CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103234s5053

Trade Name: Epogen/Procrit

Generic Name: Epoetin Alfa

Sponsor: Amgen, Inc.

Approval Date: June 30, 2004

Indications: For the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103234s5053

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103234/5053

JUN 30 2004

Amgen, Incorporated
Attention: Douglas Hunt
Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Hunt:

Your request to supplement your biologics license application for Epoetin alfa to update the Clinical Pharmacology, Indications and Usage, Precautions, Adverse Reactions, and Dosage Administration sections of the package insert to incorporate an alternative weekly dosing regimen for the treatment of anemia due to chemotherapy in patients with non-myeloid malignancies, has been approved.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages five to eighteen years until December 31, 2004. We are also deferring submission of your pediatric studies for ages zero to less than five years until June 30, 2005.

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The statuses of these postmarketing studies shall be reported annually according to 21 CFR 601.70. These commitments are listed below.

1. To obtain efficacy and safety data to evaluate weekly dosing of Procrit (Epoetin alfa) in children with solid tumors, Hodgkin's disease, ALL, or NHL, in study PR99-11-034/044 a Randomized Double-Blind, Placebo Controlled Study to Evaluate the Effect of Weekly Procrit (Epoetin alfa) on Anemia and Quality of Life in Children with Cancer Undergoing Myelosuppressive Chemotherapy. The study was completed on February 18, 2004, and the final study report will be submitted by December 31, 2004.

2. To evaluate the feasibility of conducting a study, in pediatric cancer patients age 0 to less than 5 years, and if appropriate, submit a pediatric study plan or request a waiver by June 30, 2005.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 103234. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA STN BL 103234. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- Postmarketing Study Protocol
- Postmarketing Study Final Report
- Postmarketing Study Correspondence
- Annual Report on Postmarketing Studies

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted), and
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Division of Drug Marketing, Advertising and Communication (HFD-42), Center for Drug Evaluation and Research, 5600 Fishers Lane/Room 8B45, Rockville, MD 20857. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

This information will be included in your biologics license application file.

Sincerely,

Patricia Keegan

Patricia Keegan, M.D.
Director
Division of Therapeutic Biological Oncology Products
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Enclosure: Package Insert

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103234s5053

LABELING

EPOGEN®
(Epoetin alfa)
FOR INJECTION

DESCRIPTION

Erythropoietin is a glycoprotein which stimulates red blood cell production. It is produced in the kidney and stimulates the division and differentiation of committed erythroid progenitors in the bone marrow. EPOGEN® (Epoetin alfa), a 165 amino acid glycoprotein manufactured by recombinant DNA technology, has the same biological effects as endogenous erythropoietin.[1] It has a molecular weight of 30,400 daltons and is produced by mammalian cells into which the human erythropoietin gene has been introduced. The product contains the identical amino acid sequence of isolated natural erythropoietin.

EPOGEN® is formulated as a sterile, colorless liquid in an isotonic sodium chloride/sodium citrate buffered solution or a sodium chloride/sodium phosphate buffered solution for intravenous (IV) or subcutaneous (SC) administration.

Single-dose, Preservative-free Vial: Each 1 mL of solution contains 2000, 3000, 4000 or 10,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 5.8 mg sodium citrate, 5.8 mg sodium chloride, and 0.06 mg citric acid in Water for Injection, USP (pH 6.9 ± 0.3). This formulation contains no preservative.

Single-dose, Preservative-free Vial: 1 mL (40,000 Units/mL). Each 1 mL of solution contains 40,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.2 mg sodium phosphate monobasic monohydrate, 4.8 mg sodium phosphate dibasic anhydrate, 0.7 mg sodium citrate, 5.8 mg sodium chloride, and 6.8 mcg citric acid in Water for Injection, USP (pH 6.9 ± 0.3). This formulation contains no preservative.

Multidose, Preserved Vial: 2 mL (20,000 Units, 10,000 Units/mL). Each 1 mL of solution contains 10,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in Water for Injection, USP (pH 6.1 ± 0.3).

Multidose, Preserved Vial: 1 mL (20,000 Units/mL). Each 1 mL of solution contains 20,000 Units of Epoetin alfa, 2.5 mg Albumin (Human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in Water for Injection, USP (pH 6.1 ± 0.3).

CLINICAL PHARMACOLOGY

Chronic Renal Failure Patients

Endogenous production of erythropoietin is normally regulated by the level of tissue oxygenation. Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis.[2] In normal subjects, plasma erythropoietin levels range from 0.01 to 0.03 Units/mL and increase up to 100- to 1000-fold during hypoxia or anemia.[2] In contrast, in patients with chronic renal failure (CRF), production of erythropoietin is impaired, and this erythropoietin deficiency is the primary cause of their anemia.[3,4]

Chronic renal failure is the clinical situation in which there is a progressive and usually irreversible decline in kidney function. Such patients may manifest the sequelae of renal dysfunction, including anemia, but do not necessarily require regular dialysis. Patients with end-stage renal disease (ESRD) are those patients with CRF who require regular dialysis or kidney transplantation for survival.

EPOGEN® has been shown to stimulate erythropoiesis in anemic patients with CRF, including both patients on dialysis and those who do not require regular dialysis.[4-13] The first evidence of a response to the three times weekly (TIW) administration of EPOGEN® is an increase in the reticulocyte count within 10 days, followed by increases in the red cell count, hemoglobin, and hematocrit, usually within 2 to 6 weeks.[4,5] Because of the length of time required for erythropoiesis — several days for erythroid progenitors to mature and be released into the circulation — a clinically significant increase in hematocrit is usually not observed in less than 2 weeks and may require up to 6 weeks in some patients. Once the hematocrit reaches the suggested target range (30% to 36%), that level can be sustained by EPOGEN® therapy in the absence of iron deficiency and concurrent illnesses.

The rate of hematocrit increase varies between patients and is dependent upon the dose of EPOGEN®, within a therapeutic range of approximately 50 to 300 Units/kg TIW.[4] A greater biologic response is not observed at doses exceeding 300 Units/kg TIW.[6] Other factors affecting the rate and extent of response include availability of iron stores, the baseline hematocrit, and the presence of concurrent medical problems.

Zidovudine-treated HIV-infected Patients

Responsiveness to EPOGEN® in HIV-infected patients is dependent upon the endogenous serum erythropoietin level prior to treatment. Patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL, and who are receiving a dose of zidovudine ≤ 4200 mg/week, may respond to EPOGEN® therapy. Patients with endogenous serum erythropoietin levels > 500 mUnits/mL do not appear to respond to EPOGEN® therapy. In a series of four clinical trials involving 255 patients, 60% to 80% of HIV-infected patients treated with zidovudine had endogenous serum erythropoietin levels ≤ 500 mUnits/mL.

Response to EPOGEN® in zidovudine-treated HIV-infected patients is manifested by reduced transfusion requirements and increased hematocrit.

Cancer Patients on Chemotherapy

A series of clinical trials enrolled 131 anemic cancer patients who received EPOGEN® TIW and who were receiving cyclic cisplatin- or non cisplatin-containing chemotherapy. Endogenous baseline serum erythropoietin levels varied among patients in these trials with approximately 75% (n = 83/110) having endogenous serum erythropoietin levels ≤ 132 mUnits/mL, and approximately 4% (n = 4/110) of patients having endogenous serum erythropoietin levels > 500 mUnits/mL. In general, patients with lower baseline serum erythropoietin levels responded more vigorously to EPOGEN® than patients with higher baseline erythropoietin levels. Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to EPOGEN® therapy, treatment of patients with grossly elevated serum erythropoietin levels (eg, > 200 mUnits/mL) is not recommended.

Pharmacokinetics

In adult and pediatric patients with CRF, the elimination half-life of plasma erythropoietin after intravenously administered EPOGEN® ranges from 4 to 13 hours.[14-16] The half-life is approximately 20% longer in CRF patients than that in healthy subjects. After SC administration, peak plasma levels are achieved within 5 to 24 hours. The half-life is similar between adult patients with serum creatinine level greater than 3 and not on dialysis and those maintained on dialysis.

The pharmacokinetic profile of EPOGEN® in children and adolescents appears to be similar to that of adults. Limited data are available in neonates.[17]

The pharmacokinetics of EPOGEN® have not been studied in HIV-infected patients.

A pharmacokinetic study comparing 150 Units/kg SC TIW to 40,000 Units SC weekly dosing regimen was conducted for 4 weeks in healthy subjects (n = 12) and for 6 weeks in anemic cancer patients (n = 32) receiving cyclic chemotherapy. There was no accumulation of serum erythropoietin after the 2 dosing regimens during the study period. The 40,000 Units weekly regimen had a higher C_{max} (3- to 7-fold), longer T_{max} (2- to 3-fold), higher $AUC_{0\text{-}168h}$ (2- to 3-fold) of erythropoietin and lower clearance (50%) than the 150 Units/kg TIW regimen. In anemic cancer patients, the average $t_{1/2}$ was similar (40 hours with range of 16 to 67 hours) after both dosing regimens. After the 150 Units/kg TIW dosing, the values of T_{max} and clearance are similar (13.3 ± 12.4 vs. 14.2 ± 6.7 hours, and 20.2 ± 15.9 vs. 23.6 ± 9.5 mL/h/kg) between Week 1 when patients were receiving chemotherapy (n = 14) and Week 3 when patients were not receiving chemotherapy (n = 4). Differences were observed after the 40,000 Units weekly dosing with longer T_{max} (38 ± 18 hours) and lower clearance (9.2 ± 4.7 mL/h/kg) during Week 1 when patients were receiving chemotherapy (n = 18) compared with those (22 ± 4.5 hours, 13.9 ± 7.6 mL/h/kg) during Week 3 when patients were not receiving chemotherapy (n = 7).

The bioequivalence between the 10,000 Units/mL citrate-buffered Epoetin alfa formulation and the 40,000 Units/mL phosphate-buffered Epoetin alfa formulation has been demonstrated after SC administration of single 750 Units/kg doses to healthy subjects.

