ONCOLOGIC DRUGS ADVISORY COMMITTEE
BRIEFING DOCUMENT

LENALIDOMIDE (REVLIMID®)

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

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1. INTRODUCTION

De novo myelodysplastic syndromes (MDS) are a diverse group of hematopoietic disorders that vary substantially with respect to clinical presentation, prognosis, and outcome. The International Prognostic Scoring System (IPSS) has categorized MDS into 4 risk groups: low, intermediate-1, intermediate-2, and high risk (Greenberg et al, 1997). Although all categories of MDS are associated with a risk of conversion to acute myeloid leukemia (AML) and with shortened survival, these risks are greatest in the higher-risk categories. Most newly diagnosed cases of MDS are categorized in the lower-risk disease categories (low- or intermediate-1 risk) and are characterized by a more chronic course of progressive cytopenias and associated morbidities, with median survival of several years from diagnosis and a lower rate of conversion to AML. Patients with low- to intermediate-1-risk MDS are primarily treated with supportive measures, including red blood cell (RBC) transfusions and myeloid or erythropoietic growth factors. Anemia is the most frequent cytopenia requiring medical management, and with progression of their illness, these patients often become dependent on repeated red cell transfusions for their refractory anemia. These supportive care measures do not treat the underlying biology of disease and are often associated with their own unique problems. Investigational new treatment strategies are targeting the fundamental mechanisms of disease that predominate in the lower-risk MDS categories; these strategies include immunosuppression, differentiation, immunomodulation, and angiogenesis inhibition.

Thalidomide, the first commercially available drug in the class of immunomodulatory (IMiD®) agents, has both antiangiogenic and immunomodulatory properties and was the first agent in this class to be studied in MDS. Several clinical trials have shown response rates of approximately 25% with thalidomide therapy in patients with lower-risk MDS, and treatment has resulted in RBC-transfusion independence in patients who had required regular red cell transfusions for refractory anemia; some patients have attained long-term transfusion independence (Moreno-Aspitia et al, 2002; Musto, 2004; Raza et al, 2001; Strupp et al, 2002). In a Phase 2 study, thalidomide was shown to restore erythropoiesis and to reduce transfusion dependence in approximately 18% (15/83) of evaluable patients with MDS who had not responded to recombinant erythropoietin (Raza et al, 2001). However, prolonged drug treatment appeared to be necessary to maximize the hematologic response, and the tolerability of the dosing regimen was problematic in some patients. Patients primarily discontinued thalidomide treatment because of fatigue, constipation, dyspnea, or disease progression.

Lenalidomide (REVLIMID™) is a novel IMiD that is more potent than thalidomide and has not demonstrated the findings of neurotoxicity or teratogenicity seen with thalidomide in available, relevant animal models. The rationale for developing lenalidomide as a treatment for MDS was based on the clinical study experience with thalidomide and on the hypothesis that lenalidomide could be an effective treatment for MDS with an improved safety profile.

The first study of lenalidomide in MDS, Study MDS-001, was notable in that a substantial proportion of the patients evidenced a major erythroid response to therapy, with hematologic improvement and prolonged transfusion independence (7 patients in this study have received treatment for 1.5 to 3 years). The results of this study suggested that patients with a particular cytogenetic abnormality (del 5q, which is seen in the diseased marrow cells in 20%-30% of patients with MDS) responded especially well to lenalidomide. This study has been followed up by 2 expanded Phase 2 studies, which have evaluated lenalidomide in the treatment of patients with lower-risk forms of MDS either with a del 5q cytogenetic abnormality (Study MDS-003) or without a del 5q cytogenetic abnormality (Study MDS-002). Additional preclinical studies have also demonstrated that the del 5q cytogenetic abnormality is associated with increased sensitivity to lenalidomide. This region of chromosome 5 includes genes for several growth factors and growth factor receptors and genes for factors that modulate gene expression. The biology of the relationship(s) between loss of this chromosomal segment and increased sensitivity to lenalidomide is under continuing investigation. Interestingly, cells with this cytogenetic abnormality do not appear to demonstrate the same level of increased sensitivity to thalidomide in preclinical studies (i.e., the biological effects of these 2 drugs are different in this regard).

Thus, the clinical program for lenalidomide for the treatment of patients with MDS currently includes results from 3 studies (see Appendix 8.2, Table 8.2.1, for a summary of the design features of these studies):

- Study MDS-001 (MDS-501-001), a Phase 1/2, pilot, dose-finding study to gain preliminary information on the efficacy and safety of lenalidomide in patients with MDS, to identify the subpopulations of patients with MDS who respond to lenalidomide, and to identify a safe and effective dose for use in subsequent confirmatory studies.
- Study MDS-002 (CC-5013-002), a Phase 2, multicenter, open-label, single-arm study to confirm the efficacy and safety of lenalidomide in patients with an IPSS diagnosis of low- or intermediate-1-risk MDS without an associated del 5 (q31-33) cytogenetic abnormality and with RBC-transfusion-dependent anemia.
- Study MDS-003 (CC-5013-003), a Phase 2, multicenter, open-label, single-arm study to confirm the efficacy and safety of lenalidomide in patients with an IPSS diagnosis of low- or intermediate-1-risk MDS associated with a del 5 (q31-33) cytogenetic abnormality and with RBC-transfusion-dependent anemia.

All 3 studies (Studies MDS-001, MDS-002, and MDS-003) have demonstrated that lenalidomide produces sustained, clinically meaningful hematological improvement in patients with lower-risk MDS, manifested clinically as RBC-transfusion independence. The hematologic improvement has been sustained for prolonged periods of time and is supported objectively by sustained elevations in hemoglobin (Hgb) values, with reduction or elimination of the need for RBC transfusions in many patients. These findings of patient benefit have been seen with the highest frequency in patients with a diagnosis of

low- or intermediate-1-risk MDS with an associated del 5 (q31-33) cytogenetic abnormality in Studies MDS-001 and MDS-003. The expanded Phase 2 study in this patient population (Study MDS-003) has also demonstrated that treatment with lenalidomide can produce improvement in bone marrow morphology and cytogenetic normalization in a substantial proportion of treated patients, suggesting that treatment with lenalidomide may have a positive effect on the natural history of the disease in this subgroup of patients with MDS. Additional clinical research, including a randomized, double-blind, placebo-controlled study (Study CC-5013-MDS-004), is in progress to confirm and extend these findings (see Section 4.7 and Appendix 8.2, Table 8.2.2). The primary treatment toxicity observed has been myelosuppression, which may be related to apoptotic clearance, early in the course of treatment, of abnormal precursor cells in the bone marrow of these patients.

As a result of these compelling findings, Celgene is seeking approval of lenalidomide for the following indication, at a recommended starting dose of 10 mg daily:

> *"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"*

Of the 408 patients who participated in the 3 clinical trials in MDS, 395 received a starting dose of 10 mg daily, either by a continuous dosing regimen (10 mg daily without a planned rest) or a cyclic[a] dosing regimen (10 mg daily for the first 21 days of repeated 28-day cycles). Lenalidomide demonstrated a generally similar safety profile when administered according to either the continuous or the cyclic dosing regimen. Grade 3/4 neutropenia and thrombocytopenia, the most common adverse events, were manageable with dose reductions and/or interruptions.

Study MDS-003 was submitted to support the approval of lenalidomide, under the provisions of 21 Code of Federal Regulations (CFR) 314, Subpart H (accelerated approval of new drugs for serious or life-threatening illnesses), for the treatment of patients with low- or intermediate-1-risk MDS and an associated del 5 (q31-33) cytogenetic abnormality with or without additional cytogenetic abnormalities. This request for approval follows discussions that the company had with representatives of the Oncology Division of the US Food and Drug Administration (FDA) on 22 August 2004 (US Food and Drug Administration, 2004). During those discussions, FDA provided guidance that transfusion independence can be considered to be an acceptable clinical benefit endpoint and that data from Study MDS-003 could serve as a basis for filing under 21 CFR 314 if the data were compelling and demonstrated sustained transfusion independence supported by additional objective findings indicating clinical benefit (e.g., histological improvement in bone marrow, increase in and stabilization of Hgb, and/or cytogenetic improvement).

Collectively, the efficacy and safety data demonstrate a consistent and very favorable benefit-to-risk ratio for lenalidomide for treatment of patients with transfusion-dependent

[a] Previously referred to as the "syncopated" regimen.

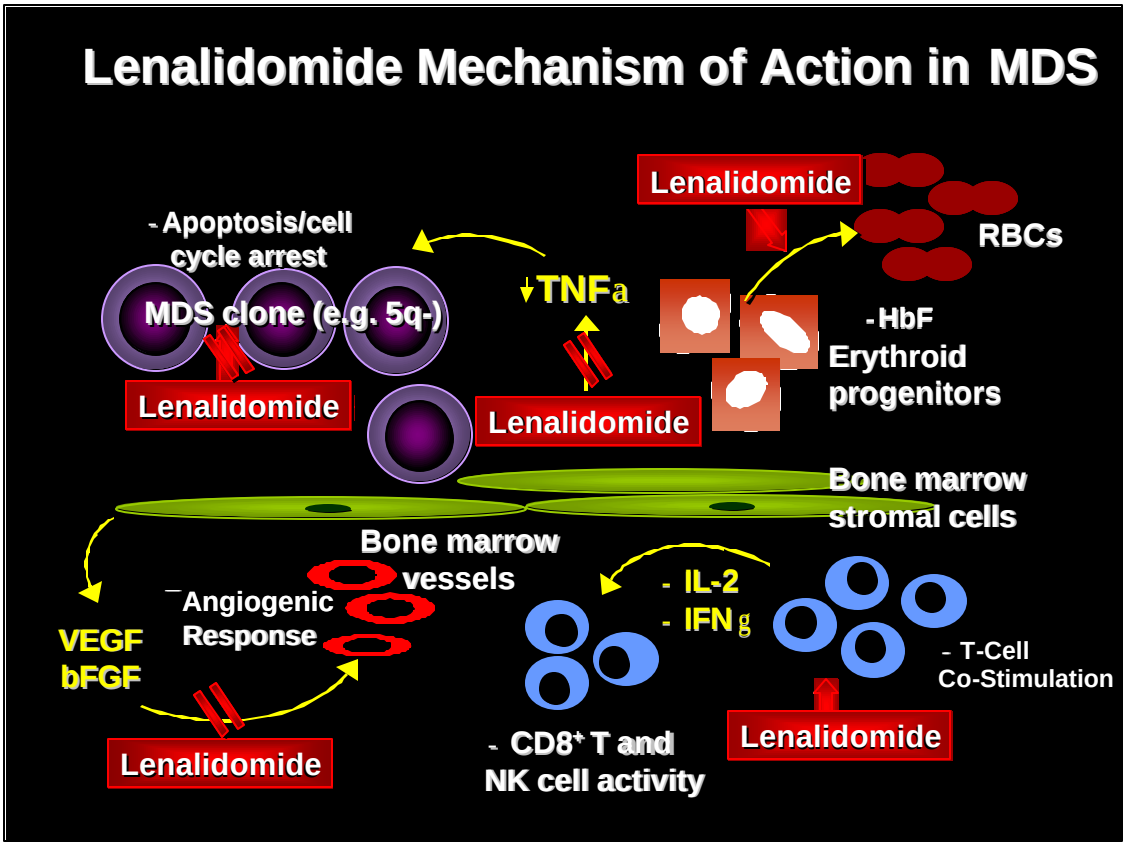
anemia due to low- or intermediate-1-risk MDS associated with a del 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. As transfusion-dependent MDS is a serious illness, with a poor prognosis and few available treatment options, an acceptably safe therapy such as lenalidomide that ameliorates the burden and consequences of long-term RBC-transfusion requirements would provide a clear clinical benefit to this population of patients.

2. NONCLINICAL SUMMARY

2.1. Mechanism of Action

Lenalidomide, a potent immunomodulator, is a 4-amino substituted analog of thalidomide. Lenalidomide affects a number of biological processes, as shown in Figure 1.

Figure 1: Mechanism of Action of Lenalidomide in MDS



Pharmacology studies of lenalidomide support the drug's efficacious use in the treatment of MDS. The MDS are associated with elevated levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) in the bone marrow; deficiencies of T cells and natural killer T cells; the presence of hematopoietic clones bearing recognizable karyotypic abnormalities such as the 5q- cytogenetic defect; refractory anemia characterized by reduced Hgb levels; and bone marrow angiogenesis resulting in increased microvessel density. Pharmacology studies of lenalidomide support its efficacy for the treatment of the complex disease state associated with MDS. These studies have demonstrated that lenalidomide:

- **Inhibits proliferation**. Patients with MDS are often diagnosed with characteristic morphologic and cytogenetic dysplastic features of the bone

marrow and peripheral blood. Among the most common cytogenetic abnormalities are clones with deletions of chromosome 5q. Lenalidomide inhibits proliferation of chromosome 5-deleted hematopoietic tumor cells. Lenalidomide induces G2/M and/or G0/G1 cell cycle arrest in Namalwa (Burkitt's lymphoma, chromosome 5 deletion) and Loucy (acute lymphoblastic leukemia, deletion 5q15::q35) cells and apoptosis in Namalwa, KG-1 (acute myeloid leukemia, chromosome 5 deletion), and Loucy cells. In Namalwa cells, lenalidomide inhibits Akt and Gab1 phosphorylation and the ability of Gab1 to associate with a receptor tyrosine kinase. Lenalidomide enhances AP-1 transcriptional activity in Namalwa cells but not in the resistant UT-7 cells.

- **Induces fetal hemoglobin.** Lenalidomide induces expression of fetal hemoglobin associated with CD34+ hematopoietic stem cell differentiation in a model of erythroid progenitor differentiation.
- **Inhibits inflammation.** Lenalidomide inhibits the secretion of pro-inflammatory cytokines, including TNF-a, interleukin (IL)-1ß, and IL-6 and IL-12, from peripheral blood mononuclear cells.
- **Induces T-cell proliferation.** Lenalidomide induces T cell proliferation and IL-2 and interferon-gamma (IFN-?) production, which stimulate cytotoxic T cell and natural killer (NK) cell activity.
- **Inhibits angiogenesis.** In vitro angiogenesis models have shown that lenalidomide inhibits angiogenesis by blocking the formation of microvessels and endothelial cell tubes, and the migration and adhesion of endothelial cells. Lenalidomide also reduces the growth of solid tumors in vivo through the inhibition of tumor-associated angiogenesis.

2.2. Toxicology

The preclinical potential toxicity of lenalidomide has been extensively investigated in in vitro and in vivo studies. Lenalidomide has relatively low toxicity after acute (single-dose) administration, as demonstrated by the high minimum oral and intravenous lethal doses (>2000 mg/kg and >40 mg/kg, respectively) in both mice and rats. The primary toxicities observed after repeated oral administration of lenalidomide were associated with the hematopoietic/lymphoreticular systems and the kidneys. In nonclinical studies, rats appeared to be more sensitive to the effects on the kidneys, whereas cynomolgus monkeys were more sensitive to the effects on the hematopoietic system. In both species, the changes noted in the kidney and/or the hematopoietic/lymphoreticular systems were generally reversible after a 4- to 7-week recovery period.

Lenalidomide did not exhibit any mutagenic or genotoxic potential in vitro or in vivo.

Studies in rats did not show selective effects of lenalidomide on male or female reproductive performance or on the viability, growth, morphology, or postnatal functional/behavioral development of the offspring. Pregnant rabbits were more

susceptible to the effects of lenalidomide than rats. There were dose-dependent increases in maternal deaths and abortions, as well as increased post-implantation loss in litters surviving to gestation day 29. Limb defects, as seen in rabbit developmental toxicology studies with thalidomide, have not been observed with lenalidomide. Finally, no adverse effects were observed on the viability, growth, or development of pups of rats administered doses of lenalidomide as high as 500 mg/kg/day in the Segment III (peri-post-natal) study in rats.

Overall, based on extensive toxicity and pharmacology studies, lenalidomide was well tolerated in the animal species evaluated and was effective in relevant pharmacology studies. These data support the clinical findings which indicate that lenalidomide is a new therapeutic option, with a favorable benefit-to-risk ratio, for the treatment of patients with MDS at the proposed therapeutic dose.

2.3. Comparison of Lenalidomide With Thalidomide

While lenalidomide and thalidomide are chemically related, these compounds are distinct chemical entities that have different metabolic profiles. The metabolic data available on lenalidomide in rats and monkeys, and on thalidomide, indicate that both compounds readily undergo in vivo chemical degradation (hydrolysis) rather than phase I oxidative metabolism. The 3 chemical reactions that are involved in the chemical hydrolysis of lenalidomide and thalidomide occur at physiological pH and consist of:

- Racemization via loss of the acidic proton at the chiral carbon atom, followed by re-protonation of the keto-enol stabilized intermediate.
- Hydrolysis of imide bonds.
- Hydrolysis of amides to carboxylic acids.

The degradation pathways of lenalidomide and thalidomide lead to no common intermediates/degradation products. In addition, it is not possible for lenalidomide to break down or convert to thalidomide. Thus, lenalidomide and thalidomide and their respective degradation products are unique and chemically different.

Lenalidomide is further differentiated from thalidomide by:

- **Clinical profile**. Lenalidomide has a distinct safety profile and activities.
- **Pharmacology.** Similar to the potency differences for the clinical dose, lenalidomide and thalidomide also differ significantly in potency in pharmacology studies. Lenalidomide was 10 to 6000 times more potent than thalidomide in various in vitro and in vivo pharmacology studies, with the exception of some angiogenesis models.
- **Developmental toxicity.** Lenalidomide has a different developmental toxicity profile than thalidomide when given to rabbits. No teratogenic effects of lenalidomide have been demonstrated in rabbit and rat embryo-fetal development (Segment II) testing. Pregnant rabbits, a species sensitive to thalidomide developmental toxicity, were orally dosed with lenalidomide to maternally toxic doses during the major organogenesis period of gestation

days 7 to 19 (inclusive). No thalidomide-like structural abnormalities were noted. At the highest dose associated with maternal toxicity, embryo-fetal loss and intrauterine deaths were observed. In the same study, thalidomide was used as the positive control and caused classic limb defects.

- **Clinical safety profile.** In clinical studies to date, lenalidomide has been associated primarily with granulocytopenia and thrombocytopenia. This is in contrast to thalidomide, which is more commonly associated with dose-limiting non-hematologic toxicities, including neurotoxicity, constipation, and sedation and is not commonly associated with thrombocytopenia.

3. THE MYELODYSPLASTIC SYNDROMES

3.1. Disease State/Etiology

The MDS are heterogenous clonal hematopoietic stem cell disorders that are characterized in most patients by refractory peripheral blood cytopenias, hypercellular bone marrows, and an increased risk of acute myelogenous leukemia transformation (Bennett et al, 1982; Greenberg, 1983; Bennett et al, 1985; Nand and Goodwin, 1988; List et al, 1990). Dysplasia, the morphological hallmark of MDS, signifies discordant nuclear-cytoplasmic maturation and accelerated apoptosis (Raza et al, 1995). The cytopenias that complicate these stem cell disorders are the result of a diminished responsiveness of bone marrow progenitor cells to normal trophic signals, which leads to premature hematopoietic progenitor cell loss and ineffective hematopoiesis (Merchav et al 1991; Hoefsloot et al, 1997). The etiology of most cases of MDS is unknown, but exposure to ionizing irradiation or bone-marrow-damaging agents, including chemotherapeutic drugs, may increase the risk of developing MDS (Kantarjian and Keating, 1987; Garfinkel and Boffeta, 1990; Stone et al, 1994; West et al, 1995; Rigolin et al, 1998).

The MDS occur primarily in older patients, with a median age at diagnosis of 65 to 75 years (Kantarjian and Estey, 2001). The prevalence of MDS is approximately 5 per 100,000 population; however, its prevalence in the population older than 70 approaches 22 to 45 per 100,000 population (Greenberg, 2000). The signs and symptoms of MDS are cytopenia-related and include fatigue, pallor, infection, and bleeding; the common associated laboratory findings are anemia, neutropenia, and thrombocytopenia (Dunbar and Nienhuis, 2001). Splenomegaly is present in approximately 20% of patients; hepatomegaly and lymphadenopathy are found less frequently.

Approximately 90% of patients present with anemia at diagnosis and, in patients with low-risk MDS, anemia is often the only significant hematologic deficiency (Greenberg et al, 1997; Greenberg, 2000). In older patients, low blood Hgb concentration may reduce quality-of-life parameters and may aggravate congestive heart failure and angina. The majority of patients with MDS develop a requirement for transfusions of RBCs, and repeated transfusions may cause iron overload with secondary hemochromatosis (Hellström-Lindberg et al, 1998). In addition, ineffective erythropoiesis stimulates increased absorption of iron (Dunbar and Nienhuis, 2001). Furthermore, high percentages of patients with MDS present with neutropenia (24%-46%), thrombocytopenia (25%-45%), or pancytopenia/bicytopenia (20%-35%) (Greenberg et al, 1997; Dunbar and Nienhuis, 2001).

The overall prognosis for patients with MDS is poor. Spontaneous complete remission or hematologic improvement rarely occurs, and the overall median survival (considering both lower-risk and higher-risk categories of MDS) is approximately 2 years (Dunbar and Nienhuis, 2001). Transformation to acute leukemia accounts for 30% of MDS mortality, and 40% of patients with MDS die of complications of bone marrow dysfunction or treatment thereof (infection, bleeding, and iron overload) (Dunbar and Nienhuis, 2001).

The remaining 30% of patients die of conditions that are not related to MDS, such as cardiovascular disease or non-hematologic malignancies. The expected survival of patients with transfusion-dependent MDS is shorter than that of those who are anemic but not yet transfusion dependent, and the achievement of transfusion independence and a cytogenetic remission are major accomplishments that might translate into prolonged survival (Cazzola and Malcovati, 2005). The high percentage of deaths attributed to causes other than MDS reflects the advanced age of the affected population. However, the chronic effects of anemia may also contribute to cardiac mortality.

3.2. MDS Associated With a Del 5 (q31-33) Cytogenetic Abnormality

Cytogenetic abnormalities are found in the dysplastic clone of 40% to 75% of patients with MDS (Noel et al, 1993). Common chromosomal changes found in MDS include trisomy 8, del (5q), del (7q), and del (20q). The del (5q) cytogenetic abnormality is perhaps the best described chromosomal aberration associated with MDS. Gene mapping experiments demonstrated that genes encoding several multipotential growth factors are located on the portion of chromosome 5 (the region between bands q31 and q33) that is generally deleted in the del (5q) cytogenetic abnormality. These genes include those that encode for IL-3, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-4, IL-5, and IL-9 (Huebner et al, 1985; Nimer and Golde, 1987). The *FMS* gene, which encodes for the receptor for macrophage colony-stimulating factor (M-CSF), is also located on this deleted region of chromosome 5 (Nienhuis et al, 1985; Le Beau et al, 1986). In addition, the chromosome deletion associated with the del (5q) cytogenetic abnormality includes the interferon regulatory factor-1 (IRF-1) coding region that encodes a DNA-binding protein that binds to a promoter element for IFN-a, IFN-ß, and other IFN-inducible genes (Boultwood et al, 1993; Willman et al, 1993; Jaju et al, 1998). One or more of these gene deletions may contribute to the pathology of MDS. Moreover, an isolated del (5q) cytogenetic abnormality is associated with a specific MDS subtype, the 5q- syndrome (Brunning et al, 2001; Vardiman et al, 2002). The 5q- syndrome was first described by Van Den Berghe et al in 5 patients with severe refractory anemia and an acquired deletion of the long arm of chromosome 5 (Van Den Berghe et al, 1974; Sokal et al, 1975). Patients with the 5q- syndrome have a refractory anemia that is associated with macrocytosis and marked dyserythropoiesis (Nimer and Golde, 1987; Horrigan et al, 1996; Brunning et al, 2001).

The recent World Health Organization (WHO) classification and criteria for MDS has designated the 5q- syndrome as a specific myelodysplastic syndrome (MDS associated with isolated del [5q] together with characteristic features) (Vardiman et al, 2002). While deletions of chromosome 5q occur in a wide spectrum of de novo and therapy-related acute myeloid leukemias and MDS, the 5q- syndrome is narrowly defined by the WHO classification as de novo MDS with an isolated cytogenetic abnormality involving deletions that include a portion of the region between bands q31 and q33 of chromosome 5 (the most common proximal breakpoints are q13, q15, and q22 and the most common distal breakpoints are q31 and q33), a normal or elevated platelet count, <5% blasts in the marrow and peripheral blood, typical dysplastic megakaryocytes (uninuclear

micromegakaryocytes), and modestly decreased to normal white blood cell counts. Additional cytogenetic abnormalities are exclusionary for the diagnosis of 5q- syndrome and are poor prognostic factors. In this regard, it should be noted that the key study, MDS-003, described herein enrolled patients with MDS with a del 5q mutation, with or without additional cytogenetic abnormalities; patients with the 5q- syndrome thus represented a subset of the MDS-003 study population.

3.3. Prognostic Features of MDS and Disease Classification

Classification systems that divide individual MDS cases into more homogeneous clinical and biologic subgroups were developed to better predict outcome and to guide management. The French-American-British (FAB), WHO, and IPSS classifications each separate patients with MDS into categories that may broadly be considered to be lower risk (IPSS low- or intermediate-1 risk) or higher risk (IPSS intermediate-2 or high risk) for leukemic transformation or death (Bennett et al, 1982; Greenberg et al, 1997; Harris et al, 1999). This is an important distinction, as treatment approaches for lower- and higher-risk MDS differ considerably with respect to intensity and type of therapy (Bowen et al, 2003).

An assessment of prognostic features by the International MDS Risk Analysis Workshop identified cytogenetic subgroups, the number of peripheral blood cytopenias, and marrow myeloblast percent to be independent predictors of survival based on multivariate analysis of data from 816 well-defined primary MDS patients across all MDS subtypes who had been evaluated in prior risk-based studies (Greenberg et al, 1997). Clinical and morphologic data were combined with cytogenetic information to identify independent factors that were predictive of survival and AML evolution (Heaney et al, 1999; Greenberg et al, 1997; Bowen et al, 2003).

Adverse factors predictive of reduced survival and earlier progression to AML were the presence of more than 10% bone marrow blasts, 2 to 3 cytopenias (defined as a Hgb level of less than 10 g/dL, an absolute neutrophil count [ANC] of less than 1,800/µL, and a platelet count of less than 100,000/µL), and complex cytogenetic abnormalities and/or chromosome 7 abnormalities. In contrast, relatively good outcomes were observed in patients with less than 5% blasts, 0 to 1 cytopenia, and bone marrow karyotypes that were normal or had isolated interstitial deletions of chromosomes 5q or 20q or a deletion of the Y chromosome (-Y). A “good” karyotype, as defined by the IPSS, was observed in 70% of the patients in the International MDS Workshop study, whereas “poor” and “intermediate” karyotypes were found in 16% and 14% of patients, respectively (Greenberg et al, 1997).

Patients were then divided into 4 prognostic categories for survival and rate of AML evolution based on percentage of bone marrow blasts: <5%, 5% to 10 %, 11% to 20%, and 21% to 30%, as shown in Table 1.

Table 1: International Prognostic Scoring System (IPSS)

Prognostic Variable	0	0.5	1.0	1.5	2.0
Marrow blasts (%)	<5	5-10	--	11-20	21-30
Karyotype	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

From: Greenberg P, et al. *Blood.* 1997;89:2079-2088.

The number of cytopenias, as an independent variable, divided patients into 2 prognostic categories, with 2 to 3 cytopenias predicting a significantly worse prognosis than 0 to 1 cytopenia. Multivariate analysis then combined the blast percentage, cytogenetic, and cytopenia subgroups to generate a prognostic model that separated patients into 4 distinctive IPSS risk categories (low, intermediate-1, intermediate-2, or high) for the median survival and time for 25% of patients to undergo evolution to AML (Greenberg et al, 1997). The IPSS low- and intermediate-1-risk groups generally correlate with the FAB subtypes refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), and refractory anemia with excess blasts (RAEB) (with <10% blasts), and the WHO categories of RA, refractory cytopenias with multilineage dysplasia (RCMD), RARS, RCMD with ringed sideroblasts (RCMD-RS), RAEB-1, unclassified MDS, and 5q- syndrome (Bennett et al, 1982; Greenberg et al, 1997; Harris et al, 1999).

