DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

Volume II

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8:00 a.m.

Holiday Inn Bethesda
8120 Wisconsin Avenue
Bethesda, Maryland

PARTICIPANTS

Silvana Martino, D.O., Chair
Johanna Clifford, M.S., R.N., Executive Secretary

MEMBERS

Ronald M. Bukowski, M.D.
Bruce D. Cheson, M.D.
James H. Doroshow, M.D.
Antonio J. Grillo-Lopez, M.D. (Industry Representative)
Pamela J. Haylock, R.N. (Consumer Representative)
Maha H.A. Hussain, M.D.
Alexandra M. Levine, M.D.
Joanne E. Mortimer, M.D.
Michael C. Perry, M.D.
Gregory H. Reaman, M.D.
Maria Rodriguez, M.D.
Robert Carroll, Ph.D. (Patient Representative)

CONSULTANTS (VOTING)

S. Gail Eckhardt, M.D.
Thomas Fleming, Ph.D.
Susan O'Brien, M.D.

FDA

Kimberly Benson, Ph.D.
Robert Justice, M.D.
Edvardas Kaminskas, M.D.
Richard Pazdur, M.D.
Anne Trontell, M.D.

C O N T E N T S

C O N T E N T S (Continued)

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order

DR. MARTINO: Good morning. I would like to get the meeting started.

The committee today will discuss New Drug Application NDA 21-880, proposed trade name Revlimid from Celgene Corporation, proposed indication for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndrome associated with a deletion of 5q cytogenetic abnormalities with or without additional cytogenetic abnormalities.

The first thing I would like to do this morning is have the committee introduce itself, and I would like to start on my left, please.

Introductions

DR. CARROLL: Robert Carroll, Patient Representative.

DR. O'BRIEN: Susan O'Brien, from M.D. Anderson.

DR. FLEMING: Thomas Fleming, Department

of Biostatistics, University of Washington.

DR. HUSSAIN: Maha Hussain, Medical Oncology, University of Michigan.

DR. BUKOWSKI: Ron Bukowski, Medical Oncology, Cleveland Clinic.

DR. CHESON: Bruce Cheson, Hematologic Oncologist, Georgetown University Hospital.

DR. ECKHARDT: Gail Eckhardt, Medical Oncologist, University of Colorado.

DR. PERRY: Michael Perry, Medical Oncology, University of Missouri, Columbia.

DR. RODRIGUEZ: Maria Rodriguez, Hematologist/Oncologist, M.D. Anderson Cancer Center in Houston, Texas.

DR. MARTINO: Silvana Martino, Medical Oncology, the Angeles Clinic in Santa Monica.

MS. CLIFFORD: Johanna Clifford, FDA, Executive Secretary to the meeting.

DR. MORTIMER: Joanne Mortimer, Medical Oncology, University of California at San Diego.

DR. LEVINE: Alexandra Levine, University of Southern California, Keck School of Medicine.

MS. HAYLOCK: Pamela Haylock, Oncology Nurse, University of Texas Medical Branch in Galveston.

DR. REAMAN: Gregory Reaman, Pediatric Oncology, Children's Oncology Group, Children's National Medical Center, Washington, D.C.

DR. BENSON: Kimberly Benson, Toxicology Reviewer, FDA.

DR. HAZARIKA: Maitreyee Hazarika, Medical Reviewer, FDA.

DR. TRONTELL: Anne Trontell, Office of Drug Safety, FDA.

DR. JUSTICE: Robert Justice, Acting Division Director, FDA.

DR. PAZDUR: Richard Pazdur, Office Director, FDA.

DR. MARTINO: Thank you.

Next, Ms. Clifford will read the Conflict of Interests.

Conflict of Interest Statement

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest and is

made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions:

In accordance with 18 U.S.C., Section 208, full waivers have been granted to the following participants:

Dr. Michael Perry for owning stock in a competitor valued at less than $5,001; Gail Eckhardt for unrelated advisory board activities for a competitor for which she receives less than 10,001 a year; Dr. Ronald Bukowski for unrelated consulting for a competitor for which he receives less than 10,001 per year; Thomas Fleming for unrelated Data, Safety, and Monitoring Board activities for competitors for which he earns less than 10,001 a year from each firm, and for

unrelated Scientific Advisory Board activities for a competitor for which he earns less than 10,001 per year.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr. Antonio Grillo-Lopez is participating in this meeting as the Non-Voting Industry Representative acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by Neoplastic and Autoimmune Disease Research.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with

any firm whose products they wish to comment upon.

Thank you.

DR. MARTINO: Thank you.

Next, Dr. Pazdur, do you have some comments you would like to make to the group?

DR. PAZDUR: Yes, I really have about three points that I would like you to focus on as you listen to these presentations.

Opening Remarks

DR. PAZDUR: First of all, we were asked whether this application is here for accelerated approval or full approval, and we are looking at this application in the terms of full approval. We have considered a reduction in transfusion requirements as clinical benefit, and, hence, this is an endpoint that would be considered for full approval.

As I stated yesterday, when we are talking about accelerated approval, the uncertainty that is expressed in the regulations have to do with the linkage between the surrogate endpoint and clinical benefit, not the effect on that endpoint.

So, here again, we believe that this is an endpoint that does represent clinical benefit to patients, and, hence, we would look at this application as a full approval.

The second point that I wanted to mention is on the design of this trial. On several occasions, as will be mentioned by the FDA reviewer, we have recommended to the sponsor before they began the study, that we look at randomized studies of this drug in MDS to have a better understanding of the disease in relationship either to other therapies or the natural history of the disease.

As we pointed out on numerous occasions, randomized trials give more information than single-arm trials. They allow us to look at alternative endpoints, such as time to event endpoints, time to progression, survival, and also and more importantly, perhaps in this application, also, it will allow us to be able to better characterize the toxicity of drugs from the natural history of the disease.

So, nevertheless, the sponsor did proceed to look at a single-arm trial in this disease, and here again, I want to point out that in order for us really to have confidence of this, we really must have a population of patients that is adequately defined, that has a known transfusion requirement.

That transfusion requirement should be a large transfusion requirement, it should be well characterized, and the effect of the drug from the natural history should be able to be distinguished from the natural history of the disease since we are comparing one patient to their previous transfusion requirements.

The third point that I would like to bring out is that the approval of a drug centers around the demonstration of safety and efficacy, but also, we have to label the drug for the indication.

In order to label the drug, we have to recommend a dose of the drug and allow adequate characterization of the toxicities of the drug to allow a risk-benefit relationship.

Frequently, in randomized trials, this is more appropriately done because one can take a look at common toxicities or adverse events between arms. In a single-arm trial, sometimes you have difficulty examining these issues, so, here again, that is a point of consideration.

So, to summarize, number one, this is for full approval. Number two, this is a single-arm trial. We have to have confidence that the effect on the endpoint is statistically persuasive and clinically meaningful.

Thirdly, we have to have adequate information on what is the appropriate dose of the drug, as well as the toxicities of the drug and adverse events, that allow us to make a risk-benefit determination.

Thanks.

DR. MARTINO: Thank you.

Next, I would like to turn to the sponsor and their presentation. I remind you that you have 45 minutes for that presentation.

Sponsor Presentation

Celgene Corporation

Introduction

DR. BURTON: Good morning, Madam Chairman, members of the Advisory Committee, ladies and gentlemen. My name is Graham Burton. I am the Senior Vice President for Regulatory Affairs at Celgene.

[Slide.]

Celgene is conducting a comprehensive development program for lenalidomide as a novel, orally available therapeutic for the treatment of myelodysplastic syndromes and a range of other hematologic malignancies.

Our initial Phase I/II trial in myelodysplastic syndromes MDS-001 set out in early 2002 to establish whether or not lenalidomide had erythroid activity in patients with MDS and to gain insights into the tolerability of the product.

The strongest signal from this trial identified a group of patients whose disease appeared very sensitive to the effects of lenalidomide. These patients all had the deletion

5q cytogenetic abnormality. This finding led us to begin a confirmatory multi-center, open-label, Phase II program starting in the middle of 2003 and involved patients with low- and intermediate-1-risk MDS.

First, MDS-003 includes patients with the deletion 5q abnormality, and the results from this trial confirm the compelling results observed in MDS-001.

Second, MDS-002 includes patients without the deletion 5q abnormality, and the results from this trial will lead to a global registration package in the future.

Finally, the development program continues with prospective double-blind, controlled multi-center trials as shown in this schema. Trials MDS-001 and 003 form the basis of our NDA.

[Slide.]

So, why are we here at this stage of development? We have a well-defined, targeted population of low- and intermediate-1-risk, transfusion-dependent patients with MDS, all of

whom have the deletion 5q cytogenetic abnormality.