INDICATIONS AND USAGE

Treatment of Anemia of Chronic Renal Failure Patients

EPOGEN® is indicated for the treatment of anemia associated with CRF, including patients on dialysis (ESRD) and patients not on dialysis. EPOGEN® is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients.

Non-dialysis patients with symptomatic anemia considered for therapy should have a hemoglobin less than 10 g/dL.

EPOGEN® is not intended for patients who require immediate correction of severe anemia. EPOGEN® may obviate the need for maintenance transfusions but is not a substitute for emergency transfusion.

Prior to initiation of therapy, the patient's iron stores should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL. Blood pressure should be adequately controlled prior to initiation of EPOGEN® therapy, and must be closely monitored and controlled during therapy.

EPOGEN® should be administered under the guidance of a qualified physician (see DOSAGE AND ADMINISTRATION).

Treatment of Anemia in Zidovudine-treated HIV-infected Patients

EPOGEN® is indicated for the treatment of anemia related to therapy with zidovudine in HIV-infected patients. EPOGEN® is indicated to elevate or maintain the red blood cell level (as manifested by the hematocrit or hemoglobin determinations) and to decrease the need for transfusions in these patients. EPOGEN® is not indicated for the treatment of anemia in HIV-infected patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding, which should be managed appropriately.

EPOGEN®, at a dose of 100 Units/kg TIW, is effective in decreasing the transfusion requirement and increasing the red blood cell level of anemic, HIV-infected patients treated with zidovudine, when the endogenous serum erythropoietin level is ≤ 500 mUnits/mL and when patients are receiving a dose of zidovudine ≤ 4200 mg/week.

Treatment of Anemia in Cancer Patients on Chemotherapy

EPOGEN® is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. EPOGEN® is indicated to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of 2 months. EPOGEN® is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding, which should be managed appropriately.

Reduction of Allogeneic Blood Transfusion in Surgery Patients

EPOGEN® is indicated for the treatment of anemic patients (hemoglobin >10 to ≤ 13 g/dL) scheduled to undergo elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.[18-20] EPOGEN® is indicated for patients at high risk for perioperative transfusions with significant, anticipated blood loss. EPOGEN® is not indicated for anemic patients who are willing to donate autologous blood. The safety of the perioperative use of EPOGEN® has been studied only in patients who are receiving anticoagulant prophylaxis.

CLINICAL EXPERIENCE: RESPONSE TO EPOGEN®

Chronic Renal Failure Patients

Response to EPOGEN® was consistent across all studies. In the presence of adequate iron stores (see IRON EVALUATION), the time to reach the target hematocrit is a function of the baseline hematocrit and the rate of hematocrit rise.

The rate of increase in hematocrit is dependent upon the dose of EPOGEN® administered and individual patient variation. In clinical trials at starting doses of 50 to 150 Units/kg TIW, adult patients responded with an average rate of hematocrit rise of:

Starting Dose (TIW IV)	Hematocrit Increase Points/Day	Points/2 Weeks
50 Units/kg	0.11	1.5
100 Units/kg	0.18	2.5
150 Units/kg	0.25	3.5

Over this dose range, approximately 95% of all patients responded with a clinically significant increase in hematocrit, and by the end of approximately 2 months of therapy virtually all patients were transfusion-independent. Changes in the quality of life of adult patients treated with EPOGEN® were assessed as part of a phase 3 clinical trial.[5,8] Once the target hematocrit (32% to 38%) was achieved, statistically significant improvements were demonstrated for most quality of life parameters measured, including energy and activity level, functional ability, sleep and eating behavior, health status, satisfaction with health, sex life, well-being, psychological effect, life satisfaction, and happiness. Patients also reported improvement in their disease symptoms. They showed a statistically significant increase in exercise capacity (VO_2 max), energy, and strength with a significant reduction in aching, dizziness, anxiety, shortness of breath, muscle weakness, and leg cramps.[8,21]

Adult Patients on Dialysis: Thirteen clinical studies were conducted, involving IV administration to a total of 1010 anemic patients on dialysis for 986 patient-years of EPOGEN® therapy. In the three

largest of these clinical trials, the median maintenance dose necessary to maintain the hematocrit between 30% to 36% was approximately 75 Units/kg TIW. In the US multicenter phase 3 study, approximately 65% of the patients required doses of 100 Units/kg TIW, or less, to maintain their hematocrit at approximately 35%. Almost 10% of patients required a dose of 25 Units/kg, or less, and approximately 10% required a dose of more than 200 Units/kg TIW to maintain their hematocrit at this level.

A multicenter unit dose study was also conducted in 119 patients receiving peritoneal dialysis who self-administered EPOGEN® subcutaneously for approximately 109 patient-years of experience. Patients responded to EPOGEN® administered SC in a manner similar to patients receiving IV administration.[22]

Pediatric Patients on Dialysis: One hundred twenty-eight children from 2 months to 19 years of age with CRF requiring dialysis were enrolled in 4 clinical studies of EPOGEN®. The largest study was a placebo-controlled, randomized trial in 113 children with anemia (hematocrit ≤ 27%) undergoing peritoneal dialysis or hemodialysis. The initial dose of EPOGEN® was 50 Units/kg IV or SC TIW. The dose of study drug was titrated to achieve either a hematocrit of 30% to 36% or an absolute increase in hematocrit of 6 percentage points over baseline.

At the end of the initial 12 weeks, a statistically significant rise in mean hematocrit (9.4% vs 0.9%) was observed only in the EPOGEN® arm. The proportion of children achieving a hematocrit of 30%, or an increase in hematocrit of 6 percentage points over baseline, at any time during the first 12 weeks was higher in the EPOGEN® arm (96% vs 58%). Within 12 weeks of initiating EPOGEN® therapy, 92.3% of the pediatric patients were transfusion-independent as compared to 65.4% who received placebo. Among patients who received 36 weeks of EPOGEN®, hemodialysis patients required a higher median maintenance dose (167 Units/kg/week [n = 28] vs 76 Units/kg/week [n = 36]) and took longer to achieve a hematocrit of 30% to 36% (median time to response 69 days vs 32 days) than patients undergoing peritoneal dialysis.

Patients With CRF Not Requiring Dialysis

Four clinical trials were conducted in patients with CRF not on dialysis involving 181 patients treated with EPOGEN® for approximately 67 patient-years of experience. These patients responded to EPOGEN® therapy in a manner similar to that observed in patients on dialysis. Patients with CRF not on dialysis demonstrated a dose-dependent and sustained increase in hematocrit when EPOGEN® was administered by either an IV or SC route, with similar rates of rise of hematocrit when EPOGEN® was administered by either route. Moreover, EPOGEN® doses of 75 to 150 Units/kg per week have been shown to maintain hematocrits of 36% to 38% for up to 6 months. Correcting the anemia of progressive renal failure will allow patients to remain active even though their renal function continues to decrease.[23-24]

Zidovudine-treated HIV-infected Patients

EPOGEN® has been studied in four placebo-controlled trials enrolling 297 anemic (hematocrit < 30%) HIV-infected (AIDS) patients receiving concomitant therapy with zidovudine (all patients were treated with Epoetin alfa manufactured by Amgen Inc). In the subgroup of patients (89/125 EPOGEN® and 88/130 placebo) with prestudy endogenous serum erythropoietin levels ≤ 500 mUnits/mL, EPOGEN® reduced the mean cumulative number of units of blood transfused per patient by approximately 40% as compared to the placebo group.[25] Among those patients who required transfusions at baseline, 43% of patients treated with EPOGEN® versus 18% of placebo-treated patients were transfusion-independent during the second and third months of therapy. EPOGEN® therapy also resulted in significant increases in hematocrit in comparison to placebo. When examining the results according to the weekly dose of zidovudine received during month 3 of therapy, there was a statistically significant ($p < 0.003$) reduction in

transfusion requirements in patients treated with EPOGEN® (n = 51) compared to placebo treated patients (n = 54) whose mean weekly zidovudine dose was ≤ 4200 mg/week.[25]

Approximately 17% of the patients with endogenous serum erythropoietin levels ≤ 500 mUnits/mL receiving EPOGEN® in doses from 100 to 200 Units/kg TIW achieved a hematocrit of 38% without administration of transfusions or significant reduction in zidovudine dose. In the subgroup of patients whose prestudy endogenous serum erythropoietin levels were > 500 mUnits/mL, EPOGEN® therapy did not reduce transfusion requirements or increase hematocrit, compared to the corresponding responses in placebo-treated patients.

In a 6 month open-label EPOGEN® study, patients responded with decreased transfusion requirements and sustained increases in hematocrit and hemoglobin with doses of EPOGEN® up to 300 Units/kg TIW.[26-27]

Responsiveness to EPOGEN® therapy may be blunted by intercurrent infectious/inflammatory episodes and by an increase in zidovudine dosage. Consequently, the dose of EPOGEN® must be titrated based on these factors to maintain the desired erythropoietic response.

Cancer Patients on Chemotherapy

Three-Times Weekly (TIW) Dosing

EPOGEN® administered TIW has been studied in a series of six placebo-controlled, double-blind trials that enrolled 131 anemic cancer patients receiving EPOGEN® or matching placebo. Across all studies, 72 patients were treated with concomitant non cisplatin-containing chemotherapy regimens and 59 patients were treated with concomitant cisplatin-containing chemotherapy regimens. Patients were randomized to EPOGEN® 150 Units/kg or placebo subcutaneously TIW for 12 weeks in each study.

The results of the pooled data from these six studies are shown in the table below. Because of the length of time required for erythropoiesis and red cell maturation, the efficacy of EPOGEN® (reduction in proportion of patients requiring transfusions) is not manifested until 2 to 6 weeks after initiation of EPOGEN®.

Proportion of Patients Transfused During Chemotherapy (Efficacy Population[a])

Chemotherapy Regimen	On Study[b]		During Months 2 and 3[c]	
	EPOGEN®	Placebo	EPOGEN®	Placebo
Regimens without cisplatin	44% (15/34)	44% (16/36)	21% (6/29)	33% (11/33)
Regimens containing cisplatin	50% (14/28)	63% (19/30)	23% (5/22)[d]	56% (14/25)
Combined	47% (29/62)	53% (35/66)	22% (11/51)[d]	43% (25/58)

[a] Limited to patients remaining on study at least 15 days (1 patient excluded from EPOGEN®, 2 patients excluded from placebo).