In the IPSS analysis, the median survival intervals and times to 25% AML evolution ranged from several years in the low-/intermediate-1-risk groups to no more than 1 year in the intermediate-2-/high-risk group. When the low- and intermediate-1 risk categories were grouped together, median survival ranged from 3 to 6 years from diagnosis, and median time to 25% AML evolution ranged from 3 years to more than 9 years from diagnosis, as shown in Table 2. Therefore, substantial variability in outcome also exists among patients with low-/intermediate-1 risk MDS.

Table 2: Survival and Evolution to AML by IPSS Risk Category

IPSS Risk Category (% IPSS Population)	Overall Score	Median Survival (y)	25% AML Progression (y)
Low (33%)	0	5.7	9.4
Intermediate-1 (38%)	0.5-1.0	3.5	3.3
Intermediate-2 (22%)	1.5-2.0	1.2	1.1
High (7%)	=2.5	0.4	0.2

From: Greenberg P, et al. *Blood.* 1997;89:2079-2088.

In the low-/intermediate-1 risk groups, the patient's age at diagnosis was found to be a significant variable for survival, with patients up to 60 years of age having substantially longer survival times than those older than 60 years of age (Greenberg et al, 1997). There were significant differences in median survival for patients both in the low- and in the intermediate-1-risk groups when stratified by age (up to 60 years vs over 60 years and up to 70 years vs over 70 years). For example, low-risk patients up to age 60 had a median survival time of 11.8 years versus 4.8 years for those over 60. Similarly, low-risk

patients up to age 70 had a median survival of 9 years versus approximately 4 years in patients over age 70. These differences in median survival based on age persisted in the intermediate-1 groups, although the differences were not as pronounced. Age was not a significant factor in survival of the intermediate-2/high-risk groups, however, nor did it affect propensity for AML evolution in any of the risk categories.

3.4. Current Therapies

The implementation of treatment strategies for MDS is difficult because of the lack of understanding of the pathogenesis of MDS, the heterogeneity of the patient population, and the advanced age of most patients with MDS. Allogeneic bone marrow transplantation (ABMT) is the only potentially curative therapy for MDS (De Witte, 1994; Anderson et al, 1996; De Witte et al, 1997; Cheson, 1998). However, due to the advanced age of the population with MDS and the need for a histocompatible donor, this treatment option is available only to a small subset of approximately 5% of patients with MDS (Anderson et al, 1993; Kernan et al, 1993; Appelbaum and Anderson, 1998; Slavin et al, 1998). Other therapies include hematopoietic growth factors, chemotherapy, immunosuppression, and cytoprotective agents (Armitage et al, 1981; Tricot and Boogaerts, 1986; Fenaux et al, 1988; Negrin et al, 1989; Miller et al, 1992; Negrin et al, 1993; Hellström-Lindberg, 1995; List et al, 1997).

Aggressive chemotherapy is generally precluded because an elderly patient with MDS often has inadequate bone marrow reserves to recover from chemotherapy-induced hypoplasia due to a lack of normal hematopoietic stem cells. The anemia in some patients may be improved by treatment with hematopoietic growth factors, but single-agent erythropoietin has only limited effectiveness, mainly confined to patients without the need for RBC transfusions. When combined with granulocyte colony-stimulating factor (G-CSF) or GM-CSF, erythropoietin may augment the erythropoietic response in selected patients with suboptimal endogenous growth factor response (Hellström-Lindberg et al, 1993; Negrin et al, 1996; Hellström-Lindberg et al, 1998). Thus far, however, no treatment modality other than ABMT in selected patients has significantly altered the natural history of MDS, and supportive care with antibiotics and blood product transfusions is still considered as the standard of care (Silverman et al, 2002).

Recently, azacitidine (Vidaza™, Pharmion) was approved in the United States for the treatment of MDS. Although azacytidine offers a new therapeutic option for patients with MDS, the overall response rate (complete and partial response) is <20% (Vidaza, 2004), and the drug is administered subcutaneously.

4. EFFICACY SUMMARY

4.1. Background and Overview of Clinical Efficacy

The efficacy of lenalidomide for the proposed indication, the treatment of transfusion-dependent anemia due to low- or intermediate-1-risk MDS associated with a del 5q cytogenetic abnormality with or without additional cytogenetic abnormalities, has been demonstrated in 2 studies:

- Study MDS-001, a Phase 1/2, pilot, dose-finding study to gain preliminary information on the efficacy and safety of lenalidomide in patients with MDS, to identify the subpopulations of patients with MDS who respond to lenalidomide, and to identify a safe and effective dose for use in subsequent confirmatory studies.
- Study MDS-003, a Phase 2, multicenter, open-label, single-arm study to confirm the efficacy and safety of lenalidomide in patients with an IPSS diagnosis of low- or intermediate-1-risk MDS associated with a del 5 (q31-33) cytogenetic abnormality (with or without other cytogenetic abnormalities) and RBC transfusion-dependent anemia.

Study MDS-003 is submitted to support the approval, under the provisions of 21 CFR 314, Subpart H (accelerated approval of new drugs for serious or life-threatening illnesses), of lenalidomide for the treatment of patients with low- or intermediate-1-risk MDS and an associated del 5 (q31-33) cytogenetic abnormality with or without additional cytogenetic abnormalities. This request for approval follows discussions held with representatives of the Oncology Division of the US FDA on 06 June 2003 (US Food and Drug Administration, 2003) and 24 August 2004 (US Food and Drug Administration, 2004). During those discussions, FDA provided guidance that transfusion independence can be considered to be an acceptable clinical benefit endpoint and that data from Study MDS-003 could serve as a basis for filing under 21 CFR 314 if the transfusion independence was sustained and supported by additional objective findings indicating clinical benefit (e.g., histological improvement in bone marrow, increase in and stabilization of Hgb, and cytogenetic improvement).

The multicenter design of Study MDS-003 (32 study centers in the United States and 1 study site in Germany) ensures that the results are applicable to the general population of patients with low- or intermediate-1-risk MDS and an associated del 5 (q31-33) cytogenetic abnormality. The bone marrow biopsy and aspirate samples, peripheral blood smear slides, and pathology reports for each patient were reviewed centrally by an independent hematologic reviewer (John M. Bennett, MD, University of Rochester Cancer Center, Rochester, NY) to confirm the baseline diagnosis of MDS, the FAB classification (Bennett et al, 1982; Bennett et al, 1985) of the MDS subtype, and the IPSS diagnosis of low- or intermediate-1-risk MDS and to determine bone marrow response to lenalidomide during the study. The cytogenetic reports and chromosome prints for each patient were centrally reviewed by an independent cytogenetic reviewer (Gordon W. Dewald, MD, The Mayo Clinic, Rochester, MN) to confirm the patient's cytogenetic eligibility at baseline and to determine cytogenetic response during the study. Thus,

although the study did not include a control arm, its multicenter design, endpoints, and execution (with extensive central review of bone marrow and cytogenetic data) minimize bias in the data that were collected and in the results that are reported.

The exposure of 148 patients to lenalidomide in Study MDS-003 represents a robust number of patients in this indication, since the MDS are syndromes that affect approximately 5 per 100,000 of population, with those with the del 5 (q31-33) karyotype representing about 20% of those cases (Greenberg, 2000). This number of lenalidomide-treated patients is sufficient to ensure the general applicability of the study results to the general population of patients with low- or intermediate-1-risk MDS associated with a del 5 (q31-33) cytogenetic abnormality. The request for approval of lenalidomide based on data from these 148 patients is consistent with the designation of lenalidomide as an orphan drug in the United States (granted on 29 January 2004) and Europe.

The primary efficacy endpoint in Study MDS-003 is RBC-transfusion independence, defined as the absence of any intravenous RBC transfusion during any consecutive 56 days during the treatment period (e.g., Days 1 to 56, Days 2 to 57, Days 3 to 58) accompanied by at least a 1-g/dL increase from screening/baseline in Hgb. The primary efficacy endpoint of RBC-transfusion independence and the secondary efficacy endpoints of the frequency of patients with a =50% decrease from baseline in RBC transfusion requirements, platelet response, neutrophil response, bone marrow response, cytogenetic response, and duration of transfusion independence were assessed based on the criteria set forth by the MDS International Working Group (IWG) (Cheson et al, 2000), thereby ensuring that an accepted international standard for the assessment of lenalidomide as therapy for MDS was used. The change from baseline in Hgb concentration (which is not required by IWG criteria for the assessment of transfusion independence) was added as an additional objective criterion for response to further quantify and confirm transfusion independence.

The designation of RBC-transfusion independence (one of the measures of patient benefit proposed by the IWG for studies in MDS) as the primary efficacy endpoint is appropriate in that patients with MDS frequently require repeated RBC transfusions to palliate the clinical symptoms of anemia. Since repeated transfusions carry risks of transfusion-related reactions, infection, and development of secondary hemochromatosis and represent a major cause of morbidity in patients with MDS, a therapy that provides an increase in Hgb concentration and allows for RBC-transfusion independence represents a clear clinical benefit for these patients. The secondary efficacy endpoints of change in Hgb, bone marrow response, and cytogenetic response provide additional objective measures indicative of the clinical benefit of lenalidomide and support the primary study endpoint of RBC-transfusion independence.

4.2. Dosage Selection for Study MDS-003

Study MDS-001 was a pilot, 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 1/2 study of lenalidomide in patients 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. Although erythroid responses were achieved within 16 weeks, a high incidence of neutropenia and thrombocytopenia was observed within the first 4 to 8 weeks of treatment. As a result of these findings, the protocol was amended to study 2 lower-dose regimens in sequential order: 1) a "continuous" dosing regimen in which 10 mg of lenalidomide was administered daily without a planned rest, and 2) a cyclic dosing regimen in which 10 mg of lenalidomide was administered on Days 1 through 21 of repeated 28-day cycles. Twelve patients were treated with the 10-mg continuous dosing regimen. Erythroid responses were observed, and the median time to dose-limiting neutropenia or thrombocytopenia was found to be 13 weeks. Enrollment into the 10-mg cyclic dosing regimen was then initiated. After 3 erythroid responses were observed among the first 5 patients who were treated with the 10-mg cyclic dosing regimen, an additional 15 patients were enrolled in that group to gain further clinical experience with the cyclic dosing regimen.

A total of 45 patients were enrolled in Study 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 patients had a diagnosis of Philadelphia chromosome-negative chronic myeloid leukemia and, therefore, were excluded from the MDS analyses). The major erythroid response rate was 44% (19/43) and the minor erythroid response rate was 7% (3/43) across the 3 lenalidomide regimens; all of the responses were observed in patients who had low- or intermediate-1-risk MDS. Patients with a del 5 (q31-33) cytogenetic abnormality appeared to be particularly responsive to lenalidomide: The major erythroid response rate was 69% (9/13) in this population, and this was associated with a median increase of 5.3 g/dL in Hgb and with major cytogenetic responses in 85% (11/13) of the patients.

Overall, the results of this study suggested that lenalidomide, administered at an initial dose of 10 mg/day, was an effective treatment for patients with low- or intermediate-1-risk MDS, particularly in MDS with an associated del 5 (q31-33) cytogenetic abnormality. As a result of the findings in this study, Study MDS-003 was initiated in patients 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 patient population. A similar study (Study MDS-002) was also initiated in patients with low- or intermediate-1-risk MDS without a del 5 (q31-33) cytogenetic abnormality and with RBC-transfusion dependence to further evaluate the efficacy and safety of lenalidomide at a dose of 10 mg/day in that patient population.

4.3. Summary of Study MDS-003

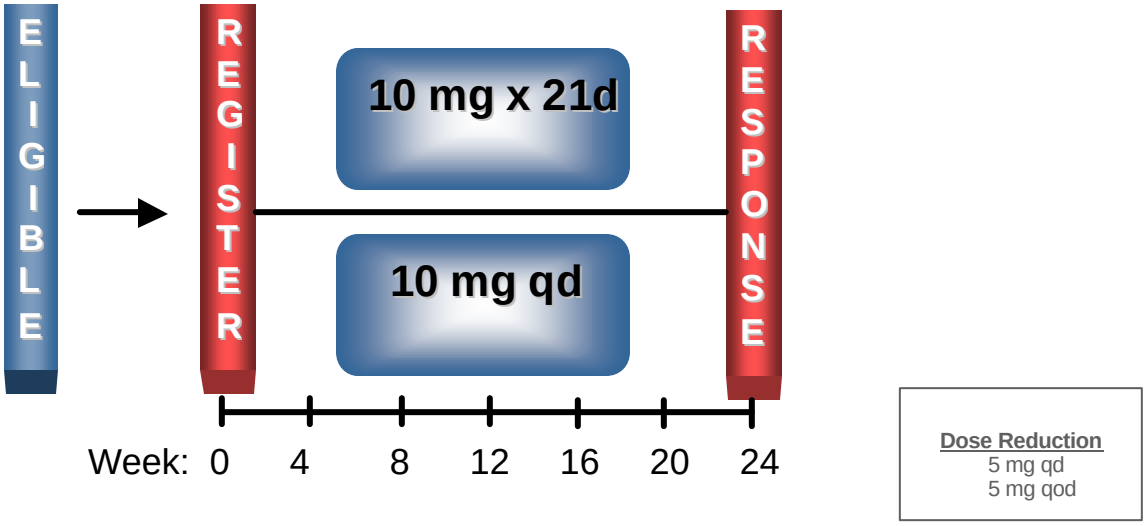
4.3.1. Study Objectives

The primary objective of the study was to evaluate the efficacy of lenalidomide for achieving hematopoietic improvement in patients with an IPSS diagnosis of low- or intermediate-1-risk MDS with a del 5 (q31-33) cytogenetic abnormality. The secondary objectives of the study were to evaluate the safety of lenalidomide in this patient population and its effects on cytogenetics and other secondary efficacy endpoints.

4.3.2. Study Design

Study MDS-003 was a Phase 2, multicenter (32 in the United States and 1 in Germany), open-label, single-arm study of the efficacy and safety of lenalidomide when administered at a dose of 10 mg daily either as a cyclic (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 148 patients with an IPSS diagnosis of low- or intermediate-1-risk MDS with an associated del 5 (q31-33) cytogenetic abnormality (as an isolated finding or associated with other cytogenetic abnormalities) and RBC-transfusion-dependent anemia. Figure 2 summarizes the study design.

Figure 2: Design of Study MDS-003



Based on preliminary data from the pilot study (Study MDS-001), the first 45 enrolled patients were treated with the 10-mg cyclic dosing regimen. However, after additional information from the pilot study suggested that the onset of response might be more rapid with the 10-mg continuous dosing regimen than with the 10-mg cyclic dosing regimen, without additional safety concerns, the 10-mg continuous dosing regimen was adopted, and 103 patients were enrolled in the study and treated with the continuous dosing regimen. Patients who began therapy on the cyclic dosing regimen and who did not experience dose-limiting adverse events were allowed to switch to the continuous dosing regimen.

Dose reductions were made based on the severity and type of the adverse events that occurred (see Appendix 8.2, Table 8.2.3, Table 8.2.4, and Table 8.2.5, for the dosage adjustment guidelines); the lowest-allowable dose was 5 mg every other day. Dose escalation above 10 mg daily was not allowed. Treatment continued until unacceptable adverse events 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. The efficacy and safety of lenalidomide were monitored at clinic visits at screening/baseline; on Day 1 of Cycles 2 through 24; on Days

8 and 22 of Cycles 1 and 2; on Day 15 of Cycles 1 through 6; and at treatment discontinuation.

The results of local review of bone marrow biopsies/aspirates, peripheral blood smear slides, pathology reports, and cytogenetic reports and chromosome prints were used to determine a patient's eligibility for the study. However, the screening/baseline information and diagnostic materials were also sent to the independent hematologic and cytogenetic reviewers for verification of the baseline diagnosis. The independent reviewers, who were blinded to the patient's transfusion response, also assessed the patients' pathologic and cytogenetic responses to lenalidomide therapy. Findings of the independent reviewers were utilized for the study analyses.

The internal Celgene Data Monitoring Committee (DMC) reviewed the efficacy and safety data to ensure that continuation of the study remained justified. The initial protocol design specified that the DMC would review the efficacy and safety data after 30 patients had completed 6 cycles of therapy. However, due to the rapid rate of enrollment and the frequency of dose interruptions, a decision was made to review the data after all of the patients had been enrolled and after 6 months of data were available. The DMC reviewed the safety and efficacy data at 2 formal meetings: 1) when all but 2 of the patients had been enrolled (30 April 2004), and 2) when all of the patients had been enrolled and all but 2 of the patients had completed 6 cycles of therapy (23 September 2004). No new previously unrecognized adverse events were identified, and the efficacy data, with the safety data, led to the conclusion that the observed risk-benefit for lenalidomide justified study continuation. In addition to these 2 formal meetings to review the efficacy and safety data, the chairman of the DMC, the principal investigator, the medical monitor, and the central hematologic and cytogenetic reviewers met in July 2004 to evaluate all of the available bone marrow histology and cytogenetics data.

4.3.3. Diagnosis and Main Criteria for Inclusion

Patients aged 18 years or older who had an IPSS diagnosis of low- or intermediate-1-risk MDS associated with a del (5q) cytogenetic abnormality that involved a deletion between bands q31 and q33 (as an isolated finding or associated with other cytogenetic abnormalities); RBC-transfusion-dependent anemia, defined as having received =2 units of RBCs within 8 weeks of the first day of study treatment; and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 were eligible for the study (see Appendix 8.2, Table 8.2.6, for a complete list of study inclusion criteria).

Exclusion criteria included proliferative chronic myelomonocytic leukemia; clinically significant anemia due to factors such as iron, vitamin B_{12}, or folate deficiencies, autoimmune or hereditary hemolysis, or gastrointestinal bleeding; ANC of <500/µL; a platelet count of <50,000/µL; compromised liver or renal function; prior grade 3 or 4 allergic or hypersensitivity reaction to thalidomide; prior grade 3 rash or desquamation while taking thalidomide; a dry bone marrow tap (aspirate); prior therapy with lenalidomide; use of hematopoietic growth factors within 7 days of the first day of treatment with the study drug; use of greater than physiologic doses of corticosteroid agents within 28 days of the first dose of study drug; and a prior history of malignancy

other than MDS unless the patient had been disease free for =3 years (pre-malignant or low-grade conditions, including cutaneous basal cell or squamous cell carcinoma or carcinoma in situ of the breast or cervix were not considered to be exclusion criteria) (see Appendix 8.2, Table 8.2.6, for a complete list of study exclusion criteria).

4.3.4 Efficacy Endpoints

4.3.4.1 Primary Endpoint

The primary efficacy endpoint was RBC-transfusion independence and was designed based on IWG criteria for transfusion independence erythroid response, with the addition of a requirement for an improvement in Hgb (independent of any recent transfusions). Transfusion independence was thus defined as the absence of any RBC transfusion during any consecutive 56 days or more during the treatment period (e.g., Days 1 to 56, Days 2 to 57, Days 3 to 58) and had to be accompanied by at least a 1-g/dL increase from screening/baseline in Hgb (see also Appendix 8.2, Table Table 8.2.7, for the IWG criteria). The requirement for a 1-g/dL increase from screening/baseline in Hgb was added to strengthen the definition of transfusion independence, after consultation with the Oncology Division of the US FDA on 06 June 2003 and before the data were analyzed

4.3.4.2 Secondary Endpoints

The secondary efficacy endpoints included the proportion of patients with a =50% decrease from baseline in RBC transfusion requirements (see Appendix 8.2, Table Table 8.2.7, for the IWG criteria), platelet response (see Appendix 8.2, Table 8.2.9, for the IWG criteria), neutrophil response (see Appendix 8.2 Table 8.2.10, for the IWG criteria), bone marrow response (see Appendix 8.2, Table 8.2.11, for the IWG criteria), and cytogenetic response (see Appendix 8.2,

Table **8.2.12**, for the IWG criteria), as determined by IWG criteria; the time to transfusion independence (see Appendix 8.2, Table 8.2.8); the duration of transfusion independence (see Appendix 8.2, Table 8.2.8); and the change from baseline in Hgb concentration.

4.3.5. Statistical Methods

The first patient was enrolled on 15 July 2003. The data cutoff date for the analysis that was included in the New Drug Application (NDA) was 15 September 2004; the median duration of follow-up for that analysis was 33 weeks (range, 1.3-59.1 weeks). The study enrollment is closed, but the study remains ongoing.

4.3.5.1. Efficacy Populations

The efficacy populations described in this briefing document are the intent-to-treat (ITT) and the modified intent-to-treat (MITT) populations. The ITT population includes all patients who were enrolled and received study drug; the MITT population focuses on a subset of patients who had more extensive documentation of transfusion dependence prior to study entry and for whom the IPSS classification of low- or intermediate-1-risk MDS with a del 5q cytogenetic abnormality was fully verified by central review. It should be noted that nearly all of the enrolled patients met the protocol-specified eligibility criteria for transfusion dependence and IPSS classification (protocol eligibility was based on local determination of transfusion dependence, IPSS score, and presence of a del 5q abnormality), and all of the enrolled patients met the eligibility criterion for presence of a del 5q abnormality both on local and central review. Thus, while the enrolled patients met the protocol patient selection criteria with few exceptions, the MITT population represented the subset of patients selected from the total enrolled patient group as having the strongest documentation of transfusion dependence and having low- or intermediate-1-risk MDS IPSS score that had been evaluated and verified on central review.

The MITT population was specified as the primary efficacy population. The MITT population was specifically defined to include all patients who 1) were documented as having received =2 units of packed RBCs (pRBC) in each of the two 8-week (56 day) periods 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 at any time during the 16 weeks prior to administration of study drug; 2) had a diagnosis of low- or intermediate-1-risk MDS that was confirmed by central hematologic review of an evaluable bone marrow aspirate/biopsy; 3) had a confirmed 5q deletion based on central cytogenetic review; and 4) took at least 1 dose of study drug. The requirement for documentation of transfusion dependence over 16 weeks prior to the study exceeded the protocol eligibility requirement (which stipulated documentation of transfusion dependence in the 8 weeks prior to the study) and was included in the definition of the MITT population after discussion with FDA (06 June 2003) to further ensure that patients were truly transfusion dependent.

Since the analysis of data from the MITT population uses this more restrictive definition of transfusion dependence and includes the data from the central reviews of bone marrow, peripheral smear, and cytogenetic findings, it is deemed to provide the most

conservative estimate of the efficacy of lenalidomide; thus, this analysis represents the primary study analysis and provides the primary evidence of the effectiveness of lenalidomide in the target population. The analysis of data for the ITT population, which constitutes the 148 enrolled patients, reveals similar findings and is provided as additional evidence of the robustness of the data demonstrating the efficacy of lenalidomide for the treatment of patients with low- or intermediate-1-risk MDS associated with a del 5 (q31-33) cytogenetic abnormality.

A third efficacy population, the per-protocol population, was also defined. This population included all patients who 1) received =2 units pRBCs during the immediate 56 days (8 weeks) prior to administration of study drug; 2) had a diagnosis of low- or intermediate-1-risk MDS that was confirmed by central hematologic review of an evaluable bone marrow aspirate/biopsy, 3) had a confirmed 5q del based on central cytogenetic review, and 4) took at least 1 dose of study drug. The efficacy results for the per-protocol population, which includes 115 patients, are consistent with those of the MITT and ITT populations and, therefore, are not presented herein.

4.3.5.2. Analytical Methods

Response rates and confidence intervals (CI) were determined for the primary (RBC-transfusion independence) and secondary (decrease of =50% in RBC-transfusion requirements; change from baseline in Hgb concentration; platelet response; neutrophil response; bone marrow response; cytogenetic response; and duration of response) endpoints. Median and mean change from baseline values and other relevant summary statistics were determined for the Hgb data. Results were presented for relevant subgroups. Kaplan-Meier estimates were provided for the duration of transfusion independence. Relevant summary statistics (mean, standard deviation [SD], median, CI, minimum, and maximum) were determined for the time to transfusion independence.

4.3.6. Results

The data cutoff date for the analysis that was summarized in the NDA was 15 September 2004. Subsequently, RBC-transfusion independence (the primary endpoint), the duration of transfusion independence response, and the median change from baseline in Hgb were analyzed using updated data (with a cutoff date of 15 March 2005) to further characterize the efficacy of lenalidomide and the durability of response; both the original and updated data are summarized in this document for these 2 key efficacy parameters.

4.3.6.1. Disposition of Patients

One hundred forty-eight patients were enrolled in the study and treated with lenalidomide: 45 patients were initially treated with the 10-mg cyclic dosing regimen, and 103 patients were initially treated with the 10-mg continuous dosing regimen. Table 3 summarizes the disposition of patients as of the 15 September 2004 data cutoff date by the initial lenalidomide regimen and overall.

Table 3: Disposition of Patients by Initial Lenalidomide Regimen and Overall (NDA Database: 15 September 2004)—Study MDS-003 (ITT Population

Disposition	10 mg Cont N=103	10 mg Cyclic N=45	Overall N=148
No. (%) of Patients Still Active in Study	77 (75%)	29 (64%)	106 (72%)
N (%) of Patients Withdrawn From Study Before Completing 24 Weeks After Completing 24 Weeks	26 (25%) 20 (20%) 6 (6%)	16 (36%) 14 (31%) 2 (4%)	42 (28%) 34 (23%) 8 (5%)
Primary Reason for Discontinuation Adverse Event Lack of Therapeutic Effect Patient Withdrew Consent Lost to Follow-up Death Protocol Violation Other	 7 (7%) 9 (9%) 1 (1%) 0 6 (6%) 0 3 (3%)	 9 (20%) 4 (9%) 1 (2%) 0 2 (4%) 0 0	 16 (11%) 13 (9%) 2 (1%) 0 8 (5%) 0 3 (2%)
No. (%) Completing 24 Weeks of Study	80 (78%)	31 (69%)	111 (75%)

As of the 15 September 2004 data cutoff date, 42 (28%) of the 148 patients had discontinued from the study: 34 (23%) of the 148 patients discontinued before completing 24 weeks of the study, and 8 (5%) discontinued treatment after completing 24 weeks of the study. The primary reasons for discontinuation were adverse events (11%; 16/148) and lack of therapeutic effect (9%; 13/148). Of the 106 patients 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%) of the 148 patients had completed at least 24 weeks of the study as of 15 September 2004.

4.3.6.2. Study Duration

Table 4 summarizes study duration by the initial lenalidomide regimen and overall.

Table 4: Study Duration by Initial Lenalidomide Regimen and Overall (NDA Database: 15 September 2004)—Study MDS-003 (ITT Population)

Study Duration [a]	10 mg Cont N=103	10 mg Cyclic N=45	Overall N=148
Mean	30.5	35.4	32.0
SD	10.78	16.22	12.83
Median	32.1	41.0	33.0
Min, Max	1.3, 55.1	5.1, 59.1	1.3, 59.1
Distribution of Patients by Duration			
At least 4 weeks	102 (99%)	45 (100%)	147 (99%)
At least 8 weeks	96 (93%)	40 (89%)	136 (92%)
At least 16 weeks	91 (88%)	38 (84%)	129 (87%)
At least 24 weeks	80 (78%)	31 (69%)	111 (75%)
At least 32 weeks	53 (52%)	29 (64%)	82 (55%)

[a] Duration (wk) = (date of discontinuation or 15-Sep-04 – date of first dose +1) / 7.

The median duration of study participation was 33.0 weeks (range, 1.3-59.1 weeks). As of the 15 September 2004 data cutoff date, 75% (111/148) of the patients had participated in the study for at least 24 weeks, and 55% (82/148) of the patients had participated in the study for at least 32 weeks.

