ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

September 14, 2005

FDA BRIEFING DOCUMENT

NDA 21-880

Revlimid® (CC-5013/Lenalidomide)

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 chromosomal abnormalities

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1 SUMMARY

The sponsor has submitted a New Drug Application for lenalidomide, a thalidomide analogue, for the 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". This ODAC briefing document provides the review team with findings from the nonclinical and clinical reviews of lenalidomide.

The key issues under consideration are:

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.

The application under review consisted of the following sections: chemistry, manufacturing and control, pharmacology/toxicology, clinical pharmacology and clinical/statistics.

Chemistry

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 chromatographic separation and mass spectral fragmentation when studied in rat and monkey.

Pharmacology/Toxicology

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.

Clinical Pharmacology
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.

Clinical
The WHO classification defines the 5q- syndrome as 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. Most patients eventually become transfusion dependent.

The sponsor submitted 3 single-arm, open-label studies in the application's clinical section. CC-5013-MDS-003 was a phase 2, multi-center study in transfusion-dependent MDS patients with an IPSS of low or intermediate-1-risk with an associated del 5 q 31-33. 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, multi-center study in transfusion-dependent MDS patients with an International

Prognostic Scoring System (IPSS) of low or intermediate-1-risk without an associated deletion of the long arm of chromosome 5 (del 5 q 31-33).

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 enrollment. Patients enrolled in study CC-501-MDS-001 required to be transfusion dependent as defined by a requirement of ≥ 4 RBC units 8 weeks before enrollment, or have less than a certain hemoglobin level.

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

Review Team's 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.

Study CC-5013-MDS-003
Study CC-5013-MDS-003 enrolled 148 patients, of which 96 (64.9%) were considered in the FDA evaluable population analyses. There were 2 dosing regimens used (10 mg daily and 10 mg every 21 days in a 28 day cycle). The FDA evaluable population included those MDS patients with a diagnosis of low or intermediate-1 risk category with a 5q deletion chromosomal abnormality with or without other cytogenetic abnormalities (20 metaphases evaluated) and were transfusion dependent (received ≥ 2 units of RBC transfusion in the 8 weeks (56 days) prior to start of study drug).

Transfusion independence was seen in 63.5% patients (95 % CI [53,73]). These responses lasted for a minimum of 8 weeks with a median duration of 30 weeks. The median hemoglobin increase from baseline to maximum level was 5.2 g/ dL. Transfusion independence was not accompanied by any platelet or neutrophil response. Bone marrow Complete Responses (CR) were seen in 40.3% patients. Transfusion independence response was accompanied by major cytogenetic responses in 41.4 % patients (95% CI of 29 and 55). An additional analysis performed by the FDA in the subgroup with isolated 5q deletion (N=72) showed similar results for transfusion independence (63.9%, 95% CI [52, 75]).

Study CC-501-MDS-001
Study CC-5013-MDS-001 enrolled 45 patients; 10 (22%) had low or intermediate-1 risk MDS with either baseline hemoglobin < 10.0 gm/dl and/or transfusion dependence and 5q 31-33 deletion. Three dosing regimens were used: 25 mg daily, 10 mg daily and 10 mg every 21 days in a 28 day cycle. For the del 5 q transfusion-dependent subpopulation, transfusion independence (for at least 8 weeks) was observed in 70% (7/10) (95% CI [35, 93]). The median duration of major erythroid response (International Working Group Criteria) was 47 weeks (95% CI [33, 88]). The median hemoglobin increase from baseline to maximum level was 5.3 g/dL. One patient who was platelet transfusion dependent at enrollment achieved a major platelet response (IWG criteria). One of 2 del 5 q patients evaluable for neutrophil response achieved a

major response (IWG criteria). Bone marrow CR was seen in 2 (20%). Major cytogenetic responses were observed in 9 (90%) of 10 who were evaluable for cytogenetic response.

