was 22 days.
The median number of days between the first and second dose reduction was 51 days (presumably that includes the duration of the first treatment interruption plus the duration of treatment with the reduced dose).
The median duration of treatment interruption after the reduced dose was stopped and a third dose reduction instituted was 21 days.

Reviewer's Comments:

- *Dose reductions and dose delays due to adverse events suggest that the starting dose may be too high for 80% of the patients for whom this drug is intended.*

Study type and design/patient enumeration

Study MDS-001 was a single center, Phase 1/2, pilot, dose-finding study in which 13 subjects received lenalidomide as a 25 mg daily dose, 12 subjects received 10 mg daily dose on a

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continuous basis, and 20 subjects received 10 mg daily dose on a syncopated regimen (on Days 1-21 of repeated 28-day cycles).

Study MDS-002 was a Phase 2, multicenter, open label, single-arm study in which 100 subjects received lenalidomide as a 10 mg daily dose on a continuous basis and 115, 10 mg dose on a syncopated regimen.

Study MDS-003 was a Phase 2, multicenter, open label, single-arm confirmatory study in which 103 subjects received lenalidomide on a 10 mg daily on a continuous basis and 45, 10 mg on a syncopated regimen.

Demographics

Demographic characteristics of subjects are summarized in Reviewer's Table below (data from Sponsor's Table 3).

Table 67 Demographic Characteristics of Subjects in Studies MDS-001, MDS-002 and MDS 003 (Reviewer's Table)

Characteristic	No. of patients 25 mg N = 13	No. of patients 10 mg Continuous, N = 215	No. of patients 10 mg Syncopated, N = 180	No. of patients 10 mg (Total) N = 395
Age (years)				
Mean	73.1	70.9	70.2	70.6
Median (range)	74.0 (51.0-85.0)	72.0 (27.0-95.0)	71.5 (27.0-92.0)	72.0 (27.0-95.0)
Age distribution				
≤ 65 years	2	59	51	110
> 65 years	11	156	129	285
Gender				
Male	7	111	97	208
Female	6	104	83	187
Race				
White	11	205	169	374
All Other	2	10	11	21

Extent of exposure (dose/duration)

Described above.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There are no 1) data derived from studies not conducted under the applicant's IND, 2) postmarketing data, or 3) literature reports on studies not conducted under the IND.

Other studies

None

Postmarketing experience

Lenalidomide has not been marketed in any country.

7.2.3 Adequacy of Overall Clinical Experience

The clinical experience with 10 mg daily dosing is contained in this review. The clinical experience with 25 mg daily dosing is not pertinent to this application. The 25 mg dose was found to be too toxic in MDS-001 and was abandoned for use in MDS

- The total number of subjects exposed to the drug was adequate,
- the duration of exposure was adequate,
- over one-half of the subjects in the three trials do not have the type of MDS for which the drug is intended (5q deletion),
- the 10 mg dose by either dosing regimen was too high for the subjects for whom the drug is intended,
- the numbers of patients > 65 years of age and ≤65 years of age was adequate,
- the numbers of males and females were adequate,
- the number of subjects exposed to the drug in races other than white was not adequate, and
- the number of subjects exposed to the drug who have renal or hepatic impairment was not adequate; these patients were excluded from the studies. Nevertheless, a few patients had transient hepatic or renal impairment due to intercurrent illnesses.

The design of studies was less than optimal to answer critical questions, since these are uncontrolled studies and the dosing is not appropriate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Since lenalidomide is closely related to thalidomide, teratogenicity studies were carried out in rats (not a susceptible species for limb abnormalities) and rabbits (who are susceptible), but were not feeding during the study. The results are summarized in Pharmacology/Toxicology review. Pharmacology/Toxicology reviewers and an FDA consultant deem the reproductive studies inadequate.

QT prolongation studies were not carried out or requested.

7.2.5 Adequacy of Routine Clinical Testing

Routine peripheral blood cell counts, bone marrow aspirates, red cell and platelet transfusion monitoring, hepatic function tests, renal function tests, thyroid function tests were performed as per protocol.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Since lenalidomide is primarily excreted by the kidney, it would be important to study the safety, as well as efficacy, in renally impaired patients.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

A placebo (best clinical care) trial would greatly help in distinguishing drug effects from the pathophysiology of MDS.

7.2.8 Assessment of Quality and Completeness of Data

Division of Scientific Investigations report is pending.

7.2.9 Additional Submissions, Including Safety Update

Safety Update was reviewed. Reports of deaths were incorporated into the section on deaths. SAE, grade 3 and 4 event, and common adverse event profiles are similar to those in the original submission.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

1. The most important limitation of data is that data supporting this application come from one single-arm Phase 2 trial, MDS-003 in *del 5q* patients. There is no control arm to compare adverse events between the treatment arm and a control arm. The supporting MDS-002 trial was carried out in *non-del 5q* population in which efficacy and safety results differ from those in the *del 5q* population.

2. Adverse events were very common. Practically all patients (99.7%) in all three MDS studies reported at least one adverse event. A very high percentage of patients (79.5%) reported a grade 3 or 4 adverse event.

3. The most commonly reported adverse events in all three studies were <u>neutropenia and thrombocytopenia.</u> They were also 1) the most common grade 3 and grade 4 adverse events, 2) the most common serious adverse events (SAEs), except for pneumonia, 3) the most

common adverse events leading to discontinuations from studies, and 4) the most common adverse events leading to dose reductions and dose interruptions.

4. Less frequently reported were infections (pneumonias, sepsis, upper respiratory, urinary tract), bleeding events (epistaxis, gingival, genitourinary, intracranial, and gastrointestinal bleeding), gastrointestinal events (diarrhea, constipation, nausea), rash, pruritus, fatigue, peripheral edema, pyrexia, respiratory symptoms, musculoskeletal symptoms, headache, dizziness, anorexia.

5. There were differences in the frequency of patients reporting neutropenia, thrombocytopenia, and infections between the *del 5q* population in the MDS-003 study and the non-*del 5q* population in the MDS-002 study. These differences are shown in the Reviewer's Table below. The *del 5q* MDS population had about double the number of subjects with neutropenia and thrombocytopenia, most of which were grade 3 or 4 compared to the non-*del 5q* population. There was also a doubling in infectious events, including pneumonias, in the *del 5q* population compared to non-*del 5q* population. Grade 3 or 4 bleeding events were rare, but occurred more frequently in the *del 5q* population than in the non-*del 5q* population.

6. Eighty percent (80%) of patients in MDS-003 had at least one dose reduction/interruption compared to 47% of patients in MDS-002. The higher incidence of dose reductions/interruptions in MDS-003 may be due to the higher incidence of neutropenia, thrombocytopenia, and infections in MDS-003, as shown in Reviewer's Table above.

7. The above findings suggest that the lenalidomide starting dose, while possibly appropriate for the *non-del 5q* MDS population, is clearly too high for the *del 5q* MDS population, for which lenalidomide is intended. A randomized clinical trial is testing 5 mg/day vs. 10 mg/day vs. placebo in *del 5q* patients. At present it is not known whether a starting 5 mg/day dose will be as effective and less toxic than the starting 10 mg dose.

8. The frequencies of SAEs were similar in the two trials (41.2% in MDS-003 and 35.8% in MDS-002). There were 18 deaths (12.2% of 148 patients) in MDS-003. Seven of the deaths in MDS-003 were possibly or probably drug-related. There were 21 deaths (9.8% of 215 patients) in MDS-002.