4.3.6.3. Primary Efficacy Populations

The MITT population includes 94 of the 148 patients who were enrolled in the study. The 54 patients who were excluded from the MITT population were excluded for the following reasons: 1) a diagnosis of low- or intermediate-1-risk MDS was not able to be verified by central review of the baseline bone marrow aspirate and biopsy slides (n=28; this generally reflected the central reviewer's determination that the specimens provided for his review were not adequate for MDS classification); 2) inability to obtain documentation to confirm that the patient received =2 units of pRBCs in the first of the two 8-week periods in the 16-week period prior to the first dose of lenalidomide (i.e., the period from 16 weeks to 8 weeks prior to first dose) (n=19); or 3) the patient was found to have been RBC-transfusion-free for a period of ≥56 days within the immediate 16 weeks prior to the start of study treatment (n=7). As noted previously, the second and third reasons for exclusion cited here reflect a more stringent definition of transfusion dependence prior to study entry, as compared with the original protocol-specified eligibility criteria.

The ITT population includes all 148 enrolled patients.

4.3.6.4. Baseline Demographic and Disease-related Characteristics

Table 5 summarizes the baseline demographic and disease-related characteristics for the MITT and ITT populations by the initial lenalidomide regimen and overall.

Table 5: Baseline Demographic and Disease-related Characteristics by Initial Lenalidomide Regimen and Overall (NDA Database: 15 September 2004)—Study MDS-003

Characteristic	MITT Population			ITT Population		
	10 mg Cont N=63	10 mg Cyclic N=31	Overall N=94	10 mg Cont N=103	10 mg Cyclic N=45	Overall N=148
Age (years)						
Mean	69.4	73.7	70.8	69.3	71.5	70.0
Median	70.0	74.0	71.5	71.0	72.0	71.0
Min, Max	41.0, 95.0	600, 91.0	41.0, 95.0	37.0, 95.0	51.0, 91.0	37.0, 95.0
=65 years	23 (37%)	8 (26%)	31 (33%)	35 (34%)	13 (29%)	48 (32%)
>65 years	40 (64%)	23 (74%)	63 (67%)	68 (66%)	32 (71%)	100 (67%)
Gender						
Male	21 (33%)	11 (36%)	32 (34%)	34 (33%)	17 (38%)	51 (35%)
Female	42 (67%)	20 (65%)	62 (66%)	69 (67%)	28 (62%)	97 (66%)
Race						
White	62 (98%)	29 (94%)	91 (97%)	100 (97%)	43 (96%)	143 (97%)
Black	0	0	0	0	0	0
Hispanic	1 (2%)	1 (3%)	2 (2%)	2 (2%)	1 (2%)	3 (2%)
Asian/Pacific Islander	0	1 (3%)	1 (1%)	1 (1%)	1 (2%)	2 (1%)
Duration of MDS (years)						
Mean	4.0	3.6	3.8	3.4	3.4	3.4
Median	3.1	3.0	3.1	2.5	2.5	2.5
Min, Max	0.2, 20.7	0.3, 14.4	0.2, 20.7	0.1, 20.7	0.2, 14.4	0.1, 20.7
5q(-) (31-33) Chromosomal Abnormality						
Yes	63 (100%)	31 (100%)	94 (100%)	103 (100%)	45 (100%	148 (100%)
IPSS Score (Based on Central Review) [a]						
Low (0)	33 (52%)	9 (29%)	42 (45%)	42 (41%)	13 (29%)	55 (37%)
Intermediate-1 (0.5-1.0)	30 (48%)	22 (71%)	53 (55%)	40 (39%)	25 (56%)	65 (44%)
Intermediate-2 (1.5-2.0)	0	0	0	4 (4%)	2 (4%)	6 (4%)
High (=2.5)	0	0	0	1 (1%)	1 (2%)	2 (1%)
Unable to Classify	0	0	0	16 (16%)	4 (9%)	20 (14%)

Table 5: Baseline Demographic and Disease-related Characteristics by Initial Lenalidomide Regimen and Overall (NDA Database: 15 September 2004)—Study MDS-003 (continued)

Characteristic	MITT Population			ITT Population		
	10 mg Cont N=63	10 mg Cyclic N=31	Overall N=94	10 mg Cont N=103	10 mg Cyclic N=45	Overall N=148
ECOG Performance Status						
0	26 (41%)	12 (39%)	38 (40%)	43 (42%)	16 (36%)	59 (40%)
1	29 (46%)	18 (58%)	47 (50%)	50 (49%)	25 (56%)	75 (51%)
2	8 (13%)	1 (3%)	9 (10%)	10 (10%)	4 (9%)	14 (10%)
FAB Classification (Based on Central Review						
RA	39 (62%)	19 (61%)	58 (62%)	53 (52%)	24 (53%)	77 (52%)
RARS	11 (18%)	3 (10%)	14 (15%)	13 (13%)	3 (7%)	16 (11%)
RA/RARS	0	1 (3%)	1 (1%)	1 (1%)	1 (2%)	2 (1%)
RAEB	11 (18%)	7 (23%)	18 (19%)	18 (18%)	12 (27%)	30 (20%)
CMML	2 (3%)	1 (3%)	3 (3%)	2 (2%)	1 (2%)	3 (2%)
Acute Leukemia	0	0	0	0	1 (2%)	1 (1%)
Not Diagnostic of MDS	0	0	0	2 (2%)	0	2 (1%)
Unable to Classify	0	0	0	14 (14%)	3 (7%)	17 (12%)

[a] IPSS score = sum of marrow blast + karyotype + cytopenia score

The demographic characteristics of the patients in the study are reflective of those of the general population of patients with MDS associated with a del 5 (q31-33) cytogenetic abnormality (Boultwood et al, 1993): The majority of the patients were female and older than 65 years of age.

4.3.6.5. Primary Efficacy Variable: RBC-transfusion Independence

Table 6 and Table 7 summarize the frequency of RBC-transfusion independence for the MITT and ITT populations as of 15 September 2004 (as provided in the original NDA) and 31 March 2005 (as provided in an update of the primary efficacy variable, submitted to the NDA).

Table 6: Frequency of RBC-transfusion Independence by Initial Lenalidomide Regimen and Overall (NDA Database: 15 September 2004)—Study MDS-003

IPSS Risk Category[a]	Statistic	MITT Population			ITT Population		
		10 mg Cont	10 mg Cyclic	Overall	10 mg Cont	10 mg Cyclic	Overall
Overall	Number of Patients Number Transfusion Independent % Transfusion Independent Exact 95% CI				103 70 68% 58.0, 76.8	45 25 56% 40.0, 70.4	148 95 64% 55.9, 71.9
Low + Int-1	Number of Patients Number Transfusion Independent % Transfusion Independent Exact 95% CI	63 41 65% 52.0, 76.7	31 16 52% 33.1, 69.8	94 57 61% 50.0, 70.6	82 57 70% 58.4, 79.2	38 23 61% 43.4, 76.0	120 80 67% 57.5, 75.0
Low	Number of Patients Number Transfusion Independent % Transfusion Independent Exact 95% CI	33 20 61% 42.1, 77.1	9 7 78% 40.0, 97.2	42 27 64% 48.0, 78.4	42 28 67% 50.5, 80.4	13 11 85% 54.6, 98.1	55 39 71% 57.1,82.4
Int-1	Number of Patients Number Transfusion Independent % Transfusion Independent Exact 95% CI	30 21 70% 50.6, 85.3	22 9 41% 20.7, 63.6	52 30 58% 43.2, 71.3	40 29 73% 56.1, 85.4	25 12 48% 27.8, 68.7	65 41 63% 50.2, 74.7
Int-2 + High	Number of Patients Number Transfusion Independent % Transfusion Independent Exact 95% CI				5 3 60% 14.7, 94.7	3 0 0% 0.0, 70.8	8 3 38% 8.5, 75.5

Note: Transfusion independence is defined as the absence of the intravenous infusion of an 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.

[a] IPSS risk category: low (combined score = 0), intermediate-1 (combined score = 0.5-1.0), intermediate-2 (combined score = 1.5-2.0), high (combined score =2.5); the combined score = marrow blast score + karyotype score + cytopenia score.

Table 7: Frequency of RBC-transfusion Independence by Initial Lenalidomide Regimen and Overall (Updated Database: 31 March 2005)—Study MDS-003

IPSS Risk Category[a]	Statistic	MITT Population			ITT Population		
		10 mg Cont	10 mg Cyclic	Overall	10 mg Cont	10 mg Cyclic	Overall
Overall	Number of Patients Number Transfusion Independent % Transfusion Independent Exact 95% CI				103 72 70% 60.1, 78.5	45 27 60% 44.3, 74.3	148 99 67% 58.7, 74.4
Low + Int-1	Number of Patients Number Transfusion Independent % Transfusion Independent 95% CI	63 42 67% 53.7, 78.0	31 18 58% 39.1, 75.5	94 60 64% 53.3, 73.5	82 58 71% 59.6, 80.3	38 25 66% 48.6, 80.4	120 83 69% 60.1, 77.3
Low	Number of Patients Number Transfusion Independent % Transfusion Independent 95% CI	33 20 61% 42.1, 77.1	9 8 89% 51.8, 99.7	42 28 67% 50.5, 80.4	42 28 67% 50.5, 80.4	13 12 92% 64.0, 99.8	55 40 73% 59.0, 83.9
Int-1	Number of Patients Number Transfusion Independent % Transfusion Independent 95% CI	30 22 73% 54.1, 87.7	22 10 46% 24.4, 67.8	52 32 62% 47.0, 74.7	40 30 75% 58.8, 87.3	25 13 52% 31.3, 72.2	65 43 66% 53.4, 77.4
Int-2 + High	Number of Patients Number Transfusion Independent % Transfusion Independent Exact 95% CI				5 3 60% 14.7, 94.7	3 0 0% 0.0, 70.8	8 3 38% 8.5, 75.5

Note: Transfusion independence is defined as the absence of the intravenous infusion of an 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.

[a] IPSS risk category: low (combined score = 0), intermediate-1 (combined score = 0.5-1.0), intermediate-2 (combined score = 1.5-2.0), high (combined score =2.5); the combined score = marrow blast score + karyotype score + cytopenia score.

As of the 15 September 2004 data cutoff date, 61% (57/94) of the patients in the MITT population had achieved RBC-transfusion independence. Similar response rates were observed both in patients with low-risk (64%; 27/42) and in patients with intermediate-1-risk (58%; 30/52) MDS and with both the 10-mg continuous (65%; 41/63) and the 10-mg cyclic (52%; 16/31) dosing regimens. The 57 responders in the MITT group had received a mean of 5.2 units (range, 1-12 units; median, 5 units) of pRBCs in each of the two 8-week periods (56 days) during the 16 weeks prior to administration of the study drug, demonstrating that these patients were transfusion dependent at baseline. The overall response rate in the ITT population as of 15 September 2004 was 64% (95/148).

The reported response rates as of 15 September 2004 represented the minimum rates of RBC-transfusion independence that would be observed, since some patients continuing in the study had already achieved a =50% reduction in their blood transfusion requirements (see Table 13) and, with continued treatment, could potentially achieve RBC-transfusion independence. Further follow-up data have shown 4 additional responses to lenalidomide therapy: As of 31 March 2005, 64% (60/94) of the patients in the MITT population and 67% (99/148) of the patients in the ITT population had become RBC-transfusion independent. Considering the NDA database, as well as the updated database, it is clear that patients who respond to lenalidomide typically show evidence of response early in the course of treatment, with a minority of patients attaining transfusion independence later, after up to 6 months of treatment (as described below, for the original NDA database).

4.3.6.6. Secondary Efficacy Endpoints

4.3.6.6.1. Time to Transfusion Independence

Table 8 summarizes the time to RBC-transfusion independence for the MITT and ITT populations based on the 15 September 2004 cutoff date.

Table 8: Time (Weeks) to RBC-transfusion Independence by Initial Lenalidomide Regimen and Overall (NDA Database: 15 September 2004)—Study MDS-003

	MITT Population			ITT Population		
Time (Weeks)	10 mg Cont N=41	10 mg Cyclic N=16	Overall N=57	10 mg Cont N=70	10 mg Cyclic N=25	Overall N=95
Median [95% CI]	5.3 [4.0, 5.9]	3.8 [2.3, 6.4]	4.7 [3.6, 5.6]	4.5 [3.6, 5.3]	3.6 [2.3, 6.1]	4.1 [3.4, 5.3]
Mean	5.8	5.2	5.6	5.0	5.1	5.0
SD	4.30	4.73	4.39	4.08	5.04	4.33
Min, Max	0.3, 19.1	0.3, 16.3	0.3, 19.1	0.3, 19.1	0.3, 18.9	0.3, 19.1

Note: Time to transfusion independence is measured from the day of the first dose of study drug to the first day of the 56-day transfusion-free period.

The median time to achieve RBC-transfusion independence was 4.7 weeks (range, 0.3-19.1 weeks) for the 57 responders in the MITT population and 4.1 weeks (range, 0.3-19.1 weeks) for the 95 responders in the ITT population.

4.3.6.6.2. Duration of Response

As of the 15 September 2004 data cutoff date, 83% (47/57) of the patients in the MITT population and 86% (82/95) of the patients in the ITT population who had become RBC-transfusion independent remained RBC-transfusion independent; 18% (10/37) of the patients in the MITT population and 14% (13/95) of the patients in the ITT population who had become RBC-transfusion independent had relapsed (i.e., required a transfusion after a response). Since so few patients had relapsed, the Kaplan-Meier procedure was unable to provide estimates of the median duration of transfusion independence (i.e., the median duration had not been reached) for either the MITT or ITT population.

As of the 31 March 2005 data cutoff date, 63% (37/59) of the patients in the MITT population and 67% (66/97) of the patients in the ITT population who had become RBC-transfusion independent remained RBC-transfusion independent; 37% (22/59) of the patients in the MITT population and 33% (32/97) of the patients in the ITT population who had become RBC-transfusion independent had relapsed (i.e., required a transfusion after a response). Based on preliminary Kaplan-Meier estimates, the median duration of RBC-transfusion independence is 74.6 weeks in both the MITT and ITT populations. This value may still change, since a substantial number of patients remain transfusion independent on treatment and are censored in the analysis.

Table 9 provides a categorization of the duration of response (measured from the date of the first of the consecutive 56 or more days during which the patient was free of RBC transfusion to the date immediately preceding the day on which the patient received the first RBC transfusion after the period of transfusion independence), as observed prior to 15 September 2004 (the NDA cutoff date). Table 9 also provides summary statistics for means and medians for the duration of response observed by the 15 September 2004 cutoff (and not taking censoring into account, i.e., for patients still responding, the duration of response was measured to the date that the last transfusion history was obtained or to the cutoff date, whichever was earlier). Table 10 summarizes these data, using the updated database (cutoff date, 31 March 2005). The estimates of duration of response provided in the summary statistics in these 2 tables are very conservative in that they represent the outcomes that would be obtained if all patients required a transfusion immediately after the last transfusion history was obtained (or on 15 September 2004 or 31 March 2005, for those patients who continued to be documented as transfusion independent as of the cutoff date).

Table 9: Duration of RBC-transfusion Independence (Weeks) by Initial Lenalidomide Regimen and Overall (NDA Database: 15 September 2004)—Study MDS 003

	MITT Population			ITT Population		
	10 mg Cont	10 mg Cyclic	Overall	10 mg Cont	10 mg Cyclic	Overall
Kaplan-Meier Estimates						
No. of Patients With Transfusion-independence Response	41	16	57	70	25	95
No.(%) Patients Who Progressed [a]	7 (17%)	3 (19%)	10 (18%)	10 (14%)	3 (12%)	13 (14%)
No. (%) Patients Who Maintained Transfusion Independence [b]	34 (83%)	13 (81%)	47 (83%)	60 (86%)	22 (88%)	82 (86%)
Median	NE	NE	NE	NE	NE	NE
95% CI	NE	NE	NE	37.9, NE	NE	NE
Summary Statistics						
Mean	26.9	35.8	29.4	27.5	34.1	29.2
SD	9.03	13.29	11.04	8.16	13.23	10.11
Median	28.0	41.1	30.1	27.5	40.7	30.0
Min, Max	8.1, 44.0+	8.1, 46.1+	8.1, 46.1+	8.1, 44.0+	8.1, 48.1+	8.1, 48.1+
Distribution of Patients by Duration of Response						
Duration of response at least 4 weeks	41 (100%)	16 (100%)	57 (100%)	70 (100%)	25 (100%)	95 (100%)
Duration of response at least 8 weeks	41 (100%)	16 (100%)	57 (100%)	70 (100%)	25 (100%)	95 (100%)
Duration of response at least 12 weeks	37 (90%)	14 (88%)	51 (90%)	65 (93%)	22 (88%)	87 (92%)
Duration of response at least 16 weeks	36 (88%)	13 (81%)	49 (86%)	64 (91%)	20 (80%)	84 (88%)
Duration of response at least 20 weeks	34 (83%)	13 (81%)	47 (83%)	61 (87%)	20 (80%)	81 (85%)
Duration of response at least 24 weeks	26 (63%)	13 (81%)	39 (68%)	50 (71%)	20 (80%)	70 (74%)
Duration of response at least 52 weeks	0	0	0	0	0	0

NE, not estimable
Note: Duration of response is measured from the first of the consecutive days during which the patient was free of RBC transfusions to the date of the first RBC transfusion after this period.
[a] Had a transfusion after a response
[b] Duration of response was censored at the date of the last visit for patients who maintained transfusion independence.

Table 10: Duration of RBC-transfusion Independence (Weeks) by Initial Lenalidomide Regimen and Overall (Updated Database: 31 March 2005)—Study MDS-003

	MITT Population			ITT Population		
	10 mg Cont	10 mg Cyclic	Overall	10 mg Cont	10 mg Cyclic	Overall
Kaplan-Meier Estimates						
No. of Patients With Transfusion-independence Response	42	18	60	72	27	99
No.(%) Patients Who Progressed [a]	16 (38%)	6 (33%)	22 (37%)	25 (35%)	7 (26%)	32 (32%)
No. (%) Patients Who Maintained Transfusion Independence [b]	26 (62%)	12 (67%)	38 (63%)	47 (65%)	20 (74%)	67 (68%)
Median	74.6	NE	74.6	74.6	NE	74.6
95% CI	52.0, 74.6	44.4, NE	52.1, 74.6	NE	NE	NE
Summary Statistics						
Mean	44.0	46.7	44.8	45.1	47.3	45.7
SD	18.07	24.94	20.19	16.40	23.51	18.51
Median	49.7	57.4	50.9	50.9	58.0	52.3
Min, Max	8.1, 74.6+	8.1, 72.7+	8.1, 74.6+	8.1, 74.6+	8.1, 72.7+	8.1, 74.6+
Distribution of Patients by Duration of Response						
Duration of response at least 4 weeks	42 (100%)	18 (100%)	60 (100%)	72 (100%)	27 (100%)	99 (100%)
Duration of response at least 8 weeks	42 (100%)	18 (100%)	60 (100%)	72 (100%)	27 (100%)	99 (100%)
Duration of response at least 12 weeks	38 (91%)	15 (83%)	53 (88%)	67 (93%)	23 (85%)	90 (91%)
Duration of response at least 16 weeks	37 (88%)	13 (72%)	50 (83%)	66 (92%)	20 (74%)	86 (87%)
Duration of response at least 20 weeks	37 (88%)	13 (72%)	50 (83%)	66 (92%)	20 (74%)	86 (87%)
Duration of response at least 24 weeks	35 (83%)	13 (72%)	48 (80%)	63 (88%)	20 (74%)	83 (84%)
Duration of response at least 52 weeks	18 (43%)	11 (61%)	29 (48%)	35 (49%)	17 (63%)	52 (53%)

NE, not estimable
Note: Duration of response is measured from the first of the consecutive days during which the patient was free of RBC transfusions to the date of the first RBC transfusion after this period.
[a] Had a transfusion after a response
[b] Duration of response was censored at the date of the last visit for patients who maintained transfusion independence.

As of the 15 September 2004 data cutoff date, the duration of response was at least 24 weeks in 68% (39/57) of the responders in the MITT population and in 74% (70/95) of the responders in the ITT population. As of 31 March 2005, the duration of response was at least 24 weeks in 80% (48/59) of the responders in the MITT population and in 84% (83/97) of the responders in the ITT population and was at least 52 weeks in 48% (29/59) of the patients in the MITT population and in 53% (52/97) of the patients in the ITT population. In both analyses, the decreasing number of patients by response duration interval (e.g., between duration of response of at least 20 weeks and at least 24 weeks in the first analysis and at least 24 weeks and at least 52 weeks in the follow-up analysis) reflects that fact that patients have been in the study for variable periods of time and responded to treatment at different times during the study (i.e., some of the responders responded earlier than others and, therefore, had a longer duration of response as of the data cutoff date). That is, this decreasing number of patients by response duration interval reflects censoring of a substantial number of patients who continue on study with ongoing response to therapy, as well as smaller numbers of patients who have experienced relapse after response or have discontinued from the study.

Figure 3 and Figure 4 provide the Kaplan-Meier plots of duration of response for the responders in the MITT population as of the 15 September 2004 (NDA database) and 31 March 2005 (updated database) cutoff dates, respectively.

Figure 3: Kaplan-Meier Plot of Duration of Response (NDA Database: 15 September 2004)—Study MDS-003 (MITT Population)

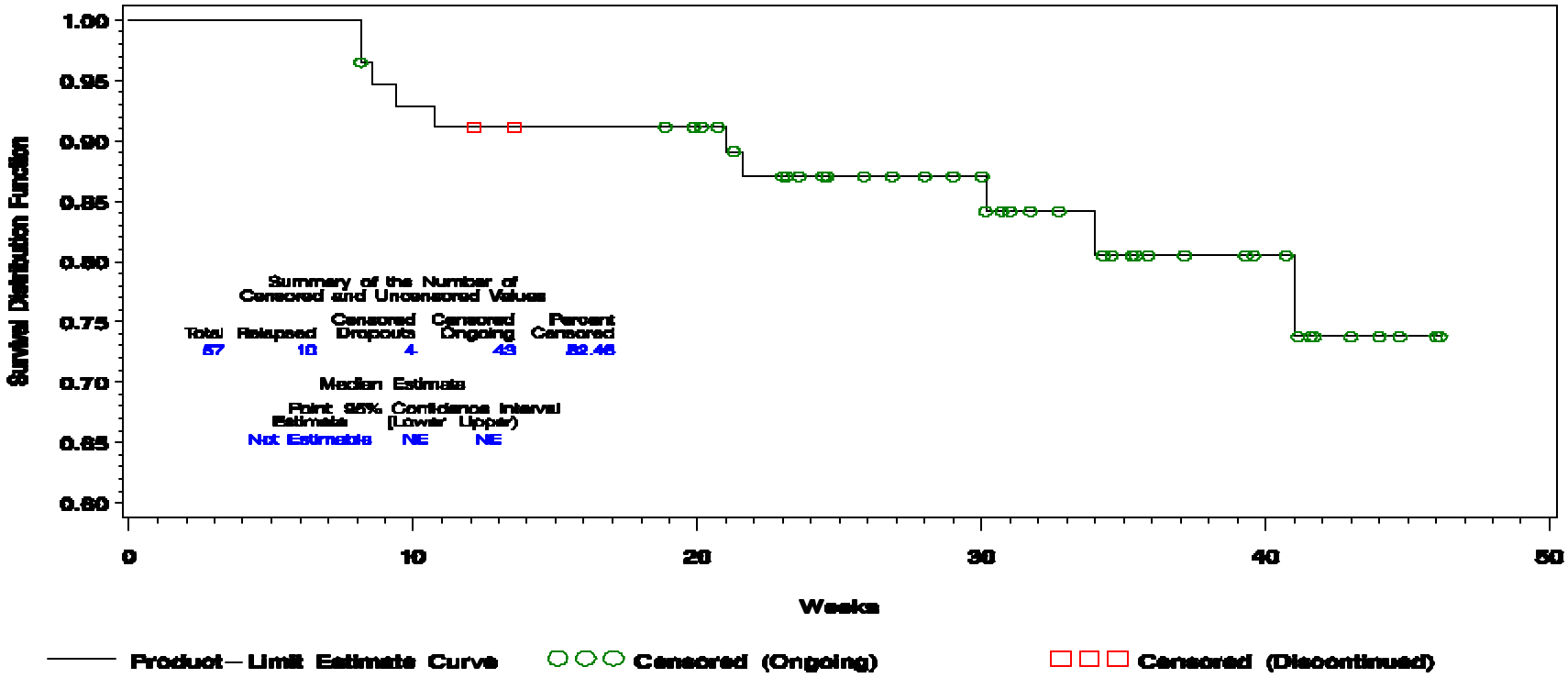
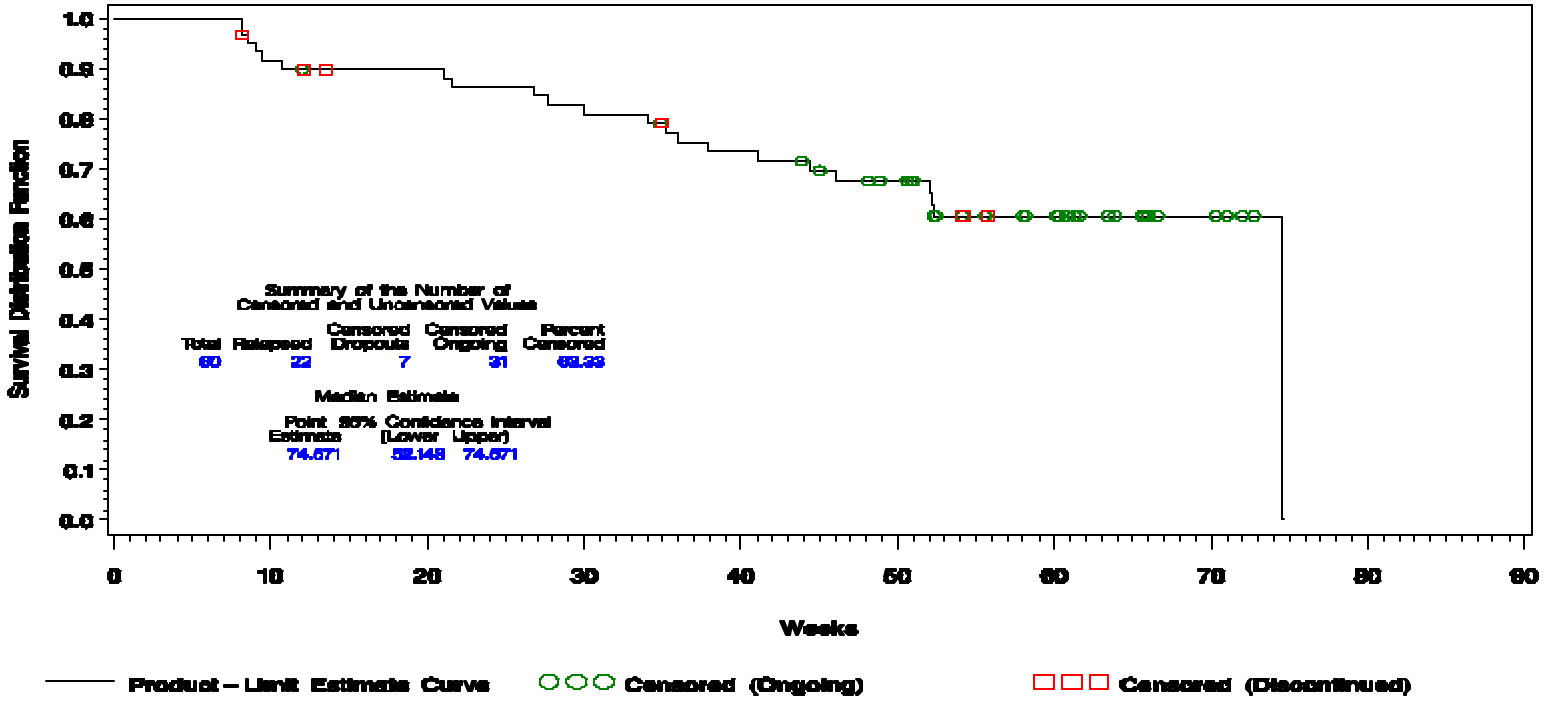


Figure 4: Kaplan-Meier Plot of Duration of Response (Updated Database: 31 March 2005)—Study MDS-003 (MITT Population)



4.3.6.6.3. Change in Hemoglobin From Baseline to Maximum Value During Response Period

Table 11 summarizes the maximum change from baseline in Hgb as of the 15 September 2004 cutoff date (NDA database) for the patients in the MITT and ITT populations who became RBC-transfusion independent analyzed for the initial lenalidomide regimen and for the overall population of responders; Table 12 summarizes these data as of the 31 March 2005 update.