Study CC-5013-MDS-002
Study CC-5013-MDS-002 enrolled 215 transfusion-dependent patients. Transfusion independence for 8 weeks was seen in 21.4 % (95% CI [16.1, 27.5]). The median duration of transfusion-dependent response was 18.9 weeks (95% CI 8, 35.9). The major platelet response rate was 8.0% (4/ 50) among the evaluable subjects. No major or minor neutrophil responses were observed. No patients demonstrated bone marrow CRs. Only 3 patients demonstrated a decrease in blast percentage from ≥ 5% to < 5%. Major cytogenetic responses were observed in 4 (5.7%) of the 70 subjects who were evaluable for cytogenetic response.

Clinical Safety
Pooled data from three studies (MDS-001, MDS-002 and MDS-003) in 408 MDS patients provide the primary safety data. Of these 408, 395 received treatment with the recommended starting dose of 10 mg/day either as a continuous regimen of daily doses (215 patients) or as a "syncopated" regimen (21 days of treatment in 28-day cycles) (180 patients). The mean exposure duration was 22.7 weeks; the median duration was 22.4 weeks; about one-half (189 or 47.8% of 395) received 10 mg/day lenalidomide for a minimum of 24 weeks. Thirteen patients received a daily 25 mg dose.

A substantial percentage of patients in all three MDS studies had reductions of the initial dose or interruption of dosing because of adverse events. The percentages of patients who had a dose reduction or dose delay at the 10 mg dose level (continuous/syncopated) ranged from 34% in MDS-001 to 80% in MDS-003. In MDS-003, 34 % experienced a second dose delay/reduction.

Review Team's Comment Regarding Dose Regimen:
Dose reductions and dose delays due to adverse events were common in these trials. In MDS-003, approximately 80% of patients had to have doses reduced or held, sometimes for very long periods. These results suggest that the starting dose may be inappropriately high for at least one-half of the patients.

At least one adverse event was reported in 407 (99.8%) of the 408 patients who were treated with lenalidomide in the 3 MDS studies. The most commonly reported AEs were neutropenia and thrombocytopenia (each in 41.5% of patients). Febrile neutropenia was rare (in 3.3% of patients). Epistaxis was reported in 10.7% of patients, ecchymoses in 3.3%, and other sites of bleeding were less common. Most of the above bleeding events were grade 1; however, epistaxis was grade 1 in 34 subjects, grade 2 in 3 subjects, and grade 3 in 2 subjects.

Of greater importance were single cases of subdural hematoma (grade 4), subarachnoid hemorrhage (grade 4), intracranial hemorrhage (grade 3), and grade 4 penile bleeding (grade 4). The patient who suffered subarachnoid hemorrhage died, and one patient who had a gastrointestinal hemorrhage discontinued treatment. Most infections were typical of this age group, such as upper respiratory infections, urinary tract infections, pneumonia, and influenza. Other commonly reported AEs were fatigue, pruritus, rash, gastrointestinal symptoms, and nervous system disorders. At least one serious adverse event (SAE) was reported in 151 (38.2%)

of the 395 patients who received the 10 mg/day starting lenalidomide dose. The most common SAE was infection followed by hematologic.

The frequency of on-study deaths (6.9% of patients) was low in the three MDS studies and consistent with that reported in the literature for the low and intermediate-1 risk MDS populations. There were 28 on-study deaths (either during the study or within 30 days after the last visit date) in 408 subjects. An additional 4 deaths were reported > 30 days after the subject completed the last study visit.

Planned Trials
The sponsor has proposed study CC-5013-MDS-004, which is 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) 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).

Risk Management
The Revlimid Risk Minimization Action plan has 2 objectives: manage the cytopenia adverse events and reduce the risk of fetal exposure in females of child bearing potential.
The sponsor proposes managing the cytopenias through the recommendation of weekly hematologic monitoring for the first 8 weeks with monthly monitoring after that. The management guidance will be included in the package insert, a medication guide, and additional educational materials.

The sponsor plans to provide information in the package insert and medication guide information regarding the benefits and potential risks of taking Revlimid during pregnancy. The sponsor proposes Category C for the labeling.

The sponsor's risk management program for physicians includes package insert, physician information brochure, Physician Frequently Asked Questions, Dosing Pocket Card, education program, and side effect management brochure. The sponsor's risk management program for patients includes medication guide, starter kit, blood count information sheet, and patient guide to transfusions, iron overload, and cytopenias. The sponsor's risk management program for nurses includes the package insert, nurse information brochure, education program, and patient information nurse training tool.