9. Reviews of deaths, SAEs, and of grade 3 – 4 adverse events led to the following conclusions: 1) Approximately 14 of 42 deaths were possibly or probably drug-related by causing neutropenia and/or thrombocytopenia with attendant consequences; 2) grade 3 or 4 neutropenia and/or thrombocytopenia can occur suddenly (e.g. within 6 days of starting therapy) or after weeks or months of therapy; hence monitoring of patients while on lenalidomide treatment is of paramount importance; and 3) the course recovery of normal or acceptable WBC and/or platelet counts after discontinuation of lenalidomide can be unpredictable: it can occur after days, weeks, or months, or it may not occur at all during the follow-up period.

10. The frequency if SAEs was higher in subjects >65 years of age than in younger subjects (42% vs. 28%). A greater proportion of subjects >65 years of age discontinued from the studies because of adverse events than the proportion of younger subjects (26% vs. 16%). There were no differences between genders in the overall frequencies of SAEs and in percentages of patients who discontinued from studies.

11. Patients with renal impairment were excluded from the studies. Because lenalidomide is mainly excreted by the kidney, renal function should be carefully monitored to avoid excess toxicity.

12. In summary, the effectiveness of lenalidomide in reducing or eliminating RBC transfusion dependence in *del 5q* MDS patients is accompanied by higher toxicity. These patients appear be more sensitive to lenalidomide than non-*del 5q* patients and have a greater incidence of grade 3 or 4 adverse events, neutropenia, thrombocytopenia, and infections.

13. The benefit of lenalidomide treatment in *del 5q* population is substantial; the incidence of severe (grade 3 or 4) adverse events, some of them life-threatening, is high. Therefore, a balanced medical evaluation is required before prescribing lenalidomide.

14. Until agreed-on and definitive toxicology studies are completed, a S.T.E.P.S.-like program, similar to that for thalidomide, needs to be implemented before lenalidomide is marketed. The program can then be continued if lenalidomide is shown to be a teratogen, and discontinued if it is not a teratogen.

15. Lenalidomide should be approved once the toxicology studies are completed and proper warnings and precautions are inserted into the product information label.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Pooled data vs. individual study data

Not applicable for reasons stated above.

Combining data

Not applicable for reasons stated above.

7.4.2 Explorations for Predictive Factors

Explorations for dose dependency for adverse findings

Described above

Explorations for time dependency for adverse findings

Described above under dose reductions/interruptions.

Explorations for drug-demographic interactions

Described above under dose reductions/interruptions.

Explorations for drug-disease interactions

Difficulty in exploring this aspect in single arm, uncontrolled trials noted. The trials excluded renally and hepatically impaired patients.

Explorations for drug-drug interactions

As noted above, lenalidomide is not metabolized by CYP450 enzymes, but excreted mainly unchanged. No interactions are known at present.

7.4.3 Causality Determination

The causality issue is discussed above in conjunction with deaths, and dose reductions/interruptions.

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8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Dosing issues are addressed in detail above. Eighty percent of patients need dose reductions and dose interruptions on the proposed dose regimens, 10 mg/day or 10 mg/day for 21 days every 28 day-cycle.

8.2 Drug-Drug Interactions

Lenalidomide is not metabolized by the CYP450 system. It is mainly excreted by the kidney. A clinical drug interaction study was performed to evaluate the effect of lenalidomide on the pharmacokinetics and activity of warfarin. Neither activities nor pharmacokinetics of either drug were altered by co-administration.

8.3 Special Populations

Efficacy
Subgroup analyses show that achievement of RBC- transfusion independence is not affected by age or gender.

The reviewer's summary of the transfusion-independent response by age and gender subgroups based on the ITT population is presented in the table below. Ninety seven (97%) of the patients were Caucasian and race was not looked at. The results confirm that the transfusion-independent responses are consistent between age and gender subgroups.

Table 68 Summary of the Transfusion Independent Response by Age and Gender Subgroups based on ITT Population (Reviewer's Table)

Subgroup	Transfusion Independence	
	N	%
Age		
≤ 65 (n=48)	31	64.6
> 65 (n= 100)	68	68.0
Gender		
Female (n=97)	68	70.1
Male (n=51)	31	60.8

Safety
The frequency if SAEs was higher in subjects >65 years of age than in younger subjects (42% vs. 28%). A greater proportion of subjects >65 years of age discontinued from the studies because of adverse events than the proportion of younger subjects (26% vs. 16%). There were no

differences between genders in the overall frequencies of SAEs and in percentages of patients who discontinued from studies.

Patients with renal or hepatic impairment were excluded. The study excluded patients with a serum creatinine >2.5 mg/dL. No renal impairment study was performed. Because lenalidomide is mainly excreted by the kidney, renal function should be carefully monitored to avoid excess toxicity.

8.4 Pediatrics

Lenalidomide has an Orphan Drug status, and pediatric studies are not required.

8.5 Advisory Committee Meeting

Lenalidomide was brought before the Oncology Drug Advisory Committee on Sept 14, 2005. A summary of the issues and questions are given below. The ODAC committee voted 10 to 5 that the benefit versus risk analyses warranted approval. For a detailed discussion, please see Committee Minutes available on the FDA website.

The key issues under consideration were:

1. Whether a single arm trial design can be used in a heterogeneous disease (myelodysplastic syndrome (MDS),
2. Whether an "8-week transfusion-free endpoint" can be used in a single arm trial to demonstrate clinical benefit,
3. Whether the dose regimen (10 mg continuous) is excessively toxic and a reduced dose regimen should be studied,
4. Whether the teratogenic potential of lenalidomide, a thalidomide analogue, has been adequately characterized,
5. Whether additional risk management measures (e.g., S.T.E.P.S. program) should be implemented until completion of further studies.

The following clinical questions with the committee votes are shown below:

1. Randomized controlled trials allow for direct comparisons of treatment effects and safety between treatment arms. A single arm study has been submitted using an 8-week run-in period to serve as a baseline for each patient's transfusion requirements. A comparison is subsequently made to a follow-up 8-week period on Revlimid to compare transfusion requirements. Does this study design allow adequate characterization of Revlimid's treatment effect in the population described in the proposed indication?

Response: *Yes=11*
No=5

2. In this single-arm trial, 80% of patients enrolled in MDS-003 had dose reductions and/or delays and 80% of patients experienced either grade 3 or 4 adverse events. Data do not exist on the efficacy and safety of lower Revlimid doses. Approval of a drug is contingent upon being able to write adequate product labeling, requiring a recommended dose and characterization of a safety profile. Do the data provided in this single-arm trial provide a basis for a recommended dose and adequate description of a safety profile?

Response : *Yes= 2*
No= 13

3. Please characterize the magnitude of Revlimid's benefit and risk in the indication being sought. After this characterization, does this risk/benefit analysis warrant approval?

Response : *Yes= 10*
No= 5

8.6 Literature Review

The following is a literature review done by the FDA efficacy reviewer.

The incidence of myelodysplastic syndromes (MDS) is about 2 cases per 100,000 people per year, with 30 cases per 100,000 people per year in patients >70 years old. At least 10,000 new cases are diagnosed annually in the United States. The overall incidence of MDS is slightly higher in males than in females (1.5-2.0:1). MDS is a disease associated with age, with a median age at diagnosis of about 70 years. MDS is rare in children. Nearly 50% of patients with MDS are asymptomatic at the time of initial diagnosis. Signs and symptoms relate to hematopoietic failure, leading to anemia, thrombocytopenia or leucopenia. Infections and bleeding manifestations also occur.