Table 11: Change in Hemoglobin (mg/dL) From Baseline to Maximum Value During the Response Period by Initial Lenalidomide Regimen and Overall (NDA Database: 15 September 2004)—Study MDS-003

	MITT Population									ITT Population								
	10 mg Cont N=41			10 mg Cyclic N=16			10 mg Overall N=57			10 mg Cont N=70			10 mg Cyclic N=25			10 mg Overall N=95		
Statistic	BL	Max	Change	BL	Max	Change	BL	Max	Change	BL	Max	Change	BL	Max	Change	BL	Max	Change
Mean	7.6	13.3	5.7	8.1	13.5	5.4	7.7	13.4	5.6	7.8	13.1	5.3	8.0	13.4	5.3	7.8	13.2	5.3
SD	0.99	2.03	1.96	0.85	1.96	2.03	0.97	2.00	1.97	1.01	1.99	1.97	0.73	1.98	2.03	0.95	1.98	1.98
Median	7.6	13.6	5.6	8.0	13.5	5.4	7.7	13.6	5.5	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	7.1	9.3	1.1	5.3	9.2	1.1	5.3	9.2	2.2	7.0	9.3	1.1	5.3	9.2	1.1
Max	10.0	17.0	11.4	10.3	16.4	9.1	10.3	17.0	11.4	10.4	18.6	11.4	10.3	16.9	9.1	10.4	18.6	11.4

BL, baseline

Note: The 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 patients who did not receive a subsequent transfusion during the study period.

Table 12: Change in Hemoglobin (mg/dL) From Baseline to Maximum Value During the Response Period by Initial Lenalidomide Regimen and Overall (Updated Database: 31 March 2005)—Study MDS-003

	MITT Population									ITT Population								
	10 mg Cont N=42			10 mg Cyclic N=18			10 mg Overall N=60			10 mg Cont N=72			10 mg Cyclic N=27			10 mg Overall N=99		
Statistic	BL	Max	Change	BL	Max	Change	BL	Max	Change	BL	Max	Change	BL	Max	Change	BL	Max	Change
Mean	7.6	13.6	5.9	8.0	13.3	5.3	7.7	13.5	5.7	7.8	13.3	5.5	8.0	13.3	5.3	7.8	13.3	5.5
SD	1.01	1.98	1.97	1.00	2.24	2.15	1.01	2.05	2.03	1.02	2.01	2.00	0.85	2.17	2.12	0.98	2.04	2.03
Median	7.6	13.7	6.0	8.0	13.4	5.3	7.8	13.7	5.6	7.7	13.4	5.4	8.0	13.4	5.3	7.8	13.4	5.3
Min	5.3	9.2	2.2	5.6	9.3	1.1	5.3	9.2	1.1	5.3	9.2	2.2	5.6	9.3	1.1	5.3	9.2	1.1
Max	10.0	17.1	11.4	10.3	16.6	9.1	10.3	17.1	11.4	10.4	18.6	11.4	10.3	16.9	9.1	10.4	18.6	11.4

BL, baseline
Note: The 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 patients who did not receive a subsequent transfusion during the study period.

The median increase in blood Hgb level from baseline to the maximum Hgb level achieved (up to the 15 September 2004 data cutoff date) during RBC-transfusion independence was 5.5 g/dL (range, 1.1-11.4 g/dL) in the 57 responders in the MITT population and 5.2 mg/dL (range, 1.1-11.4 g/dL) in the 95 responders in the ITT population. Based on updated data as of 31 March 2005, the median increase in blood Hgb from baseline from baseline to the maximum Hgb level achieved during RBC-transfusion independence was 5.7 g/dL (range, 1.1-11.4 g/dL) in the 60 responders in the MITT population and 5.5 mg/dL (range, 1.1-11.4 mg/dL) in the 99 responders in the ITT population.

4.3.6.6.4. Decrease of =50% in RBC-transfusion Requirements

Table 13 summarizes the frequency of patients in the MITT and ITT populations who had achieved a =50% decrease in RBC transfusions as of 15 September 2004 (NDA database) by the initial lenalidomide regimen and for the overall study population.

Table 13: Frequency of Patients With 50% or Greater Decrease in RBC-transfusion Requirements by Initial Lenalidomide Regimen and Overall (NDA Database: 15 September 2004)—Study MDS-003

IPSS Risk Category[a]	Statistic	MITT Population			ITT Population		
		10 mg Cont	10 mg Cyclic	Overall	10 mg Cont	10 mg Cyclic	Overall
Overall	Number of Patients Number With Reduction Response % With Reduction Response Exact 95% CI				103 79 77% 67.3, 84.5	45 31 69% 53.4, 81.8	148 110 74% 66.5, 81.1
Low + Int-1	Number of Patients Number With Reduction Response % With Reduction Response Exact 95% CI	63 46 73% 60.3, 83.4	31 22 71% 52.0, 85.8	94 68 72% 62.2, 81.1	82 63 77% 66.2, 85.4	38 29 76% 59.8, 88.6	120 92 77% 68.1, 83.9
Low	Number of Patients Number With Reduction Response % With Reduction Response Exact 95% CI	33 22 67% 48.2, 82.0	9 8 89% 51.8, 99.7	42 30 71% 55.4, 84.3	42 30 71% 55.4, 84.3	13 12 92% 64.0, 99.8	55 42 76% 63.0, 86.8
Int-1	Number of Patients Number With Reduction Response % With Reduction Response Exact 95% CI	30 24 80% 61.4, 92.3	22 14 64% 40.7, 82.8	52 38 73% 59.0, 84.4	40 33 83% 67.2, 92.7	25 17 68% 46.5, 85.1	65 50 77% 64.8, 86.5
Int-2 + High	Number of Patients Number With Reduction Response % With Reduction Response Exact 95% CI				5 4 80% 28.4, 99.5	3 0 0% 0.0, 70.8	8 4 50% 15.7, 84.3

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

[a] IPSS risk category: low (combined score = 0), intermediate-1 (combined score = 0.5-1.0), intermediate-2 (combined score = 1.5-2.0), high (combined score =2.5); the combined score = marrow blast score + karyotype score + cytopenia score.

Overall, as of the 15 September 2004 data cutoff date, 72% (68/94) of the patients in the MITT population and 74% (110/148) of the patients in the ITT population had achieved a =50% decrease in their pretreatment RBC-transfusion requirements during lenalidomide therapy. Seventy-one percent (30/42) of the patients in the MITT population with low-risk MDS and 73% (38/52) of the patients in the MITT population with intermediate-1-risk MDS had achieved a =50% decrease in their pretreatment RBC-transfusion requirements as of 15 September 2004. The transfusion reduction response rates among patients with low- or intermediate-1-risk MDS were 76% (42/55) and 77% (50/65), respectively, in the ITT population.

4.2.6.6.5. Platelet Response

As of the 15 September 2004 data cutoff date, no major or minor platelet responses had been observed among the 16 patients in the MITT population who were evaluable for platelet response (see Appendix 8.2, Table 8.2.9, for the criteria for response). Although platelet responses meeting IWG criteria were not achieved, stable platelet counts were achieved in patients during RBC-transfusion independence, as patients generally did not require platelet transfusions during periods of RBC-transfusion independence (see Section 5.3.2.1 for a discussion of platelet transfusions).

4.3.6.6.6. Neutrophil Response

As of the 15 September 2004 data cutoff date, 1 major neutrophil response had been observed among the 6 patients in the MITT population who were evaluable for neutrophil response (see Appendix 8.2, Table 8.2.10, for the criteria for response).

4.3.6.6.7. Bone Marrow Effects

At least 1 bone marrow specimen was sent to central review for 147 (>99%) of the 148 patients in the ITT population. This included 102 of the 103 patients in the 10-mg continuous dosing group and all 45 of the patients in the 10-mg cyclic dosing group.

Bone Marrow Biopsy Results

Baseline bone marrow slides adequate for interpretation by the central reviewer were available for 138 (94%) of the 147 patients. The marrow cellularity at baseline was packed in 9 (6%) patients, hypercellular in 41 (30%) patients, normocellular in 63 (46%) patients, and hypocellular in 25 (18%) patients.

Red blood cell-transfusion independence was achieved in 5 (56%) of the patients with packed marrows, in 27 (66%) of the patients with hypercellular marrows, in 45 (71%) of the patients with normocellular marrows, and in 15 (60%) of the patients with hypocellular marrows at baseline. Red blood cell-transfusion relapse occurred in 1 (20%) of 5 major erythroid responders with packed marrows at baseline, in 3 (11%) of 27 major erythroid responders with hypercellular marrows at baseline, in 8 (18%) of 45 major erythroid responders with normocellular marrows at baseline, and in 2 (13%) of 15 major erythroid responders with hypocellular marrows at baseline.

Eighty-three patients with packed, hypercellular, or normocellular marrows at baseline had follow-up bone marrow biopsy specimens that were adequate for central review.

After lenalidomide therapy (3-6 months), the marrow cellularity was found to be hypocellular at follow-up marrow biopsy in 29 (35%) patients and aplastic in 3 (4%) patients. All 3 patients who developed aplasia were treated in the 10-mg continuous dosing group. One aplastic patient was found to have atypical chronic myelogenous leukemia (CML) instead of MDS at central review. The development of AML coincided with the development of aplasia in the second aplastic patient. The third aplastic patient achieved RBC-transfusion independence and experienced a decrease in marrow blasts from 6% (RAEB) to 1% (RA).

None of the 25 patients with hypocellular marrows at baseline have developed aplasia.

Sixty-five (78%) of the 83 patients with packed, hypercellular, or normocellular marrows at baseline who had follow-up bone marrow biopsy specimens that were adequate for central review achieved RBC-transfusion independence. Among the 65 patients with RBC-transfusion independence, 25 (38%) were patients who had a hypocellular/aplastic marrow at follow-up and 40 (62%) were patients who had a packed, hypercellular, or normocellular marrow at follow-up. Among the 83 patients with follow-up marrows, 32 patients had hypocellular/aplastic marrows at follow-up, and 51 patients had packed, hypercellular, or normocellular marrows at follow-up. Thus, 78% (25/32) of patients with hypocellular/aplastic marrows at follow-up achieved RBC-transfusion independence, and 78% (40/51) of patients with packed, hypercellular, or normocellular marrows at follow-up achieved RBC-transfusion independence.

These findings demonstrate that lenalidomide-induced RBC-transfusion independence was achieved in patients with MDS associated with a del 5q abnormality who presented with packed, hypercellular, normocellular, or hypocellular bone marrows. The achievement of RBC-transfusion independence was independent of the cellularity at the follow-up marrow biopsy.

Bone Marrow Aspirate Results

A baseline bone marrow aspirate specimen from 127 patients was adequate for central review assessment. Dysplastic changes were found by the central reviewer to be present in at least 2 hematopoietic cell lines of 120 (94%) of the 127 patients at baseline. Baseline and follow-up bone marrow aspirate specimens from 81 patients were adequate for central review comparative assessment.

Among the 81 patients with available follow-up bone marrow aspirate specimens, the follow-up bone marrow aspirates from 27 (33%) patients were assessed by the central reviewer to have no evidence of MDS (morphologic and pathologic complete remission). In addition, dysplastic changes had resolved in all 3 hematopoietic cell lines of 5 other patients. The baseline bone marrow aspirate was inadequate for interpretation in 3 patients; the central reviewer assessed the follow-up marrow findings to remain consistent with RA in 1 patient; and a few (3%) ringed sideroblasts remained in 1 patient with chronic myelomonocytic leukemia (CMML). All 32 of these above-noted patients, who had no evidence of MDS on follow-up bone marrow aspiration or who had

resolution of dysplastic changes in all 3 hematopoietic cell lines, achieved RBC-transfusion independence, and only 1 of these patients developed RBC-transfusion relapse (the relapse occurred during a period when the study drug was interrupted).

In 9 (30%) of 30 patients with RAEB, the follow-up bone marrow aspirate revealed a decrease in the marrow blast count compared with that observed at baseline and the FAB classification improved to RA or RARS according to the central reviewer. In 7 (44%) of 16 patients with RARS, decreases in the percentages of ringed sideroblasts were observed in the follow-up bone marrow aspirate by the central reviewer (in 3 patients ringed sideroblasts completely resolved) so that the FAB classification was changed to RA. Among these 16 patients with evidence of bone marrow improvement following lenalidomide treatment, 13 achieved RBC-transfusion independence; 2 of these 13 patients subsequently developed RBC-transfusion relapse; the relapses occurred during periods when the study drug was interrupted.

Disease progression in the bone marrow was observed in 8 (5%) patients. In 3 (2%) of these patients the follow-up marrow aspirate was diagnostic of AML. The 3 cases of transformation to AML occurred at 1 clinical site. The baseline FAB classifications for these patients were RAEB (IPSS classification of intermediate-2-risk), marrow too hypocellular to assign, and RA (IPSS classification of intermediate-1-risk). The times from the diagnosis of MDS to study entry for these patients were 5.6 years, 3.2 years, and 5.6 years, respectively. Follow-up marrow aspirates showed that 4 other patients progressed from RA or RARS at baseline to RAEB and that 1 additional patient progressed from RAEB at baseline to refractory anemia with excess blasts in transition (RAEB-t). The time from diagnosis of MDS to study entry for these 5 patients who developed disease progression ranged from 2.4 to 6.8 years.

One 1 of the 8 patients who developed disease progression achieved RBC-transfusion independence during study treatment. The development of disease progression in this patient coincided with RBC-transfusion relapse.

These findings demonstrate that histologically confirmed bone marrow improvement was induced by lenalidomide in a substantial proportion of patients and that the observed histological bone marrow improvement was associated with durable periods of RBC-transfusion independence. Only a small percentage of patients developed evidence of disease progression on follow-up bone marrow examination.

4.3.6.6.8. Cytogenetic Response

Overall Cytogenetic Response Rates

All of the patients who were enrolled in the study were required to have cytogenetic evidence of a del 5q abnormality. Although not all of the patients had 20 analyzable metaphases at baseline, all had evidence of a del 5q abnormality in at least 2 metaphases (147 patients) or by fluorescent in situ hybridization (FISH; 1 patient) based on central review. The analysis of cytogenetic response considered all patients for whom follow-up data were available, including data from karyotype analysis in which fewer than 20 metaphases were analyzed. In this analysis, patients were categorized based only on the number of abnormal metaphases: Those who had no abnormal metaphases during treatment were categorized as "major" responders, and those who had a =50% reduction in the number of abnormal metaphases were categorized as "minor" responders; patients with no baseline or postbaseline evaluations were non-evaluable in this analysis.

Based on this analysis (which was presented in the NDA), as of 15 September 2004, major cytogenetic responses had been observed in 41% (46/111) and minor cytogenetic responses had been observed in 26% (29/111) of the patients who were evaluable for cytogenetic response, as shown in Table 14.

Table 14: Cytogenetic Response by Initial Lenalidomide Regimen and Overall (NDA Database: 15 September 2004)—Study MDS-003 (ITT Population)

Response Category	10 mg Overall
Evaluable	111
Major Response [95% CI]	46 (41%) [32.2, 51.2]
Minor Response [95% CI]	29 (26%) [18.2, 35.3]

A subsequent analysis was conducted to determine the cytogenetic response rate in patients who had at least 20 analyzable metaphases in repeated karyotype analyses, with karyotype analyses performed both at baseline and during treatment. In this analysis, a "major" cytogenetic response required zero abnormal metaphases out of at least 20 analyzable metaphases at postbaseline evaluations, and a "minor" cytogenetic response required a =50% reduction in abnormal metaphases (compared with the baseline karyotype) at one or more one postbaseline evaluation. Patients who did not meet either of these criteria were categorized as nonresponders, and those who were without 20 measurable metaphases both at baseline and postbaseline were nonevaluable (this includes patients with only baseline evaluations).

Based on this analysis, as of 15 September 2004, major cytogenetic responses were observed in 44% (32/72) and minor cytogenetic responses were observed in 29% (21/72) of the patients who were evaluable for cytogenetic response, as shown in Table 15. The Central Reviewer also evaluated cytogenetic response among 99 patients who had evidence of a del 5q abnormality in at least 2 metaphases at baseline (regardless of the total number of analyzable metaphases at baseline) and at least 20 analyzable metaphases in a follow-up evaluation. This evaluation, also shown in Table 15, revealed similar results, with major cytogenetic response (i.e., absence of abnormal metaphases in the follow-up evaluation) in 37 patients (37%).

Table 15: Cytogenetic Response in Patients With Twenty Analyzable Metaphases (NDA Database: 15 September 2004)—Study MDS-003 (ITT Population)

Patients With 20 Evaluable Metaphases [a]	
Evaluable	72
Major Cytogenetic Response [95% CI]	32 (44%) [32.7, 56.6]
Minor Cytogenetic Response [95% CI]	21 (29%) [19.1, 41.1]
Central Reviewer Criteria	
Evaluable	99
Major Cytogenetic Response [95% CI]	37 (37%) [27.8, 47.7]

[a] 20 evaluable metaphases at baseline and at one or more on-study evaluations

Correlation of Cytogenetic Findings and Clinical Outcomes

Samples of hematopoietic cells obtained from bone marrow aspirate specimens underwent standard cytogenetic testing (banding techniques) at baseline in 147 patients (>99%) of the 148 patients in the ITT population. Among these 147 patients, 110 (75%) had an MDS clone with an isolated del 5q cytogenetic abnormality, while 37 (25%) had an MDS clone with a del 5q abnormality and one or more additional cytogenetic abnormalities. The additional cytogenetic abnormalities included the following: poor prognostic cytogenetic abnormalities (IPSS karyotype score of 1.0) in 10 patients (complex abnormalities in 7 patients and abnormalities of chromosome 7 in 3 patients); intermediate prognostic cytogenetic abnormalities in 25 patients (IPSS karyotype score of 0.5); and a –Y chromosomal abnormality in 2 patients (IPSS karyotype score of 0).

RBC-transfusion Independence by Baseline Cytogenetic Findings. Seventy-four (67%) of the 110 patients with an isolated del 5q abnormality and 21 (57%) of the 37 patients with a del 5q abnormality and an additional cytogenetic abnormality achieved RBC-transfusion independence. Five (50%) of 10 patients with poor prognostic cytogenetic abnormalities achieved RBC-transfusion independence, and 16 (59%) of the remaining 27 patients with other cytogenetic abnormalities in addition to a del 5q abnormality achieved RBC-transfusion independence. All patients whose additional chromosomal abnormalities were trisomy 8, -Y, or del 13q achieved RBC-transfusion independence (3/3, 2/2, and 3/3, respectively). In contrast, no patient with a monosomy 7 or a del 11q abnormality achieved RBC-transfusion independence (0/3 and 0/3, respectively). One patient had an MDS clone with a del 7q abnormality in addition to a del 5q abnormality; this patient achieved a period of RBC-transfusion independence that lasted for 328 days before again requiring transfusions of RBCs.

Association of Cytogenetic Response With RBC-transfusion Independence. Among the 75 patients with a cytogenetic response and the 3 cytogenetic nonresponders who achieved a complete resolution of the del 5q abnormality (n=78), 74 (95%) also achieved RBC-transfusion independence. In contrast, only 11 (33%) 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 (96%; 44/46) and minor cytogenetic responders (93%; 27/29). All 7 minor cytogenetic responders who had a complete resolution of the del 5q abnormality achieved RBC-transfusion independence. In addition, the 3 cytogenetic nonresponders who experienced a complete resolution of the del 5q abnormality also achieved RBC-transfusion independence.

Only 8 (11%) of the 74 patients who achieved both cytogenetic improvement and RBC-transfusion independence, compared with 5 (45%) of 11 patients who achieved RBC-transfusion independence in the absence of cytogenetic improvement, have experienced relapse, i.e., subsequently required transfusions of RBCs. One additional patient has required transfusions of RBCs after a period of RBC-transfusion independence (follow-up cytogenetic testing was not available for this patient). None of the 7 minor cytogenetic responders who had a complete resolution of the del 5q abnormality have had a relapse (requiring further RBC transfusions) despite the presence of other cytogenetic abnormalities. The 3 cytogenetic nonresponders who had a complete resolution of the del 5q abnormality also remain RBC-transfusion independent.

These results demonstrate that lenalidomide is effective treatment for patients with MDS with dysplastic hematopoietic clones who have an isolated del 5q abnormality, as well as for patients with MDS who have dysplastic clones that have an additional cytogenetic abnormality associated with a del 5q abnormality. These findings also demonstrate that lenalidomide-induced cytogenetic improvement is associated with achievement of durable RBC-transfusion independence in patients with MDS associated with a del 5q cytogenetic abnormality.

4.3.7. Comparison of Results of Subpopulations

Table 16 summarizes the analysis of erythroid response to lenalidomide by subgroup and by initial lenalidomide regimen and overall.

Table 16: Analysis of Erythroid Response to Lenalidomide by Subgroup, Initial Dosage Regimen, and Overall (NDA Database: 15 September 2004)—Study MDS-003 (MITT Population)

Prognostic Variable	10 mg Cont	10 mg Cyclic	Overall
Age			
=65 years	57% (13/23)	63% (5/8)	58% (18/31)
>65 years	70% (28/40)	48% (11/23)	62% (39/63)
p-value	0.411	0.685	0.823
Gender			
Male	67% (14/21)	36% (4/11)	56% (18/32)
Female	64% (27/42)	60% (12/20)	63% (39/62)
p-value	1.000	0.273	0.656
Race			
White	65% (40/62)	55% (16/29)	62% (56/91)
other	100% (1/1)	0% (0/2)	33% (1/3)
p-value	1.000	0.226	0.559
ECOG at Baseline			
0	69% (18/26)	58% (7/12)	66% (25/38)
1	59% (17/29)	50% (9/18)	55% (26/47)
2	75% (6/8)	0% (0/1)	67% (6/9)
p-value	0.706	0.716	0.672
FAB Classification [a]			
RA	69% (27/39)	58% (11/19)	66% (38/58)
RARS	46% (5/11)	33% (1/3)	43% (6/14)
RAEB	73% (8/11)	43% (3/7)	61% (11/18)
CMML	50% (1/2)	100% (1/1)	67% (2/3)
p-value	0.400	0.677	0.378
IPSS Risk Category [a]			
Low	61% (20/33)	78% (7/9)	64% (27/42)
Int-1	70% (21/30)	41% (9/22)	58% (30/52)
p-value	0.597	0.113	0.533

[a] Based on Central Review.
Note: P-values are from a 2-sided Fishers Exact Test. Data are based on the 25-Sep-04 cutoff date.

No significant differences in response (i.e., RBC-transfusion independence) were observed by age, gender, race, ECOG performance status, FAB classification, or IPSS risk factor when examined for the MITT population.

Table 17 summarizes the response to lenalidomide for the ITT population overall and by FAB classification, by the initial lenalidomide regimen and for the total ITT population.

Table 17: Frequency of RBC-transfusion Independence by French-American-British (FAB) Classification and by Initial Lenalidomide Regimen and Overall (NDA Database: 15 September 2005)—Study MDS-003 (ITT Population)

FAB at Baseline	Statistic	10 mg Cont	10 mg Cyclic	Overall
Overall	No. of Patients No. (%) Transfusion Independent [95% CI]	103 70 (68%) [58.0, 76.8]	45 25 (56%) [40.0, 70.4]	148 95 (64%) [55.9, 71.9]
RA	No. of Patients No. (%) Transfusion Independent [95% CI]	53 39 (74%) [59.7, 84.7]	24 16 (67%) [44.7, 84.4]	77 55 (71%) [60.0, 81.2]
RARS	No. of Patients No. (%) Transfusion Independent [95% CI]	13 7 (54%) [25.1, 80.8]	3 1 (33%) [0.8, 90.6]	16 8 (50%) [24.7, 75.3]
RA/RARS	No. of Patients No. (%) Transfusion Independent [95% CI]	1 0 [0.0, 97.5]	1 0 [0.0, 97.5]	2 0 [0.0, 84.2]
RAEB	No. of Patients No. (%) Transfusion Independent [95% CI]	18 13 (72%) [46.5, 90.3]	12 5 (42%) [15.2, 72.3]	30 18 (60%) [40.6, 77.3]
CMML	No. of Patients No. (%) Transfusion Independent [95% CI]	2 1 (50%) [1.3, 98.7]	1 1 (100%) [2.5, 100.0]	3 2 (67%) [9.4, 99.2]
Acute Leukemia	No. of Patients No. (%) Transfusion Independent [95% CI]	0 — —	1 0 [0.0, 97.5]	1 0 [0.0, 97.5]
Not Diagnostic of MDS	No. of Patients No. (%) Transfusion Independent [95% CI]	2 1 (50%) [1.3, 98.7]	0 — —	2 1 (50%) [1.3, 98.7]
Unable to Classify	No. of Patients No. (%) Transfusion Independent [95% CI]	14 9 (64%) {35.1, 87.2]	3 2 (67%) [9.4, 99.2]	17 11 (65%) [38.3, 85.8]

Note: Transfusion independence is defined as the absence of the intravenous infusion of an 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.

Evaluation of response to lenalidomide by FAB classification shows that patients with an FAB classification of RA, RARS, RAEB, or CMML responded to lenalidomide therapy.

4.4. Analysis of Clinical Information Relevant to Dosing Recommendations

Both Study MDS-001 and Study MDS-003 demonstrate that lenalidomide 10 mg daily is an effective dose to treat anemia in patients with transfusion-dependent low- or intermediate-1-risk MDS associated with a 5 (q31-33) cytogenetic abnormality. Though neither Study MDS-001 nor Study MDS-003 was designed or powered to prospectively compare the efficacy of the lenalidomide regimens to other treatments, both regimens demonstrated impressive activity, which was accompanied by a favorable safety profile. Hematological improvement, which was manifested as RBC-transfusion independence

and which was supported by sustained elevations and improvement in Hgb values, histologic bone marrow improvement, and cytogenetic normalization, was observed with both the continuous and cyclic dosing regimens, as summarized for Study MDS-003 in Table 18.

Table 18: Summary of Efficacy Variables by Initial Lenalidomide Regimen and Overall (MITT Population)—Study MDS-003

Efficacy Parameter[a]	10 mg Cont	10 mg Cyclic	Overall
RBC-transfusion Independence[b, c]	65% (41/63) 67% (42/63)	52% (16/31) 58% (18/31)	61% (57/94) 64% (60/94)
Median Change From Baseline in Hgb at Maximum Value During Response Period	5.6	5.4	5.5
=50% Reduction in Pretreatment RBC Transfusion Requirements	73% (46/63)	71% (22/31)	72% (68/94)
Cytogenetic Response[d] Major Minor	27% (12/45) 38% (17/45)	44% (10/23) 22% (5/23)	32% (22/68) 32% (22/68)

[a] Unless otherwise specified, results represent data available as of the 15 September 2004 data cutoff date.
[b] The absence of any RBC transfusion during any consecutive rolling 56 days in the evaluation period and an increase in hemoglobin of at least 1 g/dL from the minimum during the 56 days prior to the maximum during the transfusion-independent period, excluding the first 30 days after the last transfusion before the transfusion-free period.
[c] The first entry in each column represents data as of the 15 September 2004 cutoff date; the second entry in each column represents data as of 31 March 2005.
[d] Based on patients who were evaluable for cytogenetic response at baseline (i.e., those who had at least 20 analyzable metaphases at baseline using conventional cytogenetic techniques). Major response = no detectable cytogenetic abnormality if a preexisting abnormality was present. Minor response = =50% reduction in the percent of abnormal metaphases.