This abnormality is identified by conventional laboratory testing. Although not randomized, this is the largest prospective multi-center trial carried out in this particular population. The results we believe are of significant clinical benefit.

Two-thirds of patients become transfusion independent with durable resolution of their chronic refractory anemia. This is accompanied by an unprecedented increase in hemoglobin, 3 to 4 grams in the intent-to-treat population and more than 5 grams in the responding population.

These findings are accompanied in a substantial number of those who respond by cytogenetic responses and complete remissions and by histologic normalizations and improvements in the bone marrow, providing evidence that lenalidomide is having a disease modifying effect.

Finally, the adverse events of note, particularly cytopenias, are what you may expect from an agent that exerts its effect on abnormal

clones in the bone marrow. Nevertheless, these are readily identifiable and manageable.

[Slide.]

This strong evidence in a well-defined target population has led us to propose this label for lenalidomide. Lenalidomide is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

[Slide.]

Today, Dr. Stirling will describe the preclinical properties of lenalidomide. Dr. Bennett will discuss the disease state and its clinical implications. Dr. List, the principal investigator for these studies, will present the efficacy results, and Dr. Knight will describe the safety results, followed by a brief discussion of the relevance of these findings by Dr. List.

[Slide.]

Additional advisors are also with us today to help answer any questions.

Now, let me pass the podium to Dr. David Stirling.

Lenalidomide Nonclinical Overview

Dr. David Stirling

DR. STIRLING: Thank you, Graham. Good morning. I am David Stirling, Chief Scientific Officer for Celgene Corporation, and for the next few minutes I would like to describe briefly some of the nonclinical aspects of the drug lenalidomide.

[Slide.]

With respect to the pharmacokinetic parameters of the drug, lenalidomide is rapidly absorbed and extensively distributed throughout most tissues. There is low protein binding, less than 36 percent, depending on the species tested.

The drug does not inhibit or induce the major cytochrome P450 systems, and in addition, does not appear to be a substrate for any of these P450 enzymes.

In terms of metabolism, the primary route is through hydrolysis, however, almost two-thirds of the drug is excreted intact in the urine as the parent molecule.

Lenalidomide is the result of a discovery program where we try to design drugs based on the positive biology of thalidomide. We succeeded in increasing the potential clinical benefit associated with thalidomide while minimizing or eliminating the classical toxicities associated with that drug.

Even though lenalidomide and thalidomide are structurally similar, they are very different drugs and are functionally distinct. This functional difference can be characterized in a number of ways.

In terms of chemistry and metabolism, as I mentioned, the primary route of breakdown is hydrolysis. There are no common hydrolysis products between the two drugs, therefore, the active species of lenalidomide and thalidomide are different and unique.

With respect to cellular biology, there are a number of activities associated with lenalidomide that I will describe shortly, however, regarding these activities, a principal difference between this drug and thalidomide is a considerably improved potency associated with lenalidomide.

In terms of molecular biology, we find that the target cells that contain the 5q chromosome deletion are very sensitive to the drug lenalidomide. This sensitivity is not observed with thalidomide.

When you examine the clinical safety profile and look at the classical dose-limiting toxicities associated with thalidomide, these are sedation, severe constipation, and peripheral neuropathy, you find that these toxicities are minimal, if not resolved, with lenalidomide.

Now, in terms of the nonclinical toxicology and, in particular, with respect to reprotox, we submitted an ICH-compliant package with the NDA including Segment 1, 2, and 3 studies in two sensitive species - rats and rabbits.

The primary conclusions from these studies are: one, that unlike thalidomide, in our animal studies, lenalidomide has no effect on the fetus at doses that are safe to the mother; secondly, and more importantly, lenalidomide did not produce malformations in the limbs including those commonly associated with thalidomide.

[Slide.]

However, considering the sensitivity to the structural similarities of these two molecules, we have conducted additional confirmatory reprotox studies that are shown in this slide.

We have completed a pulse dosing study where we used a high dose of lenalidomide 4 to 5 times the dose normally required for maternal toxicity. This was administered on the sensitive days of gestation, days 8 through 10. Again, we saw no thalidomide-like or any other limb malformations in this study.

We have also completed an additional Segment 2 study in rabbits including a dose ranging study with associated toxicokinetics. We have

completed the end-life portion of the developmental toxicity study and have analyzed the data. We are currently preparing reports.

This recent information has not yet been submitted to, or reviewed by, the agency. However, the results confirm the findings of the original Segment 2 study submitted with the NDA. Therefore, the overall weight of reprotox evidence supports the conclusions that lenalidomide is (a) not selectively toxic to development, and (b) does not produce thalidomide-like malformations in sensitive animal tests.

[Slide.]

As I mentioned earlier, there are a number of biological activities associated with lenalidomide, and these are summarized on this slide.

A number of these biologies are potentially important in terms of controlling the pathology of the disease in question, MDS. The drug is anti-proliferative, and that is the result of both inducing apoptosis and cell cycle arrest.

The drug is proerythropoietic, it can stimulate hemoglobin synthesis, and we have shown that it can selectively stimulate fetal hemoglobin synthesis.

Lenalidomide can control various cytokines and growth factors, some or all of which are associated with the pathology of the disease MDS. For example, lenalidomide can downregulate the proinflammatory cytokine tumor necrosis factor alpha, yet stimulate the anti-inflammatory cytokine interleukin-10.

Lenalidomide can also stimulate T-cell cytokines, such as interleukin-2 and interferon gamma. These effects promote an overall immune stimulation and results in the proliferation of both T cells and NK cells with a concomitant increase in their function.

Lenalidomide has been shown to be anti-angiogenic, a potentially important activity as the bone marrow patients with MDS have increased levels of microvessel density that is associated with the pathology of MDS.

Finally, the drug has been shown to induce proliferation of normal progenitor cells found in the bone marrow. Therefore, this potentially helps to reconstitute a normal bone marrow function.

In conclusion, you can see that lenalidomide can modulate a number of biologies, all of which could be important in modifying the pathology of the disease MDS.

Thank you.

At this time, I would like to turn over the podium to Dr. John Bennett, who will give an overview of myelodysplastic syndromes.

MDS Classification and Prognosis

DR. BENNETT: Thank you, David. Good morning. I serve two functions this morning, one as the hematomorphologist for the trials, and, second, to provide a brief overview of the myelodysplastic syndromes, focusing on the low and intermediate risk groups and to express my enthusiasm for the exciting results of the trials to date.

[Slide.]

MDS can be defined as a group of hematopoietic malignant disorders with ineffective production of one or more myeloid cell lines with a variable percentage of leukemic blasts.

The majority of patients present with moderate to severe anemia. The median age is 70, and 30 percent will progress to acute myeloid leukemia. In the United States, we estimate there are about 15,000 cases annually, which leads to a prevalence of between 35,000 and 55,000 cases.

[Slide.]

We are using the International Prognostic Scoring System, or IPSS, extensively in evaluating these patients. I want to define this for you using as a basis the Greenberg paper published in 1997, which we have modified somewhat.

The prognostic variables are listed on the left side of the column. They are based on bone marrow blasts, karyotype, and number of cytopenias. The bone marrow blasts reflect the FAB classification, which was based on the percentage of blasts in the bone marrow to establish the

various subtypes of the FAB system, which you will hear referred to by Dr. List.

The score value goes from zero to 2.0 as the percentage of blasts increases and as we identify the worst prognostic features, such as multiple chromosome abnormalities or increasing numbers of cytopenias.

I have listed under Karyotype, deletion 5q, which when it presents as a single abnormality, has a good prognosis. When it presents with 1 additional abnormality, it has an intermediate prognosis, and when it presents with multiple abnormalities, it has a poor prognosis.

We then developed a numeric scoring system based on a multivariate analysis ranging from zero, which is the best category, to greater or equal to 2.5, which would be high grade.

[Slide.]

The survival in the IPSS risk category analysis ranges from low to high, with the low risk group obviously doing better with a median survival of 71 months, but notice that all groups eventually

come down to a similar bottom line with a survival that ranges from virtually no survival for the high risk to 15 or 20 percent for the other three categories.

The 5q minus population that we are studying in the 003 study falls between low and intermediate categories.

Now, we are illustrating here, in the upper right, an example taken from an individual karyotype of a patient with deletion 5q MDS. All of these patients demonstrate an abnormality that involves a long arm, or the q arm of chromosome 5. The arrow points to where the reassociation of the chromosome occurs, after the proximal and distal break points have taken place. The most common deletion illustrated here is deletion(5)(q13q33).

[Slide.]

So, how we manage low risk patients with MDS? By and large, these patients have anemia, moderate to severe fatigue which limits their ability to function in a normal way. The standard treatment is recombinant erythroid growth factors,

5-azacitidine, or transfusion management.