The vast majority of MDS cases (80-90%) occur *de novo*, whereas 10-20% is secondary. Exposure to radiation and/or cytotoxic agents is a recognized etiologic factor in secondary disease forms. Cumulative exposure to environmental toxins, genetic differences in leukemogen susceptibility and metabolism, and genomic senescence may contribute to disease pathogenesis in de novo cases. Exposure to benzene and its derivatives results in karyotypic abnormalities often seen in MDS. Therapy related myelodysplasias are recognized long-term complications of cancer therapy and radiation therapy which usually develops 3-7 years after exposure and is most frequently related to complete or partial loss of chromosome 7. Exposure is usually to alkylating agents or nitrosoureas. Autologous bone marrow transplantation has also been associated with a risk of MDS.

The French-American-British (FAB) group proposed a classification system for MDS that consists of 5 subgroups, based on the percentage of blast cells in the peripheral blood and bone marrow, presence of ringed sideroblasts in the bone marrow, and monocyte count in the peripheral blood. The 5 subgroups are refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess of blasts (RAEB), refractory anemia with excess of blasts in transformation (RAEB-t) and chronic myelomonocytic leukemia (CMML). Subsequently, the new WHO classification was proposed which omitted RAEB-t and recommended that all patients that have > 20% blast count in the bone marrow be diagnosed as having acute myeloid leukemia (AML) (6).

Clonal cytogenetic abnormalities are found at diagnosis in 50-60% of patients with de novo MDS and 75-85% of secondary MDS. Common cytogenetic abnormalities are deletion of the long arm of chromosome 5 (5q-), monosomy of chromosome 7, trisomy of chromosome 8, deletion of the long arm of chromosome 5 (20q-) and loss of Y chromosome. The karyotype is one of the most significant prognostic markers in MDS. Steidl et al conducted a retrospective analysis in 529 patients with MDS to address the question of how many metaphases need to be analyzed to detect even small cell clones (5). They found a statistically significant difference of the frequency of normal karyotypes in the patient group with 19 or less analyzed metaphases compared to the group with 20 or more metaphases analyzed (56% versus 47%, $p = 0.041$). It was also shown that especially when less than 15 metaphases are analyzed the frequency of abnormal karyotypes declines dramatically. It has been shown that the karyotype alone is a strong and independent predictor for outcome defined by mean survival times and risk of transformation to acute leukemia. In a study by Sole et al., patients with normal karyotypes had a significantly higher mean survival time (4.15 years) in contrast to patients showing abnormal karyotypes (1.25 years) regardless of the particular aberration (7). Furthermore, detecting karyotype abnormalities is crucial for follow-up examinations.

The FAB/WHO classification has been used most frequently to evaluate survival and risk for AML transformation. The WHO classification defines the 5q syndrome as a separate entity (8). An International MDS Risk Analysis Workshop proposed a system that combines clinical, morphologic and cytogenetic data to generate a prognostic system called the International Prognostic Scoring System (IPSS) (9). Scores are noted based on the percentage bone marrow blasts, karyotype and cytopenias. Based on the scores, 4 risk groups are identified with distinctive subgroups evolution to AML; low risk, 9.4 years, intermediate-1, 3.3 years, intermediate-2, 1.1 years and high risk, 0.2 year. Patients were also separated into distinctive risk groups for median survival: low risk, 5.7 years, intermediate-1, 3.5 years, intermediate-2, 1.2 years and high risk, 0.4 year.

Allogeneic stem cell transplantation is the only potentially curative therapy but available only to younger patients (10). Azacitidine was approved by the FDA in 2004 for the treatment of all subtypes of MDS (11). Therapy includes supportive care that consists of RBC or platelet transfusions or the use of growth factors (erythropoietin, G-CSF, GM-CSF) (12).

The 5q- Syndrome

The 5q- syndrome is a distinct hematological disorder with typical laboratory, morphological, cytogenetic, molecular, and prognostic features. It is defined as a myelodysplastic syndrome with a medullary blast count <5% and an isolated interstitial deletion of the long arm of chromosome 5, including bands q31-q33.

Giagounidis et al. analyzed data in 60 patients with the 5q- syndrome as defined by WHO followed over a period of up to 28 years (13). There was a female preponderance with a male to female ratio of 1:1.5. Median age was 66.8 years (range, 32 – 83 years). Most patients eventually become transfusion dependent. The time between diagnosis and first transfusion varied between a few months and several years. Anemia is usually macrocytic and combined with low reticulocyte counts and high erythropoietin levels. Most of the patients present with refractory anemia, but refractory anemia with ringed sideroblasts also occur. Three types of cytogenetic deletion are most prevalent: del (5) (q13q33), del (5) (q13q31) and del (5) (q22q33). The molecular basis of this disease has not yet been fully elucidated, but there is evidence that a commonly deleted region of 1.5 Mb harbors one or several tumor suppressor genes, the loss of which is the basic event leading to disease activity. The 5q deletion has been demonstrated in very early hematopoietic precursors, including CD34+ CD133+ and CD34+CD38-Thyl+ cells.

The median prospective survival was 107 months for a median follow-up of 53 months, and a low probability (10%) of transformation to AML. An increase of the medullary blast count to ≥5% or the addition of one karyotypic anomaly severely reduced median overall survival (23 to 47 months). Development of leukemia accounted for 25% of deaths. Other causes of death were heart failure, bleeding and infection. Data of 76 consecutive patients with myelodysplastic syndrome (MDS) and isolated del (5q) (n=66) or del(5q) plus one additional chromosomal abnormality (n=10) were reported (14). The projected median survival of patients with isolated del (5q) was 146 months for a median follow-up of 67 months. Patients with an increased medullary blast count and those with an additional chromosomal abnormality have a significantly shorter overall survival (24 and 45 months, respectively) than patients with isolated del (5q). Deaths occurred primarily due to transformation into acute leukemia, infection, or cardiac failure.

Patients with del (5q) as the sole karyotypic abnormality have previously been well defined as having a relatively good prognosis, whereas poor prognoses were found when it was combined with other anomalies (9). Treatments with a variety of agents have met with poor success. Not every patient with 5q- has the syndrome with 5q deletion as the sole karyotypic abnormality and its associated good prognosis.

8.7 Postmarketing Risk Management Plan

The sponsor proposed the RevAssist® program to the FDA for use with lenalidomide. This program will be for minimization of fetal exposure and the management of potential cytopenias. Pregnancy tests will be done prior to each prescription in women of child-bearing age.

The distribution of lenalidomide will be limited through multiple specialty pharmacies. The specialty pharmacies will be required to contact patients who have been prescribed lenalidomide prior to shipping the prescription. During this phone contact, patients will be educated on the unknown potential risk of exposure to a human fetus, the signs and symptoms of cytopenias, and the need for routine blood tests.

Reviewer's Comment:

1. *Since lenalidomide is a thalidomide analogue and due to the inadequacy of the reproductive safety assessment, FDA has a concern regarding the risk of teratogenicity and the potential fetal exposure to lenalidomide. An adequate toxicology study is necessary to determine whether or not lenalidomide is teratogenic. Until the results of the Toxicology study are known, a risk management plan such as the S.T.E.P.S. program for thalidomide should be implemented.*
2. *The high incidence of neutropenias and thrombocytopenias necessitating dose modifications is also of concern. Risk management should include close monitoring of cytopenias.*

8.8 Other Relevant Materials

N/A

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9 OVERALL ASSESSMENT

9.1 Conclusions

The NDA submission consisted of two single-arm, phase 2 clinical studies relevant to the proposed indication, one very small. The patient population consisted of patients with transfusion-dependent anemia due to low or intermediate-1 risk MDS associated with del 5q cytogenetic abnormalities with or without additional cytogenetic abnormalities. The transfusion entry criterion is based on the RBC units transfused in the 8 weeks prior to start of study drug. The median number units of RBC transfused was six. The main study enrolled 148 patients using oral lenalidomide as a single agent given in 2 dose regimens, 10 mg daily or 10 mg for 21 days in a 28-day cycle.