2 INTRODUCTION AND BACKGROUND

2.1 Drugs for the Treatment of MDS

FDA Approvals

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 (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia and requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-t), and chronic myelomonocytic leukemia (CMML). 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 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.

Review Team's Comment:
The trial did not include cytogenetic analyses so it is not known whether the clinical benefit seen with azacitidine applies only to certain MDS subpopulations.

Other Non-Approved Drugs in Current Usage in MDS

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 after 7-22 months in 13 of the responders (1).

Antithymocyte globulin (Atgam, ATG) has been associated with transfusion independence in 44% of patients, with a median duration of 10 months (range 3-38 months). Overall survival was 84% at 38 months (2).

2.2 MDS and 5q- Syndrome

The natural history of MDS is variable with some MDS patients having a prolonged survival while others progress rapidly to acute myeloid leukemia (AML) and have a short survival. Due to this fact, several classification schemes have been devised to address this variability. The FAB/WHO classification has been used most frequently to evaluate survival and risk for AML transformation. 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) (5). 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, median 9.4 years, intermediate-1, median 3.3 years, intermediate-2, median 1.1 years and high risk, median 0.2 year. Patients are 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.

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. 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).

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 (6). 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.

Allogeneic stem cell transplantation is the only potentially curative therapy but available only to younger patients (8). Azacitidine was approved by the FDA in 2004 for the treatment of all subtypes of MDS (9). Therapy includes supportive care that consists of RBC or platelet transfusions or the use of growth factors (erythropoietin, G-CSF, GM-CSF) (10).

The 5q- Syndrome

The WHO classification defines the 5q- syndrome as a separate entity (4). 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 (11). 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. One RBC transfusion dependent female patient lost transfusion dependence for about three years without having received any medication, but became RBC transfusion dependent again after that time. Anemia was usually macrocytic and combined with low reticulocyte counts and high erythropoietin levels. Most of the patients presented with refractory anemia, but refractory anemia with ringed sideroblasts also occurred. Three types of cytogenetic deletion were most prevalent: del (5) (q13q33), del (5) (q13q31) and del (5) (q22q33).

The prognosis is excellent compared to other forms of MDS. 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 > or =5% or the addition of one karyotypic anomaly severely reduces 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.

Giagounidis et al analyzed 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) (12). 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 had a significantly shorter overall survival (24 and 45 months, respectively) than patients with isolated del (5q). In total, 29 patients had died. Deaths occurred primarily due to transformation into acute leukemia, infection, or cardiac failure.

Patients with del (5q) as the sole karyotypic abnormality had previously been well defined as having relatively good prognoses, whereas poor prognoses were found when it was combined with other anomalies (5).

2.3 Product Information

Established name and proposed trade name:	Lenalidomide/CC-5013 (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 regimens:	10 mg daily or 10 mg 21 days/7 days rest

2.4 Important Issues with Pharmacologically Related Products: Thalidomide

The most serious toxicity associated with thalidomide is its documented human teratogenicity. The risk of severe birth defects, primarily phocomelia or death to the fetus, 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 peripheral neuropathy, orthostatic hypotension, neutropenia, and HIV viral load increase. Hypersensitivity and bradycardia in patients treated with thalidomide have been reported.

Of major concern to the FDA is whether lenalidomide, a thalidomide analogue, has been studied sufficiently to allow its safe and effective use without additional risk-management activities such as the STEPS Program.

2.5 Chemistry Summary

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 chromatographic separation and mass spectral fragmentation when studied in rat and monkey.

2.6 Pharmacology/Toxicology Summary

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.

2.7 Clinical Pharmacology Summary

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 ranges from 3 - 9 hours and the pharmacokinetic disposition of lenalidomide is linear: C_{max} and AUC increase proportionately with increases in dose. Approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore entails an active component.

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 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.

3 SUMMARY OF CLINICAL STUDIES

Six studies were submitted in the lenalidomide NDA. Diseases in which lenalidomide have been studied have included MDS, malignant melanoma, multiple myeloma and Complex Regional Pain Syndrome.