Recombinant erythroid growth factors, or EPO for short, does not have a major role to play in patients with 5q minus because they have a very high endogenous erythropoietin level and their red blood cell production in the bone marrow is very limited.

5-azacitidine, or Vidaza, is the only FDA-approved drug for the treatment of patients with MDS, but most of the patients receiving this agent have advanced disease, or if they have low-risk disease, have severe thrombocytopenia or neutropenia. Transfusion management surely is the most popular way of managing patients with a transfusion need.

[Slide.]

Are transfusions the solution? No. They are at best a very imperfect solution. Number one, the improvement is transient, lasting no more than a few weeks. A normal hematocrit is virtually never restored in these patients because of the prohibitive cost of multiple transfusions and the

drain on the United States blood supply.

Each unit of blood provides 250 milligrams of iron per unit, and it is not at all uncommon for patients with deletion 5q to have an excess iron burden above 10 and as high as 30 grams, which means they begin to behave like patients with hemochromatosis and can die of complications of cardiac failure, pancreatic insufficiency, or liver failure.

There is a continual risk of infectious disease of a variety of types, which is increasing in the U.S. blood supply including the West Nile Virus. Transfusion reactions are common. There is a big demand on the blood supply. Quality of life is significantly affected because this takes time for patients to come to the transfusion center, the cost of transportation, and on their care providers.

Obviously, there is a real cost of providing transfusions which, at the University of Rochester, is in excess of $500 per unit.

[Slide.]

Allow me to give you an example of one of our patients who was on the MDS 003 study with deletion 5q. This is an 84-year-old female referred by her Ohio-based hematologist who heard about the trial from the MDS Foundation.

Prior to entering the study, she had required 116 units of red blood cells over a 54-month period, averaging approximately 2 units per month, and was on chelation therapy.

She began lenalidomide in December of 2003 with a baseline hemoglobin of 8.2 grams percent. The last red cell transfusion occurred in February 2004. Her hemoglobin gradually rose and was at a height of 13.0 grams percent in April 2004, and has remained at that level with maintenance therapy to the current date.

In addition, her bone marrow and cytogenetics normalized and we have been phlebotomizing her to lower her excess iron stores that she has accumulated over the years.

So, in this example, one sees a patient who was red blood cell dependent, was extremely

fatigued, was on chelation therapy, and now has a normal hemoglobin, and will hopefully be able to avoid the consequences of long-term iron overload.

[Slide.]

At this point, I would like to turn the podium over to Dr. Alan List.

Thank you.

Lenalidomide Efficacy

DR. LIST: Good morning.

[Slide.]

I will review with you the results of the key clinical trial supporting the efficacy of lenalidomide in patients with MDS. The current studies in MDS have shown an unprecedented rate of erythroid activity in a specifically targeted patient population.

These patients have transfusion-dependent anemia due to low- or intermediate-1-risk MDS by the IPSS Scoring System and an interstitial deletion of a long arm of chromosome 5, the so-called deletion 5q cytogenetic abnormality.

The rationale that led to the

investigation of lenalidomide in MDS was based upon studies showing modest activity of thalidomide in this disorder.

This submission consists of 3, Phase II studies performed in patients with myelodysplastic syndrome. MDS-001 was a single-center pilot study in which lenalidomide was first found to have significant activity in MDS and to be especially effective in patients with MDS associated with the 5q deletion.

Based on these findings, 2 prospective multi-center, confirmatory Phase II studies were conducted. MDS-003 enrolled patients with transfusion-dependent MDS and a chromosome 5q deletion.

The second Phase II trial, MDS-002, had the same design, but was restricted to patients without the deletion 5q abnormality. The 002 study is included in the submission for additional safety data and includes data for efficacy up to June of last year before patients completed their evaluations. 003 is the pivotal study.

[Slide.]

I will begin with the pilot study that was published earlier this year. This began in March 2002 and enrolled patients of all FAB types who had a hemoglobin less than 10 g/dL. Patients with Grade 4 neutropenia or thrombocytopenia according to Version 2 of the NCI Common Toxicity Criteria were excluded.

The primary objective was erythroid response defined as International Working Group criteria. Three oral lenalidomide dosing regimens were evaluated, 25 mg daily, 10 mg daily, and a cyclic regimen of 10 mg for 21 days of every 4-week cycle.

Patients were assessed at Week 16 and responders continued treatment until either response failure or disease progression.

[Slide.]

Forty-three patients with MDS were enrolled with the majority of patients having low- or intermediate-1-risk disease. Twelve patients had the deletion 5q abnormality and 9 of these

patients achieved both a major erythroid response and a complete cytogenetic response at a median interval of 8 weeks.

Among patients without a deletion 5q abnormality, one-third of the patients had a major erythroid response, and 12 percent had a cytogenetic response. The erythroid responses were clinically significant with a sustained improvement in median hemoglobin to over 13 g/dL, and 14 patients have maintained their response for over 2 years.

Based on the results in this study, the starting dose of lenalidomide for subsequent Phase II studies was established as 10 mg.

To confirm these results, 2 prospective multi-center, single-arm, confirmatory studies were initiated in July of 2003. Two dosing schedules were studied sequentially. The first is the cyclic regimen of 10 mg for 21 days every 4 weeks, and the second is the 10 mg daily or continuous regimen.

Bone marrow and transfusion response was assessed after 24 weeks of treatment, and

responders continued treatment until either relapse or disease progression.

[Slide.]

In the pivotal MDS-003 study, eligibility included a confirmed diagnosis of low- or intermediate-1-risk MDS associated with the chromosome 5q deletion and transfusion-dependent anemia as defined by requiring at least 2 units of packed red blood cells within 8 weeks of study initiation.

Other requirements included age greater than 18 years, ECOG Performance Status of 0 to 2, and a negative pregnancy test for women of childbearing potential.

[Slide.]

Key exclusions were neutropenia less than 500/ microliter or a platelet count less than 50,000, proliferative chronic myelomonocytic leukemia, which was defined as a white blood cell count above 12,000, anemia due to other factors, secondary or treatment-induced MDS, and finally, any non-transfusion therapy within 28 days of

enrollment.

[Slide.]

The primary endpoint for the study was red blood cell transfusion independence. Secondary endpoints included the duration of red blood cell transfusion independence, change in hemoglobin level, the frequency of minor erythroid response, cytogenetic and pathologic bone marrow response, and the safety profile.

[Slide.]

During study treatment, patients were monitored with complete blood counts every 2 weeks during the first 8 weeks, then, monthly thereafter. This was later amended to include weekly monitoring of blood counts during the initial 8 weeks.

Treatment with recombinant erythropoietin was prohibited, however, myeloid growth factors were permitted at the investigator's discretion.

The protocol provided guidelines for transfusions, recommending red blood cell transfusion for a hemoglobin of 8 g/dL or lower or when the hemoglobin fell below the pre-study

transfusion threshold for that individual.

[Slide.]

The baseline characteristics of the 148 patients who were enrolled in the study are summarized here. The median age was 71 years with a female predominance, which is consistent with the gender distribution previously reported for this abnormality in patients with MDS.

The median duration of MDS from the date of initial diagnosis to the time of study entry was 2.5 years. Median number of red blood cell transfusions or units over the last 8 weeks prior to enrollment was 6 with 71 percent of the patients requiring at least 2 units or more every 4 weeks.

Twenty-nine percent of the patients entered the study with relative neutropenia and 17 percent had a platelet count less than 100,000.

[Slide.]

The distribution of patients by IPSS category and by FAB type according to Central Pathology Review is illustrated in this slide.

Eighty-one percent of patients were

characterized as low- or intermediate-1-risk MDS, 5 percent had higher risk disease, and in 14 percent of patients, the prognostic category could not be determined either because Central Review did not confirm MDS or because the slides that were provided were inadequate.

By morphologic type, 64 percent of the patients were classified as either refractory anemia or refractory anemia with ringed sideroblasts. Twenty percent of the patients had refractory anemia with excess blasts with the remaining diagnoses including chronic myelomonocytic leukemia, atypical chronic myeloid leukemia, and 1 patient with acute myeloid leukemia.

Sixteen patients, or 11 percent, were unclassifiable on Central Review.

[Slide.]

Overall, the vast majority of patients had received prior therapy other than transfusion support for management of their disease. Seventy-three percent had failed prior treatment

with recombinant erythropoietin with a higher proportion of patients in EPO failures in the United States.

Thirty-nine percent of patients had received chemotherapy treatment for their MDS, and 37 percent of patients were receiving iron chelation therapy. Only 12 percent of patients were previously untreated.

[Slide.]