The primary endpoint was the determination of RBC transfusion independence. A rolling 56 day (8 week) transfusion free period was used for transfusion independence response. The RBC transfusion independence response of 67% (99/148) was seen with ≥ 1.0 g/dL increase in hemoglobin. These responses lasted for a minimum of 8 weeks with a median duration of transfusion independence in responders was 52 weeks. Major cytogenetic responses were seen in 43% (52/120) patients in whom follow-up bone marrows were present. The study was not designed or powered to prospectively compare the efficacy of the 2 lenalidomide dosing regimens.

The supportive study had 10 evaluable patients supporting the proposed indication.

FDA performed an analysis in those patients who met the major eligibility criteria. Ninety six patients had transfusion-dependent anemia due to a diagnosis of low or intermediate-1 risk MDS associated with a del 5q chromosomal abnormality with or without additional cytogenetic abnormalities. The results were consistent with the ITT population.

The demonstration of the clinical benefit of RBC transfusion independence, although substantial, is based mainly on one single-arm, multicenter trial. A randomized controlled trial is ongoing at present and the sponsor has a Phase IV commitment.

All MDS patients, those with 5q deletion (*del 5q*) and those without 5q deletion (*non-del 5q*), had adverse events during treatment with lenalidomide. In absence of a best supportive care control arm, it is not possible to assign adverse events to lenalidomide instead of MDS. The most common reported adverse events were neutropenia and thrombocytopenia. They were also the most common grade 3 or 4 adverse events, the most common serious adverse events (except for pneumonia), the most common events leading to discontinuations from studies, and the most common events leading to dose interruptions and dose reductions. Less frequently reported were rashes, infectious events, fatigue, bleeding events, gastrointestinal events, and others. A very high percentage (about 80%) of patients reported grade 3 or 4 events. There was a markedly different adverse event profile in the *del 5q* population from that in *non-del 5q* population. The *del 5q* patients had approximately twice as high frequencies of neutropenia and of thrombocytopenia (all grades and grades 3 – 4 in both cases), a one-third higher frequency of

infections, and higher incidences of bleeding and of venous thromboembolism than *non-del 5q* patients.

The increased sensitivity to lenalidomide in the *del 5q* population may account for the much greater need for dose reductions and dose interruption of the 10 mg/day starting dose (administered by either of the two schedules) in the *del 5q* population compared to *non-del 5q* population (80% of patients vs. 47% of patients). These data suggest that the starting dose of lenalidomide is too high for the *del 5q* population, and that careful monitoring is required for dose adjustment. Because neutropenia and thrombocytopenia can occur rapidly and unpredictably in some cases, and because the rate of recovery can be delayed, lenalidomide should be administered only during the period during which it maintains patients free of transfusions. In cases of patients who do not respond to lenalidomide treatment, the treatment should be discontinued once a response is unlikely to occur (about 16 weeks).

Patients with renal impairment were excluded from the studies. Because lenalidomide is mainly excreted by the kidney, renal function should be carefully monitored to avoid excess toxicity.

Until definitive toxicology studies have determined that lenalidomide, unlike thalidomide, does not pose risk as a human teratogen, the S.T.E.P.S.program should be implemented.

The benefit vs. risk profile of lenalidomide treatment in the del 5q population is substantial; the incidence of severe adverse events, some life-threatening, is high. Therefore, a balanced medical evaluation is required before prescribing lenalidomide followed by careful monitoring and dose adjustment.

A Black Box Warning should be placed in the label to include the unknown pregnancy risk and the recommendation to prevent fetal exposure and should also include weekly monitoring of neutropenias and thrombocytopenias.

9.2 Recommendation on Regulatory Action

Lenalidomide (Revlimid®) should receive regular approval for the treatment of patients with transfusion dependent anemia due to low or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Lenalidomide was brought before the Oncology Drug Advisory Committee on Sept 14, 2005. The ODAC committee agreed that the benefit versus risk analysis warranted approval.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Due to the inadequacy of the reproductive safety assessment, FDA has a concern regarding the risk of teratogenicity and the potential fetal exposure to lenalidomide. Of concern is also the

high incidence and dose modification due to neutropenias and thrombocytopenias. The sponsor should implement a risk management activity similar to the S.T.E.P.S. program until toxicology studies determine that lenalidomide is not a teratogen in species that predict human teratogenicity.

A Black Box Warning should be placed in the label to include the unknown pregnancy risk and the recommendation to prevent fetal exposure and should also include weekly monitoring of neutropenias and thrombocytopenias.

9.3.2 Required Phase 4 Commitments

Not applicable.

9.3.3 Other Phase 4 Requests

Celgene has a planned phase 3 study ongoing in Europe in MDS patients with a 5q deletion. It is a randomized, double-blind, placebo-controlled 3-arm study evaluating a lower dose of 5 mg daily versus 10 mg syncopated. The primary endpoint is RBC transfusion independence for ≥26 weeks. At the time of the advisory committee meeting, 20 patients had been enrolled.

The safety of lenalidomide in patients with renal impairment should be determined.

Reproductive safety assessments in this drug was inadequate as reviewed by the Pharmacology/toxicology team. Celgene is required to conduct further tests to adequately assess the risk of teratogenicity.

9.4 Labeling Review

In process.

9.5 Comments to Applicant

In process.

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10 APPENDICES

10.1 Review of Individual Study Reports: Study CC-5013-MDS-002

10.1.1 Study Design

This study was a multi-center, single-arm, open-label study of oral CC-5013 monotherapy administered at a dose of 10 mg daily on Days 1- 28 every 28 days (28- day cycles) to RBC transfusion- dependent subjects with low or intermediate-1 risk MDS who do not have a del (5q31- 33) cytogenetic abnormality.

Protocol Title: A multi- center, single- arm, open- label study of the efficacy and safety of cc-5013 monotherapy in red blood cell (RBC) transfusion-dependent subjects with myelodysplastic syndromes.

Study Objectives
Primary: To evaluate the efficacy of CC-5013 treatments to achieve hematopoietic improvement in subjects with low or intermediate-1 risk International Prognostic Scoring System (IPSS) myelodysplastic syndromes (MDS) who do not have a del (5q31- 33) cytogenetic abnormality.

Secondary: To evaluate the safety of CC- 5013 treatments in subjects with low or intermediate- 1 risk myelodysplastic syndromes who do not have a del (5q31-33) cytogenetic abnormality.

Central laboratory or local laboratory assessments were used to determine subject eligibility during screening. Local bone marrow and cytogenetic assessments determined subject eligibility during screening.

Bone marrow biopsy/ aspirate, peripheral blood smear slides and pathology reports from all subjects were sent to an independent hematologic reviewer for pathologic review. All screening/ baseline bone marrow, peripheral blood smear slides, and pathology reports were reviewed to confirm the diagnosis of MDS, and the French-British-American (FAB) classification of MDS subtype. On-study and discontinuation bone marrow biopsy/ aspirate, peripheral blood smear slides and pathology reports from subjects who achieve any MDS response were reviewed for bone marrow response by the independent hematologic reviewer. This review was not required to define eligibility during the screening period for individual subjects.