[b] Includes all transfusions from day 1 through the end of study.

[c] Limited to patients remaining on study beyond week 6 and includes only transfusions during weeks 5-12.

[d] Unadjusted 2-sided $p < 0.05$

ntensity of chemotherapy in the above trials was not directly assessed, however the degree and timing of neutropenia was comparable across all trials. Available evidence suggests that patients with lymphoid and solid cancers respond similarly to EPOGEN® therapy, and that patients with or without tumor infiltration of the bone marrow respond similarly to EPOGEN® therapy.

Weekly (QW) Dosing

EPOGEN® was also studied in a placebo-controlled, double-blind trial utilizing weekly dosing in a total of 344 anemic cancer patients. In this trial, 61 (35 placebo arm and 26 in the EPOGEN® arm) patients were treated with concomitant cisplatin containing regimens and 283 patients received concomitant chemotherapy regimens that did not contain cisplatinum. Patients were randomized to EPOGEN® 40,000 Units weekly (n = 174) or placebo (n = 170) SC for a planned treatment period of 16 weeks. If hemoglobin had not increased by > 1 g/dL, after 4 weeks of therapy or the patient received RBC transfusion during the first 4 weeks of therapy, study drug was increased to 60,000 Units weekly. Forty-three percent of patients in the Epoetin alfa group required and increase in EPOGEN® dose to 60,000 Units weekly.[25]

Results demonstrated that EPOGEN® therapy reduced the proportion of patients transfused in day 29 through week 16 of the study as compared to placebo. Twenty-five patients (14%) in the EPOGEN® group received transfusions compared to 48 patients (28%) in the placebo group (p = 0.0010) between day 29 and week 16 or the last day on study.

Comparable intensity of chemotherapy for patients enrolled in the two study arms was suggested by similarities in mean dose and frequency of administration for the 10 most commonly administered chemotherapy agents, and similarity in the incidence of changes in chemotherapy during the trial in the o arms.

Surgery Patients

EPOGEN® has been studied in a placebo-controlled, double-blind trial enrolling 316 patients scheduled for major, elective orthopedic hip or knee surgery who were expected to require ≥ 2 units of blood and who were not able or willing to participate in an autologous blood donation program. Based on previous studies which demonstrated that pretreatment hemoglobin is a predictor of risk of receiving transfusion,[20,26] patients were stratified into one of three groups based on their pretreatment hemoglobin [≤ 10 (n = 2), > 10 to ≤ 13 (n = 96), and > 13 to ≤ 15 g/dL (n = 218)] and then randomly assigned to receive 300 Units/kg EPOGEN®, 100 Units/kg EPOGEN® or placebo by SC injection for 10 days before surgery, on the day of surgery, and for 4 days after surgery.[18] All patients received oral iron and a low-dose post-operative warfarin regimen.[18]

Treatment with EPOGEN® 300 Units/kg significantly (p = 0.024) reduced the risk of allogeneic transfusion in patients with a pretreatment hemoglobin of > 10 to ≤ 13; 5/31 (16%) of EPOGEN® 300 Units/kg, 6/26 (23%) of EPOGEN® 100 Units/kg, and 13/29 (45%) of placebo-treated patients were transfused.[18] There was no significant difference in the number of patients transfused between EPOGEN® (9% 300 Units/kg, 6% 100 Units/kg) and placebo (13%) in the > 13 to ≤ 15 g/dL hemoglobin stratum. There were too few patients in the ≤ 10 g/dL group to determine if EPOGEN® is useful in this hemoglobin strata. In the > 10 to ≤ 13 g/dL pretreatment stratum, the mean number of units transfused per EPOGEN®-treated patient (0.45 units blood for 300 Units/kg, 0.42 units blood for 100 Units/kg) was less than the mean transfused per placebo-treated patient (1.14 units) (overall p = 0.028). In addition, mean hemoglobin, hematocrit, and reticulocyte counts increased significantly during the presurgery period in patients treated with EPOGEN®.[18]

EPOGEN® was also studied in an open-label, parallel-group trial enrolling 145 subjects with a pretreatment hemoglobin level of ≥ 10 to ≤ 13 g/dL who were scheduled for major orthopedic hip or knee surgery and who were not participating in an autologous program.[19] Subjects were randomly assigned to receive one of two SC dosing regimens of EPOGEN® (600 Units/kg once weekly for 3 weeks prior to surgery and on the day of surgery, or 300 Units/kg once daily for 10 days prior to surgery, on the day of surgery and for 4 days after surgery). All subjects received oral iron and appropriate pharmacologic anticoagulation therapy.

From pretreatment to presurgery, the mean increase in hemoglobin in the 600 Units/kg weekly group (1.44 g/dL) was greater than observed in the 300 Units/kg daily group.[19] The mean increase in absolute reticulocyte count was smaller in the weekly group ($0.11 \times 10^6/mm^3$) compared to the daily group ($0.17 \times 10^6/mm^3$). Mean hemoglobin levels were similar for the two treatment groups throughout the postsurgical period.

The erythropoietic response observed in both treatment groups resulted in similar transfusion rates [11/69 (16%) in the 600 Units/kg weekly group and 14/71 (20%) in the 300 Units/kg daily group].[19] The mean number of units transfused per subject was approximately 0.3 units in both treatment groups.

CONTRAINDICATIONS

EPOGEN® is contraindicated in patients with:

1. Uncontrolled hypertension.
2. Known hypersensitivity to mammalian cell-derived products.
3. Known hypersensitivity to Albumin (Human).

WARNINGS

Pediatric Use

The multidose preserved formulation contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in premature infants which are sometimes fatal.

Thrombotic Events and Increased Mortality

A randomized, prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure) was conducted in which patients were assigned to EPOGEN® treatment targeted to a maintenance hematocrit of either 42 ± 3% or 30 ± 3%.[42] Increased mortality was observed in 634 patients randomized to a target hematocrit of 42% [221 deaths (35% mortality)] compared to 631 patients targeted to remain at a hematocrit of 30% [185 deaths (29% mortality)]. The reason for the increased mortality observed in these studies is unknown, however, the incidence of non-fatal myocardial infarctions (3.1% vs 2.3%), vascular access thromboses (39% vs 29%), and all other thrombotic events (22% vs 18%) were also higher in the group randomized to achieve a hematocrit of 42%.

Increased mortality was also observed in a randomized placebo-controlled study of EPOGEN® in adult patients who did not have CRF who were undergoing coronary artery bypass surgery (7 deaths in 126 patients randomized to EPOGEN® versus no deaths among 56 patients receiving placebo). Four of these deaths occurred during the period of study drug administration and all four deaths were associated with thrombotic events. While the extent of the population affected is unknown, in patients at risk for thrombosis, the anticipated benefits of EPOGEN® treatment should be weighed against the potential for increased risks associated with therapy.

...a randomized, prospective trial conducted with another Epoetin alfa product, in 939 women with metastatic carcinoma of the breast who were receiving chemotherapy, patients were assigned to receive either Epoetin alfa or placebo for up to a year, in a weekly schedule, with the primary goal of showing improved survival and improved quality of life in the Epoetin alfa treatment arm.[25] This study utilized a treatment strategy designed to maintain hemoglobin levels of 12 to14 g/dL (hematocrit 36 to 42%). Increased mortality in the first 4 months after randomization was observed among 469 patients who received the erythropoietin product [41 deaths (8.7% mortality)] compared to 470 patients who received placebo [16 deaths (3.4% mortality)]. In the first four months of the study, the incidence of fatal thrombotic vascular events (1.1% vs 0.2%) and death attributed to disease progression (6.0% vs 2.8%) were both higher in the group randomized to receive Epoetin alfa as compared to placebo. Based on Kaplan-Meier estimates, the proportion of subjects surviving at 12 months after randomization was lower in the Epoetin alfa group than in the placebo group (70% vs 76%), p = 0.012, log rank. However, due to insufficient monitoring and data collection, reliable comparisons cannot be made concerning the effect of Epoetin alfa on overall time to disease progression, progression-free survival, and overall survival.

Pure Red Cell Aplasia
Pure red cell aplasia (PRCA), in association with neutralizing antibodies to native erythropoietin, has been observed in patients treated with recombinant erythropoietins. PRCA has been reported in a limited number of patients exposed to EPOGEN®. This has been reported predominantly in patients with CRF. Any patient with loss of response to EPOGEN® should be evaluated for the etiology of loss of effect (see PRECAUTIONS: LACK OR LOSS OF RESPONSE). EPOGEN® should be discontinued in any patient with evidence of PRCA and the patient evaluated for the presence of binding and neutralizing antibodies to EPOGEN® native erythropoietin, and any other recombinant erythropoietin administered to the patient. Amgen should be contacted to assist in this evaluation. In patients with PRCA secondary to neutralizing antibodies to erythropoietin, EPOGEN® should not be administered and such patients should not be switched to another product as anti-erythropoietin antibodies cross-react with other erythropoietins (see ADVERSE REACTIONS).

Albumin (Human)
EPOGEN® contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Chronic Renal Failure Patients
Hypertension: Patients with uncontrolled hypertension should not be treated with EPOGEN®; blood pressure should be controlled adequately before initiation of therapy. Up to 80% of patients with CRF have a history of hypertension.[29] Although there does not appear to be any direct pressor effects of EPOGEN®, blood pressure may rise during EPOGEN® therapy. During the early phase of treatment when the hematocrit is increasing, approximately 25% of patients on dialysis may require initiation of, or increases in, antihypertensive therapy. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with EPOGEN®.

Special care should be taken to closely monitor and aggressively control blood pressure in patients treated with EPOGEN®. Patients should be advised as to the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control by initiation of appropriate measures, the hemoglobin may be reduced by decreasing or withholding the dose of EPOGEN®. A clinically significant decrease in hemoglobin may not be observed for several weeks.