The outcome analyses include 2 study populations. The first is an intent-to-treat population, which includes all registered patients, and the second is a modified intent-to-treat population that is limited to those patients with documentation of transfusion dependence for at least 4 months pre-study, and who were confirmed by Central Review to have low- or intermediate-1-risk MDS and the deletion 5q abnormality.

There are two additional datasets that are referred to in the analyses. One is the original NDA submission date of September of last year, and the second is an efficacy update from March 31st of

this year that was provided in the briefing supplement.

[Slide.]

The primary endpoint of transfusion independence was defined using a more stringent classification of the International Working Group criteria that required absence of red blood cell transfusions for 8 consecutive weeks and a corresponding rise in hemoglobin of at least 1 g/dL over baseline.

The latter was included to lessen any possible bias introduced by a physician's subjectivity in transfusion decisions.

The duration of transfusion independence was measured from the day following the last transfusion until the day before the next date of transfusion.

[Slide.]

A high rate of transfusion independence was observed in both of the study populations. In the intent-to-treat population, 99 patients, or 67 percent, achieved transfusion independence by the

March update, compared to 64 percent of the 94 patients with more rigorous documentation of transfusion requirements in the modified ITT subset.

The median time to response was 4.6 and 5.1 weeks respectively. These updated data are very similar to those from the initial NDA submission data analysis shown in the column on the left-hand side.

[Slide.]

Achievement of transfusion independence was associated with a precipitous decline in the mean number of red blood cell transfusions every 8 weeks, as illustrated here, and was sustained long term.

The dotted line marks the date of treatment initiation. The bars to the left, in orange, represent the prestudy treatment frequency, and the bars to the right representing transfusions that were administered on study.

[Slide.]

As you can see in this figure, which

illustrates the mean untransfused hemoglobin by treatment cycle, transfusion independence was accompanied by a meaningful increase in hemoglobin, reaching near normal or normal levels by cycles 3 and 4 that have been maintained for up to 18 months.

These hemoglobin changes provide strong justification for the reduction in red blood cell transfusions that I showed you on the previous slide.

[Slide.]

For responding patients, the median peak hemoglobin achieved during transfusion independence was 13.4 g/dL, corresponding to a median increase in hemoglobin from baseline of 5.3 g/dL.

[Slide.]

Transfusion independence with lenalidomide treatment has been durable. Kaplan-Meier estimate of the duration of transfusion independence as of March 2005 shows that the median duration of transfusion independence has not been reached. Overall, 83 of the 99 patients achieving

transfusion independence remained transfusion free for over 6 months, and 52 patients remained transfusion free for over 1 year with 57 responders continuing to be monitored.

[Slide.]

Transfusion independence was achieved whether or not patients presented with an isolated 5q deletion or accompanied by additional chromosome abnormalities as shown in the right-hand column.

At baseline, three-quarters of patients had an isolated 5q deletion, while 25 percent of patients had additional chromosome abnormalities.

The transfusion independence rate exceeded 60 percent in the isolated 5q population, over 50 percent in patients with additional chromosome abnormalities. These findings support the notion that the chromosome 5q deletion identifies a distinct subset of patients with MDS selectively responsive to lenalidomide treatment.

[Slide.]

Like transfusion response, cytogenetic responses were common. Among 72 patients who had a

minimum of 20 analyzable metaphases both at baseline and at follow-up, 74 percent experienced a cytogenetic response. Overall, 44 percent achieved a complete cytogenetic response and 29 percent had a partial response characterized by a decrease of abnormal metaphases by 50 percent or greater.

The frequency of either complete or partial study genetic response showed no difference based upon karyotype complexity with a comparable frequency of cytogenetic response in patients with isolated deletion 5q and in those patients with additional chromosome abnormalities.

[Slide.]

There was a close correlation between achievement of a cytogenetic response and achievement of transfusion independence. Ninety-five percent or more of the cytogenetic responders also achieved transfusion independence, while only 26 percent of cytogenetic non-responders achieved transfusion independence.

[Slide.]

Improvement in bone marrow histologic

findings were also common. Among 84 patients with adequate baseline and follow-up specimens, 35 percent achieved a complete histologic response characterized by resolution of cytologic dysplasia in all lineages and a blast percentage less than 5 percent. All but 1 of these patients achieved transfusion independence.

In addition, 9 of 16 patients who presented with refractory anemia with excess blasts had reductions in blast percentage to less than 5 percent.

As of the NDA submission date, 6 of 13 patients with refractory anemia with ringed sideroblasts had a corresponding reduction in ringed sideroblasts.

Overall, since the study began in July 2003, only 8 patients experienced disease progression, 3 evolved to acute myeloid leukemia, and 5 progressed to a more advanced phase of MDS.

[Slide.]

From the results of this study, we conclude that lenalidomide is a highly active agent

in lower risk transfusion-dependent MDS patients with deletion 5q. Resolution of anemia is rapid and durable, and associated with normalization of hemoglobin and the resolution of cytologic dysplasia in a high proportion of patients.

Hematologic and cytogenetic responses are closely correlated and occur without relation to karyotype complexity. These data support the proposed label indication for lenalidomide for the treatment of low- and intermediate-1-risk MDS, that is transfusion dependent with a chromosome 5q deletion with or without additional chromosome abnormalities.

Thank you.

At this time, I will turn the podium over to Dr. Robert Knight, who will discuss the safety data.

Lenalidomide Safety Assessment

DR. KNIGHT: Thank you, Alan.

My name is Robert Knight, and I am the head of Clinical Oncology at Celgene.

[Slide.]

The safety data presented here are data that are included in the sponsor's briefing document.

[Slide.]

All 148 patients enrolled into the deletion 5q trial, Study 003, received at least 1 dose of 10 mg of lenalidomide, 71 percent of patients received lenalidomide for at least 6 months, and the median exposure to study drug was approximately 44 weeks in both dosage regimen cohorts.

[Slide.]

Patients were started at a dose of lenalidomide of 10 mg daily, and sequential dose reductions to 5 mg daily and then to 5 mg every other day were allowed.

The protocol designated dose-limiting toxicities that were to trigger a reduction in dose are listed here. Thus, this study was designed to initiate therapy at a lenalidomide dose of 10 mg daily and to treat these MDS patients to Grade 4 neutropenia or a platelet count less than 30,000 in

an attempt to adequately suppress the abnormal deletion 5q clone. Most dose adjustments during the study were due to cytopenias.

[Slide.]

Three-quarters of the total study population required a dose reduction from the initial induction dose of 10 mg daily to 5 mg daily. Most of these dose reductions occurred by the second month of treatment, and approximately 20 percent of patients remained on 10 mg out through 6 months.

Approximately 25 percent of patients required a dose reduction to 5 mg every other day by the end of 6 months of therapy.

[Slide.]

Consistent with a rapid induction of apoptosis in the abnormal deletion 5q clone in the marrow, neutropenia and thrombocytopenia were the most common Grade 3 or 4 adverse events reported.

Despite the frequency of Grade 4 neutropenia, febrile neutropenia occurred in only 8, or 5.4 percent, of patients. Despite the

frequency of thrombocytopenia, Grade 3 or 4 hemorrhagic events occurred in only 6, or 4.1 percent, of patients.

[Slide.]

Platelet counts fell to less than 10,000 in 9 patients and to between 10,000 and 20,000 in 16 patients. Among these 25 patients, 6 patients required platelet transfusions for clinically significant events, which consisted of epistaxis and gingival bleeding, and 15 patients were given platelet transfusions prophylactically or for petechiae.

Another 50 patients had platelet counts less than 50,000, and 6 of these patients received platelet transfusions.

[Slide.]

Now, this slide breaks down the Grade 3/4 hematologic adverse events by dosage cohort regimen. While Grade 4 neutropenia was reported more frequently in the continuous versus the cyclic regimen, there was no difference between the cohorts in regard to the development of febrile

neutropenia.

Grade 4 thrombocytopenia adverse events occurred somewhat more frequently in the cyclic group. Two, Grade 3 hemorrhagic events occurred in the continuous cohort, and three, Grade 3 events occurred in the cyclic cohort.

In addition, a Grade 4 hemorrhagic event that was associated with trauma in a patient who entered the trial with a platelet count of 99,000, and then a few days before the accident, the platelet count was 76,000 also occurred.

[Slide.]

The median absolute neutrophil and platelet counts for transfusion-independent responders over time are represented on this slide.

In these responders, a substantial fall in both neutrophil and platelet counts can be seen during the first 8 weeks of lenalidomide treatment.

This is followed by a recovery and a prolonged period during transfusion independence in which the neutrophil and platelet counts remained at stable and acceptable levels, around 1,500 for

the neutrophil counts and slightly above 100,000 for the platelets.