Based on the overall assessment of response and on the findings that the safety profiles of the 10-mg continuous and 10-mg cyclic dosing regimens are similar (see Section 5), the recommended starting dose of lenalidomide is 10 mg daily, either administered continuously or for 21 days of repeated 28-day cycles. The dose of lenalidomide may be reduced to 5 mg/day in patients who cannot tolerate the 10-mg dose.

No formal studies have been conducted to assess the effects of age, gender, race, renal dysfunction, or hepatic impairment on the pharmacokinetics of lenalidomide. However, the available clinical data do not indicate that adjustments in dose are needed for efficacy- or safety-related reasons based on age, gender, or race. Specifically, subgroup analyses show that achievement of RBC-transfusion independence is not affected by age, gender, ECOG performance status, FAB classification, or IPSS classification (see Table 16), suggesting that no dosage adjustments are needed based on demographic or prognostic factors.

4.5. Persistence of Efficacy and/or Tolerance Effects

The median duration of response for the 57 responders in the MITT population had not been reached as of the 15 September 2004 data cutoff date for the NDA (see Table 9 and Figure 3). As of the data cutoff date, 82% (47/57) of the responders remained transfusion independent, and 18% (10/57) had relapsed (i.e., required a transfusion after a response). The duration of response was at least 24 weeks in 39 (68%) of the 57 responders. Thus, response to lenalidomide has been durable in the responders who met the prespecified criteria for transfusion dependence (over the 16 prior weeks) at baseline.

The response data for the ITT population further supported the durability of the response to lenalidomide. As of the 15 September 2004 data cutoff date for the NDA, 64% (95/148) of the patients in the ITT population had achieved RBC-transfusion independence. Eighty-two (86%) of the 95 responders in the ITT population remained transfusion independent, and 13 (85%) had relapsed (i.e., required a transfusion after a response) as of the 15 September 2004 data cutoff date. As with the MITT population, the median duration of response had not yet been reached in the ITT population. However, the duration of RBC-transfusion independence was at least 24 weeks in 70 (74%) of the 95 responders in the ITT population.

Additional follow-up data for the MITT population through 31 March 2005 have shown the durability of the response to lenalidomide. Based on preliminary Kaplan-Meier estimates, the median duration of transfusion independence response is 74.6 weeks in both the MITT and ITT populations (see Table 10 and Figure 4). As of 31 March 2005, the duration of transfusion independence response was already at least 52 weeks in 48% (29/59) of the responders in the MITT population and in 52% (52/97) of the responders in the ITT population.

4.6. Other Information Relative to Efficacy

Study MDS-002 is identical in design to Study MDS-003 except that the study population comprises patients with RBC-transfusion dependent, low- or intermediate-1-risk MDS without an associated del 5 (q31-33) cytogenetic abnormality. Two hundred fifteen patients were enrolled in this study and treated with 10 mg of lenalidomide daily either by the cyclic (115 patients) or continuous dosing regimen (100 patients). Of these 215 patients, 118 (55 and 63, respectively, in the continuous and cyclic dosing groups) met the criteria for inclusion in the MITT population (as specified in Section 4.3.5.1). Table 19 summarizes the frequency of RBC-transfusion independence in Study MDS-002 as of the 15 June 2004 data cutoff date by the initial lenalidomide regimen and for the overall MITT study population.

Table 19: Frequency of RBC-transfusion Independence by Initial Lenalidomide Regimen and Overall (MITT Population)—Study MDS-002

IPSS Risk Category[a] at Baseline	Statistic	10mg Cont.	10mg Cyclic	Overall
Overall (Low+Int-1)	Number of Patients	55	63	118
	Number Transfusion Independent[b]	10	15	25
	% Transfusion Independent[b]	18	24	21
	Exact 95% CI	[9.1, 30.9]	[14.0, 36.2]	[14.2, 29.7]
Low	Number of Patients	29	36	65
	Number Transfusion Independent[b]	7	9	16
	% Transfusion Independent[b]	24	25	25
	Exact 95% CI	[10.3, 43.5]	[12.1, 42.2]	[14.8, 36.9]
Int-1	Number of Patients	26	27	53
	Number Transfusion Independent[b]	3	6	9
	% Transfusion Independent[b]	12	22	17
	Exact 95% CI	[2.4, 30.2]	[8.6, 42.3]	[8.1, 29.8]

[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] The absence 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

As of the 15 June 2004 cutoff date, 21% (25/118) of the patients with low- or intermediate-1 risk MDS without an associated del 5 (q31-33) cytogenetic abnormality had achieved RBC-transfusion independence during lenalidomide therapy. The response to lenalidomide was 18% (10/55) in the 10-mg continuous dosing group and 24% (15/63) in the 10-mg cyclic dosing group; however, the seemingly higher response rate in the cyclic dosing group may reflect the longer time of drug exposure for patients in this dosing group. 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 and resulted in a =50% decrease from pretreatment in RBC-transfusion requirements in 38% (45/118) of the patients. These reported response rates represent the minimum rates of RBC-transfusion independence that will be observed in this study, since a number of patients who were continuing in the study had already achieved a =50% reduction in their blood transfusion requirements as of the data cutoff date.

The interim results of this study suggest that lenalidomide is an effective treatment for a significant proportion of patients with low- or intermediate-1-risk MDS without an associated del 5 (q31-33) cytogenetic abnormality, although the observed response rates are lower than the response rates observed in patients with a del 5q cytogenetic abnormality. These results further corroborate and extend the major findings of the earlier pilot study (Study MDS-001) and the Phase 2 study patients with low- or intermediate-1-risk MDS with an associated del 5 (q31-33) cytogenetic abnormality (Study MDS-003).

4.7 Phase 4 Commitments

Additional clinical research is in progress to confirm and extend the findings that have been observed in the Phase 2 studies of lenalidomide in RBC-transfusion-dependent patients with low- or intermediate-1-risk MDS with or without a del 5q cytogenetic abnormality (see Appendix 8.2, Table 8.2.2, for descriptions of these studies).

Study CC-5013-MDS-004, the confirmatory study for Study MDS-003, is a multicenter, randomized, double-blind, placebo-controlled, 3-arm study of the efficacy and safety of lenalidomide versus placebo in RBC-transfusion-dependent patients with low- or intermediate-1-risk MDS associated with a del 5q cytogenetic abnormality. Transfusion-dependent anemia is defined as documentation that a subject with anemia due to MDS did not have any consecutive 56 days (8 weeks) that were RBC transfusion free during at least the 112 days (16 weeks) prior to Day 1 of the pre-randomization phase. The primary endpoint is RBC-transfusion independence for =26 weeks. The secondary endpoints include erythroid response; duration of RBC-transfusion independence; the change in Hgb concentration in patients who achieve a major erythroid response; the change in platelet count and ANCs from baseline; cytogenetic response; bone marrow response; safety; and quality-of-life assessments.

One hundred sixty-two patients are planned for enrollment. Patients will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups: 1) lenalidomide, 5 mg daily for 28 days of repeated 28-day cycles; 2) lenalidomide, 10 mg daily on Days 1 to 21 of repeated 28-day cycles (and matching placebo on Days 22-28); or 3) placebo daily for 28 days of repeated 28-day cycles. Double-blind treatment will continue for up to 52 weeks unless prevented by disease progression or unacceptable toxicity, after which patients who have responded to therapy may continue to receive lenalidomide in an open-label extension phase for up to an additional 52 weeks. Patients will be evaluated for response at Week 16 of the double-blind period of the study. Patients in the placebo group who have not attained at least a minor response at Week 16 will be offered the opportunity to receive treatment with lenalidomide (at a starting dose of 5 mg daily) in the open-label extension phase of the study; patients in the lenalidomide 5-mg/day group who have not attained at least a minor response at Week 16 and who have not required a reduction in the lenalidomide dose will be offered the opportunity to receive treatment with lenalidomide at dose of 10 mg/day in the open-label extension phase of the study. Patients in the lenalidomide 10 mg/day group who have not attained at least a minor response to therapy at Week 16 will be discontinued from the study. Enrollment in the study has begun.

A study of similar design (Study CC-5013-MDS-005) is planned in RBC-transfusion-dependent patients with low- or intermediate-1-risk MDS without a del 51[31] cytogenetic abnormality as a confirmatory study for Study MDS-002. A third study of lenalidomide alone and in combination with recombinant erythropoietin in patients with low or intermediate-1-risk MDS and symptomatic anemia, to be conducted by the ECOG, is also planned.

5. SAFETY SUMMARY

Pooled data from 3 studies of lenalidomide (Studies MDS-001, MDS-002, and MDS-003) in 408 patients with MDS that were available as of 31 December 2004 (as presented in the 120-day Safety Update Report) are provided to establish the safety of lenalidomide for the proposed indication; 395 of these 408 patients received treatment with the recommended starting dose of 10 mg/day, and 13 received treatment with 25 mg/day of lenalidomide, which represents the first dose that was explored in the pilot study (Study MDS-001). Since the recommended starting dose of lenalidomide for the treatment of patients with MDS is 10 mg/day, administered continuously or for the first 21 days of repeated 28-day cycles, the discussions of safety data focus on the overall experience with the 10-mg dose. Lenalidomide has also been the subject of a number of other clinical studies, in a variety of malignant and non-malignant conditions. However, the safety data presented here focus on findings from the studies in MDS, as these findings are of primary relevance to the use of this drug in the proposed indication; and other studies (which have been included in NDA submission) have not revealed additional relevant safety findings.

The incidence of adverse events was generally similar across the 3 MDS studies, and the data presentations provided here thus focus on the pooled data from the 3 studies. Higher grades of myelosuppression (neutropenia and thrombocytopenia) were observed in Study MDS-003 study (MDS with the del 5q cytogenetic abnormality) than in Study MDS-002 study (MDS without del 5q). For this reason, adverse event data are presented separately for Studies MDS-002 and MDS-003 for these and other selected adverse events of interest with lenalidomide.

5.1. Exposure to the Drug

A total of 408 patients received at least 1 dose of lenalidomide (25 mg, 10-mg continuous, or 10-mg cyclic) in the 3 MDS studies. Of these, 395 patients received the recommended starting dose of 10 mg/day either in a continuous (215 patients) or cyclic (180 patients) dosing regimen. Table 20 summarizes the duration of exposure to lenalidomide in the 3 MDS studies.

Table 20: Duration of Exposure to Lenalidomide in the MDS Studies (MDS-001, MDS-002, and MDS-003) (Data Cutoff: 31 December 2004)

	Over All MDS Studies			
Treatment Duration	25mg (N=13)	10mg Cont. (N=215)	10mg Cyclic (N=180)	10mg Overall (N=395)
Duration (weeks) [a]				
n	13	215	180	395
Mean	40.5	31.3	31.4	31.3
SD	42.48	20.42	22.69	21.46
Median	20.6	28.0	25.6	26.7
Min, Max	1.3, 127.0	0.4, 107.0	0.7, 85.1	0.4, 107.0
Distribution of Treatment Duration	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Entered (received at least one dose)	13 (100)	215 (100)	180 (100)	395 (100)
At least 4 weeks	10 (77)	199 (93)	159 (88)	358 (91)
At least 8 weeks	9 (69)	179 (83)	144 (80)	323 (82)
At least 16 weeks	8 (62)	153 (71)	123 (68)	276 (70)
At least 24 weeks	6 (46)	127 (59)	100 (56)	227 (58)
At least 32 weeks	6 (46)	101 (47)	75 (42)	176 (45)
At least 48 weeks	4 (31)	58 (27)	56 (31)	114 (29)

[a] Duration (weeks) = (date of last dose - date of first dose + 1) / 7

The mean duration of exposure to lenalidomide in these patients was 31.3 weeks, and the median duration of exposure was 26.7 weeks; 227 (58%) of the 395 patients who received the 10-mg/day starting dose were administered treatment for at least 24 weeks, and 29% (114/395) were administered treatment for at least 48 weeks.

Table 21 summarizes the duration of exposure in Studies MDS-003 (MDS with an associated del 5 q cytogenetic abnormality) and MDS-002 (MDS without an associated del 5 q cytogenetic abnormality).

Table 21: Duration of Exposure in Studies MDS-003 and MDS-002 (Data Cutoff: 31 December 2004)

	Study MDS-003 [a]	Study MDS-002 [b]
Treatment Duration	10 mg Overall N=148	10 mg Overall N=215
Duration (Weeks)		
Mean	37.0	26.2
SD	19.76	19.22
Median	43.9	23.0
Min, Max	0.4, 69.9	0.6, 73.9
Distribution of Treatment Duration		
Entered (received at least 1 dose)	148 (100)	215 (100)
At least 4 weeks	137 (93)	191 (89)
At least 8 weeks	130 (88)	166 (77)
At least 16 weeks	119 (80)	136 (63)
At least 24 weeks	105 (71)	103 (48)
At least 32 weeks	90 (61)	72 (34)
At least 48 weeks	60 (41)	43 (20)

[a] Included patients with MDS associated with a del 5q cytogenetic abnormality.
[b] Included patients with MDS without a del 5q cytogenetic abnormality.

As of 31 December 2004, the mean and median duration of exposure to lenalidomide were longer in Study MDS-003 than in Study MDS-002; 41% (60/148) of the patients in Study MDS-003, compared with 20% (43/215) of the patients in Study MDS-002 had received at least 48 weeks of treatment with lenalidomide.

Table 22 summarizes the frequency of reasons for discontinuation from the 3 MDS studies.

Table 22: Frequency of Reasons for Discontinuation From the MDS Studies (MDS-001, MDS-002, and MDS-003) (Data Cutoff: 31 December 2004)

	Over All MDS Studies			
	25mg (N=13)	10mg Cont. (N=215)	10mg Cyclic (N=180)	10mg Overall (N=395)
Patients enrolled	13	215	180	395
Discontinued study medication [a]	11 (85)	134 (62)	131 (73)	265 (67)
Primary reason for discontinuation				
Adverse event	6 (46)	45 (21)	47 (26)	92 (23)
Lack of therapeutic effect	1 (8)	58 (27)	56 (31)	114 (29)
Patient withdrew consent	1 (8)	16 (7)	8 (4)	24 (6)
Patient lost to follow-up	1 (8)	1 (1)	2 (1)	3 (1)
Death	2 (15)	8 (4)	9 (5)	17 (4)
Protocol violation	0	1 (1)	1 (1)	2 (1)
Other	0	5 (2)	8 (4)	13 (3)

[a] Discontinued either during core treatment period or during follow-up period

Table 23 summarizes the frequency of reasons for discontinuation in Studies MDS-003 (MDS with an associated del 5 q cytogenetic abnormality) and MDS-002 (MDS without an associated del 5 q cytogenetic abnormality).

Table 23: Frequency of Reasons for Discontinuation in Studies MDS-003 and MDS-002 (Data Cutoff: 31 December 2004)

	Study MDS-003 [a]	Study MDS-002 [b]
Treatment Duration	**10 mg Overall N=148**	**10 mg Overall N=215**
Discontinued Study Medication	69 (47)	169 (79)
Primary Reason for Discontinuation		
Adverse Event	26 (18)	57 (27)
Lack of Therapeutic Effect	26 (18)	74 (34)
Patient Withdrew Consent	3 (2)	19 (9)
Patient Lost to Follow-up	0	2 (1)
Death	9 (6)	7 (3)
Protocol Violation	0	2 (1)
Other	5 (3)	8 (4)

[a] Included patients with MDS associated with a del 5q cytogenetic abnormality.
[b] Included patients with MDS without a del 5q cytogenetic abnormality.

As of 31 December 2004, 47% (69/148) of the patients in Study MDS-003 and 79% (169/215) of the patients in Study MDS-002 had discontinued treatment, primarily due to adverse events and lack of therapeutic effect. More patients in Study MDS-002 than in Study MDS-003 discontinued for these reasons.

5.2. Demographic and Other Characteristics of Study Population

Table 24 summarizes the demographics of the patients in the 3 MDS studies.

Table 24: Demographic Characteristics of Patients in the MDS Studies (MDS-001, MDS-002, and MDS-003) (Data Cutoff: 31 December 2004)

	Over All MDS Studies			
	25mg (N=13)	10mg Cont. (N=215)	10mg Cyclic (N=180)	10mg Overall (N=395)
Age (years)				
n	13	215	180	395
Mean	73.1	70.9	70.2	70.6
SD	8.88	10.72	10.28	10.52
Median	74.0	72.0	71.5	72.0
Min, Max	51.0, 85.0	27.0, 95.0	27.0, 92.0	27.0, 95.0
Age distribution	**n (%)**	**n (%)**	**n (%)**	**n (%)**
<=65	2 (15)	59 (27)	51 (28)	110 (28)
>65	11 (85)	156 (73)	129 (72)	285 (72)
Missing	0	0	0	0
Gender	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Male	7 (54)	111 (52)	97 (54)	208 (53)
Female	6 (46)	104 (48)	83 (46)	187 (47)
Missing	0	0	0	0
Race	**n (%)**	**n (%)**	**n (%)**	**n (%)**
White	11 (85)	205 (95)	169 (94)	374 (95)
All Other	2 (15)	10 (5)	11 (6)	21 (5)
Missing	0	0	0	0

The safety population includes both patients with (from Studies MDS-001 and MDS-003) and without (from Study MDS-001 and Study MDS-002) a del 5 (q31 33) cytogenetic abnormality. In contrast to the efficacy population (which included a larger proportion of female patients, reflecting the gender distribution of MDS with a del 5 (q31-33) cytogenetic abnormality; see Section 4.3.6.4), the overall safety population is approximately half male (53%; 208/395) and half female (47%; 187/395), reflecting the counterbalancing effect of the non-del 5q MDS population, the majority of which is male.

5.3. Adverse Events

5.3.1. Analysis of Adverse Events

All adverse events that were reported by the patients or observed by the investigators were to be recorded in the patient's case report form. 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 adverse events and laboratory abnormalities was graded according to National Cancer Institute (NCI) Common Toxicity Criteria (CTC) (Version 2.0). If NCI CTC were not available for an adverse event, the severity was graded as follows: mild = grade 1, moderate = grade 2, and severe = grade 3.

Treatment-emergent adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The frequencies of adverse events were tabulated by body system, MedDRA term, and treatment regimen, with patients reporting the same event more than once counted only once in the tabulations. Adverse events were summarized by the worst grade. Grade 3/4 adverse events, serious adverse events, and discontinuations due to adverse events were also tabulated by the initial lenalidomide regimen and overall for each dose regimen. Deaths were listed, with a description of the circumstances.

5.3.2. Grade 1-4 Adverse Events

5.3.2.1. Adverse Events Reported in =5% of Patients Treated With the 10-mg/day Starting Dose

Table 25 summarizes, for all lenalidomide dose groups, the frequency of adverse events that were reported in ≥5% of the 395 patients who were treated with the 10-mg/day starting dose in the 3 MDS studies.

Table 25: Frequency of Adverse Events Reported in 5% or More of Patients Treated With 10 mg of Lenalidomide in the MDS Studies (MDS-001, MDS-002, and MDS-003) (Data Cutoff: 31 December 2004)

	Over All MDS Studies			
System organ class/ Preferred term [a]	25mg (N=13)	10mg Cont. (N=215)	10mg Cyclic (N=180)	10mg Overall (N=395)
PATIENTS WITH AT LEAST ONE ADVERSE EVENT	**13 (100)**	**215 (100)**	**180 (100)**	**395 (100)**
GASTROINTESTINAL DISORDERS				
DIARRHEA NOS	7 (54)	92 (43)	68 (38)	160 (41)
CONSTIPATION	3 (23)	59 (27)	45 (25)	104 (26)
NAUSEA	4 (31)	49 (23)	42 (23)	91 (23)
VOMITING NOS	1 (8)	20 (9)	20 (11)	40 (10)
ABDOMINAL PAIN NOS	3 (23)	23 (11)	13 (7)	36 (9)
ABDOMINAL PAIN UPPER	1 (8)	20 (9)	15 (8)	35 (9)
DRY MOUTH	0	15 (7)	16 (9)	31 (8)
DYSPEPSIA	0	13 (6)	10 (6)	23 (6)
ABDOMINAL DISTENSION	1 (8)	11 (5)	9 (5)	20 (5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
FATIGUE	9 (69)	74 (34)	70 (39)	144 (37)
EDEMA PERIPHERAL	4 (31)	31 (14)	49 (27)	80 (20)
PYREXIA	2 (15)	45 (21)	30 (17)	75 (19)
ASTHENIA	3 (23)	24 (11)	15 (8)	39 (10)
EDEMA NOS	0	14 (7)	16 (9)	30 (8)
PAIN NOS	3 (23)	14 (7)	12 (7)	26 (7)
CHEST PAIN	1 (8)	16 (7)	6 (3)	22 (6)
RIGORS	2 (15)	9 (4)	9 (5)	18 (5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
PRURITUS	8 (62)	74 (34)	53 (30)	127 (32)
RASH NOS	5 (39)	75 (35)	48 (27)	123 (31)
DRY SKIN	1 (8)	23 (11)	16 (9)	39 (10)
NIGHT SWEATS	1 (8)	17 (8)	16 (9)	33 (8)
CONTUSION	4 (31)	16 (7)	7 (4)	23 (6)
URTICARIA NOS	2 (15)	12 (6)	11 (6)	23 (6)
RASH PRURITIC	0	10 (5)	11 (6)	21 (5)
SWEATING INCREASED	0	15 (7)	4 (2)	19 (5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
THROMBOCYTOPENIA	7 (54)	106 (49)	68 (38)	174 (44)
NEUTROPENIA	9 (69)	117 (54)	55 (31)	172 (44)
ANEMIA NOS	1 (8)	23 (11)	20 (11)	43 (11)
RESPIRATORY, THORACIC AND Mediastinal DISORDERS				
COUGH	6 (46)	36 (17)	41 (23)	77 (20)
DYSPNEA NOS	5 (39)	36 (17)	31 (17)	67 (17)
NASOPHARYNGITIS	1 (8)	40 (19)	19 (11)	59 (15)
PHARYNGITIS	0	30 (14)	22 (12)	52 (13)
EPISTAXIS	1 (8)	21 (10)	23 (13)	44 (11)
DYSPNEA EXERTIONAL	2 (15)	11 (5)	11 (6)	22 (6)
BRONCHITIS NOS	0	11 (5)	9 (5)	20 (5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
ARTHRALGIA	3 (23)	48 (22)	37 (21)	85 (22)
MUSCLE CRAMP	1 (8)	38 (18)	37 (21)	75 (19)
BACK PAIN	2 (15)	38 (18)	33 (18)	71 (18)
PAIN IN LIMB	2 (15)	22 (10)	25 (14)	47 (12)
MYALGIA	3 (23)	16 (7)	14 (8)	30 (8)
PERIPHERAL SWELLING	0	14 (7)	9 (5)	23 (6)
NERVOUS SYSTEM DISORDERS				
HEADACHE	3 (23)	42 (20)	37 (21)	79 (20)
DIZZINESS	2 (15)	38 (18)	36 (20)	74 (19)
DYSGEUSIA	0	16 (7)	7 (4)	23 (6)
HYPOESTHESIA	0	12 (6)	10 (6)	22 (6)
PARAESTHESIA	1 (8)	9 (4)	12 (7)	21 (5)
PERIPHERAL NEUROPATHY	0	5 (2)	14 (18)	19 (5)
INFECTIONS AND INFESTATIONS				
UPPER RESPIRATORY TRACT INFECTION NOS	5 (39)	31 (14)	29 (16)	60 (15)
URINARY TRACT INFECTION NOS	3 (23)	22 (10)	24 (13)	46 (12)
PNEUMONIA NOS	2 (15)	21 (10)	15 (8)	36 (10)
SINUSITIS NOS	1 (8)	18 (8)	11 (6)	29 (7)
CELLULITIS	0	7 (3)	12 (7)	19 (5)

Table 25: Frequency of Adverse Events Reported in 5% or More of Patients Treated With 10 mg of Lenalidomide in the MDS Studies (MDS-001, MDS-002, and MDS-003) (Data Cutoff: 31 December 2004) (continued)

	Over All MDS Studies			
System organ class/ Preferred term [a]	25mg (N=13)	10mg Cont. (N=215)	10mg Cyclic (N=180)	10mg Overall (N=395)
METABOLISM AND NUTRITION DISORDERS				
ANOREXIA	1 (8)	26 (12)	17 (9)	43 (11)
APPETITE DECREASED NOS	1 (8)	13 (6)	15 (8)	28 (7)
HYPOKALEMIA	1 (8)	16 (7)	7 (4)	23 (6)
DEHYDRATION	1 (8)	11 (5)	7 (4)	18 (5)
INVESTIGATIONS				
WEIGHT DECREASED	0	15 (7)	11 (6)	26 (7)
EYE DISORDERS				
VISION BLURRED	0	7 (3)	18 (10)	25 (6)
PSYCHIATRIC DISORDERS				
INSOMNIA	0	18 (8)	19 (11)	37 (9)
ANXIETY	0	12 (6)	10 (6)	22 (6)
DEPRESSION	1 (8)	14 (7)	7 (4)	21 (5)

[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 patient with multiple occurrences of an AE is counted only once in the AE category.

Neutropenia was reported at least once in 44% (172/395) of the patients who were treated with the 10-mg/day starting dose (see Table 25). Despite the high frequency of neutropenia, the frequency of febrile neutropenia was low (4%; 15/395). At least one infection or infestation was reported in 201 (51%) of the 395 patients; these primarily represented upper respiratory tract infections and other types of infections that are expected in an elderly population (e.g., urinary tract infections, pneumonia not otherwise specified [NOS], influenza). Bacteremia was reported in 3 patients, and *Staphylococcal* bacteremia, *Enterobacter* sepsis, *Enterococcal* infection NOS, *Klebsiella* infection, *Staphylococcal* sepsis, and septic shock were reported in 1 patient each.

Thrombocytopenia was reported at least once in 44% (174/395) of the patients who were treated with the 10-mg/day starting dose (see Table 25). Few patients required platelet transfusions to treat thrombocytopenia, and few bleeding events were reported.[b] One of the 363 patients treated with the 10-mg/day starting dose of lenalidomide in Studies MDS-002 and MDS-003 discontinued treatment due to a bleeding event (gastrointestinal hemorrhage NOS). One death was attributed to a bleeding event (multi-organ failure due to thrombocytopenia-induced hemorrhage in a patient who had a central review classification of AML); this death was judged by the investigator to be unrelated to lenalidomide.

Overall, including patients who did and did not receive platelet transfusions during the study, the most commonly reported bleeding adverse events were epistaxis, which was reported in 41 (11%) of the 363 patients (grade 1, 34 patients; grade 2, 3 patients; and

[b] The discussion of platelet transfusions is limited to data from Studies MDS-002 and MDS-003. Therefore, the number of patients treated with the 10-mg/day starting dose is 363, rather than 395, in these discussions.

grade 3, 4 patients); gingival bleeding, which was reported in 9 (3%) patients (all grade 1); and ecchymoses, which were reported in 13 (4%) patients (all grade 1). Intracranial hemorrhage (grade 3), subarachnoid hemorrhage (grade 4), subdural hematoma (grade 4), and penile bleeding (grade 4) were reported in 1 patient each.

Seven (2%) of the 363 patients received platelet transfusions during in the 8 weeks prior to study entry (screening period; platelet transfusion data were systematically collected for 8 weeks prior to baseline), and 63 (17%) of the 363 patients were administered platelet transfusions over the course of the treatment phase of the study (1 of these 63 patients was found to have AML instead of MDS at study entry).

Among these 63 patients, the baseline platelet count was =100,000/mL in 29 (46%) of the patients and <100,000/mL in 33 (52%) of the patients. Evidence of bleeding was reported in 20 (32%) of the 63 patients at the time of the platelet transfusions. The majority of these were reported to be grade 1 adverse events; there was 1 case of grade 4 intestinal perforation, 1 case of grade 4 gastrointestinal hemorrhage, 1 case of grade 3 subdural hematoma (sustained when the patient fell out of bed), 1 case of grade 3 penile bleeding, 1 case of grade 3 epistaxis, 1 case of grade 3 rectal hemorrhage, 1 case of grade 3 hematoma, 1 case of grade 3 coagulopathy, and 1 case of grade 2 pedal petechiae.