It is recommended that the dose of EPOGEN® be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period, because of the possible association of excessive rate of rise of hemoglobin with an exacerbation of hypertension. In CRF patients on hemodialysis with clinically evident ischemic heart disease or congestive heart failure, the hemoglobin should be managed carefully, not to exceed 12 g/dL (see THROMBOTIC EVENTS).

Seizures: Seizures have occurred in patients with CRF participating in EPOGEN® clinical trials.

In adult patients on dialysis, there was a higher incidence of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients) as compared with later timepoints.

Given the potential for an increased risk of seizures during the first 90 days of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. Patients should be cautioned to avoid potentially hazardous activities such as driving or operating heavy machinery during this period.

While the relationship between seizures and the rate of rise of hemoglobin is uncertain, it is recommended that the dose of EPOGEN® be decreased if the hemoglobin increase exceeds 1 g/dL in any 2-week period.

Thrombotic Events: During hemodialysis, patients treated with EPOGEN® may require increased anticoagulation with heparin to prevent clotting of the artificial kidney (see ADVERSE REACTIONS for more information about thrombotic events).

Other thrombotic events (eg, myocardial infarction, cerebrovascular accident, transient ischemic attack) have occurred in clinical trials at an annualized rate of less than 0.04 events per patient year of EPOGEN® therapy. These trials were conducted in adult patients with CRF (whether on dialysis or not) in whom the target hematocrit was 32% to 40%. However, the risk of thrombotic events, including vascular access thrombosis, was significantly increased in adult patients with ischemic heart disease or congestive heart failure receiving EPOGEN® therapy with the goal of reaching a normal hematocrit (42%) as compared to a target hematocrit of 30%. Patients with pre-existing cardiovascular disease should be monitored closely.

Zidovudine-treated HIV-infected Patients
In contrast to CRF patients, EPOGEN® therapy has not been linked to exacerbation of hypertension, seizures, and thrombotic events in HIV-infected patients.

PRECAUTIONS
The parenteral administration of any biologic product should be attended by appropriate precautions in case allergic or other untoward reactions occur (see CONTRAINDICATIONS). In clinical trials, while transient rashes were occasionally observed concurrently with EPOGEN® therapy, no serious allergic or anaphylactic reactions were reported (see ADVERSE REACTIONS for more information regarding allergic reactions).

The safety and efficacy of EPOGEN® therapy have not been established in patients with a known history of a seizure disorder or underlying hematologic disease (eg, sickle cell anemia, myelodysplastic syndromes, or hypercoagulable disorders).

In some female patients, menses have resumed following EPOGEN® therapy; the possibility of pregnancy should be discussed and the need for contraception evaluated.

Hematology
Exacerbation of porphyria has been observed rarely in patients with CRF treated with EPOGEN®. However, EPOGEN® has not caused increased urinary excretion of porphyrin metabolites in normal volunteers, even in the presence of a rapid erythropoietic response. Nevertheless, EPOGEN® should be used with caution in patients with known porphyria.

In preclinical studies in dogs and rats, but not in monkeys, EPOGEN® therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of CRF in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of adult patients on dialysis who were treated with EPOGEN® for 12 to 19 months, compared to the incidence of bone marrow fibrosis in a matched group of patients who had not been treated with EPOGEN®.

Hemoglobin in CRF patients should be measured twice a week; zidovudine-treated HIV-infected and cancer patients should have hemoglobin measured once a week until hemoglobin has been stabilized, and measured periodically thereafter.

Lack or Loss of Response
If the patient fails to respond or to maintain a response to doses within the recommended dosing range, the following etiologies should be considered and evaluated:
1. Iron deficiency: Virtually all patients will eventually require supplemental iron therapy (see IRON EVALUATION).
2. Underlying infectious, inflammatory, or malignant processes.
3. Occult blood loss.
4. Underlying hematologic diseases (ie, thalassemia, refractory anemia, or other myelodysplastic disorders).
5. Vitamin deficiencies: Folic acid or vitamin B12.
6. Hemolysis.
7. Aluminum intoxication.
8. Osteitis fibrosa cystica.
9. Pure Red Cell Aplasia (PRCA): In the absence of another etiology, the patient should be evaluated for evidence of PRCA and sera should be tested for the presence of antibodies to recombinant erythropoietins.

Iron Evaluation
During EPOGEN® therapy, absolute or functional iron deficiency may develop. Functional iron deficiency, with normal ferritin levels but low transferrin saturation, is presumably due to the inability to mobilize iron stores rapidly enough to support increased erythropoiesis. Transferrin saturation should be at least 20% and ferritin should be at least 100 ng/mL.

Prior to and during EPOGEN® therapy, the patient's iron status, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels which will adequately support erythropoiesis stimulated by EPOGEN®. All surgery patients being treated with EPOGEN® should receive adequate iron supplementation throughout the course of therapy in order to support erythropoiesis and avoid depletion of iron stores.

Drug Interaction
No evidence of interaction of EPOGEN® with other drugs was observed in the course of clinical trials.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenic potential of EPOGEN® has not been evaluated. EPOGEN® does not induce bacterial gene mutation (Ames Test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus. In female rats treated IV with EPOGEN®, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg.

Pregnancy Category C

EPOGEN® has been shown to have adverse effects in rats when given in doses 5 times the human dose. There are no adequate and well-controlled studies in pregnant women. EPOGEN® should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

In studies in female rats, there were decreases in body weight gain, delays in appearance of abdominal hair, delayed eyelid opening, delayed ossification, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. In female rats treated IV, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg. EPOGEN® has not shown any adverse effect at doses as high as 500 Units/kg in pregnant rabbits (from day 6 to 18 of gestation).

Nursing Mothers

Postnatal observations of the live offspring (F1 generation) of female rats treated with EPOGEN® during gestation and lactation revealed no effect of EPOGEN® at doses of up to 500 Units/kg. There were, however, decreases in body weight gain, delays in appearance of abdominal hair, eyelid opening, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. There were no EPOGEN®-related effects on the F2 generation fetuses.

It is not known whether EPOGEN® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when EPOGEN® is administered to a nursing woman.

Pediatric Use

See WARNINGS: PEDIATRIC USE.

Pediatric Patients on Dialysis: EPOGEN® is indicated in infants (1 month to 2 years), children (2 years to 12 years), and adolescents (12 years to 16 years) for the treatment of anemia associated with CRF requiring dialysis. Safety and effectiveness in pediatric patients less than 1 month old have not been established (see CLINICAL EXPERIENCE: CHRONIC RENAL FAILURE, PEDIATRIC PATIENTS ON DIALYSIS). The safety data from these studies show that there is no increased risk to pediatric CRF patients on dialysis when compared to the safety profile of EPOGEN® in adult CRF patients (see ADVERSE REACTIONS and WARNINGS). Published literature[30-33] provides supportive evidence of the safety and effectiveness of EPOGEN® in pediatric CRF patients on dialysis.

Pediatric Patients Not Requiring Dialysis: Published literature[33,34] has reported the use of EPOGEN® in 133 pediatric patients with anemia associated with CRF not requiring dialysis, ages 3 months to 20 years, treated with 50 to 250 Units/kg SC or IV, QW to TIW. Dose-dependent increases in hemoglobin and hematocrit were observed with reductions in transfusion requirements.

Pediatric HIV-infected Patients: Published literature [35,36] has reported the use of EPOGEN® in 20 zidovudine-treated anemic HIV-infected pediatric patients ages 8 months to 17 years, treated with 50 to 400 Units/kg SC or IV, 2 to 3 times per week. Increases in hemoglobin levels and in reticulocyte counts, and decreases in or elimination of blood transfusions were observed.

ediatric Cancer Patients on Chemotherapy: Published literature[37,38] has reported the use of EPOGEN® in approximately 64 anemic pediatric cancer patients ages 6 months to 18 years, treated with 25 to 300 Units/kg SC or IV, 3 to 7 times per week. Increases in hemoglobin and decreases in transfusion requirements were noted.

Chronic Renal Failure Patients
Patients with CRF Not Requiring Dialysis
Blood pressure and hemoglobin should be monitored no less frequently than for patients maintained on dialysis. Renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients.

Hematology
Sufficient time should be allowed to determine a patient's responsiveness to a dosage of EPOGEN® before adjusting the dose. Because of the time required for erythropoiesis and the red cell half-life, an interval of 2 to 6 weeks may occur between the time of a dose adjustment (initiation, increase, decrease, or discontinuation) and a significant change in hemoglobin.

In order to avoid reaching the suggested target hemoglobin too rapidly, or exceeding the suggested target range (hemoglobin of 10 g/dL to 12 g/dL), the guidelines for dose and frequency of dose adjustments (see DOSAGE AND ADMINISTRATION) should be followed.

For patients who respond to EPOGEN® with a rapid increase in hemoglobin (eg, more than 1 g/dL in any 2-week period), the dose of EPOGEN® should be reduced because of the possible association of excessive rate of rise of hemoglobin with an exacerbation of hypertension.

he elevated bleeding time characteristic of CRF decreases toward normal after correction of anemia in adult patients treated with EPOGEN®. Reduction of bleeding time also occurs after correction of anemia by transfusion.

Laboratory Monitoring
The hemoglobin should be determined twice a week until it has stabilized in the suggested target range and the maintenance dose has been established. After any dose adjustment, the hemoglobin should also be determined twice weekly for at least 2 to 6 weeks until it has been determined that the hemoglobin has stabilized in response to the dose change. The hemoglobin should then be monitored at regular intervals.

A complete blood count with differential and platelet count should be performed regularly. During clinical trials, modest increases were seen in platelets and white blood cell counts. While these changes were statistically significant, they were not clinically significant and the values remained within normal ranges.

In patients with CRF, serum chemistry values (including blood urea nitrogen [BUN], uric acid, creatinine, phosphorus, and potassium) should be monitored regularly. During clinical trials in adult patients on dialysis, modest increases were seen in BUN, creatinine, phosphorus, and potassium. In some adult patients with CRF not on dialysis treated with EPOGEN®, modest increases in serum uric acid and phosphorus were observed. While changes were statistically significant, the values remained within the ranges normally seen in patients with CRF.