[Slide.]

For non-responders, the median neutrophil and platelet counts also fall with initial lenalidomide treatment, and then level off at stable levels around 1,000 for neutrophil counts and somewhat below 100,000 for platelet counts.

[Slide.]

In addition, Grade 3 non-hematologic adverse events occurred relatively uncommonly, and Grade 4 events, including pneumonias, were very infrequent.

[Slide.]

This slide lists the most common serious adverse events. Most serious events occurred in fewer than 5 patients. All individual serious adverse events, including pneumonia and neutropenia, were reported in less than 10 percent of the study population.

Events were assessed by the treating physicians to be due both to MDS and to

lenalidomide therapy.

[Slide.]

After almost 18 months of study duration, from July 2003 to the end of December 2004, and a median time on study of nearly a year, more than half the patients, or 53 percent, remained on study.

Eighteen percent of patients discontinued the study due to adverse events, and another 18 percent for lack of response.

Nine patients, or 6 percent, of the study population died while on study. A handful of patients terminated the study for other reasons.

[Slide.]

These are the adverse events that led to study discontinuation. Only 8 patients, or 5.4 percent, terminated the study due to thrombocytopenia, and only 4 patients, or 2.7 percent, due to neutropenia. Four patients discontinued the study due to rash, and 2 due to pneumonia.

All other adverse events leading to

discontinuation were reported in one patient each.

[Slide.]

Among the patients in the deletion 5q trial, Study 003, there were 11 deaths or approximately 7 percent of the study population, that occurred either on study or within 30 days after drug termination.

Three deaths were due to infection associated with neutropenia and were assessed by the treating physicians to be related to lenalidomide. These 3 deaths occurred early during induction of lenalidomide therapy when there was a rapid decrease in the neutrophil counts.

The last death attributed to lenalidomide occurred in March 2004, and none have occurred since, as the protocol was modified to follow CBCs weekly during the first several weeks of treatment. The rest of the deaths were not unexpected in an elderly population with MDS.

[Slide.]

Safety data have also been included in the non-deletion 5q trial, Study 002, in the sponsor's

briefing document. Lenalidomide has also demonstrated activity in this MDS patient population.

[Slide.]

In the non-deletion 5q patients, Grade 3/4 thrombocytopenia and neutropenia occurred at approximately half the rate as in the patients that participated in the deletion 5q study. The non-hematologic safety profile between the two studies was similar.

[Slide.]

Overall, 3 MDS studies, 001, 002, and 003, 6 percent of patients have died on study. Five or slightly more than 1 percent of the study population of 408 patients were suspected to be related to lenalidomide therapy by the treating physicians, and this includes 3 patients described in a previous slide for the deletion 5q study.

The median age at death was 80 years, and the median time from initial diagnosis to death was 2.8 years.

[Slide.]

We conclude lenalidomide has a favorable safety profile in this deletion 5q MDS population. The most common adverse events associated with lenalidomide treatment are neutropenia and thrombocytopenia, and that these cytopenias are easily managed by hematologists experienced with treating patients with hematologic disorders by monitoring blood counts and utilizing dose interruptions and dose reductions.

Neutropenia and thrombocytopenia commonly develop early in the course of lenalidomide therapy, and this effect is consistent with the induction of widespread apoptosis in the abnormal deletion 5q clone, and responders' recovery may be aided by the repopulation of the marrow with normal hematopoietic progenitors as indicated by the cytogenetic and histologic bone marrow responses.

Non-hematologic adverse events were generally mild and infrequently dose limiting.

[Slide.]

We recommend that for the treatment of deletion 5q MDS patients, lenalidomide be initiated

at a dose of 10 mg once daily with frequent monitoring of blood counts especially during the first 8 weeks of therapy.

We recommend further that the 10 mg daily dose be continued and dose reduction to 5 mg be dictated by tolerance. This dosage regimen has resulted in durable transfusion independent responses in a high proportion of deletion 5q MDS patients with large increases in blood hemoglobin levels, as well as cytogenetic and bone marrow histologic responses.

Thank you.

Now, Dr. List will present a summary of the implications of lenalidomide.

Study Conclusion

DR. LIST: I have a few slides I would like to share to summarize the clinical benefit of lenalidomide treatment in MDS and also offer a perspective as a clinician and investigator as to the impact the treatment can have for individuals dealing with complications from MDS.

[Slide.]

The results of the MDS-003 study confirm and extend the observations from the pilot study that lenalidomide is highly active in patients with the deletion 5q in low- and intermediate-1-risk disease.

Analysis of numerous parameters consistently demonstrates the clinical benefit of lenalidomide in this target population. This includes the durable resolution of anemia in the majority of patients, corresponding rise in hemoglobin to normal or near normal levels, and a high frequency of cytogenetic response with improvement or resolution of the diagnostic hallmark of this disease cytologic dysplasia.

These benefits are achieved with predictable adverse effects, primarily myelosuppression that occurs early in the treatment course with suppression of deletion 5q clone, and is manageable with dose adjustment.

[Slide.]

This figure that was produced by a patient with deletion 5q, who entered the MDS-001 trial

early in 2002, provides some insight into what this treatment can mean for the individual.

Disregarding the potential complications from iron loading, this patient who was struggling to maintain employment while receiving regular transfusions, achieved transfusion independence that has now been sustained for over 3 1/2 years of treatment.

This patient received the 25 mg dosage and after an early decline in white blood cell count and platelet count experienced a rise in hemoglobin, as well as platelet count and white blood cell count as his disease remains in sustained cytogenetic remission.

[Slide.]

The disease remitting activity of lenalidomide suggests that it has potential to favorably impact the natural history of disease in higher risk patients. Indeed, patients with deletion 5q and 1 or more additional chromosome abnormalities have an unfavorable prognosis compared to those with an isolated 5q deletion, as

illustrated here in the figure on the right from data that was published by Dr. Dewald at the Mayo Clinic.

Patients with additional chromosome abnormalities in this series had a median survival of 264 days compared to 2 to 3 years for those with the isolated 5q deletion. These data are consistent with the cytogenetic data reported by other investigators.

When overall survival is analyzed from the date of initial diagnosis for patients treated on the MDS-003 trial, you can see from the figure on the left that median survival has not been reached, and exceeds 18 months even in patients with additional chromosome abnormalities as shown here in the green.

These data suggest that treatment with lenalidomide may alter the natural history of disease in this unfavorable disease subset.

I will turn the podium over to Dr. Burton to conclude.

Conclusions

[Slide.]

DR. BURTON: We recognize the unique public sensitivities and awareness of the relationship of lenalidomide to thalidomide, and so we have proposed a risk management program specifically tailored for lenalidomide.

This program, called the RevAssist program, continues to be reviewed and refined in consultation with the FDA. RevAssist is centered on educating patients, physicians, and healthcare practitioners about the overall risk-benefit profile of lenalidomide.

Additional education will focus on the need to conduct pregnancy testing for females of childbearing potential before and during lenalidomide therapy.

Education and evaluation of RevAssist will be the priority of our medical affairs and commercial groups, and will be accomplished by limiting distribution of lenalidomide to dedicated specialty pharmacies.

[Slide.]

Finally, I now would like to leave you with a reminder of our proposed label for lenalidomide.

Lenalidomide is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

This completes our presentation this morning, Madam Chairman, and Dr. Robert DeLap will be moderating our questions, which I believe will be after the FDA's presentation.

Thank you.

DR. MARTINO: Thank you.

Next, I would like the FDA to do their presentation.

DR. GRILLO-LOPEZ: Madam Chairman, if I may, while the FDA is preparing for the presentation, may I please ask that the record show that I joined the meeting before the sponsor started their presentation.

I am Antonio Grillo-Lopez. I am a hematologist/oncologist, Industry Representative, and I do not receive any support from industry for attending this meeting.

DR. MARTINO: Thank you.

We have one additional member to the committee that has joined us.

DR. DOROSHOW: Yes. I am Jim Doroshow, Director of the Division of Cancer Treatment and Diagnosis at the NCI, and I have no support.

FDA Presentation

DR. HAZARIKA: Good morning. This NDA application is for lenalidomide. There will be three speakers for this presentation.

I am Maitreyee Hazarika and will present the Clinical Review, Kimberly Benson will present the Reproductive Safety Assessment, and Ed Kaminskas will present the Safety Review.

Clinical Review

[Slide.]

DR. HAZARIKA: The proposed indication is treatment of patients with transfusion-dependent

anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

[Slide.]

We request the ODAC Committee to focus on the following issues:

Can a single-arm trial design be used in a heterogenous disease like MDS? FDA had recommended a randomized controlled trial.

Is an 8-week transfusion-free endpoint appropriate to demonstrate clinical benefit?