Copies of cytogenetic reports and glossy prints from all subjects were sent to an independent reviewer for cytogenetic review. All screening/baseline cytogenetic reports and glossy prints were reviewed to confirm cytogenetic eligibility. On-study and discontinuation cytogenetics from all subjects were reviewed for cytogenetic response by the independent cytogenetic reviewer. This review was not required to define eligibility during the screening period for individual subjects.

A data monitoring committee (DMC) that comprised a statistician, safety monitor, and clinician from Celgene Corporation as well as an external central hematologic reviewer, reviewed ongoing safety and efficacy data to assess benefit-to-risk considerations throughout the study.

Study Endpoints
Response endpoints are based on IWG Criteria:
Primary: RBC transfusion independence
Secondary endpoints included >50 % decrease in RBC transfusion requirements; Change of hemoglobin concentration from baseline; Safety (type, frequency, severity, and relationship of adverse events to CC- 5013); Platelet response; Neutrophil response ; Bone marrow response; Cytogenetic response; Duration of response.

Dosing Regimens: Oral CC- 5013 10 mg (two 5 mg capsules) daily on Days 1- 28 every 28 days for up to 24 cycles. Subjects who have been started on the syncopated regimen (Days 1- 21 every 28 days) and have not experienced dose-limiting toxicity may be switched to an every day dose of 10 mg.

Study Population
Inclusion Criteria:

1. Must understand and voluntarily sign an informed consent form.
2. Age ≥ 18 years at the time of signing the informed consent form.
3. Must be able to adhere to the study visit schedule and other protocol requirements.
4. Diagnosis of low or intermediate-1 risk IPSS MDS without an abnormality of chromosome 5 involving a deletion between bands q31 and q33.
5. Red blood cell (RBC) transfusion-dependent anemia defined as having received ≥ 2 units of RBCs within 8 weeks of the first day of study drug treatment.
6. Eastern Cooperative Oncology Group (ECOG) (Appendix IV) performance status score of 0, 1, or 2.
7. Women of childbearing potential (WCBP) must have a negative serum or urine pregnancy test within 7 days of starting study drug. In addition, sexually active WCBP must agree to use adequate contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) while on study drug. WCBP must agree to have pregnancy tests every 4 weeks while on study drug.

Exclusion Criteria:

1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form or that will place the subject at unacceptable risk if he/ she were to participate in the study or confound the ability to interpret the data.
2. Pregnant or lactating females.
3. Prior therapy with CC- 5013.
4. Inability to aspirate bone marrow (dry tap).
5. Proliferative (WBC ≥ 12,000/ uL) chronic myelomonocytic leukemia (CMML).
6. An abnormality of chromosome 5 involving a deletion between bands q31 and q33.

7. Any of the following lab abnormalities:
    - Absolute neutrophil count (ANC) <500 cells/ mm^3 (0.5×10^9/L).
    - Platelet count <50,000/ mm^3 (50×10^9/ L).
    - Serum creatinine >2.5 mg/dL (221 μmol/ L).
    - Serum SGOT/ AST or SGPT/ ALT >3.0 x upper limit of normal (ULN).
    - Serum direct bilirubin >2.0 mg/dL (34 μmol/ L).
8. Prior ≥grade 3 National Cancer Institute (NCI) Common Toxicity Criteria (CTC) allergic reaction/hypersensitivity to thalidomide.
9. Prior ≥grade 3 NCI CTC rash or any desquamation (blistering) while taking thalidomide.
10. Clinically significant anemia due to factors such as iron, B12 or folate deficiencies, autoimmune or hereditary hemolysis or gastrointestinal bleeding (if a marrow aspirate is not evaluable for storage iron, transferrin saturation must be >20 % and serum ferritin not less than 50ng/mL).
11. Use of hematopoietic growth factors within 7 days of the first day of study drug treatment.
12. Chronic use (>2 weeks) of greater than physiologic doses of a corticosteroids agent dose equivalent to >10 mg/day of prednisone) within 28 days of the first day of study drug treatment.
13. Use of experimental or standard drugs (i. e. chemotherapeutic, immunosuppressive, and cytoprotective agents) for the treatment of MDS within 28 days of the first day of study drug treatment.
14. Prior history of malignancy other than MDS (except basal cell or squamous cell carcinoma or carcinoma in situ of the cervix or breast) unless the subject has been free of disease for ≥3 years.
15. Use of any other experimental therapy within 28 days of the first day of study drug treatment.

The sample size was based on a single-stage design to test the null hypothesis that the true RBC transfusion- independent rate in low or intermediate-1 risk MDS subjects without a del (5q31- 33) cytogenetic abnormality was ≤15% versus the alternative hypothesis that the true rate is ≥25%. The sample size and corresponding decision rule were selected so that the probability of rejecting the null hypothesis is less than 0.025 if the null hypothesis is true and the probability of rejecting the alternative hypothesis is less than 0.20 if the alternative hypothesis is true. This criterion requires that the two-sided 95% confidence interval (normal approximation) for the percentage of subjects who become RBC transfusion- independent during the study lies above 15%. A sample size of 114 evaluable subjects is sufficient to meet these requirements. If it is assumed that 20% of the subjects are not evaluable then the total sample size becomes 136 subjects.

Primary efficacy analyses will be performed on the modified intent-to-treat population that includes all subjects with a confirmed diagnosis of MDS, who have documented need for transfusions during the baseline period and who took study medication.

Kaplan-Meier estimates will be provided for the duration of response.

Adverse events, vital sign measurements, clinical laboratory information, concomitant medications, and ECG interpretations, will be tabulated and summarized. All toxicities will be summarized by frequency, severity grade based on the NCI CTC and relationship to study drug.

Amendments
Amendment #1(September 12, 2003)
increased the treatment period from 6 cycles to 24 cycles; changed the dosing regimen from 10 mg daily on days 1-21 (syncopated dose) to 10 mg daily on days 1-28; changed to allow use of local cytogenetic testing results; added a central cytogenetic reviewer; excluded subjects from whom a bone marrow aspirate cannot be obtained (dry tap) at screening / baseline; excluded subjects with proliferative (WBC ≥ 12,000/ uL) CMML; changed exclusion criteria for bilirubin from total to direct; modified platelet count requirement for re-starting study drug following an interruption due to thrombocytopenia from ≥50,000/uL to ≥ 30,000/uL (without evidence of hemostatic failure); changed dose modification for hyperthyroidism/hypothyroidism from interrupt the dose and contact Celgene to omit CC-5013 for the remainder of the cycle, assess etiology, initiate appropriate therapy, and re- start at the next cycle and the next lower dose level; added interim data monitoring plan; modified the "Modified Intent to Treat Population" to include " received at least two transfusions in each of the eight week periods during the 16 week pre-treatment period (in addition, subjects must not have been transfusion- free for any 56 consecutive days during the 16 week pre-treatment period").

Amendment #2 (January 13, 2004)
added the requirement to perform a complete blood cell count (CBC) weekly during the first 8 weeks of therapy to monitor for early hematologic AEs; provided additional dose modification guidelines for neutropenia and thrombocytopenia that occurred during the first 4 weeks of therapy; clarified the procedures for the central cytogenetic review; expanded the secondary efficacy measures to include the change from baseline in Hgb concentration; and allowed the use of a value from a local laboratory if the value from the central laboratory was missing or invalid.

Reviewer's Comment:

1. *There was no protocol amendment submitted to the FDA when the number of patients in the study was increased from 136 to 215. There was no modified statistical analysis plan and statistical methods for the increase in the sample size.*

10.1.2 Datasets Analyzed

The sponsor analyzed data in the MITT population (i.e., those subjects with low or intermediate-1 risk MDS without a del 5q cytogenetic abnormality, as confirmed by Central Review, and for whom documented evidence existed that there was no 56-day, RBC transfusion-free period during the immediate 16 weeks prior to the start of study therapy) and the per-protocol and efficacy evaluable population.