Among the 63 patients who received platelet transfusions during lenalidomide therapy, 23 (37%) were patients who achieved RBC-transfusion independence. The platelet transfusions were given prior to or on the same day as the last RBC transfusion prior to achievement of RBC-transfusion independence in 12 of the 23 patients (in all 12 patients, the platelet transfusions were administered within 56 days of starting lenalidomide treatment). The platelet transfusions were given at the time of or after RBC-transfusion relapse in 7 (30%) patients (in one patient RBC-transfusion relapse was coincident with the development of disease progression from RA to RAEB). Platelet transfusions were administered to only 4 patients during a period of RBC-transfusion independence for the following reasons: acute episode of intestinal perforation (1 patient), grade 3 thrombocytopenia and grade 1 epistaxis (2 patients), and grade 4 thrombocytopenia (1 patient).

Among the 40 patients who were given platelet transfusions and who did not achieve RBC-transfusion independence, 23 (58%) received their first transfusion of platelets within the first 56 days of lenalidomide treatment.

Forty-eight (76%) of the 63 patients who were treated with platelet transfusions during the study were subsequently discontinued from study treatment. None of the 48 patients were discontinued from the study for hemorrhagic adverse events.

In summary, although thrombocytopenia was reported in approximately 44% of patients, few of the patients who were treated with the 10-mg/day starting dose of lenalidomide in Studies MDS-002 and MDS-003 required platelet transfusions for a thrombocytopenia-associated bleeding event. Thirty-one (49%) of 63 thrombocytopenic patients received platelet transfusions to prevent possible bleeding events, while 13 (21%) were given platelet transfusions to treat a bleeding episode (9 grade 1, 1 grade 2, and 3 grade 3 bleeding events). No patient discontinued the study due to a bleeding event.

Table 26 summarizes the frequency of selected adverse events in Studies MDS-003 (MDS with an associated del 5 q cytogenetic abnormality) and MDS-002 (MDS without an associated del 5 q cytogenetic abnormality).

Table 26: Frequency of Selected Adverse Events in Studies MDS-003 and MDS-002 (Data Cutoff: 31 December 2004)

Adverse Event	Study MDS-003 [a] 10 mg Overall N=148	Study MDS-002 [b] 10 mg Overall N=215
At Least One Adverse Event	**148 (100)**	**215 (100)**
Thrombocytopenia	91 (62)	65 (30)
Neutropenia	87 (59)	69 (32)
Diarrhea NOS	72 (49)	72 (34)
Pruritus	62 (42)	55 (26)
Rash NOS	53 (36)	62 (29)
Fatigue	46 (31)	73 (34)
Constipation	35 (24)	61 (28)
Nausea	35 (24)	47 (22)
Nasopharyngitis	34 (23)	25 (12)
Arthralgia	32 (22)	38 (18)

[a] Included patients with MDS associated with a del 5q cytogenetic abnormality.
[b] Included patients with MDS without a del 5q cytogenetic abnormality.

The incidence of thrombocytopenia or neutropenia was higher in the patients with MDS associated with a del 5q cytogenetic abnormality (Study MDS-003) than in those with MDS without a del 5q cytogenetic abnormality (Study MDS-002).

5.3.2.2. Analysis of Adverse Events by Demographic Characteristics

No significant difference was noted between patients =65 years of age (100%; 110/110) and those >65 years of age (100%; 285/285) or between males (100%; 208/208) and females 100%; 187/187) in the percentage of patients who had at least one adverse event based on the pooled database (Studies MDS-001, MDS-002, and MDS-003). Of the frequently reported adverse events (i.e., those listed in Table 25), constipation and epistaxis were reported significantly more frequently in patients >65 years of age than in those =65 years of age (p=0.05; Fisher's exact test), whereas headache was reported significantly more frequently in patients =65 years of age than in those >65 years of age. Diarrhea, nausea, vomiting, dizziness, and urinary tract infection were reported significantly more frequently in females than in males (p=0.05; Fisher's exact test), whereas arthralgia, night sweats, and upper respiratory tract infection were reported significantly more frequently in males than in females. The number of non-white patients (21 vs 374 white patients) is too small to allow for an evaluation of the effects of race on the frequency of any individual adverse event.

5.3.3. Drug-related Adverse Events

Table 27 summarizes the drug-related adverse events that were reported in =5% of the patients who were treated with the 10-mg/day starting dose in the 3 MDS studies.

Table 27: Frequency of Drug-related Adverse Events Reported in 5% or More of Patients Treated With 10-mg/day Dose in the MDS Studies (MDS-001, MDS-002, and MDS-003) (Data Cutoff: 31 December 2004)

Preferred Term	25 mg (N=13)	10 mg Cont. (N=215)	10 mg Cyclic (N=180)	10 mg Overall (N=395)
At Least 1 Drug-related Event	**13 (100)**	**205 (95)**	**158 (88)**	**363 (92)**
Neutropenia	9 (69)	106 (49)	50 (28)	156 (40)
Thrombocytopenia	7 (54)	94 (44)	60 (33)	154 (39)
Pruritus	8 (62)	57 (27)	45 (25)	102 (26)
Rash NOS	2 (15)	58 (27)	38 (21)	96 (24)
Diarrhea NOS	5 (39)	43 (20)	31 (17)	74 (19)
Fatigue	7 (54)	32 (15)	28 (16)	60 (15)
Constipation	2 (15)	27 (13)	22 (12)	49 (12)
Muscle Cramp	1 (8)	18 (8)	17 (9)	35 (9)
Nausea	0	18 (8)	14 (8)	32 (8)
Edema Peripheral	1 (8)	6 (3)	25 (14)	31 (8)
Dry Skin	1 (8)	13 (6)	9 (5)	22 (6)
Arthralgia	1 (8)	9 (4)	12 (7)	21 (5)

Note: Drug-related adverse events are those that the investigator suspected to be related to the study medication.

Not all of the cases of neutropenia and thrombocytopenia that were reported (see Table 25) were suspected to be related to lenalidomide therapy. Rather, in some patients, these events were judged to be related to the underlying medical condition.

Table 28 summarizes the frequency of selected drug-related adverse events in Studies MDS-003 (MDS with an associated del 5 q cytogenetic abnormality) and MDS-002 (MDS without an associated del 5 q cytogenetic abnormality).

Table 28: Frequency of Selected Drug-related Adverse Events in Studies MDS-003 and MDS-002 (Data Cutoff: 31 December 2004)

	Study MDS-003 [a]		Study MDS-002 [b]	
	10 mg Overall N=148		10 mg Overall N=215	
Drug-related Adverse Event	Grade 1-4	Grade 3/4	Grade 1-4	Grade 3/4
At Least One Drug-related Adverse Event	142 (96)	131 (89)	193 (90)	154 (72)
Thrombocytopenia	86 (58)	73 (49)	53 (25)	41 (19)
Neutropenia	84 (57)	82 (55)	58 (27)	51 (24)
Pruritus	48 (32)	3 (2)	47 (22)	2 (1)
Rash NOS	42 (28)	10 (7)	47 (22)	9 (4)
Diarrhea	35 (24)	3 (2)	30 (14)	3 (1)
Fatigue	18 (12)	4 (3)	28 (13)	5 (2)

[a] Included patients with MDS associated with a del 5q cytogenetic abnormality.
[b] Included patients with MDS without a del 5q cytogenetic abnormality.

Grade 1 to 4 and grade 3/4 drug-related thrombocytopenia, neutropenia, pruritus, rash NOS, diarrhea, and fatigue were reported more frequently in the patients with MDS associated with a del 5q cytogenetic abnormality (Study MDS-003) than in those with MDS without an associated del 5q cytogenetic abnormality (Study MDS-002).

5.3.4. Grade 3/4 Adverse Events

5.3.4.1. Grade 3/4 Adverse Events Reported in =1% of Patients Treated With the 10-mg/day Starting Dose

Table 29 summarizes the frequency of grade 3/4 adverse events that were reported in ≥2% of the 395 patients who were treated with the 10-mg/day starting dose in the MDS studies.

Table 29: Frequency of Grade 3/4 Adverse Events Reported in 2% or More of Patients Treated With 10-mg Lenalidomide Starting Dose in the MDS Studies (MDS-001, MDS-002, and MDS-003) (Data Cutoff: 31 December 2004)

	Over All MDS Studies			
System organ class/ Preferred term [b]	25mg (N=13)	10mg Cont. (N=215)	10mg Cyclic (N=180)	10mg Overall (N=395)
PATIENTS WITH AT LEAST ONE NCI CTC GRADE 3 OR 4 ADVERSE EVENT	**13 (100)**	**185 (86)**	**147 (82)**	**332 (84)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
NEUTROPENIA	9 (69)	110 (51)	52 (29)	162 (41)
THROMBOCYTOPENIA	7 (54)	84 (39)	61 (34)	145 (37)
ANEMIA NOS	0	18 (8)	13 (7)	31 (8)
FEBRILE NEUTROPENIA	0	5 (2)	8 (4)	13 (3)
LEUKOPENIA NOS	0	10 (5)	2 (1)	12 (3)
PANCYTOPENIA	1 (8)	4 (2)	2 (1)	6 (2)
INFECTIONS AND INFESTATIONS				
PNEUMONIA NOS	0	13 (6)	12 (7)	25 (6)
URINARY TRACT INFECTION NOS	1 (8)	5 (2)	3 (2)	8 (2)
SEPSIS NOS	1 (8)	3 (1)	4 (2)	7 (2)
CELLULITIS	0	2 (1)	4 (2)	6 (2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
FATIGUE	4 (31)	15 (7)	13 (7)	28 (7)
PYREXIA	0	4 (2)	3 (2)	7 (2)
CHEST PAIN	1 (8)	6 (3)	0	6 (2)
GASTROINTESTINAL DISORDERS				
DIARRHEA NOS	1 (8)	9 (4)	8 (4)	17 (4)
NAUSEA	0	10 (5)	2 (1)	12 (3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
DYSPNEA NOS	2 (15)	11 (5)	4 (2)	15 (4)
HYPOXIA	0	3 (1)	3 (2)	6 (2)
PLEURAL EFFUSION	0	2 (1)	4 (2)	6 (2)
CARDIAC DISORDERS				
ATRIAL FIBRILLATION	0	7 (3)	7 (4)	14 (4)
CARDIAC FAILURE CONGESTIVE	0	5 (2)	9 (5)	14 (4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
BACK PAIN	1 (8)	9 (4)	6 (3)	15 (4)
ARTHRALGIA	0	6 (3)	5 (3)	11 (3)
PAIN IN LIMB	0	3 (1)	4 (2)	7 (2)
NERVOUS SYSTEM DISORDERS				
DIZZINESS	0	6 (3)	2 (1)	8 (2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
RASH NOS	0	7 (3)	12 (7)	19 (5)
METABOLISM AND NUTRITION DISORDERS				
HYPOKALEMIA	1 (8)	6 (3)	1 (1)	7 (2)
VASCULAR DISORDERS				
DEEP VEIN THROMBOSIS	0	5 (2)	4 (2)	9 (2)
HYPERTENSION NOS	0	5 (2)	2 (1)	7 (2)
INVESTIGATIONS				
ALANINE AMINOTRANSFERASE INCREASED	0	4 (2)	2 (1)	6 (2)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)				
ACUTE LEUKANEMIA NOS	0	6 (3)	0	6 (2)

[a] NCI CTC=National Cancer Institute Common Toxicity Criteria version 2. NCI Common Toxicity Criteria are listed in Appendix I of the protocol.
[b] System Organ Class and Preferred Terms are coded using the MedDRA dictionary. A patient with multiple occurrences of an AE is counted only once in the Preferred term category.

Neutropenia, thrombocytopenia, and anemia NOS were the most frequently reported grade 3/4 adverse events, grade 4 events. Table 30 summarizes selected grade 3/4 hematologic events by grade.

Table 30: Frequency of Selected Grade 3 and Grade 4 Hematologic Events in the MDS Studies (MDS-001, MDS-002, and MDS-003) (Data Cutoff: 31 December 2004)

	25 mg (N=13)		10 mg Cont. (N=215)		10 mg Cyclic (N=180)		10 mg Overall (N=395)	
	Grade		Grade		Grade		Grade	
Preferred Term [a]	3	4	3	4	3	4	3	4
Neutropenia	0	9 (69)	26 (12)	84 (39)	18 (10)	34 (19)	44 (11)	118 (30)
Thrombocytopenia	6 (46)	1 (8)	71 (33)	13 (6)	46 (26)	15 (8)	117 (30)	28 (7)
Anemia NOS	0	0	10 (5)	8 (4)	10 (6)	3 (2)	20 (5)	11 (3)
Febrile Neutropenia	0	0	5 (2)	0	6 (3)	2 (1)	11 (3)	2 (1)
Leukopenia	0	0	5 (2)	5 (2)	2 (1)	0	7 (2)	5 (1)
Pancytopenia	0	1 (8)	1 (1)	3 (1)	0	2 (1)	1 (<1)	5 (1)

[a] Events that were reported as grade 3/4 in =1% of patients treated with the 10-mg/day dose (as shown in Table 29).

At least one grade 3/4 infection or infestation was reported in 67 (17%) of the 395 patients who were treated with the 10-mg dose of lenalidomide. Grade 3/4 pneumonia was reported in 6% (25/395), and grade 3/4 cellulitis was reported in 2% (6/395) of the patients. All other types of infections (including infection NOS, sepsis NOS, bacteremia, and respiratory tract infections) were reported in 4 or fewer patients.

Relatively few patients received platelet transfusions for bleeding events (see Section 5.3.2.1 for a discussion of platelet transfusions and bleeding events of all grades), and individual grade 3/4 bleeding adverse events were infrequent. Grade 3/4 epistaxis and grade 3/4 hematuria were reported in 4 (1%) patients each; grade 3/4 upper gastrointestinal (GI) hemorrhage, lower GI hemorrhage, rectal hemorrhage, subarachnoid hemorrhage, subdural hematoma, hemorrhage NOS, and penile hemorrhage were each reported in 1 (<1%) patient.

Grade 3/4 hemolytic anemias, including warm-type hemolytic anemia (1%; 3/395) hemolytic anemia NOS (1%; 3/395), autoimmune hemolytic anemia (1%; 2/395), and hemolysis and hemolytic anemia (<1%; 1/395 each), were occasionally observed in this heavily transfused population.

There were no reports of grade 3/4 constipation or grade 4 diarrhea. Grade 3 diarrhea was reported in 4% (17/395), and grade 3/4 fatigue (primarily grade 3) was reported in 7% (28/395) of the patients. No cases of grade 3 somnolence were reported. Grade 3 peripheral neuropathy was reported in 3 (1%) patients, and grade 3 neuropathy was reported in 1 (<1) patient.

Table 31 summarizes the frequency of grade 4 hematologic adverse events in Studies MDS-003 (MDS with an associated del 5 q cytogenetic abnormality) and MDS-002 (MDS without an associated del 5 q cytogenetic abnormality).

Table 31: Frequency of Grade 4 Hematologic Adverse Events in Studies MDS-003 and MDS-002 (Data Cutoff: 31 December 2004)

Grade 4 Adverse Event	Study MDS-003 [a] 10 mg Overall N=148	Study MDS-002 [b] 10 mg Overall N=215
Neutropenia	60 (41)	47 (22)
Thrombocytopenia	15 (10)	10 (5)
Anemia NOS	6 (4)	4 (2)
Leukopenia NOS	5 (3)	0
Granulocytopenia	2 (1)	0
Pancytopenia	2 (1)	3 (1)
Febrile Neutropenia	1 (1)	1 (1)
Coagulopathy	0	0
Hemolytic Anemia	0	1 (1)

[a] Included patients with MDS associated with a del 5q cytogenetic abnormality.
[b] Included patients with MDS without a del 5q cytogenetic abnormality.

The incidence of grade 4 hematologic adverse events—in particular, the incidence of grade 4 neutropenia and thrombocytopenia—was higher among the patients with MDS associated with a del 5q cytogenetic abnormality (Study MDS-003) than among those without a del 5q cytogenetic abnormality (Study MDS-002).

5.3.4.2. Analysis of Grade 3/4 Adverse Events by Demographic Characteristics

No significant difference was noted between patients =65 years of age (82%; 90/110) and those >65 years of age (85%; 242/285) or between males (79%; 165/208) and females (80%; 149/187) in the percentage of patients who had at least one grade 3/4 adverse event or in the frequency of any individual grade 3/4 adverse event based on the pooled database (Studies MDS-001, MDS-002, and MDS-003). The number of non-white patients (21 vs 374 white patients) is too small to allow for an evaluation of the effects of race on the frequency of any individual grade 3/4 adverse event.

5.3.5. Deaths

The frequency of on-study death (6%; 25/408) was relatively low in the 3 MDS studies considering the prolonged duration of study treatment and appeared consistent with the survival reported in the literature for the low- to intermediate-1-risk MDS population (Greenberg et al, 1997). Table 32 summarizes the deaths that were reported in the 3 MDS studies.

Table 32: Deaths in the MDS Studies (MDS-001, MDS-002, and MDS-003)

Patient No.	Age/Gender IPSS Score	Initial Regimen	Date of Last Dose	Date of Death	Cause	Related
MDS-001						
108	69/Female Low	25mg	10Sep2002	23Sep2002	Multi-organ failure	No
112	82/Male Int-1	25mg	17May2002	25May2002	Multi-organ failure Systemic inflammatory response syndrome	No
134	72/Female Int-1	10mg Cyclic	20Apr2003	27Apr2003	Splenic infarction	No
MDS-002						
0052001	80/Female Int-1	10mg Cont	29Dec2003	03Jan2004	Intestinal perforation NOS	No
0102005	79/Male Int-1	10mg Cont	18Feb2004	04Mar2004	Disease progression NOS	No
0112005	87/Male Unknown	10mg Cont	06Jan2004	28Jan2004	Acute myeloid leukemia NOS	No
0122003	77/Male Unknown	10mg Cont	12Feb2004	16Feb2004	Pneumonia NOS	No
0152009	72/Female Unknown	10mg Cont	17Feb2004	05Mar2004	Hepatic failure	No
0262008	80/Female Low	10mg Cont	13May2004	11Jun2004	Urosepsis Pancytopenia Septic shock Renal failure NOS	Suspected Suspected Suspected No
0322001	75/Male Int-1	10mg Cont	02Feb2004	15Feb2004	Pneumonia NOS	No
0042003	82/Female Unknown	10mg Cyclic	24Dec2003	28Dec2003	Melena Anemia NOS	No No
0092001	76/Female Low	10mg Cyclic	13Sep2003	14Sep2003	Cardiogenic shock	No
0152003	92/Male Unknown	10mg Cyclic	23Feb2004	23Feb2004	Cardiac arrest	No
0292004	85/Male Int-1	10mg Cyclic	13Oct2003	04Nov2003	Renal failure NOS Disease progression NOS	No No
0312004	65/Male Unknown	10mg Cyclic	09Apr2004	09May2004	Respiratory failure	Suspected
MDS-003						
0233008	65/Male Low	10mg Cont	09Apr2004	13Apr2004	Pancytopenia Sepsis NOS Respiratory distress	Suspected No Suspected
0293011	88/Female Unknown	10mg Cont	19Apr2004	19Apr2004	Cardiac failure NOS	No
0323002	79/Female Low	10mg Cont	18Feb2004	06Mar2004	Klebsiella sepsis	Suspected
0323004	69/Female Unknown	10mg Cont	08Apr2004	08Apr2004	Sudden death	No
0373011	83/Female Low	10mg Cont	02Feb2004	08Feb2004	Pneumonia NOS	Suspected
0373024	72/Male Int-1	10mg Cont	20Jun2004	03Jul2004	Acute leukemia NOS	No
0373031	79/Female Low	10mg Cont	23May2004	24May2004	Intestinal perforation NOS	No
0373033	84/Male Low	10mg Cont	26Oct2004	21Nov2004	Cardiac failure NOS	No
0113003	85/Male Int-1	10mg Cyclic	16Mar2004	22Mar2004	Cardiac failure congestive Atrial fibrillation Pneumonitis NOS	No No No
0303003	88/Female Int-1	10mg Cyclic	16Sep2004	03Oct2004	Multi-organ failure	No

Of the 25 on-study deaths, 20 were judged by the investigators to be unrelated to lenalidomide therapy, and 5 (due to urosepsis and shock secondary to pancytopenia, respiratory failure, respiratory distress secondary to pancytopenia, sepsis, and pneumonia, respectively) were suspected by the investigators to be potentially related to lenalidomide

administration (see Table 32). All patients whose deaths were judged to be potentially related to lenalidomide therapy were treated with the 10-mg/day starting dose. The frequency of potentially drug-related death (as assessed by study investigators) among those who were treated with the 10-mg/day starting dose is, therefore, estimated at 1% (5/395). The median age at the time of the death was 80 years (mean, 79 years; range, 66-93 years).

In addition to the deaths listed in Table 32, the Company has received reports of 19 deaths that have occurred more than 30 days from the date of the last dose of lenalidomide (3 of these deaths occurred after the reporting period for the 120-day Safety Update Report). None of these deaths was judged by the investigators to be related to lenalidomide therapy. The causes of death were disease progression (7 patients), thrombocytopenia (2 patients), cardiac arrest (2 patients), cardiomyopathy (1 patient), multi-organ failure (1 patient), pulmonary embolism (1 patient), acute renal failure (1 patient), gastrointestinal hemorrhage (1 patient), subarachnoid hemorrhage (1 patient), metastatic lung cancer (1 patient), and infection (1 patient).

5.3.6. Other Serious Adverse Events

5.3.6.1. Serious Adverse Events Reported in =1% of Patients Treated With the 10-mg/day Starting Dose

The frequency of most individual serious adverse events was low, with most individual serious adverse events occurring in <5 patients in any treatment group. Table 33 summarizes the frequency of serious adverse events that were reported in =1% of the patients who were treated with the 10-mg/day starting dose in the 3 MDS studies.

Table 33: Frequency of Serious Adverse Events Reported in 1% or More of Patients Treated With the 10-mg Lenalidomide Starting Dose in the MDS Studies (MDS-001, MDS-002, and MDS-003) (Data Cutoff: 31 December 2004)

	Over All MDS Studies			
Overall System organ class/ Preferred term [a]	25mg (N=13)	10mg Cont. (N=215)	10mg Cyclic (N=180)	10mg (N=395)
PATIENTS REPORTING AT LEAST ONE SERIOUS ADVERSE EVENT	**5 (39)**	**99 (46)**	**80 (44)**	**179 (45)**
INFECTIONS AND INFESTATIONS				
PNEUMONIA NOS	2 (15)	15 (7)	12 (7)	27 (7)
SEPSIS NOS	0	2 (1)	4 (2)	6 (2)
URINARY TRACT INFECTION NOS	0	4 (2)	2 (1)	6 (2)
CELLULITIS	0	2 (1)	2 (1)	4 (1)
INFECTION NOS	0	1 (1)	2 (1)	3 (1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
ANEMIA NOS	0	9 (4)	9 (5)	18 (5)
NEUTROPENIA	0	10 (5)	3 (2)	13 (3)
THROMBOCYTOPENIA	0	5 (2)	5 (3)	10 (3)
FEBRILE NEUTROPENIA	2 (15)	5 (2)	4 (2)	9 (2)
PANCYTOPENIA	0	4 (2)	1 (1)	5 (1)
WARM TYPE HEMOLYTIC ANEMIA	0	1 (1)	2 (1)	3 (1)
SPLENIC INFARCTION	0	0	2 (1)	2 (1)
CARDIAC DISORDERS				
CARDIAC FAILURE CONGESTIVE	0	4 (2)	6 (3)	10 (3)
ATRIAL FIBRILLATION	0	5 (2)	4 (2)	9 (2)
CARDIAC ARREST	0	0	2 (1)	2 (1)
MYOCARDIAL ISCHAEMIA	0	0	2 (1)	2 (1)
GASTROINTESTINAL DISORDERS				
DIARRHEA NOS	0	4 (2)	2 (1)	6 (2)
NAUSEA	0	4 (2)	1 (1)	5 (1)
ABDOMINAL PAIN NOS	1	3 (1)	1 (1)	4 (1)
VOMITING NOS	0	2 (1)	2 (1)	4 (1)
GASTROINTESTINAL HEMORRHAGE NOS	0	1 (1)	2 (1)	3 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
PYREXIA	1 (8)	7 (3)	4 (2)	11 (3)
ASTHENIA	0	2 (1)	4 (2)	6 (2)
CHEST PAIN	1 (8)	4 (2)	0	4 (1)
DISEASE PROGRESSION NOS	0	0	3 (2)	3 (1)
MULTI-ORGAN FAILURE	2 (15)	0	2 (1)	2 (1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
PLEURAL EFFUSION	0	3 (1)	2 (1)	5 (1)
DYSPNEA NOS	0	3 (1)	1 (1)	4 (1)
HYPOXIA	0	1 (1)	2 (1)	3 (1)
PULMONARY EMBOLISM	0	1 (1)	2 (1)	3 (1)
PULMONARY HYPERTENSION NOS	0	0	3 (2)	3 (1)
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED	0	0	2 (1)	2 (1)
NERVOUS SYSTEM DISORDERS				
DIZZINESS	0	3 (1)	1 (1)	4 (1)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)				
ACUTE LEUKEMIA NOS	0	6 (3)	0	6 (2)
ACUTE MYELOID LEUKEMIA NOS	0	3 (1)	0	3 (1)
METABOLISM AND NUTRITION DISORDERS				
DEHYDRATION	0	6 (3)	1 (1)	7 (2)
VASCULAR DISORDERS				
DEEP VEIN THROMBOSIS	0	1 (1)	3 (2)	4 (1)
HYPOTENSION NOS	1 (8)	1 (1)	1 (1)	2 (1)
RENAL AND URINARY DISORDERS				
RENAL FAILURE NOS	0	3 (1)	1 (1)	4 (1)
RENAL FAILURE ACUTE	0	0	2 (1)	2 (1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
BACK PAIN	1 (8)	2 (1)	1 (1)	3 (1)

Table 33: Frequency of Serious Adverse Events Reported in 1% or More of Patients Treated With the 10-mg Lenalidomide Starting Dose in the MDS Studies (MDS-001, MDS-002, and MDS-003) (Data Cutoff: 31 December 2004) (continued)

	Over All MDS Studies			
Overall System organ class/ Preferred term [a]	25mg (N=13)	10mg Cont. (N=215)	10mg Cyclic (N=180)	10mg Overall (N=395)
HEPATOBILIARY DISORDERS				
HYPERBILIRUBINEMIA	0	1 (1)	2 (1)	3 (1)
IMMUNE SYSTEM DISORDERS				
HYPERSENSITIVITY NOS	0	0	3 (2)	3 (1)
PSYCHIATRIC DISORDERS				
CONFUSIONAL STATE	0	0	2 (1)	2 (1)

[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 patient with multiple occurrences of an AE is counted only once in the AE category.

Table 34 summarizes the frequency of selected serious adverse events in Studies MDS-003 (MDS with an associated del 5 q cytogenetic abnormality) and MDS-002 (MDS without an associated del 5 q cytogenetic abnormality).

Table 34: Frequency of Serious Adverse Events in Studies MDS-003 and MDS-002 (Data Cutoff: 31 December 2004)

	Study MDS-003 [a]		Study MDS-002 [b]	
	10 mg Overall N=148		10 mg Overall N=215	
Serious Adverse Event	Total Reports	Related [c]	Total Reports	Related [c]
Any Serious Adverse Event	**71 (48)**	**69 (47)**	**93 (43)**	**82 (38)**
Pneumonia NOS	14 (10)	6 (4)	10 (5)	2 (1)
Neutropenia	10 (7)	9 (6)	3 (1)	1 (1)
Pyrexia	6 (4)	4 (3)	1 (1)	1 (1)
Febrile Neutropenia	6 (4)	4 (3)	3 (1)	2 (1)
Thrombocytopenia	6 (4)	4 (3)	2 (1)	1 (1)
Dehydration	6 (4)	0	0	0
Anemia NOS	5 (3)	2 (1)	9 (4)	2 (1)
Congestive Heart Failure	5 (3)	1 (1)	5 (2)	2 (1)
Sepsis NOS	5 (3)	0	1 (1)	0
Diarrhea NOS	4 (3)	0	2 (1)	1 (1)
Vomiting NOS	4 (3)	1 (1)	0	0
Acute Leukemia NOS	0	0	0	0

[a] Included patients with MDS associated with a del 5q cytogenetic abnormality.
[b] Included patients with MDS without a del 5q cytogenetic abnormality.
[c] Suspected by the investigator to be related to the study medication.