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As the hemoglobin increases and patients experience an improved sense of well-being and quality of life, the importance of compliance with dietary and dialysis prescriptions should be reinforced. In particular, hyperkalemia is not uncommon in patients with CRF. In US studies in patients on dialysis, hyperkalemia has occurred at an annualized rate of approximately 0.11 episodes per patient-year of EPOGEN® therapy, often in association with poor compliance to medication, diet, and/or dialysis.

Dialysis Management
Therapy with EPOGEN® results in an increase in hematocrit and a decrease in plasma volume which could affect dialysis efficiency. In studies to date, the resulting increase in hematocrit did not appear to adversely affect dialyzer function[9,10] or the efficiency of high flux hemodialysis.[11] During hemodialysis, patients treated with EPOGEN® may require increased anticoagulation with heparin to prevent clotting of the artificial kidney.

Patients who are marginally dialyzed may require adjustments in their dialysis prescription. As with all patients on dialysis, the serum chemistry values (including BUN, creatinine, phosphorus, and potassium) in patients treated with EPOGEN® should be monitored regularly to assure the adequacy of the dialysis prescription.

Information for Patients
In those situations in which the physician determines that a home dialysis patient can safely and effectively self-administer EPOGEN®, the patient should be instructed as to the proper dosage and administration. Home dialysis patients should be referred to the full "Information for Home Dialysis Patients" insert; it is not a disclosure of all possible effects. Patients should be informed of the signs and symptoms of allergic drug reaction and advised of appropriate actions. If home use is prescribed for a home dialysis patient, the patient should be thoroughly instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, or drug product. A puncture-resistant container for the disposal of used syringes and needles should be available to the patient. The full container should be disposed of according to the directions provided by the physician.

Renal Function
In adult patients with CRF not on dialysis, renal function and fluid and electrolyte balance should be closely monitored, as an improved sense of well-being may obscure the need to initiate dialysis in some patients. In patients with CRF not on dialysis, placebo-controlled studies of progression of renal dysfunction over periods of greater than 1 year have not been completed. In shorter term trials in adult patients with CRF not on dialysis, changes in creatinine and creatinine clearance were not significantly different in patients treated with EPOGEN® compared with placebo-treated patients. Analysis of the slope of 1/serum creatinine versus time plots in these patients indicates no significant change in the slope after the initiation of EPOGEN® therapy.

Zidovudine-treated HIV-infected Patients
Hypertension
Exacerbation of hypertension has not been observed in zidovudine-treated HIV-infected patients treated with EPOGEN®. However, EPOGEN® should be withheld in these patients if pre-existing hypertension is uncontrolled, and should not be started until blood pressure is controlled. In double-blind studies, a single seizure has been experienced by a patient treated with EPOGEN®.[25]

Cancer Patients on Chemotherapy
Hypertension

Hypertension, associated with a significant increase in hemoglobin, has been noted rarely in patients treated with EPOGEN®. Nevertheless, blood pressure in patients treated with EPOGEN® should be monitored carefully, particularly in patients with an underlying history of hypertension or cardiovascular disease.

Seizures
In double-blind, placebo-controlled trials, 3.2% (n = 2/63) of patients treated with EPOGEN® TIW and 2.9% (n = 2/68) of placebo-treated patients had seizures. Seizures in 1.6% (n = 1/63) of patients treated with EPOGEN® TIW occurred in the context of a significant increase in blood pressure and hematocrit from baseline values. However, both patients treated with EPOGEN® also had underlying CNS pathology which may have been related to seizure activity.

In a placebo-controlled, double-blind trial utilizing weekly dosing with EPOGEN®, 1.2% (n = 2/168) of safety-evaluable patients treated with EPOGEN® and 1% (n = 1/165) of placebo-treated patients had seizures. Seizures in the patients treated with weekly EPOGEN® occurred in the context of a significant increase in hemoglobin from baseline values however significant increases in blood pressure were not seen. These patients may have had other CNS pathology.

Thrombotic Events
In double-blind, placebo-controlled trials, 3.2% (n = 2/63) of patients treated with EPOGEN® TIW and 11.8% (n = 8/68) of placebo-treated patients had thrombotic events (eg, pulmonary embolism, cerebrovascular accident), (See WARNINGS; Thrombotic Events and Increased Mortality).

In a placebo-controlled, double-blind trial utilizing weekly dosing with EPOGEN®, 6.0% (n = 10/168) of safety-evaluable patients treated with EPOGEN® and 3.6% (n = 6/165) (p = 0.444) of placebo-treated patients had clinically significant thrombotic events (deep vein thrombosis requiring anticoagulant therapy, embolic event including pulmonary embolism, myocardial infarction, cerebral ischemia, left ventricular failure and thrombotic microangiopathy). A definitive relationship between the rate of hemoglobin increase and the occurrence of clinically significant thrombotic events could not be evaluated due to the limited schedule of hemoglobin measurements in this study.

Tumor Growth Factor Potential
EPOGEN® is a growth factor that primarily stimulates red cell production. Erythropoietin receptors are also found to be present on the surface of some malignant cell lines and tumor biopsy specimens. However, it is not known if these receptors are functional. A randomized, placebo-controlled trial was conducted in 224 chemotherapy-naïve, non-anemic patients with small cell lung cancer receiving cisplatin-based combination chemotherapy, to investigate whether the concurrent use of EPOGEN® stimulated tumor growth as assessed by impact on overall response rate. Patients were randomized to receive EPOGEN® 150 Units/kg or placebo subcutaneously TIW during chemotherapy. The overall response rates, after 3 cycles of treatment, were 72% and 67%, in the EPOGEN® and placebo arms, respectively. Complete response rates (17% vs. 14%) and median overall survival (10.5 mos vs. 10.4 mos) were similar in the EPOGEN® and placebo arms.[25]

Two additional studies explored effect on survival and/or progression of administrations of other exogenous erythropoietin with higher hemoglobin targets.

In a randomized, placebo-controlled study using another Epoetin alfa product, conducted in 939 women with metastatic breast cancer, study drug dosing was titrated to attempt to maintain hemoglobin levels between 12 and 14 g/dL. At four months, death attributed to disease progression was higher (6% vs 3%) in women receiving Epoetin alfa. Overall mortality was significantly higher at 12 months in the Epoetin alfa arm (See WARNINGS; Thrombotic Events and Increased Mortality).

In a randomized, placebo-controlled study using Epoetin beta, conducted in 351 patients with head and neck cancer, study drug was administered with the aim of achieving a hemoglobin level of 14 g/dL in women and 15 g/dL in men. Locoregional progression-free survival was significantly shorter (median PFS: 406 days Epoetin beta vs 745 days placebo, p = 0.04) in patients receiving Epoetin beta.[43]

There is insufficient information to establish whether use of Epoetin products, including EPOGEN®, have an adverse effect on time to tumor progression or progression-free survival.

These trials permitted or required dosing to achieve hemoglobin of greater than 12 g/dL. Until further information is available, the recommended target hemoglobin should not exceed 12 g/dL in men or women.

Surgery Patients

Thrombotic/Vascular Events

In perioperative clinical trials with orthopedic patients, the overall incidence of thrombotic/vascular events was similar in Epoetin alfa and placebo-treated patients who had a pretreatment hemoglobin of > 10 g/dL to ≤ 13 g/dL. In patients with a hemoglobin of > 13 g/dL treated with 300 Units/kg of Epoetin alfa, the possibility that EPOGEN® treatment may be associated with an increased risk of postoperative thrombotic/vascular events cannot be excluded.[18-20,28]

In one study in which Epoetin alfa was administered in the perioperative period to patients undergoing coronary artery bypass graft surgery, there were 7 deaths in the group treated with Epoetin alfa (n = 126) and no deaths in the placebo-treated group (n = 56). Among the 7 deaths in the patients treated with Epoetin alfa, 4 were at the time of therapy (between study day 2 and 8). The 4 deaths at the time of therapy (3%) were associated with thrombotic/vascular events. A causative role of Epoetin alfa cannot be excluded (see WARNINGS).

Hypertension

Blood pressure may rise in the perioperative period in patients being treated with EPOGEN®. Therefore, blood pressure should be monitored carefully.

ADVERSE REACTIONS

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EPOGEN® with the incidence of antibodies to other products may be misleading.

A few cases of PRCA associated with antibodies with neutralizing activity have been reported in patients receiving EPOGEN® (see WARNINGS: PURE RED CELL APLASIA). These cases were observed in patients treated by either SC or IV routes of administration and occurred predominantly in CRF patients.

Chronic Renal Failure Patients

EPOGEN® is generally well-tolerated. The adverse events reported are frequent sequelae of CRF and are not necessarily attributable to EPOGEN® therapy. In double-blind, placebo-controlled studies involving over 300 patients with CRF, the events reported in greater than 5% of patients treated with EPOGEN® during the blinded phase were:

Percent of Patients Reporting Event

Event	Patients Treated With EPOGEN® (n = 200)	Placebo-treated Patients (n = 135)
Hypertension	24%	19%
Headache	16%	12%
Arthralgias	11%	6%
Nausea	11%	9%
Edema	9%	10%
Fatigue	9%	14%
Diarrhea	9%	6%
Vomiting	8%	5%
Chest Pain	7%	9%
Skin Reaction (Administration Site)	7%	12%
Asthenia	7%	12%
Dizziness	7%	13%
Clotted Access	7%	2%

Significant adverse events of concern in patients with CRF treated in double-blind, placebo-controlled trials occurred in the following percent of patients during the blinded phase of the studies:

Seizure	1.1%	1.1%
CVA/TIA	0.4%	0.6%
MI	0.4%	1.1%
Death	0%	1.7%

In the US EPOGEN® studies in adult patients on dialysis (over 567 patients), the incidence (number of events per patient-year) of the most frequently reported adverse events were: hypertension (0.75), headache (0.40), tachycardia (0.31), nausea/vomiting (0.26), clotted vascular access (0.25), shortness of breath (0.14), hyperkalemia (0.11), and diarrhea (0.11). Other reported events occurred at a rate of less than 0.10 events per patient per year.