Is the 10-mg dose excessively toxic?

Is there a benefit versus risk of the drug for this population?

Should additional risk management measures be implemented?

[Slide.]

The recent drug approval for MDS will be presented. The FDA analysis of Reproductive Safety Assessment, Efficacy, and Safety will then be presented, followed by the Risk Management Plan and

Summary.

[Slide.]

There has been one approval in recent years, azacitidine injection. It received regular approval in 2004 for the treatment of patients with all MDS subtypes as shown. Effectiveness was demonstrated in 1 randomized, controlled trial comparing azacitidine with best supportive care and in 2 single-arm studies.

The primary efficacy endpoint was the overall response rate defined as complete or partial response of bone marrow and peripheral blood, and the response rate in the azacitidine arm of 16 percent with no responses in the observation arm.

The endpoint used in this azacitidine application is different from that in the current application.

[Slide.]

Lenalidomide is a thalidomide analogue with similarities in structure. Lenalidomide is an amide and bears an amino group in the aromatic

ring, whereas, thalidomide is an imide.

[Slide.]

In in-vitro studies, lenalidomide was not a substrate of cytochrome P450. The presence and identity of circulating metabolites was not studied in humans. The primary route of elimination is renal excretion of parent drug.

Dr. Benson will now present the Reproductive Safety Assessment.

Reproductive Safety Assessment

[Slide.]

DR. BENSON: With oncologic drugs, the developmental safety assessment that we require for NDA filing is the embryo-fetal development study. This usually consists of two studies conducted in a rodent and a non-rodent, usually, the rabbit.

If negative results are seen in the rodent study, they should be confirmed in a second species. If clear evidence of an effect on development is seen in the first study, a second species is not required.

[Slide.]

Two main embryo-fetal development studies were submitted for lenalidomide. A rat study was conducted under standard design. In this study, no adverse effects of lenalidomide were seen in the embryo or fetus including limb bud defects.

[Slide.]

It should be noted that historical data tells us that with thalidomide, the rat is not a sensitive species for the associated limb bud developmental effects.

While this study does provide some information regarding possible effects of exposure to lenalidomide during embryo-fetal development, it is considered to be an inadequate model for the full assessment of lenalidomide's effects on embryo-fetal development.

[Slide.]

The second species chosen to study lenalidomide's effects on embryo-fetal development was the New Zealand White rabbit. This species has been shown to be sensitive to the thalidomide limb bud malformation.

This study was also conducted under standard design and it included a thalidomide dose group.

Acceptable study endpoints, either maternal or developmental, were not achieved for the lenalidomide dose groups. Limb bud defects were seen in the thalidomide group, but were not evident in the lenalidomide dose groups.

[Slide.]

This study was inadequate. The drug-related effects seen with the highest dose tested did not meet the standard criteria for sufficient exposure.

There was also a confounding variable in this study. A dozen rabbits spread out among all dose groups were not eating when they first arrived in the laboratory. Each of these rabbits had a negative outcome in this study. This confounding variable makes these data difficult to analyze.

[Slide.]

In conclusion, the structural similarities between lenalidomide and thalidomide, a known human

teratogen, suggests a developmental risk. At this time, there is insufficient information for lenalidomide regarding effects on embryo-fetal development.

The rat is not an appropriate model for the full assessment of embryo-fetal effects of lenalidomide, and the submitted rabbit study was inadequate.

[Slide.]

It is our recommendation that if lenalidomide is approved, it receive a Pregnancy Category D classification, similar to most other oncologic agents. The sponsor should conduct additional studies to fully assess the potential embryo-fetal development effects of lenalidomide.

Thank you.

Clinical Review

[Slide.]

DR. HAZARIKA: MDS-003 is the main study submitted. It is a single-arm trial in 96 evaluable patients which uses two, 10-mg doses, and a primary endpoint of RBC transfusion independence.

MDS-001 contains supportive data in 10 patients. It started with 25 mg, then, dose-reduced to 10 mg doses. The primary endpoint is major or minor erythroid response.

MDS-002 is not relevant to the proposed indication, but serves as a reference for the response rate in MDS patients without the 5q deletion.

[Slide.]

The efficacy data analysis for this study are based on the updated efficacy data submitted on August 15th and differ slightly from the FDA's briefing package.

[Slide.]

MDS-003 is a single-arm, multi-center, Phase II study. The results of local or central laboratory were used to determine the eligibility for the patient.

Adjudication was done by independent hematologic and cytogenetic reviewers. Response criteria were based on the International Working Group Standardized Response Criteria for MDS.

[Slide.]

The primary endpoint was RBC transfusion independence. There were several secondary endpoints including change in hemoglobin from baseline, duration of response, greater than 50 percent decrease in RBC transfusion requirements, cytogenetic, platelet, and neutrophil responses.

[Slide.]

Eligibility required the diagnosis of low- or intermediate-1-risk IPSS-MDS with a cytogenetic abnormality of chromosome 5. The 5q deletion could be isolated or be associated with other cytogenetic abnormalities.

RBC transfusion-dependent anemia was defined as requiring at least 2 units of RBCs within 8 weeks of study treatment.

[Slide.]

148 patients were enrolled. Lenalidomide was given orally. Celgene examined two doses. The first 45 patients received a dose of 10 mg daily for 21 days of a 28-day cycle referred to as syncopated.

The next 103 patients received a dose of 10 mg daily referred to as continuous.

[Slide.]

All patients had a 5q deletion, 74 percent had an isolated 5q deletion, and 26 percent had associated additional cytogenetic abnormalities, 80 percent patients had at least 20 metaphases analyzed for karyotypic analysis.

[Slide.]

For the proposed indication, there were 80 percent patients adjudicated to the low- and intermediate-1 IPSS risk category as required by the protocol.

[Slide.]

As per the protocol, 95 percent patients received at least 2 units within 8 weeks prior to start of study drug, 72 percent received more than 3 units. The median was 6 units, and the range 0 to 18.

[Slide.]

FDA reviewed the data for the 148 patients in the intent-to-treat population and also

conducted an analysis in 96 patients that were evaluable. These differed from the sponsor's 94 patients in the definition of transfusion-independent anemia.

[Slide.]

The FDA evaluable population excluded patients who were not adjudicated a diagnosis of MDS by an independent hematologic reviewer, who were not adjudicated an IPSS score or the risk category was intermediate-2 or high by an independent cytogenetic reviewer, patients who did not receive at least 2 units RBC within 8 weeks of start of study drug, and patients whose karyotype analysis was not based on at least 20 banded metaphase analysis at baseline.

These 96 patients constituted 65 percent of patients.

[Slide.]

The International Working Group response criteria includes the major erythroid response, which for RBC transfusion-dependent patients is transfusion independence, and for patients with

pretreatment hemoglobin less than 11 grams is a greater than 2 g/dL increase.

The minor erythroid response is a 50 percent decrease in transfusion requirements and 1 to 2 gram increase in hemoglobin.

[Slide.]

The IWG also states that improvements must last at least 2 months in the absence of ongoing cytotoxic therapy.

[Slide.]

RBC transfusion independence was defined as the absence of any RBC transfusion during any consecutive "rolling" 56 days, or 8 weeks, during the treatment period, and must last 2 months.

Included afterwards was an at least 1 gram increase in hemoglobin.

[Slide.]

Sixty-seven percent patients achieved RBC transfusion independence with 95 percent confidence intervals of 59 and 74 percent in both the ITT and the FDA evaluable population.

[Slide.]

The hemoglobin change was calculated by the sponsor using the minimum hemoglobin value in the 8-week period preceding the first dose of study drug or baseline, and the maximum hemoglobin value during the response period.

The median change was 3.3 g/dL in the ITT population, and 5.2 in the responders.

[Slide.]

Although the 50 percent decrease in transfusion requirements was 76 percent, please note that this included the primary transfusion independence response.

[Slide.]

The response duration was measured from the last of the consecutive 56 days during which the subject was free of transfusions to the date of the first transfusion. The median duration was 52 weeks in the responders, in the ITT and the FDA evaluable population, with a range of 8 to 75 weeks.

[Slide.]

Relapses from transfusion independent to

transfusion dependent occurred in 32 out of the 99 responders, of which 13 occurred within the treatment period.

[Slide.]

The IWG response criteria defines a major cytogenetic response to have no detectable cytogenetic abnormality if pre-existing abnormality was present, and required 20 analyzable metaphases using conventional techniques.

[Slide.]

Cytogenetic responses were calculated in patients who had follow-up bone marrows with karyotype analysis in at least 20 metaphases. Greater than 40 percent major cytogenetic responses were seen in the ITT and the FDA evaluable population.

[Slide.]