Table 1 Safety Studies

Study ID	Total Patients	Study Design and Dosing Regimen
CC-5013-MDS-003	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 and 10 mg 21d/7 d rest
CC-501-MDS-001	45	Pilot phase 1/2, single arm, open-label, single center, 2-stage dose-finding MDS 3 dosing regimens Oral 25 mg daily, 10 mg daily and 10 mg 21d/7 d rest

CC-5013-MDS-002	215	Single arm open-label phase 2 in low or intermediate-1 risk MDS without 5q deletion 2 dosing regimens Oral 10 mg daily and 10 mg 21d/7 d rest
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 submitted to demonstrate lenalidomide's efficacy in MDS are summarized in the table below. Efficacy results in the MDS del 5 q subpopulation are most relevant for the indication proposed. All three studies were single-arm, non-randomized trials.

Table 2 Clinical Efficacy Studies for MDS

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	RBC transfusion Independence	96/148[a]
CC-501-MDS-001	Pilot, phase 1/2 single arm, open-label, single center , 2-stage, dose finding	25 mg 10 mg daily 10 mg 21d/7 d rest	Major and minor Erythroid Response (IWG)	10/45[b]
CC-501-MDS-002	Single arm, open-label, multicenter phase 2	10 mg daily 10 mg 21d/7 d rest	RBC transfusion independence	118/215[c]

[a] Number of patients evaluated by FDA 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 and FDA 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

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

4 STUDY CC-5013-MDS-003 STUDY DESIGN

Study CC-5013-MDS-003 is a multicenter, single-arm, open-label study of oral CC-5013 monotherapy administered to red blood cell (RBC) transfusion-dependent patients with low- or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a del 5q31-33) cytogenetic abnormality. Red-cell blood transfusion-dependence for purposes of study entry included patients who received 2 or more units of PRBC in the 8 weeks prior to start of study drug. Initially, a dose of 10 mg daily on days 1-21 every 28 days was used, later amended to a dose of 10 mg daily every 28 days.

Objective: To evaluate the efficacy and safety of CC-5013 treatments to achieve hematopoietic improvement in subjects with low- or intermediate-1 risk International Prognostic Scoring System (IPSS) MDS associated with a del (5q31-33) cytogenetic abnormality.

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 efficacy endpoints included cytogenetic response, ≥ 50% decrease in RBC transfusion requirements, change in hemoglobin concentration from baseline, platelet response, neutrophil response, bone marrow response and duration of response.

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 (0.5×10^9/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)
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.

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.

Response endpoints were based on International MDS Working Group (IWG) Criteria.
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.

5 STUDY CC-5013-MDS-003 EFFICACY

5.1 Population and Baseline Characteristics

The FDA reviewed the data for all patients and considered 96 patients who met the following criteria to be evaluable. This 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 adequately analyzed in at least 20 metaphases. An additional analysis was done by the FDA reviewer in the subgroup of patients with isolated 5q deletion only. The table below shows a summary of the sponsor's and FDA's patient populations.

Table 3 Summary of Patient Populations

Patient Population	Number of Patients	
	Sponsor N (%)	FDA N (%)
All enrolled (ITT)	148 (100.0)	148 (100.0)
Per Protocol	115 (77.7)	115 (77.7)
Transfusion dependent low or intermediate-1 risk MDS with 5q deletion or additional abnormalities	94[a] (63.5)	96[b] (64.9)
Isolated 5q deletion MDS	-	72 (48.6)

[a]This is the sponsor's modified intent-to-treat population(MITT): 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.

[b]This is the 'FDA evaluable' population and includes 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

5.2 Dosing Regimens

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. 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.

Table 4 Dosing Regimens in ITT Population

Study	10 mg syncopated	10 mg continuous
CC-5013-MDS-003	45	103

5.3 MDS Subtypes, IPSS Score and Risk Category

The IPSS score and risk category in the ITT population are summarized in the table below. The FDA reviewer included the distribution of patients who had a 5q deletion as an isolated abnormality or had additional karyotypes (20 metaphases examined). The sponsor's analysis includes all patients who had evidence of a deletion 5q abnormality in at least 2 (two) metaphases, or by FISH alone.