Events reported to have occurred within several hours of administration of EPOGEN® were rare, mild, and transient, and included injection site stinging in dialysis patients and flu-like symptoms such as arthralgias and myalgias.

In all studies analyzed to date, EPOGEN® administration was generally well-tolerated, irrespective of the route of administration.

Pediatric CRF Patients: In pediatric patients with CRF on dialysis, the pattern of most adverse events was similar to that found in adults. Additional adverse events reported during the double-blind phase in >10% of pediatric patients in either treatment group were: abdominal pain, dialysis access complications including access infections and peritonitis in those receiving peritoneal dialysis, fever, upper respiratory infection, cough, pharyngitis, and constipation. The rates are similar between the treatment groups for each event.

Hypertension: Increases in blood pressure have been reported in clinical trials, often during the first 90 days of therapy. On occasion, hypertensive encephalopathy and seizures have been observed in patients with CRF treated with EPOGEN®. When data from all patients in the US phase 3 multicenter trial were analyzed, there was an apparent trend of more reports of hypertensive adverse events in patients on dialysis with a faster rate of rise of hematocrit (greater than 4 hematocrit points in any 2-week period). However, in a double-blind, placebo-controlled trial, hypertensive adverse events were not reported at an increased rate in the group treated with EPOGEN® (150 Units/kg TIW) relative to the placebo group.

Seizures: There have been 47 seizures in 1010 patients on dialysis treated with EPOGEN® in clinical trials, with an exposure of 986 patient-years for a rate of approximately 0.048 events per patient-year. However, there appeared to be a higher rate of seizures during the first 90 days of therapy (occurring in approximately 2.5% of patients) when compared to subsequent 90-day periods. The baseline incidence of seizures in the untreated dialysis population is difficult to determine; it appears to be in the range of 5% to 10% per patient-year.[39-41]

Thrombotic Events: In clinical trials where the maintenance hematocrit was 35 ± 3% on EPOGEN®, clotting of the vascular access (A-V shunt) has occurred at an annualized rate of about 0.25 events per patient-year, and other thrombotic events (eg, myocardial infarction, cerebral vascular accident, transient ischemic attack, and pulmonary embolism) occurred at a rate of 0.04 events per patient-year. In a separate study of 1111 untreated dialysis patients, clotting of the vascular access occurred at a rate of 0.50 events per patient-year. However, in CRF patients on hemodialysis who also had clinically evident ischemic heart disease or congestive heart failure, the risk of A-V shunt thrombosis was higher (39% vs 29%, $p < 0.001$), and myocardial infarctions, vascular ischemic events, and venous thrombosis were increased, in patients targeted to a hematocrit of 42 ± 3% compared to those maintained at 30 ± 3% (see WARNINGS).

In patients treated with commercial EPOGEN®, there have been rare reports of serious or unusual thrombo-embolic events including migratory thrombophlebitis, microvascular thrombosis, pulmonary embolus, and thrombosis of the retinal artery, and temporal and renal veins. A causal relationship has not been established.

Allergic Reactions: There have been no reports of serious allergic reactions or anaphylaxis associated with EPOGEN® administration during clinical trials. Skin rashes and urticaria have been observed rarely and when reported have generally been mild and transient in nature.

There have been rare reports of potentially serious allergic reactions including urticaria with associated respiratory symptoms or circumoral edema, or urticaria alone. Most reactions occurred in situations where a causal relationship could not be established. Symptoms recurred with rechallenge in a few instances, suggesting that allergic reactivity may occasionally be associated with EPOGEN® therapy. If an anaphylactoid reaction occurs, EPOGEN® should be immediately discontinued and appropriate therapy initiated.

Zidovudine-treated HIV-infected Patients

Adverse events reported in clinical trials with EPOGEN® in zidovudine-treated HIV-infected patients were consistent with the progression of HIV infection. In double-blind, placebo-controlled studies of 3 months duration involving approximately 300 zidovudine-treated HIV-infected patients, adverse events with an incidence of ≥ 10% in either patients treated with EPOGEN® or placebo-treated patients were:

	Percent of Patients Reporting Event	
Event	Patients Treated With EPOGEN® (n = 144)	Placebo-treated Patients (n = 153)
Pyrexia	38%	29%
Fatigue	25%	31%
Headache	19%	14%
Cough	18%	14%
Diarrhea	16%	18%
Rash	16%	8%
Congestion, Respiratory	15%	10%
Nausea	15%	12%
Shortness of Breath	14%	13%
Asthenia	11%	14%
Skin Reaction, Medication Site	10%	7%
Dizziness	9%	10%

In the 297 patients studied, EPOGEN® was not associated with significant increases in opportunistic infections or mortality.[25] In 71 patients from this group treated with EPOGEN® at 150 Units/kg TIW, serum p24 antigen levels did not appear to increase.[27] Preliminary data showed no enhancement of HIV replication in infected cell lines in vitro.[25]

Peripheral white blood cell and platelet counts are unchanged following EPOGEN® therapy.

Allergic Reactions: Two zidovudine-treated HIV-infected patients had urticarial reactions within 48 hours of their first exposure to study medication. One patient was treated with EPOGEN® and one was treated with placebo (EPOGEN® vehicle alone). Both patients had positive immediate skin tests against their study medication with a negative saline control. The basis for this apparent pre-existing hypersensitivity to components of the EPOGEN® formulation is unknown, but may be related to HIV-induced immunosuppression or prior exposure to blood products.

Seizures: In double-blind and open-label trials of EPOGEN® in zidovudine-treated HIV-infected patients, 10 patients have experienced seizures.[25] In general, these seizures appear to be related to underlying pathology such as meningitis or cerebral neoplasms, not EPOGEN® therapy.

Cancer Patients on Chemotherapy

Adverse experiences reported in clinical trials with EPOGEN® administered TIW in cancer patients were consistent with the underlying disease state. In double-blind, placebo-controlled studies of up to 3 months duration involving 131 cancer patients, adverse events with an incidence > 10% in either patients treated with EPOGEN® or placebo-treated patients were as indicated below:

Percent of Patients Reporting Event

Event	Patients Treated With EPOGEN® (n = 63)	Placebo-treated Patients (n = 68)
Pyrexia	29%	19%
Diarrhea	21%*	7%
Nausea	17%*	32%
Vomiting	17%	15%
Edema	17%*	1%
Asthenia	13%	16%
Fatigue	13%	15%
Shortness of Breath	13%	9%
Parasthesia	11%	6%
Upper Respiratory Infection	11%	4%
Dizziness	5%	12%
Trunk Pain	3%*	16%

* Statistically significant

Although some statistically significant differences between patients being treated with EPOGEN® and placebo-treated patients were noted, the overall safety profile of EPOGEN® appeared to be consistent with the disease process of advanced cancer. During double-blind and subsequent open-label therapy in which patients (n = 72 for total exposure to EPOGEN®) were treated for up to 32 weeks with doses as high as 927 Units/kg, the adverse experience profile of EPOGEN® was consistent with the progression of advanced cancer.

Three hundred thirty-three (333) cancer patients enrolled in a placebo-controlled double-blind trial utilizing Weekly dosing with EPOGEN® for up to 4 months were evaluable for adverse events. The incidence of adverse events was similar in both the treatment and placebo arms.

Surgery Patients

Adverse events with an incidence of ≥ 10% are shown in the following table:

	Percent of Patients Reporting Event				
Event	Patients Treated With EPOGEN® 300 U/kg (n = 112)[a]	Patients Treated With EPOGEN® 100 U/kg (n = 101)[a]	Placebo-treated Patients (n = 103)[a]	Patients Treated With EPOGEN® 600 U/kg (n = 73)[b]	Patients Treated With EPOGEN® 300 U/kg (n = 72)[b]
Pyrexia	51%	50%	60%	47%	42%
Nausea	48%	43%	45%	45%	58%
Constipation	43%	42%	43%	51%	53%
Skin Reaction, Medication Site	25%	19%	22%	26%	29%
Vomiting	22%	12%	14%	21%	29%
Skin Pain	18%	18%	17%	5%	4%
Pruritus	16%	16%	14%	14%	22%
Insomnia	13%	16%	13%	21%	18%
Headache	13%	11%	9%	10%	19%
Dizziness	12%	9%	12%	11%	21%
Urinary Tract Infection	12%	3%	11%	11%	8%
Hypertension	10%	11%	10%	5%	10%
Diarrhea	10%	7%	12%	10%	6%
Deep Venous Thrombosis	10%	3%	5%	0%[c]	0%[c]
Dyspepsia	9%	11%	6%	7%	8%
Anxiety	7%	2%	11%	11%	4%
Edema	6%	11%	8%	11%	7%

[a] Study including patients undergoing orthopedic surgery treated with EPOGEN® or placebo for 15 days

[b] Study including patients undergoing orthopedic surgery treated with EPOGEN® 600 Units/kg weekly x 4 or 300 Units/kg daily x 15

[c] Determined by clinical symptoms

Thrombotic/Vascular Events: In three double-blind, placebo-controlled orthopedic surgery studies, the rate of deep venous thrombosis (DVT) was similar among Epoetin alfa and placebo-treated patients in the recommended population of patients with a pretreatment hemoglobin of > 10 g/dL to ≤ 13 g/dL.[18,20,28] However, in 2 of 3 orthopedic surgery studies the overall rate (all pretreatment hemoglobin groups combined) of DVTs detected by postoperative ultrasonography and/or surveillance venography was higher in the group treated with Epoetin alfa than in the placebo-treated group (11% vs 6%). This finding was attributable to the difference in DVT rates observed in the subgroup of patients with pretreatment hemoglobin > 13 g/dL. However, the incidence of DVTs was within the range of that reported in the literature for orthopedic surgery patients.

In the orthopedic surgery study of patients with pretreatment hemoglobin of > 10 g/dL to ≤ 13 g/dL which compared two dosing regimens (600 Units/kg weekly x 4 and 300 Units/kg daily x 15), 4 subjects in the 600 Units/kg weekly EPOGEN® group (5%) and no subjects in the 300 Units/kg daily group had a thrombotic vascular event during the study period.[19]

In a study examining the use of Epoetin alfa in 182 patients scheduled for coronary artery bypass graft surgery, 23% of patients treated with Epoetin alfa and 29% treated with placebo experienced thrombotic/vascular events. There were 4 deaths among the Epoetin alfa-treated patients that were associated with a thrombotic/vascular event. A causative role of Epoetin alfa cannot be excluded (see WARNINGS).