Among the 14 patients evaluable for a platelet response in the FDA evaluable population, none had a major platelet response.

[Slide.]

Among the 6 patients evaluable for a

neutrophil response, 1 patient had a major response which occurred 26 days after the transfusion independence response.

[Slide.]

MDS-001 was a dose-finding, Phase I/II, single-arm, single-center study of lenalidomide in patients with MDS. The primary endpoint was major or minor erythroid response. There were 45 patients enrolled in the study.

The initial starting dose was 25 mg daily based on the findings of a Phase I study in myeloma, and the first 13 patients were enrolled at this dose. A high incidence of neutropenia and thrombocytopenia was observed within the first 4 to 8 weeks of treatment as a result of which the protocol was amended to study the 10 mg continuous dose.

The median time to dose-limiting neutropenia or thrombocytopenia was found to be 13 weeks, and the syncopated dose was then initiated.

[Slide.]

The primary endpoint was a major or minor

erythroid response. Secondary endpoints included cytogenetic, platelet, and neutrophil responses.

[Slide.]

Eligibility required the diagnosis of de novo MDS of the subtypes shown. RBC transfusion-dependent anemia was defined as requiring at least 4 units of RBCs within 8 weeks of study treatment, or baseline mean hemoglobin less than 10 in untransfused patients.

[Slide.]

There were 10 patients with transfusion-dependent anemia in low- or intermediate-1 MDS with 5q deletion.

[Slide.]

Of these 10 patients, 7 experienced a major erythroid response, and there were no minor responses.

[Slide.]

Of the 7 patients who achieved a response, the median duration of major erythroid response was 41 weeks with a range of 31 to 88 weeks. The median change in hemoglobin values was 5.3 g/dL.

Major cytogenetic responses were observed in 9 out of 10 patients and all responders. There was 1 patient each with a platelet and neutrophil response.

[Slide.]

MDS-002 had an identical study design to 003 except that the study population patients did not have a 5q deletion. There were 215 patients enrolled. Two doses were used. 115 patients received the 10 mg syncopated, and 100 patients received the 10 mg continuous dose.

[Slide.]

RBC transfusion independence was achieved in 21 percent in the ITT population. The median increase in hemoglobin level from baseline in the responders was 3 g/dL. The median duration of response was 19 weeks.

[Slide.]

Dr. Kaminskas will now present the Safety Summary.

Safety Summary

DR. KAMINSKAS: Good morning.

[Slide.]

The safety review is based on 408 patients who participated in the three MDS trials. Thirteen patients received the 25 mg/day starting dose; 215 patients, 10 mg/day starting dose; 180 patients received the 10 mg for 21 days every 28-day cycle starting dose.

[Slide.]

One key issue in this safety assessment is shown on this slide. If you would look at the MDS-003 trial, which is for the population, MDS 5q deletion population for which the approval is sought, about 80 percent of patients had at least one dose reduced or interrupted, and about 34 percent of patients had two doses reduced or interrupted.

In practice, what this meant was that following an adverse event serious enough to stop the medicine, there was a period of dose interruption that may have lasted days, weeks, or months. The median duration was 22 days, followed by a starting lower dose 5 mg.

If a second dose reduction was needed that followed an interruption, median duration was 51 days before the second lower dose, 5 mg every other day, started.

Dose reductions and interruptions were less frequent in the MDS-002 trial on the right, the population without the 5q deletion. Still, almost half of the patients had 1 dose reduced or interrupted, and 23 percent of patients had 2 doses reduced or interrupted.

In the dose-ranging trial, the MDS-001 trial, dose reduction rate was 38 percent in the 10 mg dose group, but in the 25 mg dose group, over half of the patients had to have 2 dose reductions with interruptions.

[Slide.]

Virtually, all patients had adverse events. Eighty percent of patients had Grade 3 or Grade 4 adverse events. The most prominent among them were hematologic, neutropenia and thrombocytopenia, infections primarily, pneumonia, sepsis, and others were 9 percent.

Fatigue was a prominent symptom even though only 6 percent of patients had Grade 4 fatigue. Rashes were impressive, some covering over 70 percent of the body that resolved on discontinuation of the drug.

[Slide.]

However, the key question is whether neutropenia, thrombocytopenia or other adverse events, are they due to the disease MDS or to the drug in an uncontrolled trial.

[Slide.]

Serious adverse events with a 10 mg starting dose occurred in 38 percent of patients in all 3 studies. The most common were hematopoietic, anemia, neutropenia, thrombocytopenia, and infectious, pneumonia, sepsis including urosepsis. The others were less common.

[Slide.]

In the 3 studies, there were 28 on-study deaths including those that occurred within 30 days of the last dose of the drug, and another 14 deaths subsequently.

Over one-half of the deaths were due to infections, bleeding, or disease progression to AML.

[Slide.]

In summary, 408 MDS patients were treated with starting doses of 25 mg/day or 10 mg/day lenalidomide. Excessive toxicity was observed in that the 10 mg/day dose was reduced and/or interrupted in 80 percent of study patients.

Single-arm trials do not permit attribution of adverse events to MDS or to the drug or to both. Eighty percent of patients had Grade 3 or Grade 4 adverse events, and 38 percent of patients had serious adverse events.

[Slide.]

Most common of these were neutropenia, thrombocytopenia, and infections. Most common reasons for discontinuations from the studies were adverse events - hematologic, gastrointestinal, and dermatologic.

Most deaths were due to infections, acute myelogenous leukemia, bleeding, and cardiac causes.

Benefits of red cell transfusion independence versus risks of neutropenia and thrombocytopenia need to be assessed.

Thank you.

DR. HAZARIKA: Celgene has a planned Phase III study ongoing in Europe in MDS patients with a 5q deletion. It is a randomized, double-blind, placebo-controlled, 3-arm study evaluating a lower dose of 5 mg daily versus 20 mg syncopated.

The primary endpoint is RBC transfusion independence for greater than 26 weeks.

[Slide.]

A major safety concern for lenalidomide is teratogenicity, and the major risk management goal is the prevention of fetal exposure to lenalidomide.

[Slide.]

Examples of other drugs with teratogenic potential and risk management plans to prevent fetal exposure include thalidomide, which has the STEPS program, and isotretinoin, which has the IPLEDGE program.

[Slide.]

In summary, azacitidine was studied in a randomized, controlled trial, while lenalidomide is a single-arm study. Azacitidine was studied in all MDS subtypes. Lenalidomide is specific for low- or intermediate-1-risk, transfusion dependent, 5q deletion. The response criteria are very different in both.

[Slide.]

The embryo-fetal development in lenalidomide, a thalidomide analogue, has not been adequately addressed. The submission consists of 2 single-arm studies, one very small. The transfusion entry criteria is based on 8 weeks prior to start of study drug. The median was 6 units.

A rolling 56-day transfusion-free period is used for transfusion independent response. The RBC transfusion independent response of 67 percent was seen with at least 1 gram increase in hemoglobin. The median duration of transfusion independence in responders was 52 weeks.

A major cytogenetic response of greater than 40 percent was seen.

[Slide.]

Almost all patients had adverse events. About 80 percent had Grade 3/4 adverse events. Eighty percent patients experienced dose delays or dose reductions. Excessive toxicities seen at the 10 mg dose raises a question about the benefit versus risk profile of this drug in this population.

The absence of a control arm makes attribution of adverse events and deaths difficult.

Thank you for your attention.

DR. MARTINO: Thank you.

At this point, I would like to turn to the committee itself, and if there are questions to either the FDA or the Company, please raise your hand, and we will call you in turn.

Dr. Levine, you may start, please.

Questions from the Committee

DR. LEVINE: I have many, so maybe I will start with a few and come back, but one question.

You didn't really state whether the drug was given for a certain point and stopped, or whether it was maintained during that week or during that year, or whatever it is, the duration of the response. Did they get treated the whole time?

DR. DeLAP: There were two different approaches that were evaluated in the course of these studies regarding the 10 mg starting dose.

I am sorry, I am Dr. Robert DeLap. As Dr. Burton mentioned, I will be moderating the question and answers for the company. I am the Vice President for Medical Research at Celgene. So, let me begin again then.

We evaluated, in the course of this research, two different ways of using the 10 mg starting dose. One was continuous dosing until the patient evidenced basically a Grade 4 toxicity at which time there was interruption, Grade 4 hematologic toxicity.

The other approach was to cycle with 21 days of dosing followed by a scheduled 7-day break. Most of our experiences with the continuous dosing

regimen--

DR. LEVINE: My question was are these responses, the duration of response that is maintained on treatment, in other words--

DR. DeLAP: Yes.

DR. LEVINE: The second question. This is excreted into the urine in its active unchanged parent compound. What is the toxicity of this drug in renal failure? Two-thirds of the drug is the parent drug in the urine, or insufficiency, renal insufficiency.