FDA reviewed the data in the ITT population. The table below summarizes the number of subjects who were included in the efficacy analyses.

Table 69 Population Analyses (Applicant's Table)

Analysis Populations	10mg Cont. n (%)	10mg Sync. n (%)	Overall n (%)
Intent-to-treat (ITT) [a]	100 (100.0)	115 (100.0)	215 (100.0)
Safety [b]	100 (100.0)	115 (100.0)	215 (100.0)
Per Protocol (PP) [c]	77 (77.0)	89 (77.4)	166 (77.2)
Modified intent-to-treat (MITT) [d]	55 (55.0)	63 (54.8)	118 (54.9)
Efficacy Evaluable (EE) [e]	26 (26.0)	56 (48.7)	82 (38.1)

Data Source: Table 14.1.1

[a] The ITT population includes all enrolled subjects.
[b] The safety population includes all subjects who took at least one dose of study drug.
[c] The PP population includes all safety subjects who were confirmed by central reviewers to have a diagnosis of low- or intermediate-1 risk MDS associated with a del (5q31-33) cytogenetic abnormality and who received at least 2 units of PRBC transfusion during the 56 days prior to starting study medication.
[d] The MITT population includes all PP subjects who received at least two transfusions in each of the eight week periods during the 16 week pre-treatment period and were not transfusion-free for any 56 consecutive days during the 16 week pre-treatment period.
[e] The EE population includes all MITT subjects who were in the study for at least 168 days or discontinued for any reason.

Source: CC-5013-MDS-002, Table 13

10.1.3 Demographic and Baseline Disease Characteristics

FDA agreed with the sponsor's ITT analysis. FDA noted that there were 2 patients (Patient ID 0312006 and 0392003) who had a karyotypic analysis with 5q deletion, one associated with other abnormalities. Of these, one patient was on the 10 mg syncopated dose and the other on the 10 mg continuous dose. There was no diagnosis of MDS in the patient 0392003 and there was no IPSS risk category assigned.

Table 70 Demographics and Baseline Disease Characteristics ITT Population (Applicant's Table)

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	10mg Cont. (N=100)	10mg Sync. (N=115)	Overall (N=215)
Age (years)			
n	100	115	215
Mean	72.6	70.1	71.2
SD	10.46	9.96	10.25
Median	74.0	71.0	72.0
Min, Max	27.0, 94.0	35.0, 92.0	27.0, 94.0
Age distribution	n (%)	n (%)	n (%)
<=65	20 (20.0)	31 (27.0)	51 (23.7)
>65	80 (80.0)	84 (73.0)	164 (76.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Sex	n (%)	n (%)	n (%)
Male	68 (68.0)	70 (60.9)	138 (64.2)
Female	32 (32.0)	45 (39.1)	77 (35.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Race [1]	n (%)	n (%)	n (%)
White	93 (93.0)	109 (94.8)	202 (94.0)
Black	5 (5.0)	2 (1.7)	7 (3.3)
Hispanic	1 (1.0)	0 (0.0)	1 (0.5)
Asian/Pacific Islander	1 (1.0)	2 (1.7)	3 (1.4)
American Indian/Alaska Native	0 (0.0)	2 (1.7)	2 (0.9)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Height (inches)			
n	97	97	194
Mean	67.1	66.7	66.9
SD	3.96	3.48	3.73
Median	67.5	67.0	67.0
Min, Max	56.0, 75.0	60.0, 76.0	56.0, 76.0
Weight (lbs)			
n	97	112	209
Mean	173.2	173.7	173.5
SD	34.42	35.61	34.98
Median	173.0	171.5	172.0
Min, Max	103.2, 282.0	87.0, 260.5	87.0, 282.0
Duration of MDS (years)			
n	99	115	214
Mean	2.9	2.7	2.8
SD	3.61	3.76	3.69
Median	2.6	1.8	2.2
Min, Max	0.0, 11.5	0.0, 12.9	0.0, 12.9
Eq(-) (31-33) Chromosomal Abnormality	n (%)	n (%)	n (%)
Yes	1 (1.0)	1 (0.9)	2 (0.9)
No	92 (92.0)	112 (97.4)	204 (94.9)
Missing	7 (7.0)	2 (1.7)	9 (4.2)
IPSS Score(based on Central Review)[2]	n (%)	n (%)	n (%)
Low (0)	40 (40.0)	53 (46.1)	93 (43.3)
Intermediate-1 (0.5-1.0)	37 (37.0)	39 (33.9)	76 (35.3)
Intermediate-2 (1.5-2.0)	2 (2.0)	4 (3.5)	6 (2.8)
High (>=2.5)	0 (0.0)	2 (1.7)	2 (0.9)
Missing	21 (21.0)	17 (14.8)	38 (17.7)
ECOG Performance Status[3]	n (%)	n (%)	n (%)
0	44 (44.0)	44 (38.3)	88 (40.9)
1	50 (50.0)	68 (59.1)	118 (54.9)
2	3 (3.0)	2 (1.7)	5 (2.3)
Missing	2 (2.0)	1 (0.9)	3 (1.4)

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	10mg Cont (N=100)		10mg Sync. (N=115)		Overall (N=215)	
FAB Classification[4]	n	(%)	n	(%)	n	(%)
RA	32	(32.0)	44	(38.3)	76	(35.3)
RARS	54	(54.0)	51	(44.3)	105	(48.8)
RAEB	8	(8.0)	15	(13.0)	23	(10.7)
CMML	6	(6.0)	4	(3.5)	10	(4.7)
RAEB-T	0	(0.0)	0	(0.0)	0	(0.0)
Missing	0	(0.0)	1	(0.9)	1	(0.5)
FAB Classification[4] from Central Hematologic Review	n	(%)	n	(%)	n	(%)
RA	18	(18.0)	22	(19.1)	40	(18.6)
RARS	42	(42.0)	44	(38.3)	86	(40.0)
RA/RARS	1	(1.0)	6	(5.2)	7	(3.3)
RAEB	9	(9.0)	15	(13.0)	24	(11.2)
CMML	11	(11.0)	9	(7.8)	20	(9.3)
RA/CMML	0	(0.0)	1	(0.9)	1	(0.5)
RARS/CMML	1	(1.0)	0	(0.0)	1	(0.5)
RAEB-T	2	(2.0)	3	(2.6)	5	(2.3)
Acute Leukemia	0	(0.0)	1	(0.9)	1	(0.5)
Not diagnostic of MDS	2	(2.0)	1	(0.9)	3	(1.4)
Unable to classify	9	(9.0)	11	(9.6)	20	(9.3)
Missing	5	(5.0)	2	(1.7)	7	(3.3)

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[1] Percents may add up to more than 100% since subjects were allowed to select more than one Race.
[2] IPSS Score = Sum of Marrow blast + Karyotype + Cytopenia Score
[3] Eastern Cooperative Oncology Group Performance Status: 0=Fully active, no restrictions (Karnofsky 90-100); 1=Restricted but ambulatory and capable of light work (Karnofsky 70-80); 2=Ambulatory and capable of self-care but unable to work (Karnofsky 50-60).
[4] French-American-British (FAB) classification of MDS. See Appendix II of the protocol for the classification criteria.
Program path: \\nasdbvm\data\prd\Projects\CC-5013\CC-5013-MDS-002\programs\tables\demog.sas

Source: CC-5013-MDS-002, Table 14.1.4.1

10.1.4 Primary Efficacy Analysis

RBC Transfusion Independence

The RBC transfusion independence rate was 21.4% (46/215) in the ITT population.