OVERDOSAGE

The maximum amount of EPOGEN® that can be safely administered in single or multiple doses has not been determined. Doses of up to 1500 Units/kg TIW for 3 to 4 weeks have been administered to adults without any direct toxic effects of EPOGEN® itself.[6] Therapy with EPOGEN® can result in polycythemia if the hemoglobin is not carefully monitored and the dose appropriately adjusted. If the suggested target range is exceeded, EPOGEN® may be temporarily withheld until the hemoglobin returns to the suggested target range; EPOGEN® therapy may then be resumed using a lower dose (see DOSAGE AND ADMINISTRATION). If polycythemia is of concern, phlebotomy may be indicated to decrease the hemoglobin.

DOSAGE AND ADMINISTRATION

Chronic Renal Failure Patients

The recommended range for the starting dose of EPOGEN® is 50 to 100 Units/kg TIW for adult patients. The recommended starting dose for pediatric CRF patients on dialysis is 50 Units/kg TIW. The dose of EPOGEN® should be reduced as the hemoglobin approaches 12 g/dL or increases by more than 1 g/dL in any 2-week period. The dosage of EPOGEN® must be individualized to maintain the hemoglobin within the suggested target range. At the physician's discretion, the suggested target hemoglobin range may be expanded to achieve maximal patient benefit.

EPOGEN® may be given either as an IV or SC injection. In patients on hemodialysis, EPOGEN® usually has been administered as an IV bolus TIW. While the administration of EPOGEN® is independent of the dialysis procedure, EPOGEN® may be administered into the venous line at the end of the dialysis procedure to obviate the need for additional venous access. In adult patients with CRF not on dialysis, EPOGEN® may be given either as an IV or SC injection.

Patients who have been judged competent by their physicians to self-administer EPOGEN® without medical or other supervision may give themselves either an IV or SC injection. The table below provides general therapeutic guidelines for patients with CRF:

Starting Dose:

Adults	50 to 100 Units/kg TIW; IV or SC
Pediatric Patients	50 Units/kg TIW; IV or SC
Reduce Dose When:	1. Hgb approaches 12 g/dL or, 2. Hgb increases > 1 g/dL in any 2-week period
Increase Dose If:	Hgb does not increase by 2 g/dL after 8 weeks of therapy, and hgb is below suggested target range
Maintenance Dose:	Individually titrate
Suggested Target Hgb Range:	10 g/dL to 12 g/dL

During therapy, hematological parameters should be monitored regularly (see LABORATORY MONITORING).

Pretherapy Iron Evaluation: Prior to and during EPOGEN® therapy, the patient's iron stores, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Transferrin saturation should be at least 20%, and ferritin should be at least 100 ng/mL. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels that will adequately support erythropoiesis stimulated by EPOGEN®.

Dose Adjustment: The dose should be adjusted for each patient to achieve and maintain a target hemoglobin not to exceed 12 g/dL.

Increases in dose should not be made more frequently than once a month. If the hemoglobin is increasing and approaching 12 g/dL, the dose should be reduced by approximately 25%. If the hemoglobin continues to increase, dose should be temporarily withheld until the hemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. If the hemoglobin increases by more than 1 g/dL in a 2-week period, the dose should be decreased by approximately 25%.

If the increase in the hemoglobin is less than 1 g/dL over 4 weeks and iron stores are adequate (see PRECAUTIONS: Laboratory Monitoring), the dose of EPOGEN® may be increased by approximately 25% of the previous dose. Further increases may be made at 4-week intervals until the specified hemoglobin is obtained.

Maintenance Dose: The maintenance dose must be individualized for each patient on dialysis. In the US phase 3 multicenter trial in patients on hemodialysis, the median maintenance dose was 75 Units/kg TIW, with a range from 12.5 to 525 Units/kg TIW. Almost 10% of the patients required a dose of 25 Units/kg, or less, and approximately 10% of the patients required more than 200 Units/kg TIW to maintain their hematocrit in the suggested target range. In pediatric hemodialysis and peritoneal dialysis patients, the median maintenance dose was 167 Units/kg/week (49 to 447 Units/kg per week) and 76 Units/kg per week (24 to 323 Units/kg/week) administered in divided doses (TIW or BIW), respectively to achieve the target range of 30% to 36%.

If the hemoglobin remains below, or falls below, the suggested target range, iron stores should be re-evaluated. If the transferrin saturation is less than 20%, supplemental iron should be administered. If the transferrin saturation is greater than 20%, the dose of EPOGEN® may be increased. Such dose increases should not be made more frequently than once a month, unless clinically indicated, as the

esponse time of the hemoglobin to a dose increase can be 2 to 6 weeks. Hemoglobin should be measured twice weekly for 2 to 6 weeks following dose increases. In adult patients with CRF not on dialysis, the maintenance dose must also be individualized. EPOGEN® doses of 75 to 150 Units/kg/week have been shown to maintain hematocrits of 36% to 38% for up to 6 months.

Lack or Loss of Response: Over 95% of patients with CRF responded with clinically significant increases in hematocrit, and virtually all patients were transfusion-independent within approximately 2 months of initiation of EPOGEN® therapy.

If a patient fails to respond or maintain a response, other etiologies should be considered and evaluated as clinically indicated (see PRECAUTIONS: LACK OR LOSS OF RESPONSE).

Zidovudine-treated HIV-infected Patients
Prior to beginning EPOGEN®, it is recommended that the endogenous serum erythropoietin level be determined (prior to transfusion). Available evidence suggests that patients receiving zidovudine with endogenous serum erythropoietin levels > 500 mUnits/mL are unlikely to respond to therapy with EPOGEN®.

Starting Dose: For adult patients with serum erythropoietin levels ≤ 500 mUnits/mL who are receiving a dose of zidovudine ≤ 4200 mg/week, the recommended starting dose of EPOGEN® is 100 Units/kg as an IV or SC injection TIW for 8 weeks. For pediatric patients, see PRECAUTIONS: PEDIATRIC USE.

Increase Dose: During the dose adjustment phase of therapy, the hemoglobin should be monitored weekly. If the response is not satisfactory in terms of reducing transfusion requirements or increasing hemoglobin after 8 weeks of therapy, the dose of EPOGEN® can be increased by 50 to 100 Units/kg TIW. Response should be evaluated every 4 to 8 weeks thereafter and the dose adjusted accordingly by 50 to 100 Units/kg increments TIW. If patients have not responded satisfactorily to an EPOGEN® dose of 300 Units/kg TIW, it is unlikely that they will respond to higher doses of EPOGEN®.

Maintenance Dose: After attainment of the desired response (ie, reduced transfusion requirements or increased hemoglobin), the dose of EPOGEN® should be titrated to maintain the response based on factors such as variations in zidovudine dose and the presence of intercurrent infectious or inflammatory episodes. If the hemoglobin exceeds 13 g/dL, the dose should be discontinued until the hemoglobin drops to 12 g/dL. The dose should be reduced by 25% when treatment is resumed and then titrated to maintain the desired hemoglobin.

Cancer Patients on Chemotherapy
Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to EPOGEN® therapy, treatment of patients with grossly elevated serum erythropoietin levels (eg, > 200 mUnits/mL) is not recommended. The hemoglobin should be monitored on a weekly basis in patients receiving EPOGEN® therapy until hemoglobin becomes stable. The dose of EPOGEN® should be titrated to maintain the desired hemoglobin.

Two EPOGEN® dosing regimens may be used in adults; 150 Units/kg SC TIW or 40,000 Units SC Weekly. For pediatric patients, see PRECAUTIONS: PEDIATRIC USE.

TIW Dosing
tarting Dose:

Adults	150 Units/kg SC TIW
Pediatric Patients	See PRECAUTIONS: Pediatric Use

Reduce Dose by 25% when:	1. Hgb approaches 12 g/dL or, 2. Hgb increases > 1 g/dL in any 2-week period
Withhold Dose if:	Hgb exceeds 13 g/dL, until the hemoglobin falls to 12 g/dL, and restart dose at 25% below the previous dose

Increase Dose to 300 Units/kg TIW if: response is not satisfactory [no reduction in transfusion requirements or rise in hemoglobin] after 8 weeks

Suggested Target Hgb Range: 10 g/dL to 12 g/dL

During therapy, hematological parameters should be monitored regularly (see PRECAUTIONS: Laboratory Monitoring).

Weekly Dosing

- The starting dose in adults is 40,000 Units SC Weekly. If after 4 weeks of therapy, the hemoglobin has not increased by ≥ 1 g/dL, in the absence of RBC transfusion, the EPOGEN® dose should be increased to 60,000 Units Weekly.
- If patients have not responded satisfactorily to an EPOGEN® dose of 60,000 Units Weekly after 4 weeks, it is unlikely that they will respond to higher doses of EPOGEN®.
- EPOGEN® should be withheld if the hemoglobin exceeds 13 g/dL and reinitiated with a 25% dose reduction when the hemoglobin is less than 12 g/dL.
- If EPOGEN® treatment produces a very rapid hemoglobin response (e.g., an increase of more than 1 g/dL in any 2-week period), the dose of EPOGEN® should be reduced by 25%.

Surgery Patients

Prior to initiating treatment with EPOGEN® a hemoglobin should be obtained to establish that it is > 10 to ≤ 13 g/dL.[18] The recommended dose of EPOGEN® is 300 Units/kg/day subcutaneously for 10 days before surgery, on the day of surgery, and for 4 days after surgery.

An alternate dose schedule is 600 Units/kg EPOGEN® subcutaneously in once weekly doses (21, 14, and 7 days before surgery) plus a fourth dose on the day of surgery.[19]

All patients should receive adequate iron supplementation. Iron supplementation should be initiated no later than the beginning of treatment with EPOGEN® and should continue throughout the course of therapy.