DR. DeLAP: We are currently embarking on studies in renal failure. We do not have a study in renal failure at the present time. You are correct that the drug is excreted primarily in renal failure, and therefore, it is a question as to whether this patient, a patient with renal failure would tolerate the drug the same way as the patient without.

I would like to show one slide. We did do an analysis within the MDS-003 study, the key study that we are talking about today, where we looked at

the patients who had relatively lower renal function as evidenced by calculating creatinine clearance versus patients who had good renal function based on calculated creatinine clearance, and we did find the response was not as good in patients who had impaired renal function.

Would you bring that slide up, please.

[Slide.]

The rate of discontinuations due to adverse experiences was, in fact, higher in patients who had impaired renal function. Despite the higher rate of discontinuation, we still did see a 50 percent transfusion independence response in these patients.

We did see first cycle cytopenias in a higher proportion of these patients, 33 percent versus 19 percent. Again, we will be doing further studies, formal studies in renal-impaired patients, as well as additional pharmacokinetic studies in MDS.

DR. LEVINE: So, what do you think your package insert would say as it relates to, you

know, as a clinician, am I supposed to put somebody on with a creatinine of 2 or not?

DR. DeLAP: The study actually evaluated patients with creatinine up to 2.5, so it's reasonable to begin patients with at least modest degrees of renal impairment on this drug, but they do need to be monitored closely, and that is exactly what the prescribing information will say.

DR. LEVINE: Can I ask one more and then I will come back? One more. How many patients were on G-CSF or GM-CSF? Did they respond as the white count went down? What are the data in that regard?

DR. DeLAP: I will ask Dr. Knight from Celgene to address that.

DR. KNIGHT: I am Robert Knight. Yes, although we allowed myeloid growth factors, only 23 patients actually received them during the study, and generally, they receive them after they had a Grade 4 neutropenia, and the neutrophil counts in large part did respond and respond relatively quickly.

DR. MARTINO: Dr. Cheson.

DR. CHESON: Thank you.

First, I would like to clarify something, and that is, as raised by Dr. Pazdur and his colleagues, this is a very heterogeneous group of diseases we are working with. Patients with 5q minus syndrome alone, which is a very uncommon entity, actually, in most series, have a median survival that approaches 9 to 12 or 14 years, and with an additional cytogenetic abnormality, you saw the results from Dr. Dewald. There are other papers in the literature which have survival as high as 3 to 4 years. So, you can pick your study and get your results.

So, it makes it a little difficult to assess these data because, for example, when you tell me that a certain number of patients progress to AML, you can say, well, certainly, that is the eventuality in MDS, but the risk of progressing to AML is only around 13 to 15 percent in 5q minus by itself.

Now, the 5q minus syndrome, by itself, is a fairly distinct entity recognized by the World

Health Organization, which is accompanied by, in fact, a normal to increased number of platelets, not thrombocytopenia, as in the other MDS conditions. Therefore, if one sees thrombocytopenia in this patient population, one is more likely to think that it is associated with the drug, and not with the disease itself.

In fact, they generally only have mild neutropenia, splenomegaly in about 20 percent of patients, but the characteristic feature is what we are facing here, and that is this profound transfusion requiring anemia. Just a little bit of intro from another perspective.

I have a toxicity question. I guess, you know, we have seen there is a lot of activity, but we have seen that there have been considerable dose modifications, and we have seen a number of deaths and adverse events that are either attributed to or not the drug.

In general, when we assess toxicities on a clinical trial, it's on a scale of unlikely, possibly, probably, or most likely related to the

drug. It is my understanding that wasn't the case in this study.

Could someone comment on this and how this might impact on the decision as to whether to attribute a major toxicity or fatality to the drug versus not?

DR. DeLAP: You are correct, Dr. Cheson. The scale that was used for assessing drug relationship by the investigators in this study was a binary system. It was either not suspected to be drug related or it was suspected to be drug related.

So, if one saw a developing neutropenia in the context of the drug administration, and then at a low white blood count, a patient developed an infection and ultimately died from that, that would be considered suspected as potentially related to the drug.

We did not use a more precise gradation of degrees of suspicion.

DR. CHESON: There is one patient that seems to be rather troubling as associated to not

related to the drug, and that was the last patient who died--I think it was the last one on the list--of an intracerebral bleed.

When a patient is thrombocytopenic, and even though it's traumatic, it is hard not to attribute this to an effect of the drug. For example, if the patient falls down and hits their head when they are thrombocytopenic, bleeds and dies, is that because they first had an acute cerebral episode, fell down and hit their head, or is it because they fell down and hit their head and died?

In any event, you have to give the benefit of the doubt to the patient and attribute that to an effect of the drug, and there was another one in there also which was sort of sudden death unknown. To say these are not drug related is difficult to accept in the absence of other sorts of documentation.

DR. DeLAP: It is very difficult to come to a final conclusion about the attribution of some of these, of individual cases. Again, as Dr.

Pazdur said at the start, if you have a randomized trial, which is in the future for this drug, you can get a much better estimate.

We actually feel that given the potential impact of this drug on the course of the disease, that the survival effect will be favorable with the magnitudes of the changes we are seeing in bone marrow and cytogenetic complete responses, and those sorts of things.

But I would like to get back to the one patient that you mentioned, that fell and hit her head, and subsequently died. Could I ask Dr. Knight to just take us through a couple of additional details on that case?

DR. KNIGHT: Yes. This patient was a 61-year-old woman. She entered the trial with RAEB, actually with 7 percent blasts, and a platelet count of 99,000. She had achieved a transfusion independent response with the drug and at follow-up marrow, her blast count had decreased to 3 percent.

Her platelet counts had remained

relatively in the same range, and a few days before her accident, her platelet count was 76,000. So, I believe the treating physician assessed this as not related because the patient had been responding to the drug and had a history of a relatively stable platelet count, and that's what I have.

DR. CHESON: But it wasn't relatively stable because it has just dropped by 20 percent, but anyhow, none of us were there, so we can't say.

DR. KNIGHT: Correct.

DR. CHESON: But my point is in this context, you have to give the patient the benefit of the doubt, and not the drug the benefit of the doubt.

Just for clarification purposes, I notice in the earlier trials, the patients were required to be EPO, as it is called here, to have failed EPO.

Number 1, was that the case on the pivotal trial? Number 2, could you define what that means, "failed EPO," does that mean they responded and then relapsed, or they were refractory to EPO,

because there are cases in the literature of 5q minus, that have responded to EPO.

The second question before I forget it is it also wasn't stated in the presentation of the pivotal trial whether they were required to have a certain level of hemoglobin prior to study entry rather than just being transfused because we all know to get a patient on a drug like this, you might give them transfusions just so they can get on the study.

DR. DeLAP: I will ask Dr. List to address these questions for us.

DR. LIST: I think the first question you asked, Dr. Cheson, and I am Dr. List, by the way, is regarding the eligibility in the initial trial, and it was defined as at least 6 weeks of therapy, if I remember right, 40,000 units per week of EPO to define a patient to be EPO-resistant.

Nearly everybody had had months of therapy, and if they did respond in the past, had then failed and when they went on the trial.

On the 003 trial, there was no requirement

for prior EPO, so the data that we showed you for the 73 percent that had prior EPO and failed was according to the local investigator when they enrolled the trial. So, there was no requirement on time of the protocol entry to define that.

The second question. The patients had to be transfusion dependent on the 003 trial. Are you talking about the 001?

DR. CHESON: I am talking about the pivotal trial.

DR. LIST: They had to have hemoglobin less than 10.

DR. CHESON: Okay, not just having received transfusion.

DR. LIST: Right, I see what you are saying, yes.

DR. MARTINO: Dr. Hussain.

DR. HUSSAIN: I have two questions for the company.

The first one is, if I am not mistaken, I saw 40 percent as an E rate, 80 percent of the patients interrupting their treatment. Why do you

think you have the right dose?

The second question is if you were asked to do a Phase III trial, why you chose not to.

DR. DeLAP: With respect to the dose question, the 10 mg dose needs to be considered in the context of the initial treatment of these patients where we are observing apoptosis of the abnormal clone of cells in the patient's bone marrow.

These patients with MDS and of the chromosome 5 deletion in their dysplastic clone, they have a cell clone that is giving rise to a lot of their neutrophils and platelets, and as we give a drug, it causes that clone to apoptose and to be suppressed or eliminated, there can be a period of time before more normal cells come back into the bone marrow where the patients actually become neutropenic, thrombocytopenic, related again to the suppression of the clone, which is actually giving rise to a lot of their neutrophils and platelets.

[Slide.]

In terms of if I can just show you one