FDA observed that among the 2 patients with the 5q deletion karyotype, one achieved a major response while the other had no response.

Among the responders, patient 0242018 did not have a transfusion history; patient 0102001 did not have an IPSS classification or a diagnosis of MDS at baseline and 0152005 did not have a classification of IPSS.

Table 71 Transfusion Independence ITT Population (Applicant's Table)

IPSS Risk Category[2] at Baseline	Statistic	10mg Cont.	10mg Sync.	Overall
Overall	Number of Subjects	100	115	215
	Number Transfusion Independent	18	28	46
	% Transfusion Independent	(18.0)	(24.3)	(21.4)
	Exact 95% CI	[11.0, 26.9]	[16.8, 33.2]	[16.1, 27.5]
Low+Int-1	Number of Subjects	77	92	169
	Number Transfusion Independent	17	27	44
	% Transfusion Independent	(22.1)	(29.3)	(26.0)
	Exact 95% CI	[13.4, 33.0]	[20.3, 39.8]	[19.6, 33.3]
Low	Number of Subjects	40	53	93
	Number Transfusion Independent	10	15	25
	% Transfusion Independent	(25.0)	(28.3)	(26.9)
	Exact 95% CI	[12.7, 41.2]	[16.8, 42.3]	[18.2, 37.1]
Int-1	Number of Subjects	37	39	76
	Number Transfusion Independent	7	12	19
	% Transfusion Independent	(18.9)	(30.8)	(25.0)
	Exact 95% CI	[8.0, 35.2]	[17.0, 47.6]	[15.8, 36.3]
Int-2+High	Number of Subjects	2	6	8
	Number Transfusion Independent	0	0	0
	% Transfusion Independent	(0.0)	(0.0)	(0.0)
	Exact 95% CI	[0.0, 84.2]	[0.0, 45.9]	[0.0, 36.9]
Int-2	Number of Subjects	2	4	6
	Number Transfusion Independent	0	0	0
	% Transfusion Independent	(0.0)	(0.0)	(0.0)
	Exact 95% CI	[0.0, 84.2]	[0.0, 60.2]	[0.0, 45.9]
High	Number of Subjects	0	2	2
	Number Transfusion Independent	0	0	0
	% Transfusion Independent		(0.0)	(0.0)
	Exact 95% CI		[0.0, 84.2]	[0.0, 84.2]

[1] The absence of the intravenous infusion of any RBC transfusion during any consecutive rolling 56 days during the treatment period and an increase in hemoglobin of at least 1 g/dL from the minimum during the screening/baseline period to the maximum during the transfusion-independent period, excluding the first 30 days after the last transfusion before the transfusion-free period
[2] IPSS Risk Category: Low (combined score = 0), Intermediate-1 (combined score = 0.5 to 1.0), Intermediate-2 (combined score = 1.5 to 2.0), High (combined score >= 2.5); Combined score = (Marrow blast score + Karyotype score + Cytopenia score)
Program path: \\sasdbvm\data\prd\Projects\CC-5013\CC-5013-MDS-002\programs\tables\transind-itt.sas

Source: CC-5013-MDS-002, Table 14.2.1.1

10.1.5 Secondary Efficacy Analysis

Duration of Response

Of the 46 subjects in the ITT population who achieved RBC transfusion independence, 33 (71.7%) remained transfusion independent, and 13 (28.3%) had relapsed (i.e., required a transfusion after a response). The median duration of RBC transfusion independence has not been reached for the 46 responders in the ITT population; however, the duration of RBC-transfusion independence was at least 16 weeks in 32 of the responders in the ITT population.

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The table below provides a categorization of the duration of response observed prior to 15 June 2004, together with means and medians for the duration of response observed by the 15 June 2004 cutoff (and not taking censoring into account, i.e., for subjects still responding, the duration of response was measured to the date that the last transfusion history was obtained or 15 June 2004 whichever was earlier). These represent the lowest outcome estimates that would be obtained if all subjects required a transfusion immediately after the last transfusion history was obtained (or 15 June 2004).

Table 72 Duration of Response ITT Population (Applicant's Table)

Duration of transfusion independence response (weeks)	10mg Cont. (N=100)	10mg Sync. (N=115)	Overall (N=215)
Kaplan-Meier estimates			
Subjects with Transfusion Independence Response	18	28	46
Subjects who progressed (had a transfusion after response)	5 (27.8)	8 (28.6)	13 (28.3)
Subjects who maintained transfusion independence (censored[2])	13 (72.2)	20 (71.4)	33 (71.7)
Median	NE	NE	NE
95% confidence interval	NE	[21.3, NE]	NE
Summary statistics			
Mean	17.1	22.2	20.2
SD	7.15	8.09	8.05
Median	15.9	20.9	18.9
Min, Max	8.0, 32.4	8.3, 35.9+	8.0, 35.9+
Duration of response at least 4 weeks	18 (100.0)	28 (100.0)	46 (100.0)
Duration of response at least 8 weeks	18 (100.0)	28 (100.0)	46 (100.0)
Duration of response at least 12 weeks	12 (66.7)	25 (89.3)	37 (80.4)
Duration of response at least 16 weeks	9 (50.0)	23 (82.1)	32 (69.6)
Duration of response at least 20 weeks	5 (27.8)	16 (57.1)	21 (45.7)
Duration of response at least 24 weeks	4 (22.2)	11 (39.3)	15 (32.6)

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[1] Measured from the first of the consecutive 56 days during which the subject was free of RBC transfusions to the date of the first RBC transfusion after this period.
[2] Duration of response was censored at the date of last visit for subjects who maintained transfusion independence.
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Source: CC-5013-MDS-002, Table 14.2.3.1

Change in Hemoglobin from Baseline to Maximum Value during Response Period

The median increase in hemoglobin (Hgb) level from baseline to maximum Hgb level during RBC-transfusion independence was 3.0 g/dL (range, 1.0-8.3 g/dL) for the 46 responders in the

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ITT population. The table below summarizes the change from baseline in Hgb for the patients in the ITT population who became RBC transfusion independent.

Table 73 Change from Baseline in Hgb for Patients who became RBC Transfusion Independent ITT Population

		10mg Cont. (N=18)			10mg Sync. (N=28)			Overall (N=46)		
	Stat	BL	Max	Change	BL	Max	Change	BL	Max	Change
Hemoglobin (g/dL)	N	18	19	18	28	29	28	46	48	46
	Mean	8.0	11.4	3.4	8.1	11.7	3.7	8.0	11.6	3.6
	SD	0.83	1.86	1.75	1.07	2.06	2.12	0.97	1.97	1.97
	Median	8.0	11.1	3.0	8.1	11.4	3.1	8.0	11.1	3.0
	Min	6.2	9.1	1.5	6.1	7.3	1.0	6.1	7.3	1.0
	Max	9.1	15.4	7.5	10.6	15.0	8.3	10.6	15.4	8.3

[1] Response period is defined as the time from 30 days after the last transfusion prior to achieving transfusion independence to the next transfusion or to the last assessment for subjects who did not receive a subsequent transfusion during the study period.
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Data source: CENLAB D RESP Run date: 03FEB2005 DB extract date: 31JAN05:20:39:22

Source: CC-5013-MDS-002, Table 14.2.4.1

Decrease of ≥50% in RBC Transfusion Requirements

Overall, 37.7% (81/215) of the subjects in the ITT population achieved a ≥50% decrease in their pretreatment RBC transfusion requirements during lenalidomide therapy. The table below summarizes the frequency of subjects in the ITT population who achieved a ≥50% decrease in RBC transfusions.