Overall, serious adverse events were reported more frequently in the patients with MDS associated with a del 5q cytogenetic abnormality (Study MDS-003) than in those with MDS without an associated del 5q cytogenetic abnormality (Study MDS-002). However, the frequency of individual drug-related serious adverse events was low both among patients with and without an associated del 5q cytogenetic abnormality.

5.3.6.2. Analysis of Serious Adverse Events by Demographic Characteristics

Significantly more patients >65 years of age (49%; 140/285) than =65 years of age (36%; 39/110) had at least one serious adverse event (p=0.05; Fisher's exact test) based on the pooled database (Studies MDS-001, MDS-002, and MDS-003), but no significant differences were observed between age groups in the frequency of any individual serious adverse event. No significant difference was observed between males (45%; 93/208) and females (46%; 86/187) in the percentage of patients who had at least one serious adverse event or in the frequency of any individual serious adverse event. The number of non-white patients (21 vs 374 white patients) is too small to allow for an evaluation of the effects of race on the frequency of any individual serious adverse event.

5.3.7. Adverse Events Leading to Discontinuation of Treatment

Table 35 summarizes the adverse events that led to discontinuation from studies for the MDS studies.

Table 35: Frequency of Adverse Events Leading to Discontinuation in 1% or More of Patients Treated With the 10-mg Lenalidomide Starting Dose in the MDS Studies (MDS-001, MDS-002, and MDS 003) (Data Cutoff: 31 December 2004)

	Over All MDS Studies			
System organ class/ Preferred term [a]	25 mg (N=13)	10 mg Cont. (N=215)	10 mg Cyclic (N=180)	10 mg Overall (N=395)
PATIENTS REPORTING AT LEAST ONE ADVERSE EVENT LEADING TO DISCONTINUATION OF STUDY DRUG	**9 (69)**	**58 (27)**	**56 (31)**	**114 (29)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
THROMBOCYTOPENIA	2 (15)	17 (8)	16 (9)	33 (8)
NEUTROPENIA	5 (39)	11 (5)	7 (4)	18 (5)
ANEMIA NOS	0	4 (2)	2 (1)	6 (2)
HEMOLYTIC ANEMIA NOS	1 (8)	1 (1)	1 (1)	2 (1)
WARM TYPE HEMOLYTIC ANEMIA	0	1 (1)	1 (1)	2 (1)
GASTROINTESTINAL DISORDERS				
DIARRHEA NOS	0	5 (2)	2 (1)	7 (2)
NAUSEA	0	4 (2)	2 (1)	6 (2)
ABDOMINAL DISTENSION	0	1 (1)	3 (2)	4 (1)
ABDOMINAL PAIN NOS	0	1 (1)	1 (1)	2 (1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
RASH NOS	0	3 (1)	5 (3)	8 (2)
DERMATITIS BULLOUS	0	1 (1)	1 (1)	2 (1)
FACE EDEMA	0	1 (1)	1 (1)	2 (1)
PRURITUS	0	1 (1)	1 (1)	2 (1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
FATIGUE	0	2 (1)	2 (1)	4 (1)
PYREXIA	0	3 (1)	1 (1)	4 (1)
DISEASE PROGRESSION NOS	0	0	2 (1)	2 (1)
FALL	0	1 (1)	1 (1)	2 (1)
GAIT ABNORMAL	0	1 (1)	1 (1)	2 (1)
CARDIAC DISORDERS				
CARDIAC FAILURE CONGESTIVE	0	2 (1)	1 (1)	3 (1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
ARTHRALGIA	0	0	2 (1)	2 (1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
DYSPNEA NOS	0	3 (1)	0	3 (2)
INFECTIONS AND INFESTATIONS				
PNEUMONIA NOS	0	3 (1)	1 (1)	4 (1)
METABOLISM AND NUTRITION DISORDERS				
ANOREXIA	0	3 (1)	0	3 (1)

[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 patient with multiple occurrences of an AE is counted only once in the AE category.

Most adverse events that led to discontinuation of treatment were reported in <5 patients each, and the rate of any event that led to discontinuation, including cytopenias, was low.

The percentage of patients who discontinued from the studies due to adverse events was significantly higher in the patients >65 years of age (32%; 92/285) than in those =65 years of age (20%; 22/110) (p=0.05; Fisher's exact test) but was not significantly different between males (29%; 61/208) and females (28%; 53/187). No significant difference was noted between age groups or genders in the frequency of any individual adverse event that led to discontinuation of treatment. The number of non-white patients (21 vs 374 white patients) is too small to allow for an evaluation of the effects of race on the incidence of any individual adverse event that led to study discontinuation.

Table 36 summarizes the frequency of discontinuations due to adverse events in Studies MDS-003 (MDS with an associated del 5 q cytogenetic abnormality) and MDS-002 (MDS without an associated del 5 q cytogenetic abnormality).

Table 36: Frequency of Discontinuations Due to Adverse Events in Studies MDS-003 and MDS-002 (Data Cutoff: 31 December 2004)

Adverse Event [c]	Study MDS-003 [a] 10 mg Overall N=148	Study MDS-002 [b] 10 mg Overall N=215
At Least One Adverse Event Leading to Discontinuation	**32 (22)**	**70(33)**
Thrombocytopenia	8 (5)	20 (9)
Neutropenia	4 (3)	12 (6)
Anemia	2 (1)	3 (1)
Rash NOS	4 (3)	4 (2)
Pneumonia NOS	2 (1)	2 (1)

[a] Included patients with MDS associated with a del 5q cytogenetic abnormality.
[b] Included patients with MDS without a del 5q cytogenetic abnormality.
[c] Adverse events reported as a reason for discontinuation in =2 patients in Study MDS-003.

The frequency of discontinuations due to adverse events was lower among the patients with MDS associated with a del 5q cytogenetic abnormality (Study MDS-003) than among those without a del 5q cytogenetic abnormality (Study MDS-002). Although thrombocytopenia and neutropenia were reported more frequently in Study MDS-003 than in Study MDS-002 (Table 26), the incidence of discontinuation of therapy for these reasons was lower in Study MDS-003 than in Study MDS-002. Except for thrombocytopenia, neutropenia, anemia, rash NOS, and pneumonia, all other adverse events that led to discontinuation of treatment in Study MDS-003 were reported in 1 patient each.

5.3.8. Analysis of Adverse Events by Organ System or Syndrome

5.3.8.1. Blood and Lymphatic System Disorders

The incidence of neutropenia and thrombocytopenia were 44% (172/395) and 44%; (174/395), respectively. However, the incidences of grade 4 neutropenia (30%; 118/395) and thrombocytopenia (7%; 28/395) and serious neutropenia (3%; 13/395) or thrombocytopenia (3%; 10/395) were low given the population under study, as were the rates of discontinuation due to neutropenia (5%; 18/395) and thrombocytopenia (8%; 33/395). Few patients developed grade 4 febrile neutropenia (<1%; 2/395). Few of the patients who were treated with the 10-mg/day starting dose of lenalidomide required platelet transfusions for a thrombocytopenia-associated with a bleeding event. Thirty-one (49%) of 63 thrombocytopenic patients received platelet transfusions to prevent possible bleeding events, while 13 (21%) were given platelet transfusions to treat a bleeding episode (9 grade 1, 1 grade 2, and 3 grade 3 bleeding events).

Approximately one third to one half of patients required a dose reduction or interruption during lenalidomide therapy. The following are the recommended dosage adjustments

for patients who develop thrombocytopenia or neutropenia within the first 4 weeks of initiation of therapy:

- Thrombocytopenia
  - For patients with a baseline platelet count of =100,000/µL, withhold lenalidomide when the platelet count decreases to <50,000/µL. Resume lenalidomide at a dose of 5 mg/day when the platelet count recovers to =50,000/µL.
  - For patients with a baseline platelet count of <100,000/µL, withhold lenalidomide when the platelet count decreases by 50% of the baseline value. Resume lenalidomide therapy at a dose of 5 mg/day when the platelet count recovers to =50,000/µL (for patients whose baseline platelet count was =60,000/µL) or to =30,000/µL (for patients whose baseline platelet count was <60,000/µL).
- Neutropenia
  - For patients with a baseline ANC of =1000/µL, withhold lenalidomide when the ANC decreases to <750/µL. Resume lenalidomide therapy at a dose of 5 mg/day when the ANC recovers to =1000/µL.
  - For patients with a baseline ANC of <1000/µL, withhold lenalidomide when the ANC decreases to <500/µL. Resume lenalidomide at a dose of 5 mg/day when the ANC recovers to =500/µL.

5.3.8.2. Cardiac Disorders

Few grade 3/4 cardiac arrhythmias were reported in this elderly population. Atrial fibrillation was observed in 14 (4%), bradycardia was observed in 3 (1%), and sinus tachycardia was observed in 2 (<1%) of the 395 patients who were treated with the 10-mg starting dose; supraventricular arrhythmia was reported in 1 (<1%) patient. Congestive heart failure (CHF) was reported in 14 (4%) of the patients. Cardiac arrest, cardio-respiratory arrest, cardiogenic shock, and myocardial ischemia/infarct were reported in 1 or 2 patients each. These rates are considered to be within the expected range for this population.

5.3.8.3. Endocrine Disorders

Acquired hypothyroidism was reported in 5% (19/395) of the patients who were treated with the 10-mg/day starting dose. Hyperthyroidism and increased levels of thyroid-stimulating hormone (TSH) were reported in <1% (1/395) of the patients.

In Study MDS-003, the pivotal study for this submission, acquired hypothyroidism (all grade 2) was reported as an adverse event in 10 (6%) of the 148 patients; all 8 patients required replacement therapy. Two of these 10 patients had elevated TSH levels at baseline, and 1 entered the study with a past medical history of hypothyroidism and abnormal thyroid function tests at baseline (this patient required replacement therapy after 124 days on study treatment). Common symptoms in these patients included weakness, fatigue, weight gain, constipation, and diarrhea. None of the cases of acquired

hypothyroidism was judged to represent a serious adverse event, and no patient discontinued treatment due to acquired hypothyroidism.

Twenty-one (14%) of the 148 patients in Study MDS-003 had laboratory thyroid function changes. Changes were noted in serum TSH levels, as well as in triiodothyronine (T_3) and/or thyroxine (T_4) levels, during treatment. Fifteen of these 21 patients developed elevated serum TSH levels during the study. Of these 15 patients, "elevation in TSH" was reported as an adverse event in 1 patient. Six of these 21 patients developed abnormal thyroid function tests that were consistent with hyperthyroidism (but hyperthyroidism was not reported as an adverse event for any patient in Study MDS-003). Two of these 6 patients were symptomatic (one was reported to have a grade 1 tremor, and one was reported to have grade 1 night sweats). Additionally, one patient had had a thyroid nodule surgically removed over 20 years ago.

Overall, thyroid abnormalities occurred in a small percentage of the patients in Study MDS-003, and when such abnormalities occurred, they did not exceed grade 2 in severity.

5.3.8.4. Gastrointestinal Disorders

Diarrhea of any grade was reported in 41% (160/395) and constipation of any grade was reported in 26% (104/395) of the patients who received the 10-mg starting dose of lenalidomide. Most of the reported cases of diarrhea and constipation were grade 1 or 2; grade 3 diarrhea was reported in 4% (17/395) and grade 3/4 constipation was reported in 1% (2/395) of the patients. Grade 4 diarrhea was not reported. Few patients discontinued treatment due to diarrhea (2%; 7/395) or constipation (<1%; 1/395).

5.3.8.5. General Disorders and Administration Site Conditions

Thirty-seven percent (144/395) of the patients were reported to have fatigue, primarily grade 1 to 2, at least once during the studies. Grade 3/4 fatigue was reported in 7% (28/395) of the patients (grade 4 in 1 patient). Few patients (1%; 4/395) discontinued treatment due to fatigue.

5.3.8.6. Nervous System Disorders

Somnolence (3%; 10/395), tremor (3%; 10/395), peripheral neuropathy NOS (5%; 19/395), neuropathy NOS (2%; 7/395), and neuropathic pain (1%; 3/395) were reported at low incidences during the 3 MDS studies.

5.3.8.7. Skin and Subcutaneous Tissue Disorders

Pruritus and rash NOS were reported in 32% (127/395) and in 31% (123/395) of the patients, respectively, during lenalidomide therapy. No cases of grade 4 pruritus or rash NOS were reported. The incidence of grade 3 pruritus (1%; 5/395) and grade 3/4 rash (5%; 19/395) was low, and few patients discontinued treatment for these reasons (pruritus, 1%; rash, 2%).

5.4. Clinical Laboratory Evaluations

5.4.1. Hematology

Table 37 summarizes the shift from baseline in hematology parameters based on the most-extreme value obtained during treatment for the patients who received the 10-mg/day starting dose.

Table 37: 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)

	CC-5013 10mg Overall (N=395) Most Extreme Values					
Baseline Grade [c]	Normal n (%)	Gr 1 n (%)	Gr 2 n (%)	Gr 3 n (%)	Gr 4 n (%)	Total n (%)
ABS NEUTROPHILS (N=389)						
Normal	39 (10)	14 (4)	43 (11)	77 (20)	61 (16)	234 (60)
Grade 1	0	1 (<1)	10 (3)	25 (6)	13 (3)	49 (13)
Grade 2	0	1 (<1)	1 (<1)	26 (7)	23 (6)	51 (13)
Grade 3	1 (<1)	0)	0	9 (2)	34 (9)	44 (11)
Grade 4	0	1 (<1)	1 (<1)	1 (<1)	8 (2)	11 (3)
Total	40 (10)	17 (4)	55 (14)	138 (36)	139 (36)	
ABS LYMPHOCYTES (N=31)						
Normal	8 (26)	6 (19.4)	2 (7)	0	0	16 (52)
Grade 1	1 (3)	1 (3)	7 (23)	2 (7)	0	11 (36)
Grade 2	0	0	2 (7)	1 (3)	0	3 (10)
Grade 3	0	0	0	1 (3)	0	1 (3)
Grade 4	0	0	0	0	0	0
Total	9 (29)	7 (23)	11 (36)	4 (13)	0	
WBC (N=389)						
Normal	52 (13)	22 (6)	74 (19)	84 (22)	12 (3)	244 (63)
Grade 1	1 (<1)	2 (1)	19 (5)	29 (8)	2 (1)	53 (14)
Grade 2	0	2 (1)	13 (3)	38 (10)	5 (1)	58 (15)
Grade 3	0	0	1 (<1)	23 (6)	9 (2)	33 (9)
Grade 4	0	1 (<1)	0	0	0	1 (<1)
Total	53 (14)	27 (7)	107 (28)	174 (45)	28 (7)	
HGB (N=389)						
Normal	0	3 (1)	6 (2)	4 (1)	0	13 (3)
Grade 1	0	16 (4)	59 (15)	39 (10)	1 (<1)	115 (30)
Grade 2	1 (<1)	8 (2)	91 (23)	95 (24)	22 (6)	217 (56)
Grade 3	0	1 (<1)	9 (2)	19 (5)	11 (3)	40 (10)
Grade 4	0	0	0	1 (<1)	3 (<1)	4 (1)
Total	1 (<1)	28 (7)	165 (42)	158 (41)	37 (10)	
PLATELETS (N=383)						
Normal	53 (14)	97 (25)	55 (14)	71 (19)	2 (1)	278 (73)
Grade 1	2 (1)	6 (2)	15 (4)	49 (13)	4 (1)	76 (20)
Grade 2	1 (<1)	2 (1)	3 (1)	12 (3)	0	18 (5)
Grade 3	0	0	0	10 (3)	1 (<1)	11 (3)
Grade 4	0	0	0	0	0	0
Total	56 (15)	105 (27)	73 (19)	142 (37)	7 (2)	

[a] Number of patients with baseline and post-baseline measurements. This number is used as the denominator for calculation of percents.
[b] NCI CTC=National Cancer Institute Common Toxicity Criteria version 2. NCI Common Toxicity Criteria are listed in Appendix 4 of the protocol.
[c] Baseline = last value before start of treatment.

The overall frequency of shifts from grade 0, 1, 2, or 3 values at baseline was low among the 389 (of 395) patients in the 3 MDS studies who received the 10-mg/day starting dose of lenalidomide and who had a baseline and at least one follow-up value.

The overall frequency of grade 4 neutropenia, based on central laboratory data (34%; 131/389), is comparable to that based on adverse event reports of grade 4 neutropenia (30%; 118/395) (see Table 30), whereas the frequency of grade 4 thrombocytopenia, based on laboratory data (2%; 7/389), is lower than that based on adverse event reports (7%; 28/395) (see Table 30). The higher frequency of anemia based on laboratory data (9%; 34/389) than based on adverse event reports (3%; 11/395) (see Table 30) may be an artifact of reporting, as anemia is both a disease feature and a clinical endpoint.

5.4.2. Serum Chemistries

Lenalidomide had no clinically meaningful effects on serum chemistries, including liver and renal function tests, in any of the 3 studies in MDS.

5.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

A review of vital sign data for individual patients who were treated with lenalidomide in the 3 MDS studies revealed no clinically important changes during treatment in blood pressure, pulse rate, or oral temperature.

5.6. Safety in Special Groups and Situations

5.6.1. Intrinsic Factors

Analysis of all adverse events (see Section 5.3.2), grade 3/4 adverse events (see Section 5.3.4), serious adverse events (see Section 5.3.6), and discontinuations due to adverse events (see Section 5.3.7) revealed no clinically important differences in the frequency of adverse events by age or gender when examined for the 3 studies in MDS; the number of non-white patients was too small to allow for conclusions to be reached.

5.6.2. Extrinsic Factors

Co-administration of 200-mg of lenalidomide with a high-fat meal resulted in a slower rate, but not in a lower extent, of absorption (Study 1398/142). The mean maximum plasma levels were 39% lower when 200 mg of lenalidomide was administered in the fed state than when the same dose was administered in the fasted state (mean maximum plasma concentration (C_{max}) values of 2239 and 3519 ng/mL, respectively). The time to maximum plasma concentration (T_{max}) occurred later in the fed state (median T_{max} at 3 hours, ranged from 2 to 4 hours) than in the fasted state (median T_{max} at 0.6 hours). No difference was observed in the extent of absorption, as reflected by the area under the concentration-time curve (AUC) value. Since lenalidomide is absorbed equally well with or without food, the drug may be taken on an empty stomach or with food.

5.6.3. Drug Interactions

Results from nonclinical and human in vitro metabolism studies show that lenalidomide is not metabolized through the cytochrome P450 pathway, suggesting that administration of lenalidomide is not likely to result in drug interactions related to this pathway in man.

Administration of 10 mg of lenalidomide daily for 4 days before administration of a single, oral 25-mg dose of warfarin had no effect on the pharmacokinetics of either R- or S-warfarin (Study CC-5013-PK-003). Conversely, administration of a single 25-mg oral dose of warfarin along with the fourth daily, 10-mg dose of lenalidomide had no effect on the pharmacokinetics of total lenalidomide. The C_{max} and $AUC_{(0\text{-}24\ h)}$ values were approximately 30% higher for the S-isomer of lenalidomide than for the R-isomer of lenalidomide, but no differences in half-life or T_{max} were observed between the isomers. As expected during warfarin therapy, elevations in prothrombin time (PT) and the International Normalized Ration (INR) were observed during the study. However, based

on a comparison of the PT and INR values that were observed during co-administration of placebo and warfarin and those that were observed during co-administration of lenalidomide and warfarin, co-administration of lenalidomide had no effect on PT or INR. The results of this study show no pharmacokinetic or pharmacodynamic interactions between lenalidomide and warfarin; therefore, it is anticipated that lenalidomide and warfarin may be safely co-administered.

5.7. Other Information Pertinent to Safety

In addition to MDS, lenalidomide has been investigated for the treatment of other indications, including multiple myeloma (Study CDC-501-001, Study CDC-501-002, Study CC-5013-MM-007, and Study CC-5013-MM-014), metastatic malignant melanoma (Study CC-5013-MEL-001 and Study CC-5013-MEL-002), solid tumors (Study CDC-501-ST-001, CDC-501-ST-002, and CDC-501-ST-003), gliomas (Study CDC-501-GLIO-001), complex regional pain syndrome (CRPS; Study CC-5013-CRPS-001), and Crohn's disease (Study CDC-501-CD-001). The adverse-event profiles of lenalidomide in these indications, particularly with regard to cytopenias, were generally more modest than in MDS. The greater susceptibility to myelosuppression in the MDS patients is presumably due to their underlying bone marrow disease. Additionally, in patients who have MDS with the del 5q cytogenetic abnormality, abnormal cell clones with the del 5q cytogenetic abnormality (which are particularly susceptible to lenalidomide) may represent a large proportion of the progenitor cells in the bone marrow prior to treatment; thus, increased myelosuppression in these patients, particularly early in treatment (before improvement in cytogenetics and bone marrow morphology is seen), may be directly related to the therapeutic effect of the drug.

Changes in thyroid function (hypo- and hyperthyroidism) have been observed during lenalidomide therapy; the relationship of these changes to lenalidomide is not clear at this time. The percentage of patients with MDS who had abnormal laboratory findings for thyroid function tests in study MDS-003 was 14% (21/148). While thyroid abnormalities are not uncommon in the US population, particularly in older individuals, it is notable that abnormal on-treatment values for TSH, T_3, and/or T_4 have also been observed in 35% (14/40) of patients with unilateral type 1 CRPS who were treated with 10 mg/day of lenalidomide for up to 12 weeks (Study CRPS-001) and in 40% (2/5) of patients with CHF who were treated with 10 mg/day of lenalidomide for up to 12 weeks (Study CC-5013-CHF-00-001). Clinical manifestations of hyperthyroidism (in terms of insomnia, dizziness, headache, tremor, nausea, heat and cold intolerance) coincided with the abnormal laboratory findings in some patients, and some patients required suppressive therapy. Although these have not represented severe adverse events, further evaluation of the effects of lenalidomide on thyroid function is warranted in future clinical studies.

6. RISK-BENEFIT ASSESSMENT

6.1. Current Therapies and Unmet Medical Need

The MDS occur predominantly in older patients, with a median age at diagnosis of 65 to 75 years (Kantarjian and Estey, 2001). The incidence of MDS is approximately 5 per 100,000 population; however, its prevalence in the population older than 70 approaches 22 to 45 per 100,000 population (Greenberg, 2000). The overall prognosis for patients with MDS is poor. Spontaneous complete remission or hematologic improvement rarely occurs, and the overall median survival is approximately 2 years (Dunbar and Nienhuis, 2001). Patients with lower grades of MDS have a somewhat longer survival and lesser rate of transformation to AML but still have progressive cytopenias with a high probability of becoming transfusion dependent for refractory anemia. The expected survival of patients with transfusion-dependent MDS is shorter than the survival of patients who are anemic but not yet transfusion dependent (Cazzola and Malcovati, 2005).

Allogeneic bone marrow transplantation is the only potentially curative therapy for MDS (Anderson et al, 1996; Cheson, 1998; De Witte, 1994; De Witte et al, 1997). However, due to the advanced age of the population with MDS and the need for a histocompatible donor, this treatment option is available only to a small subset of approximately 5% of patients with MDS (Anderson et al, 1993; Appelbaum and Anderson, 1998; Slavin et al, 1998; Kernan et al, 1993). Other therapies include hematopoietic growth factors, chemotherapy, immunosuppression, and cytoprotective agents (Armitage et al, 1981; Tricot and Boogaerts, 1986; Fenaux et al, 1988; Negrin et al, 1989; Hellström-Lindberg, 1995; List et al, 1997; Miller et al, 1992). Aggressive chemotherapy is generally precluded because older patients with MDS often have inadequate bone marrow reserves to recover from chemotherapy-induced hypoplasia, due to a lack of normal hematopoietic stem cells.

The anemia in some patients may be improved by treatment with hematopoietic growth factors, but single-agent erythropoietin has demonstrated limited effectiveness, mainly confined to patients without the need for RBC transfusions. When combined with G-CSF or GM-CSF, erythropoietin may augment the erythropoietic response in selected patients with suboptimal endogenous growth factor response (Hellström-Lindberg et al, 1998; Hellström-Lindberg et al, 1993; Negrin et al, 1996). Thus far, however, no treatment modality, other than ABMT in selected patients, has significantly altered the natural history of MDS, and supportive care with antibiotics and transfusions is still considered to be the standard of care (Silverman et al, 2002).

Recently, azacitidine (Vidaza™, Pharmion) was approved in the United States for the treatment of MDS. Although azacytidine offers a new therapeutic option for patients with MDS, the overall response rate (complete and partial response) is <20% (see Vidaza, 2005), and the drug is administered subcutaneously.

6.2. Benefits

The results of Study MDS-003 demonstrate that lenalidomide, administered at a dose of 10 mg/day, is effective in producing RBC-transfusion independence in a high proportion of patients with low- or intermediate-1-risk MDS associated with a del 5 (q31-33) cytogenetic abnormality, with or without additional cytogenetic abnormalities. As of the 15 September 2004 NDA cutoff date, 61% (57/94) of the patients in the MITT population and 64% (95/148) of the patients in the ITT population had achieved RBC-transfusion independence; as of 31 March 2005, the response rates were 64% (60/94) in the MITT population and 67% (99/148) in the ITT population. Lenalidomide-induced RBC-transfusion independence was associated with a median increase from baseline in blood Hgb concentration of 5.5 mg/dL (ITT population) to 5.7 g/dL (MITT population) in the responders (based on data available as of 31 March 2005) and with histologic improvement and cytogenetic normalization, further quantifying and confirming the clinical observation of transfusion independence.

The response to lenalidomide is durable. The median duration of response had not yet been reached as of the 15 September 2004 data cutoff date. Transfusion independence was ongoing in 82% (47/57) of the responders in the MITT population and in 86% (82/95) of the 95 responders in the ITT population. As of the 15 September 2004 data cutoff date, the duration of RBC-transfusion independence was at least 24 weeks in 68% (39/57) of the responders in the MITT population and in 74% (70/95) of the 95 responders in the ITT population. Additional follow-up through 31 March 2005 further confirms the durability of the response to lenalidomide; as of that date, 63% (38/59) of the patients in the MITT population and 68% (67/99) of the patients in the ITT population remained RBC-transfusion independent, and 37% (22/59) in the MITT population and 32% (32/99) of the patients in the ITT population had progressed. Based on preliminary Kaplan-Meier estimates using data from the 31 March 2005 update, the median duration of response is 74.6 weeks, both for the MITT and ITT populations.

Red blood cell-transfusion dependency requires repeated insertion of intravenous lines, and is attended by discomfort and inconvenience for patients. Additionally, RBC transfusions expose patients to possible transfusion-related reactions and to an increased risk of infection. Chronic RBC-transfusion therapy can also lead to in the development of secondary hemochromatosis. As noted previously, patients enrolled in the pivotal study (Study MDS-003) were receiving a median of 5 units of red cells per 8 weeks at study entry (average number of units transfused in each of 2 consecutive 8-week periods prior to study entry; MITT population). The achievement of prolonged RBC-transfusion independence with lenalidomide therapy, in a large proportion of these patients, represents a clear clinical benefit.

The RBC-transfusion independence achieved during lenalidomide therapy was also accompanied by histologic bone marrow improvement, including resolution of dysplastic morphologic changes and normalization of blast percentages in many patients. Not surprisingly, histologic bone marrow improvement correlated with durable RBC-transfusion independence. Also, it is notable that only a small percentage of patients developed disease progression during the course of these studies.