An MDS clone with an isolated 5 q deletion cytogenetic abnormality only was seen in 110 (74.3 %) patients and 38 (25.7 %) patients had the 5q deletion associated with additional cytogenetic abnormalities. 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. 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.

Table 5 MDS Subtypes, IPSS Scores and Risk Category at Baseline ITT Population (Reviewer's Table)

Category	10 mg Sync N=45	10 mg Cont N=103	ITT N=148 (%)
MDS Subtypes			
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)
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)

5.4 RBC Transfusion Dependent Anemia at Baseline

RBC transfusion- dependent anemia was defined as having received ≥ 2 units of RBCs within 8 weeks of study treatment. There were 7 (4.7%) patients who received less than 2 units RBC within 8 weeks of start of study drug.

Table 6 Transfusion Dependence at Baseline ITT Population (Reviewer's table)

Transfusion Dependence	**N=148**	**%**
≥ 2 RBC units within 1-8 weeks	141	95.3
< 2 units within 8 weeks	7	4.7

5.5 Reasons for Patient Exclusions

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

Table 7 Reasons For Exclusions (Reviewer's table)

Reasons For Exclusions	**Number of patients (n=148)**	**%**

Unable to assign IPSS score due to missing myeloblast percent or laboratory values	20	13.5
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
< 20 metaphases analyzed at baseline	29	19.6

Reviewer's Comment:
The FDA considered an evaluable population analysis in those patients 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.

5.6 Primary Efficacy Analysis

5.6.1 RBC Transfusion Independence

FDA analyzed the primary endpoint of transfusion independence in the ITT population as well as the evaluable population of 98 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 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 81 patients, 51 (63.0%) of patients achieved transfusion independence. The table below summarizes and compares the frequency of RBC transfusion independence in the different populations analyzed.

Table 8 RBC Transfusion Independence in Various Populations (Reviewer's Table)

Population	Number Transfusion Independent	% Transfusion Independent	95% CI
Sponsor/FDA ITT			
Overall (N=148)	95	64.2	0.56, 0.72
10 mg cont (N=103)	70	68.0	0.58, 0.77
10 mg sync (N=45)	25	55.6	0.40, 0.70
FDA Evaluable			
Overall (N=96)	61	63.5	0.53, 0.73

10 mg cont (N=67)	44	65.7	0.53, 0.77
10 mg sync (N=29)	17	58.6	0.39, 0.76
Isolated 5q deletion MDS			
Overall (N=72)	46	63.9	0.52, 0.75
10 mg cont (N=53)	35	60.0	0.52, 0.78
10 mg sync (N=19)	11	57.9	0.34, 0.80

5.7 Secondary Efficacy Analysis

5.7.1 Duration of Response

The response duration was measured 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 after this 56-day RBC transfusion-free period. 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.

The 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 9 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

5.7.2 Change of Hemoglobin Concentration from Baseline

The baseline hemoglobin (Hgb) from which a change was computed used by the sponsor was the minimum Hgb value in the 56 days prior to start of study drug which could be either taken from the central laboratory values or the local laboratory values. FDA noted that only 25 screen/baseline Hgb records are from central laboratory data; almost all the screen/baseline Hgb data are from local laboratory. The sponsor reported the median increase in Hgb level from baseline to maximum Hgb 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 as shown below.

Table 10 Change of Hemoglobin Concentration from Baseline 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

[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.
Program path: \\sasdbvm\data\prd\Projects\CC-5013\CC-5013-MDS-003\programs\tables\hgb-resp-summary.sas

Source: CC-5013-MDS-003, Table 14.2.4.1.

5.7.3 Decrease of ≥ 50% in RBC Transfusion Requirements

There is no working definition from the IWG criteria for 50% reduction of RBC transfusion requirement. FDA noted that the sponsor's definition of 50% reduction of RBC transfusion requirement overlapped with the transfusion independence definition (i.e., all transfusions independent responders had greater than 50% requirement of RBC transfusion). The table below summarizes the frequency of patients in the ITT and evaluable populations who achieved a ≥ 50% decrease in RBC transfusions.