Table 74 Patients with ≥ 50% Decrease in RBC Transfusions ITT Population (Applicant's Table)

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IPSS Risk Category[2] at Baseline	Statistic	10mg Cont.	10mg Sync.	Overall
Overall	Number of Subjects	100	115	215
	Number of Responders[1]	31	50	81
	% Responders	(31.0)	(43.5)	(37.7)
	Exact 95% CI	[22.1, 41.0]	[34.3, 53.0]	[31.2, 44.5]
Low+Int-1	Number of Subjects	77	92	169
	Number of Responders[1]	28	47	75
	% Responders	(36.4)	(51.1)	(44.4)
	Exact 95% CI	[25.7, 48.1]	[40.4, 61.7]	[36.8, 52.2]
Low	Number of Subjects	40	53	93
	Number of Responders[1]	14	29	43
	% Responders	(35.0)	(54.7)	(46.2)
	Exact 95% CI	[20.6, 51.7]	[40.4, 68.4]	[35.8, 56.9]
Int-1	Number of Subjects	37	39	76
	Number of Responders[1]	14	18	32
	% Responders	(37.8)	(46.2)	(42.1)
	Exact 95% CI	[22.5, 55.2]	[30.1, 62.8]	[30.9, 54.0]
Int-2+High	Number of Subjects	2	6	8
	Number of Responders[1]	0	1	1
	% Responders	(0.0)	(16.7)	(12.5)
	Exact 95% CI	[0.0, 84.2]	[0.4, 64.1]	[0.3, 52.7]
Int-2	Number of Subjects	2	4	6
	Number of Responders[1]	0	0	0
	% Responders	(0.0)	(0.0)	(0.0)
	Exact 95% CI	[0.0, 84.2]	[0.0, 60.2]	[0.0, 45.9]
High	Number of Subjects	0	2	2
	Number of Responders[1]	0	1	1
	% Responders		(50.0)	(50.0)
	Exact 95% CI		[1.3, 98.7]	[1.3, 98.7]

[1] At least a 50% reduction in the number of transfusions reflected over any 56-day rolling period during the study as compared to the 56-day period prior to start of study medication.
[2] IPSS Risk Category: Low (combined score = 0), Intermediate-1 (combined score = 0.5 to 1.0), Intermediate-2 (combined score = 1.5 to 2.0), High (combined score >= 2.5); Combined score = (Marrow blast score + Karyotype score + Cytopenia score)
Program path: \\sasdbvm\data\prd\Projects\CC-5013\CC-5013-MDS-002\programs\tables\resp-50-itt.sas

Source: CC-5013-MDS-002, Table 14.2.1.5

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Platelet Response, Neutrophil Response, Cytogenetic Response and Bone Marrow Effects

The major platelet response rate was 8.0% (4/50) among the evaluable subjects in the ITT population. No major or minor neutrophil responses were observed among the evaluable subjects in the ITT population.

Adequate standard cytogenetic studies (at least 20 evaluable metaphases) of the MDS clone were available for Central Review at baseline for 178 (82.8%) of 215 subjects (studies were inadequate in 31 cases and missing in 6 cases). Among the 178 subjects who had evaluable baseline cytogenetic studies, 137 (77%) had an MDS clone with a normal karyotype and 41 (23%) had an MDS clone with an abnormal karyotype. The abnormal karyotypes included the following cytogenetic abnormalities: 1) trisomy 8 (n= 9); 2) – Y (n= 8); 3) del 20q (n= 6); 4) del 7 (n= 3); 5) trisomy 19 (n= 2); 6) del 11q (n= 1); 7) del 17p (n= 1); 8) del 5q (n= 1); 9) Inv 5 (n= 1); 10) + X (n= 1); 11) intermediate abnormalities (2 cytogenetic abnormalities) (n= 7); and 12) complex abnormalities (≥3 cytogenetic abnormalities) (n= 1). In the ITT population, major cytogenetic responses were observed in 4 and minor cytogenetic responses were observed in 4 of the 70 subjects who were evaluable for cytogenetic response.

No morphologic or pathologic complete responses were observed among the 82 subjects who had adequate baseline and follow-up bone marrow aspirates.

The table below summarizes the platelet, neutrophil and cytogenetic responses in the ITT population.

Table 75 Patients with Platelet, Neutrophil and Cytogenetic responses ITT population (Applicant's Table)

Secondary Efficacy Endpoint	Response Category [1]	10mg Cont. N [2]	n	(%)	[Ex. 95% CI]	10mg Sync. N [2]	n	(%)	[Ex. 95% CI]	Overall N [2]	n	(%)	[Ex. 95% CI]
Platelet Response	Major	23	3	(13.0)	[2.8, 33.6]	27	1	(3.7)	[0.1, 19.0]	50	4	(8.0)	[2.2, 19.2]
	Minor		0	(0.0)	[0.0, 14.8]		0	(0.0)	[0.0, 12.8]		0	(0.0)	[0.0, 7.1]
	None		20	(87.0)			26	(96.3)			46	(92.0)	
Neutrophil Response	Major	16	1	(6.3)	[0.2, 30.2]	21	0	(0.0)	[0.0, 16.1]	37	1	(2.7)	[0.1, 14.2]
	Minor		0	(0.0)	[0.0, 20.6]		0	(0.0)	[0.0, 16.1]		0	(0.0)	[0.0, 9.5]
	None		15	(93.8)			21	(100.0)			36	(97.3)	
Cytogenetic Response	Major	26	3	(11.5)	[2.4, 30.2]	44	1	(2.3)	[0.1, 12.0]	70	4	(5.7)	[1.6, 14.0]
	Minor		4	(15.4)	[4.4, 34.9]		0	(0.0)	[0.0, 8.0]		4	(5.7)	[1.6, 14.0]
	None		19	(73.1)	[52.2, 88.4]		43	(97.7)	[88.0, 99.9]		62	(88.6)	[78.7, 94.9]

[1] See Appendix I of the protocol for the definitions of the response criteria.
[2] Number of subjects evaluable for response. For platelet response, the patient must have a baseline platelet count <100 x10^9/L to be included in the analysis. For neutrophil response, the patient is required to have a baseline ANC <1 x10^9/L. For cytogenetic response, only subjects with both a baseline and post-baseline evaluation of abnormal metaphases are included in the analysis.
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Data source: D_RESP Run date: 03FEB2005 DB extract date: 31JAN05:20:29:22

Source: CC-5013-MDS-002, Table 14.2.6.1

10.1.6 Efficacy Conclusions

Lenalidomide achieves RBC- transfusion independence in subjects with low or intermediate-1 risk MDS without a del 5 cytogenetic abnormality in 21.4% (46/215) patients in the ITT population.

Lenalidomide-induced RBC transfusion independence was associated with a median increase from baseline in blood Hgb concentration of 3.0 g/dL in the responders in the ITT population. The median duration of transfusion independence has not been reached. As of the data cutoff date, the duration of RBC- transfusion independence is at least 16 weeks in 32 subjects in the ITT population.

Lenalidomide therapy resulted in a ≥50% decrease from pretreatment in RBC transfusion requirements in 37.7% of the subjects in the ITT population. These included the transfusion-independence responses.

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Reviewer's Comments:
1. This study is not relevant to the proposed indication but serves as a reference for MDS patients without the 5q deletion. RBC transfusion independence responses and major cytogenetic responses are lower than in the MDS patients with a 5q deletion.

10.2 Line-by-Line Labeling Review.

In process.

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11 REFERENCES

Reference List

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