The cytogenetic data available also show that lenalidomide is a highly effective treatment for patients with MDS with an isolated del 5q cytogenetic abnormality, as well as for patients with MDS who have dysplastic clones that have a del 5q abnormality together with additional cytogenetic abnormalities. Further, the data suggest that lenalidomide-induced cytogenetic improvement correlates with both the achievement and durability of RBC-transfusion independence in patients with MDS associated with a del 5q cytogenetic abnormality.

Lenalidomide thus provides an effective, orally available therapy for patients with transfusion-dependent MDS and an associated del 5 (q31-33) cytogenetic abnormality, a population with significant morbidity for which few therapeutic options exist. Lenalidomide induces sustained and durable RBC-transfusion independence, accompanied by substantial increases in and stabilization of Hgb, bone marrow improvement, and cytogenetic normalization. Additionally, the cytogenetic findings indicate that lenalidomide may have a positive effect on the natural history of the disease.

6.3. Risks

Lenalidomide, administered at the recommended dose of 10 mg/day, demonstrated a favorable safety profile in the population of 395 patients who were treated with this dose in the 3 MDS studies. The adverse events were easily monitored and managed clinically.

Grade 3/4 neutropenia and thrombocytopenia were the most common adverse events associated with the administration of lenalidomide. These events may correlate with the therapeutic effect of lenalidomide in inducing apoptosis of abnormal precursor cell clones in the bone marrow of treated MDS patients. However, the rates of adverse event reports of serious neutropenia (7%) or thrombocytopenia (4%) and discontinuation from the study due to neutropenia (3%) and thrombocytopenia (5%) were low in Study MDS-003, indicating that these adverse events were effectively managed through dose reductions or the use of appropriate supportive care. To minimize the risk of serious adverse events related to neutropenia or thrombocytopenia, the proposed labeling recommends that a complete blood cell (CBC) count, including white blood cell (WBC) count with differential, platelet count, Hgb, and hematocrit be performed weekly for the first 8 weeks of lenalidomide treatment. The proposed labeling also recommends a dosage reduction scheme for patients who develop grade 3/4 neutropenia or thrombocytopenia.

Pruritus, rash, diarrhea, constipation, and fatigue were reported in =10% of the patients who were treated with the 10 mg/day starting dose. These were primarily of grade 1, 2, or 3 in severity. The discontinuation rate from the study due to these events was low (=3%) in Study MDS-003, indicating that these adverse events are tolerable to the patients, resolve, or are manageable with appropriate supportive care.

The overall frequency of on-study death among the patients who were treated with lenalidomide (25 mg/day or 10 mg/day) was low (6%; 25/408), considering the prolonged duration of the study, and the survival reported in the literature for the low- to intermediate-1-risk MDS population (Greenberg et al, 1997). Five deaths (due to urosepsis and shock secondary to pancytopenia, respiratory failure, respiratory distress secondary to pancytopenia, sepsis, and pneumonia, respectively) were suspected by the

investigators to be related to lenalidomide administration. All 5 of the potentially related deaths occurred in patients who were treated with the 10-mg/day starting dose. Thus, the overall frequency of drug-attributed death was approximately 1% (5/395) among the patients who received the 10-mg/day starting dose. Review of these cases, together with the overall safety database, indicates that careful monitoring of blood counts is important, particularly early in treatment when the abnormal clone (which may represent most of the progenitor cells in the marrow, at the start of treatment) is undergoing apoptosis in response to lenalidomide therapy.

Although lenalidomide is an IMiD with some similar physiologic activities to thalidomide (a known teratogen), no teratogenic effects of lenalidomide have observed in rabbit and rat embryo-fetal development (Segment II) testing. Embryotoxicity was observed in the rabbit study when given in doses up to 100 times the recommended human dose of 10 mg on a milligram-per-kilogram basis. Physician judgment and an appropriately informed patient are key components of a decision to treat all patients, but are particularly key for women of childbearing potential to ensure that the benefit to the patient justifies the potential risk to the fetus should a pregnancy occur during treatment.

Celgene has developed a Risk Management Plan for lenalidomide. Celgene plans to balance the risks of lenalidomide therapy by safety signal monitoring of all patients and by providing enhanced labeling information, including a medication guide, targeted medical and patient education, and medical treatment guidelines and management plans. Celgene also plans to control the distribution of lenalidomide as it is introduced into the marketplace in order to support the safe and effective use of this drug, including appropriate patient monitoring and provision of comprehensive education and counseling. The details of this plan will be finalized in consultation with FDA.

In summary, the safety profile of lenalidomide in patients with MDS is well characterized. The adverse events (neutropenia, thrombocytopenia, pruritus, rash, diarrhea, constipation, and fatigue) are easily monitored and clinically manageable. Appropriate screening of prospective patients and comprehensive patient education and counseling is expected to minimize the risks associated with lenalidomide therapy.

6.4. Conclusions

Transfusion-dependent MDS is associated with substantial patient morbidity, and few treatment options exist. Lenalidomide can safely and effectively ameliorate the burden and consequences of long-term RBC-transfusion requirements for many of these patients, providing a clear and durable clinical benefit. The data provided demonstrate that lenalidomide is a safe and effective, orally available therapy that successfully reduces dependency on RBC-transfusions for patients with transfusion-dependent MDS and an associated del 5 (q31-33) cytogenetic abnormality.

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Study CC-5013-MDS-002: A multicenter, single-arm, open-label study of the efficacy and safety of CC-5013 monotherapy in RBC transfusion-dependent patients with myelodysplastic syndromes. 01 February 2005.

Study CC-5013-MDS-003: A multicenter, single-arm, open-label study of the efficacy and safety of CC 5013 monotherapy in red blood cell transfusion-dependent patients with myelodysplastic syndromes. 07 March 2005.

Study CC-5013-MEL-001: Multicenter, randomized, double-blind, parallel-group study to compare the efficacy and safety of two CC-5013 dose regimens in patients with

metastatic malignant melanoma whose disease has progressed on treatment with DTIC, IL-2, IFN-a and/or IFN-ß based therapy. 07 March 2005.

Study CC-5013-MEL-002: Multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of CC-5013 vs. placebo in patients with metastatic malignant melanoma whose disease has progressed on treatment with DTIC, IL-2, IFN-a and/or IFN-ß based therapy. 07 March 2005.

Study MDS-501-001: A phase II open label study of the safety and efficacy of CC 5013 (Revimid™) treatment for patients with myelodysplastic syndrome. 24 September 2004.

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8. APPENDICES

8.1. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
5q31-33	Chromosome 5, long arm, band 31 to band 33
ABMT	Allogenic bone marrow transplant
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AUC	Area under the concentration-time curve
BL	Baseline
CBC	Complete blood cell count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
C_{max}	Maximum plasma concentration
CML	Chronic myelogenous leukemia
CMML	Chronic myelomonocytic leukemia
CRPS	Complex regional pain syndrome
CTC	Common Toxicity Criteria
del	Deletion
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
FAB	French-American-British
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
G-CSF	Granulocyte colony-stimulating factor
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony-stimulating factor
Hgb	Hemoglobin
IFN-?	Interferon-gamma
IL	Interleukin
IMiD	Immunomodulatory drug

Abbreviation	Definition
INR	International Normalized Ratio
Int-1	Intermediate-1
IPSS	International Prognostic Scoring System
IRF-1	Interferon regulatory factor-1
ITT	Intent to treat
IWG	International Working Group
M-CSF	Macrophage colony-stimulating factor
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified intent to treat
NCI	National Cancer Institute
NDA	New Drug Application
NE	Not estimable
NOS	Not otherwise specified
pRBC	Packed red blood cells
PT	Prothrombin time
q	Every
qd	Every day
qod	Every other day
RA	Refractory anemia
RAEB	Refractory anemia with excess blasts
RAEB-t	Refractory anemia with excess blasts in transition
RBC	Red blood cell
RCMD	Refractory cytopenias with multilineage dysplasia
RCMD-RS	Refractory cytopenias with multilineage dysplasia with ringed sideroblasts
RARS	Refractory anemia with ringed sideroblasts
SD	Standard deviation
T_3	Triiodothyronine
T_4	Thyroxine
T_{max}	Time to maximum plasma concentration
TNF-a	Tumor necrosis factor-alpha
TSH	Thyroid-stimulating hormone

Abbreviation	Definition
WBC	White blood cell
WHO	World Health Organization

8.2. Supportive Information

Table 8.2.1: Description of Clinical Efficacy and Safety Studies of Lenalidomide in MDS

Study ID	Number of Study Centers Location(s)	Study Start Enrollment Status, Date Enrollment Total/Goal	Design Control Type	Study & Ctrl Drugs Dose, Route & Regimen	Study Objective	No. Patients by Arm Entered/ Completed	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
MDS-001	1 USA	19-Feb-02 Ongoing 45/45	Phase 1/2, single-center, open-label, single-arm, noncontrolled, 2-stage	Lenalidomide 25 mg qd x 28 d 10 mg qd x 28 d (10-mg cont) 10 mg qd on Days 1-21 (10-mg cyclic)	To estimate the percent of patients with MDS who experienced erythroid response and the interval to response after treatment	25 mg: 13/2 [a] 10-mg cont: 12/3 [a] 10-mg cyclic: 20/8 [a]	16 wk, followed by an extension that allowed treatment until disease progression	7/6 74 y (51-85 y) 9/3 69.5 y (56-85 y) 10/10 71.5 y (27-82 y)	Age =18 y; de novo MDS of =12 wk in duration and FAB classification of RA, RARS, RAEB, RAEB-t), or CMML; ECOG PS of =2	Major and minor erythroid response, AEs, and safety labs.
MDS-002	38 USA	30-Jun-04 Ongoing 215/99	Phase 2, multicenter, open-label, single-arm, non-controlled	Lenalidomide 10 mg qd x 28 d (10-mg cont) 10 mg qd on Days 1-21 (10-mg cyclic) Repeated 28-d cycles	To evaluate the efficacy and safety of lenalidomide treatments for achieving hematopoietic improvement in patients who have low- or intermediate-1 risk MDS without a del 5 (q31-33) cytogenetic abnormality	10-mg cont: 100/52 [b] 10-mg cyclic: 115/47 [b]	24 cycles	68/32 74 y (27-94 y) 70/45 71 y (35-92 y)	Age =18 y IPSS diagnosis of low- or intermediate-1-risk MDS without a del 5 (q31-33) cytogenetic abnormality; RBC-transfusion dependent; ECOG PS of ≥2	RBC-transfusion independence, AEs, and safety labs

Table 8.2.1: Description of Clinical Efficacy and Safety Studies of Lenalidomide in MDS (continued)

Study ID	Number of Study Centers Location(s)	Study Start Enrollment Status, Date Enrollment Total/Goal	Design Control Type	Study & Ctrl Drugs Dose, Route & Regimen	Study Objective	No. Patients by Arm Entered/ Completed	Duration	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoint(s)
MDS-003	33 USA (32) Germany (1)	30-Jun-04 Ongoing 148/90	Phase 2, multicenter, open-label, single-arm, non-controlled	Lenalidomide 10 mg qd x 28 d (10-mg cont) 10 mg qd on Days 1-21 (10-mg cyclic) Repeated 28-d cycles	To evaluate the efficacy and safety of lenalidomide in patients with low- or intermediate-1-risk MDS with a del 5 (q31-33) cytogenetic abnormality	10-mg cont: 104/90 [c] 10-mg cyclic: 44/28 [c]	24 cycles	35/69 71 y (37-95 y) 16/28 72 y (51-91 y)	Age =18 y; IPSS diagnosis of low- or intermediate-1-risk MDS with a del 5 (q31-33) cytogenetic abnormality; RBC-transfusion anemia; ECOG PS of =2	RBC-transfusion independence, AEs, and safety labs

AE, adverse event; CMML, chronic myelomonocytic leukemia; cont., continuous; ECOG PS, Eastern Cooperative Oncology Group performance status; FAB, French-American-British; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; qd, once daily; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess blasts; RAEB-t, refractory anemia with excess blasts in transition; RBC, red blood cell

[a] Number completes as of data cutoff date of 05 February 2004.
[b] Number completed as of data cutoff date of 15 June 2004.
[c] Number completed as of data cutoff date of 15 September 2004.

Table 8.2.2: Ongoing or Planned Studies of Lenalidomide in MDS

Protocol No.	Study Title	No. of Pts (Planned/ Enrolled[a])	Study Design	Lenalidomide Doses/Treatment Length	Date Initiated	Study Status
CC-5013-MDS-004	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, 3-Arm Study of the Efficacy and Safety of 2 Doses of Lenalidomide Versus Placebo in Red Blood Cell (RBC) Transfusion-Dependent Patients With Low-or-Intermediate-1-Risk Myelodysplastic Syndromes With a Deletion 5q Cytogenetic Abnormality	162/8	Phase 3, multicenter, randomized, placebo controlled safety/ efficacy	10 mg 21 x 28 days vs. 5 mg daily vs placebo	08-Jul-2005	Ongoing
CC-5013-MDS-005	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, 3-Arm Study of the Efficacy and Safety of 2 Doses of Lenalidomide Versus Placebo in Red Blood Cell (RBC) Transfusion-Dependent Patients with Low- or Intermediate-1-Risk EPO Refractory Myelodysplastic Syndromes Without A Deletion 5q Cytogenetic Abnormality	372/0	Phase 3, multicenter, randomized, placebo controlled safety/ efficacy	10 mg 21 x 28 days vs. 5 mg daily vs placebo	-	Planned
ECOG	Randomized Phase III Trial Comparing the Frequency of Major Erythroid Response (MER) to Treatment With Lenalidomide Alone and in Combination With Recombinant Erythropoietin in Patients with Low- or Intermediate-1 Risk MDS and Symptomatic Anemia.	212/0	Phase 3, multicenter, randomized, safety/ efficacy	10 mg 21x 28 days vs 10 mg 21 x 28 day + rhu-EPO 60,000U SC weekly	-	Planned

EPO, erythropoietin; SC, subcutaneous

Table 8.2.3: Dose Reductions in Patients by Initial Lenalidomide Regimen

Initial Regimen [a]	Starting Dose Level	Dose Reduction 1	Dose Reduction 2 [b]
Cyclic Dose[c]	10 mg qd on Days 1-21 q 28 days	5 mg qd	5 mg qod
Continuous Dose	10 mg qd	5 mg qd	5 mg qod

q, every; qd, every day; qod, every other day
[a] Treatment is in 28-day cycles.
[b] Lowest-allowable dosage; patients who cannot tolerate this dosage are discontinued from the study.
[c] If a patient is switched to the continuous-dose regimen, dosage adjustments are made as shown for the continuous-dose regimen.

Table 8.2.4: Dose Modification Guidelines for Neutropenia and/or Thrombocytopenia Within the First 4 Weeks of Starting Lenalidomide Therapy

Adverse Event/Baseline Value	On-therapy Value	Action
Neutropenia		
Absolute Neutrophil Count (ANC) =1000/µL	ANC <750/µL	• Hold dose • Restart at dose of 5 mg/d when ANC recovers to =1000/µL
ANC <1000/µL	ANC <500/µL	• Hold dose • Restart at a dose of 5 mg/d when ANC recovers to =500/µL
Thrombocytopenia		
Platelet count =100,000/µL	Platelet count <50,000/ µL	• Hold dose • Restart at a dose of 5 mg/d when platelet count recovers to =50,000/µL
Platelet count <100,000/µL	Decrease of 50% in baseline platelet count	• Hold dose • For patients with baseline platelet count of >60,000/µL, resume at a dose of 5 mg/d when platelet count recovers to =50,000/µL • For patients with baseline platelet count of <60,000/µL, resume at a dose of 5 mg/d when platelet count recovers to =30,000/µL

Table 8.2.5: Dose Modification Guidelines for Adverse Events During Lenalidomide Therapy

Adverse Event	NCI CTC Criteria	Action[a]
Neutropenia	Grade 4 neutropenia for =7 d or grade 4 neutropenia plus fever of 38.5ºC	• Omit lenalidomide for remainder of cycle • Restart lenalidomide at the next -lower dose level at planned start of next cycle if ANC is =500/µL
Thrombocytopenia	Platelet count =30,000/µL or platelet count <50,000/µL that requires platelet transfusion	• Omit lenalidomide for remainder of cycle • Restart lenalidomide at the next -lower dose level at the planned start of the next cycle if the platelet count is =30,000/µL, without evidence of hemostatic failure • If hemostatic failure is present, consult with the Celgene medical monitor
Desquamating (blistering) rash	—	• Discontinue lenalidomide
Nondesquamating rash	Grade 3	• Omit lenalidomide for remainder of cycle • Restart lenalidomide at the next -lower dose level at the planned start of the next cycle if toxicity reduces to grade =2
	Grade 4	• Discontinue lenalidomide
Erythema multiforme	Grade 3	• Discontinue lenalidomide
Neuropathy	Grade 3	• Omit lenalidomice for remainder of cycle for grade 3 • Restart lenalidomide at the next -lower dose level at the planned start of the next cycle if toxicity reduces to grade =2
	Grade 4	• Discontinue lenalidomide
Sinus bradycardia/other cardiac arrhythmia	Grade 2	• Omit lenalidomide for remainder of cycle • Re-start lenalidomide at planned start of next cycle (if toxicity reduces to less than or equal to grade 2) at the next lower dose level.
	Grade 3 or 4	• Discontinue lenalidomide
Allergic reaction or hypersensitivity	Grade 3	• Omit lenalidomide for remainder of cycle • Restart lenalidomide at the next -lower dose level at the planned start of the next cycle if toxicity reduces to grade 0 or 1
	Grade 4	• Discontinue lenalidomide

Table 8.2.5: Dose Modification Guidelines for Adverse Events During Lenalidomide Therapy (continued)

Adverse Event	NCI CTC Criteria	Action[a]
Constipation	Grade 1 or 2	• Initiate bowel regimen and maintain lenalidomide dose level
	Grade 3	• Omit lenalidomide for remainder of cycle • Restart lenalidomide at the next-lower dose level at the planned start of the next cycle if toxicity reduces to grade =2
Venous thrombosis/embolism	Grade 3	• Omit lenalidomide for remainder of cycle and start anticoagulation therapy • Restart on Day 1 of next cycle at the same dose level, at the investigator's discretion
Hepatic or other non-hematologic adverse event assessed as lenalidomide related	Grade 3 or 4	• Omit lenalidomide for remainder of cycle • Restart lenalidomide at the next-lower dose level at the planned start of the next cycle if toxicity reduces to grade =2
Hyperthyroidism or hypothyroidism	—	• Omit lenalidomide for remainder of cycle • Evaluate etiology and initiate appropriate therapy • Restart lenalidomide at the next-lower dose level at the planned start of the next cycle

ANC, absolute neutrophil count; NCI CTC, National Cancer Institute Common Toxicity Criteria

[a] The Celgene medical monitor is notified if an adverse event does not resolve to grade 2 (grade =2 for sinus bradycardia or cardiac arrhythmia) within 4 weeks.

Table 8.2.6: Inclusion/Exclusion Criteria for Study MDS-003

Inclusion Criteria	Exclusion Criteria
1. Age, 18 years or older (at the time the informed consent is signed) 2. IPSS diagnosis of low- (combined marrow blast, karyotype, and cytopenia score of 0) or intermediate 1- (combined marrow blast, karyotype, and cytopenia score of 0.5 1) risk MDS associated with an abnormality of chromosome 5 that involves a deletion between bands q31 and q33, with the del (5q) cytogenetic abnormality either representing an isolated cytogenetic finding (the 5q- syndrome) or being associated with other cytogenetic abnormalities 3. RBC-transfusion-dependent anemia, defined as receiving 2 or more units of RBCs within 8 weeks of the first day of study treatment 4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 (fully active, able to carry on all predisease performance without restriction), 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of light or sedentary nature, e.g., light housework, office work), or 2 (ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours) 5. For women of childbearing potential (defined as a sexually mature woman who had not undergone a hysterectomy or who had had menses at any time during the preceding 24 months before study entry), a negative serum or urine pregnancy test within 7 days of starting study drug and willingness to use an adequate contraceptive method (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) and to have pregnancy tests every 4 weeks while on the study drug 6. Ability to adhere to the study -visit schedule and to other protocol requirements 7. Ability to understand and willingness to sign an informed consent statement	1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from signing the informed consent statement, place the patient at an unacceptable risk if he/she were allowed to participate in the study, or confound the interpretation of the study data 2. Pregnancy or breast-feeding 3. Prior therapy with lenalidomide 4. Inability to obtain bone marrow aspirate (dry tap) 5. Proliferative chronic myelomonocytic leukemia, defined as a white blood cell (WBC) count of =12000/µL 6. Any of the following laboratory abnormalities: • Absolute neutrophil count (ANC) of <500 cells/mm3 (0.5 x 109 L) • Platelet count of <50,000/mm3 (50 x 109 L) • Serum creatinine of >2.5 mg/dL (221 µmol/L) • Serum alanine aminotransferase (ALT; SGPT) or aspartate aminotransferase (AST; SGOT) of >3 times the upper limit of the normal range • Serum direct bilirubin of >2.0 mg/dL (34 µmol/L) 7. Prior grade 3 or 4 allergic reaction or hypersensitivity to thalidomide 8. Prior grade 3 or 4 rash or desquamation while taking thalidomide 9. Clinically significant anemia due to factors, such as iron, B12, or folate deficiencies; autoimmune or hereditary hemolysis; or gastrointestinal bleeding (if a marrow aspirate was not available to determine storage iron, the transferrin saturation must have been =20%, and the serum ferritin must not have been <50 ng/mL) 10. Use of hematopoietic growth factors within 7 days of the first day of treatment with the study drug 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 dose of the study drug 12. Use of experimental or standard drugs (e.g., chemotherapeutic, immunosuppressive, or cytoprotective agents) for the treatment of MDS within 28 days of the first dose of study drug 13. Prior history of malignancy other than MDS, except basal cell or squamous cell carcinoma or carcinoma in situ of the breast or cervix, unless the patient had been disease free for =3 years 14. Use of any experimental therapy within 28 days of the first day of study drug treatment

Table 8.2.7: International Working Group (IWG) Criteria for Red Blood Cell Response in Patients With Myelodysplastic Syndrome

Outcome	Criteria
Transfusion Independence	• No need for red blood cell (RBC) transfusions for any consecutive 56 days during the evaluation period. • Increase in hemoglobin (Hgb) of at least 1 g/dL from the minimum value that was observed during the 56 days prior to start of treatment to the maximum that was observed during the transfusion-independent period, excluding the first 30 days after the last transfusion before the transfusion-free period [a, b]
=50% Decrease in RBC-transfusion Requirements	• =50% decrease from pretreatment requirements, defined as the number of RBC units required over the 56-day period before the start of the study mediation (i.e., Day -54 through Day 1 in the counting system used in the analysis) over any consecutive 56 days during the evaluation period

[a] The change in Hgb was measured from the minimum Hgb value that was obtained from either the local or central laboratory during the 56-day period immediately preceding the first day of drug administration to the maximum value observed during the transfusion-free interval, excluding any Hgb values that were obtained within 30 days of the last transfusion that immediately preceded the transfusion-free period. Change was post-value minus pre-value, so a positive change indicates an increase.

[b] The requirement for a 1-g/dL increase from screening/baseline in Hgb was added as an additional requirement for transfusion independence after consultation with the Oncology Division of the US Food and Drug Administration (FDA) on 06 June 2003 and before the data were analyzed.

Table 8.2.8: Definitions of Time to Transfusion Independence and Duration of Response

Outcome[a]	Criteria
Time to Transfusion Independence	• For those patients who become transfusion independent, the time to transfusion independence is measured from the first dose of study drug to the first day of the 56-day, red blood cell (RBC)-transfusion-free period.
Duration of Response	• The duration of response is measured from the date of the first of the consecutive 56 days during which the patient is free of RBC transfusions to the day before the date of the first RBC transfusion after this 56-day, RBC-transfusion-free period. If a patient who responds has not received an RBC transfusion, the duration of response is censored at the date on which the last Blood Component Transfusion History case report form (CRF) was completed or at 15 June 2004, whichever is earlier.

Table 8.2.9: International Working Group (IWG) Criteria for Platelet Response in Patients With Myelodysplastic Syndrome

Outcome	Criteria
Major Response	• For patients with a mean pretreatment platelet count <100,000/mm^3, for all readings taken within 56 days of start of treatment, an absolute increase of =30,000/mm^3 sustained for at least 56 consecutive days (i.e., at least 2 readings 56 or more days apart and all reading in-between) that are at least 30,000/mm^3 larger than the mean pretreatment count. • For patients with a mean pretreatment platelet count <100,000/mm^3, a =50% increase in platelet count with a net increase >10,000/mm^3 but <30,000/mm^3 for all readings in a consecutive 56-day period.
Minor Response	• For platelet transfusion-dependent patients, stabilization of platelet counts (all values in a 56-day period greater than the pretreatment mean) and platelet transfusion independence.

Table 8.2.10: International Working Group (IWG) Criteria for Neutrophil Response in Patients With Myelodysplastic Syndrome

Outcome	Criteria
Major Response	• For patients with mean pretreatment absolute neutrophil count (ANC) <1500/mm^3, over all values obtained within 56 days of start of treatment, a =100% increase or an absolute increase of =500/mm^3, whichever is greater, sustained for 56 consecutive days (at least 2 readings 56 or more days apart and all readings in-between showing a =100% increase or an absolute increase of =500/mm^3 whichever is greater).
Minor Response	• For patients with a mean pretreatment ANC <1500/mm3, an ANC increase of =100%, with an absolute increase <500/mm^3 sustained for 56 consecutive days as defined above.

Table 8.2.11: International Working Group (IWG) Criteria for Bone Marrow Response in Patients With Myelodysplastic Syndrome

Outcome	Criteria
Complete Remission (CR)	• *Bone marrow evaluation.* Bone marrow showing <5% myeloblasts with normal maturation of all cell lines, with no evidence for dysplasia (see qualifier under peripheral blood evaluation). When erythroid precursors constitute <50% of bone marrow nucleated cells, the percent of blasts is based on all nucleated cells; when there are =50% erythroid cells, the percent blasts should be based on the non-erythroid cells. • *Peripheral blood evaluation.* Absolute values as follows for =2 months: o Hemoglobin, >11 g/dL (untransfused; not on erythropoietin) o Neutrophils, =1500/mm^3 (not on a myeloid growth factor) o Platelets, =100,000/ mm^3 (untransfused; not on a thrombopoietic agent) o Blasts, -0% o No dysplasia. The presence of mild megaloblastoid changes may be permitted if they are thought to be consistent with treatment effect. However, persistence of pretreatment abnormalities (e.g., pseudo-Pelger-Hüet cells, ringed sideroblasts, dysplastic megakaryocytes) is not consistent with CR.
Partial Remission (PR)	• All of the criteria for CR (if abnormal prior to treatment), except for the bone marrow evaluations, blasts decreased by =50% over pretreatment or a less advanced MDS French-American-British (FAB) Classification than pretreatment. Cellularity and morphology are not relevant.
Stable Disease	• Failure to achieve at least a PR but with no evidence of progression for =2 months.
Failure	• Death during treatment or disease progression characterized by worsening of cytopenias, increase in the percent of bone marrow blasts (as defined for Disease Transformation, or progression to an MDS FAB subtype that is more advanced than at pretreatment.
Relapse (After CR or PR)	One or more of the following: • Return to pretreatment bone marrow blast percentage • Decrement of =50% form maximum remission response levels in neutrophils or platelets • Red blood cell (RBC)-transfusion dependence (=2 units RBC transfusions over an 8-week period) or reduction in hemoglobin concentration by =2 g/dL in the absence of acute infection, gastrointestinal bleeding, hemolysis, etc.
Disease Progression	A =50% increase in blasts, depending on the baseline blast percent • For patients with <5% blasts, increase to =10% blasts. • For patients with 5%- to 10% blasts, =50% increase to >10% blasts. • For patients with 10% to 20% blasts, =50% increase to >20% blasts • For patients with 20% to 30% blasts, =50% increase to >30% blasts
Disease Transformation	Transformation to acute monocytic leukemia (=30% blasts)

Table 8.2.12: International Working Group (IWG) Criteria for Cytogenic Response in Patients With Myelodysplastic Syndrome

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

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.