Table 11 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	0.67, 0.81

10 mg cont (N=103)	79	76.7	0.67, 0.84
10 mg sync (N=45)	31	68.9	0.53, 0.82
FDA evaluable			
Overall (N=96)	71	74.0	0.64, 0.82
10 mg cont (N=67)	50	74.6	0.63, 0.84
10 mg sync (N=29)	21	72.4	0.53, 0.87
Isolated 5q deletion MDS			
Overall (N=72)	55	76.4	0.65, 0.86
10 mg cont (N=53)	41	77.4	0.64, 0.88
10 mg sync (N=19)	14	73.7	0.49, 0.91

5.7.4 Platelet Response, Neutrophil Response , Cytogenetic Response, Bone Marrow Response

Platelet and Neutrophil Response

Among the 14 patients who were platelet transfusion dependent and thus evaluable for a platelet response in the FDA evaluable population, there were no platelet responses, major or minor. Among the 6 patients evaluable for a neutrophil response, one patient had a major response. The table below shows the FDA analyses results of the platelet response and neutrophil response in the evaluable population.

Table 12 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

Although the IWG criteria specified at least 20 metaphases be analyzed for cytogenetic response, the sponsor considered patients for cytogenetic response who had at least 2 (two) metaphases analyzed.

FDA considered those patients evaluable for a cytogenetic response that 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. Where interphase FISH without conventional cytogenetics was used for response, it was considered insufficient for the diagnosis of 5q deletion; since although deletion of 5q may be confirmed, other abnormalities

would not have been ruled out. The table below shows a comparison of the cytogenetic responses in various populations.

Table 13 Comparison of Cytogenetic Response in Various Populations (Reviewer's Table)

Population Evaluable Number Cytogenetic Response	Analysis	Major Response (%)	95% CI	Minor Response (%)	95% CI
ITT (N=111)	Sponsor	46 (41.4)	[32.2, 51.2]	29 (26.1)	[18.2,35.3]
10 mg cont (N=78)		32 (41.0)	[30.0, 52.7]	21 (26.9)	[17.5, 38.2]
10 mg sync (N=33)		14 (42.4)	[25.5, 60.8]	8 (24.2)	[11.1, 42.3]
ITT (N=93)	FDA	37 (39.8)	[29.8, 50.5]	25 (26.9)	[18.2, 37.1]
10 mg cont (N=73)		30 (41.1)	[29.7, 53.2]	19 (26.0)	[16.5, 37.6]
10 mg sync (N=20)		7 (35.0)	[15.4, 59.2]	6 (30.0)	[11.9, 54.3]
FDA Evaluable (N=58)	FDA	24 (41.4)	[28.6, 55.1]	19 (32.8)	[21.0, 46.3]
10 mg cont (N=43)		18 (41.9)	[27.0, 57.9]	15 (34.9)	[21.0, 50.9]
10 mg sync (N=15)		6 (40.0)	[16.3, 67.7]	4 (26.7)	[7.8, 55.1]
Isolated 5q deletion MDS (N=21)	FDA	0 (0.0)	[0, 16.1]	11 (52.4)	[29.8, 74.3]
10 mg cont (N=15)		0 (0.0)	[0, 21.8]	8 (53.3)	[26.6, 78.7]
10 mg sync (N=6)		0 (0.0)	[0, 45.9]	3 (50.0)	[11.8, 88.2]

Bone Marrow Response
FDA considered a bone marrow Complete Response (CR) in patients who had a follow-up bone marrow aspirate done and which showed ≤ 5% myeloblasts with normal maturation of all cell lines and no evidence of dysplasia. Follow-up bone marrow aspirates were available in 57 (93.4%) of the 61 responders. A CR was seen in 23 (40.3%) patients.

6 STUDY CC-5013-MDS-001

This was a pilot, phase 1/2, single-arm, single-center, open-label, 2-stage, dose-finding study of CC-5013 in 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 levels (10 mg/day, 10 mg 21days/7days rest).

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.

Study Population:
Major 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/ μ L); Chronic myelomonocytic leukemia (CMML)
- Baseline mean hemoglobin < 10.0 g/ dL (untransfused) or transfusion dependent defined by 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 ≤ 1.5x ULN) and hepatic function: bilirubin < 2.5 mg/ dL; AST/ALT < 2x ULN
- 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.

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 blast > 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

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. All responses required that values be sustained above the response threshold for a minimum of 8 consecutive weeks.

6.1 Population and Baseline Characteristics

Population Analysis

There were 45 patients enrolled in the study which made up the ITT population. The sponsor also looked at the population of interest for the proposed indication which 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. The table below summarizes the number of patients who were included in the efficacy analyses submitted by the sponsor. FDA reviewed and agreed with the 10 patients in the population of interest.

Table 14 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.

Baseline Disease Characteristics

The FDA reviewer analyzed 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 15 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

6.2 Dosing Regimens

The first 13 patients who were enrolled in the study were treated with 25 mg daily. Twelve patients 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.

Table 16 Dosing Regimens in ITT Population (Reviewer's Table)

Study	25 mg daily	10 mg continuous	10 mg syncopated

CC-501-MDS-001	13	12	18

6.3 Primary Efficacy Analysis

6.3.1 Response Rate

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 MDS IWG.

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 with 95% CI of 35 and 93%. 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. In the 9 patients with isolated 5 q deletion, response rate was 77.8%. The FDA assessment confirmed the sponsor's assessment.

6.4 Secondary Efficacy Analysis

6.4.1 Duration of Response

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. Thus 7 (77.8%) had progressed (i.e., required a transfusion after a response). The median duration of major erythroid response was 47.4 weeks with a 95% CI of 38.6 and 88.1 weeks.

6.4.2 Change in Hemoglobin Values

For all responders with an isolated 5 q deletion cytogenetic abnormality, the median change in hemoglobin concentration from baseline was 5.3 g/dL.

6.4.3 Platelet Response, Neutrophil Response, Cytogenetic Response, Bone Marrow Response

Out of the 10 del 5 q patients, 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.

Complete histologic remission was observed in 2 (33.3%) of the 6 patients who were evaluable for bone marrow response. FDA agreed with the sponsor's analysis.

Reviewer's Comment:
Bone marrow response and cytogenetics response did not always coincide.

7 STUDY CC-5013-MDS-002

Study CC-5013-MDS-002 had an identical study design to CC-5013-MDS-003 except that the study population included patients without a del 5q cytogenetic abnormality: transfusion dependent, low - or intermediate- 1- risk IPSS MDS without an abnormality of chromosome 5 involving a deletion between bands q31 and q33.

7.1 Population and Baseline Characteristics

Datasets Analyzed
There were 215 patients enrolled and were included in the efficacy analyses by the sponsor. FDA confirmed the data in the ITT population.

Baseline Disease Characteristics
Baseline disease and demographic characteristics were similar to those in MDS-003 except for a higher percentage of males and cytogenetics.

The FDA reviewer noted that there were 2 patients (Patient ID 0312006 and 0392003) who had a karyotypic analysis with 5q deletion, one isolated and 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. Patient 0392003 did not have a diagnosis of MDS or IPSS risk category assigned.

7.2 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 transfusion independence 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.

7.3 Secondary Efficacy Analysis

Duration of Response
Of the 46 subjects in the ITT population who achieved RBC- transfusion independence, 33/46 (71.7%) remained transfusion independent, and 13/46 (28.3%) had relapsed (i.e., required a transfusion after a response). The minimum duration was for 8 weeks. The duration of RBC-transfusion independence was at least 16 weeks in 32 of the responders.

Change in Hemoglobin From Baseline
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.

Decrease of ≥ 50% in RBC Transfusion Requirements
Overall, 37.7% (81/215) of the patients in the ITT population achieved a ≥50% decrease in their pretreatment RBC- transfusion requirements during lenalidomide therapy. This included patients with a transfusion independence response.

Platelet Response, Neutrophil Response, Cytogenetic Response, Bone marrow Response
Among the evaluable patients in the ITT population, the major platelet response rate was 8.0% (4/50) and there were no major or minor neutrophil responses observed.

Standard cytogenetic studies with at least 20 evaluable metaphases of the MDS clone were available for Central Review at baseline for 178 (82.8%) of 215 patients. In the ITT population, major cytogenetic responses were observed in 4 (5.7%) and minor cytogenetic responses were observed in 4 (5.7%) 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.

8 INTEGRATED REVIEW OF SAFETY

8.1 Drug Exposure

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 17 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
At least 8 weeks	9	175	143	318
At least 16 weeks	8	142	121	263
At least 24 weeks	6	102	87	189
At least 32 weeks	6	50	47	97
At least 48 weeks	4	7	11	18
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)

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 18 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.

In the population treated with 10 mg/day lenalidomide about 59% (232/395) of patients had to have the dose reduced at least one time, and about 25% (99/395) had to have a second dose reduced or delayed. In the population treated with 25 mg/day lenalidomide about 60% of patients had to have first and second dose reduction/interruption.

Reviewer's Comments:
Dose reductions and dose delays due to adverse events were common in these trials, especially in MDS-003 in which about 80% of patients had to have doses reduced or held, sometimes for very long periods. These results suggest that the starting dose may be too high for at least one-half of the patients.

8.2 Common Adverse Events

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.

Table 19 Frequency of Adverse Events in the MDS Studies (Sponsor's Table 4)

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)	71 (33.0)	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)

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)

	Over All MDS Studies			
System organ class/ Preferred term [a]	25mg (N=13)	10mg Cont. (N=215) Over All MDS Studies	10mg Sync. (N=180)	10mg Overall (N=395)
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 was rare (in 3.3% of patients) and bleeding events were not

common. Epistaxis was reported in 10.7% of subjects, ecchymoses in 3.3%, petechiae 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 1 in 34 subjects, grade 2 in 3 subjects, and grade 3 in 2 subjects.

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

Most of the infections were typical in this age group, such as upper respiratory infections, urinary tract infections, pneumonia, and influenza. Other commonly reported AEs were fatigue, pruritus, rash, gastrointestinal symptoms, and nervous system disorders.

8.3 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 lenalidomide. Most SAEs occurred in fewer than 5 subjects in any treatment group. The table below summarizes the SAEs.

Table 20 Frequency of Serious Adverse Events in the MDS Studies (Sponsor's Table 9)

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.

Reviewer's Comments:

Most of the SAEs related to pancytopenias and infections are most likely due both to MDS and to lenalidomide therapy.

Sponsor's sub-group analyses:
Subgroup 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 > 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 >94% of subjects were white.

8.4 Deaths

The frequency of on-study deaths (6.9% of patients) was low in the three MDS studies and consistent with that reported in the literature for the low and INT-1 risk MDS population (Greenberg, 1997). There were 28 on-study deaths (either during the study or within 30 days after the last visit date) in 408 subjects. An additional 4 deaths were reported > 30 days after the subject completed the last study visit.

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:
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. Three of the above cases fall into this category. Pancytopenia is recognized as definite risk to treatment but also a definite risk of the disease. Different observers would differ in assigning causality in three of the four cases. The fourth case, that of a patient who died of respiratory failure, appears to this reviewer as definitely unrelated to lenalidomide.

All four patients were treated with 10 mg/day lenalidomide, three on continuous dosing, one on syncopating dosing.

Relationship to lenalidomide dose and schedule: 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 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.

9 PLANNED PHASE 3 STUDY

An IND has been submitted for study CC-5013-MDS-004, which is 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) 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 done in Europe. The primary endpoint is RBC transfusion independence for ≥26 weeks (182 days).

10 RISK MANAGEMENT PLAN

The Revlimid Risk Minimization Action plan has 2 objectives: manage the cytopenia adverse events and reduce the risk of fetal exposure in females of child bearing potential.
The sponsor proposes managing the cytopenias through the recommendation of weekly hematologic monitoring for the first 8 weeks with monthly monitoring after that. The management guidance will be included in the package insert, a medication guide, and additional educational materials.

The sponsor plans to provide information in the package insert and medication guide information regarding the benefits and potential risks of taking Revlimid during pregnancy. The sponsor proposes Category C for the labeling.

The sponsor's risk management program for physicians includes Package insert, physician information brochure, Physician Frequently Asked Questions, Dosing Pocket Card, education program, and side effect management brochure. The sponsor's risk management program for patients includes medication guide, starter kit, blood count information sheet, and patient guide to transfusions, iron overload, and cytopenias. The sponsor's risk management program for nurses includes the package insert, nurse information brochure, education program, and patient information nurse training tool.

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