PREPARATION AND ADMINISTRATION OF EPOGEN®

1. Do not shake. It is not necessary to shake EPOGEN®. Prolonged vigorous shaking may denature any glycoprotein, rendering it biologically inactive.

2. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.

3. Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the vial containing EPOGEN®, and wipe the septum with a disinfectant. Insert the needle into the vial, and withdraw into the syringe an appropriate volume of solution.

4. **Single-dose:** 1 mL vial contains no preservative. Use one dose per vial; do not re-enter the vial. Discard unused portions.

   Multidose: 1 mL and 2 mL vials contain preservative. Store at 2° to 8° C after initial entry and between doses. Discard 21 days after initial entry.

5. Do not dilute or administer in conjunction with other drug solutions. However, at the time of SC administration, preservative-free EPOGEN® from single-use vials may be admixed in a syringe with bacteriostatic 0.9% sodium chloride injection, USP, with benzyl alcohol 0.9% (bacteriostatic saline) at a 1:1 ratio using aseptic technique. The benzyl alcohol in the bacteriostatic saline acts as a local anesthetic which may ameliorate SC injection site discomfort. Admixing is not necessary when using the multidose vials of EPOGEN® containing benzyl alcohol.

HOW SUPPLIED

EPOGEN®, containing Epoetin alfa, is available in the following packages:

1 mL **Single-dose, Preservative-free** Solution
- 2000 Units/mL (NDC 55513-126-10)
- 3000 Units/mL (NDC 55513-267-10)
- 4000 Units/mL (NDC 55513-148-10)
- 10,000 Units/mL (NDC 55513-144-10)
- 40,000 Units/mL (NDC 55513-823-10)

Supplied in dispensing packs containing 10 single-dose vials.

mL **Multidose, Preserved** Solution
- 10,000 Units/mL (NDC 55513-283-10)

1 mL **Multidose, Preserved** Solution
- 20,000 Units/mL (NDC 55513-478-10)

Supplied in dispensing packs containing 10 multidose vials.

STORAGE

Store at 2° to 8 ° C (36 ° to 46 ° F). Do not freeze or shake.

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Manufactured by:
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3XXXXXX – VXX

Issue Date: XX/XX/XX

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103234s5053

MEDICAL REVIEW

Clinical Review

Date: June 13, 2004

Type: s-BLA

STN: 103234/5053

Product: Epogen/Procrit

Sponsor: Amgen

Kaushik A. Shastri, M.D.
CDER/ODE VI/DTBOP

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Director, CDER/ODE VI/DTBOP

MaPP VERSION
3-12-03

Primary Clinical Review

Cover Sheet

Submission Type:	s-BLA
Submission Number	STN 103234/5053
Letter Date	August 29, 2003
Stamp Date	September 4, 2003
Review Completion Date:	June 13, 2003
Established Name:	Epoetin alfa
Trade Name :	Epogen, Procrit
Therapeutic Class	
Sponsor	Amgen Inc.
Priority Designation (S or P)	S

Sponsor's Proposed:

Formulation:	sterile, colorless liquid in isotonic sodium chloride/sodium citrate buffered solution or a sodium chloride/sodium phosphate buffered solution for intravenous (IV) or subcutaneous administration; strengths 2000, 3000, 4000, 10000, 20000, 40000 Units/mL
Dosing Regimen	40,000 Units SC weekly
Indication	treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy
Intended Population:	anemic cancer patients on chemotherapy

Table of Contents

1.0 Executive Summary

Recommendation on Clinical Approvability

Based on the review of this supplemental BLA. I recommend approval of the sponsor proposed alternative weekly dosing of Epogen/Procrit for treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. This recommendation is based on the results of a multicenter double-blinded placebo controlled trial (PR98-27-008) enrolling 344 anemic cancer patients undergoing chemotherapy who were randomized to Epogen/Procrit 40,000 IU/week (n=174) or placebo (n=170) SC for a planned treatment period of 16 weeks. If hemoglobin had not increased by > 1 g/dL, after 4 weeks of therapy or the patient received an RBC transfusion during the first 4 weeks of therapy, study drug was increased to 60,000 IU/week. Forty-three percent of patients in the Epoetin alfa group required an increase in their dose to 60,000 IU weekly. Results demonstrated that Epogen/Procrit therapy reduced the proportion of patients transfused in day 29 through week 16 of the study as compared to placebo. Twenty-five patients (14%) in the Epogen/Procrit group received transfusions compared to 48 patients (28%) in the placebo group (p=0.0010) between day 29 and week 16 or the last day on study. The safety data from this study were comparable between the placebo and the treatment arm. In addition, the sponsor also conducted pharmacokinetics/pharmacodynamic study, which showed although serum levels of erythropoietin were higher with the 40,000 IU weekly dosing regimen as compared to the 150 IU/kg three times/week regimen, the two regimens produced similar pharmacodynamic responses, i.e., changes in percent reticulocytes, hemoglobin, and red cells.

Review of Literature suggests frequent use of once weekly dosing in clinical practice. It is possible that a 3 times-per-week dosing regimen is inconvenient in many patient populations, including oncology patients, largely because of shift in medical practice towards outpatient management of patients. A major benefit of once-a-week dosing would be to reduce the frequency of injections and thereby improve compliance. The published studies also bolster the argument that once weekly dosing of epoetin alfa is safe and effective.

1.2 Recommendation on Postmarketing Actions

The specific post-marketing studies deemed necessary for this particular supplement are the pediatric usage studies. The sponsor has already agreed to perform post-marketing studies and devise risk management strategy related to increased thrombotic events and potential for tumor growth for another related and recently approved supplement STN 103234/5033.

1.3 Summary of Clinical Findings

1.3.1 Overview of Clinical Review

The data regarding safety and efficacy of alternative once weekly dosing are primarily and exclusively derived from [redacted] PR98-27-008, which was a Phase 3 placebo-controlled trial in 344 cancer patients receiving chemotherapy and has been reviewed in detail in the subsequent sections.

The submission also includes another clinical study EPO-CA-480 that is listed as supportive study. This study, discontinued due to slow enrollment, was an open label study that compared no treatment (control group, n=11) with epoetin alfa for 12 weeks administered in the following

regimens: 150 IU/kg t.i.w (n=9), 300 IU/kg q.w.(n=5), 450 IU/kg q.w.(n=10), 600 IU/kg q.w. (n=9), and 900 IU/kg q.w. (n=10), in subjects with cancer who were receiving platinum-containing chemotherapy for the treatment of solid tumors. Because of the small sample size, data analysis was relegated to descriptive statistics and no meaningful conclusions can be drawn from this study.

The pharmacokinetics/pharmacodynamic data are derived from study EPO-PHI-377, which was a Phase 1 pharmacokinetic/pharmacodynamic study to compare once-weekly and three-times weekly dosing in anemic cancer patients as well as in healthy volunteers. Safety data in this small population of cancer patients in the study (n=15 Epoetin alfa 150 units/kg 3 times/week for six weeks; n=18 Epoetin alfa 40,000 units weekly for 6 weeks) were also provided which have been included in this review in section 6.2. A supportive pharmacokinetic/pharmacodynamic study (EPO-PHI-370) was also included in the submission. In depth review of both these PK/PD studies can be found in Dr. Hong Zhao's clinical pharmacology review and is not included here.

1.3.2 Efficacy

The randomized study PR-98-008 provides statistical support for the sponsor's efficacy claim. The primary efficacy analysis was based on the difference in proportions transfused in the ITT population. The pre-specified non-responder (worst outcome) imputation analysis of subjects receiving RBC transfusions after treatment Day 28 until individual study end (i.e., subjects who withdrew from the study after Day 28, with no transfusion after Day 28, were imputed as transfused for purposes of analysis) yielded an estimated difference of –9.8% favoring the Epoetin alfa group which reached borderline statistical significance (p=0.069, Chi square test; p=0.071, adjusted logistic regression analysis). The sponsor presented a rationale that indicated that using non-responder imputation biased results against the Epoetin alfa treatment arm. This reviewer agrees with the sponsor's rationale described in section 3.3.2. Five additional imputation analyses, previously discussed with the FDA, yielded estimated rate differences that consistently favored the Epoetin alfa group over the placebo group (range: -10% to –16%); all of these differences were statistically significant ($p < 0.05$). In addition to the primary endpoint described above, the mean number of RBC units transfused/subject in the placebo group (1.5 units) was approximately twice that in the Epoetin alfa group (0.7 units). The mean number of units transfused/100 subject-days was statistically significantly lower in the Epoetin alfa group ($p < 0.0001$). There was a marked difference in hemoglobin response, favoring the Epoetin alfa group.

1.3.3 Safety

The safety findings in the pivotal trial PR98-008, which was a randomized double blinded placebo controlled trial, showed that the safety profile in the treatment arm was comparable to the placebo group. Specifically, the survival experience was similar in the two study arms. Although there were more subjects with thrombotic vascular events (TVE's) in the Epoetin alfa group than in the placebo group (i.e., 10 vs.6), examination of TVE occurrences in relation to hemoglobin increases did not reveal any consistent findings suggesting a relationship between the rate of hemoglobin rise and the occurrence of TVE's, although exploration of this relationship was hampered by the limited schedule of hemoglobin measurements in the study.

1.3.4 Dosing, Regimen, and Administration

Epogen/ Procrit is already approved for three times/week dosing. Under this supplement, it can also be used in the following manner. The starting dose is 40,000 units per week. If after 4

weeks of therapy, the hemoglobin has not increased by ≥ 1 g/dL, in the absence of RBC transfusion, the Epogen/Procrit dose should be increased to 60,000 IU/week. If patients have not responded satisfactorily to a dose of 60,000 Units weekly after 4 weeks, it is unlikely that they will respond to higher doses. Epogen/Procrit should be withheld if the hemoglobin exceeds 13 g/dL and reinitiated with a 25% dose reduction when the hemoglobin is less than 12 g/dL. If Epogen/Procrit treatment produces a very rapid hemoglobin response (e.g., an increase of more than 1.3 g/dL in any 2-week period), the dose should be reduced by 25%.

1.3.5 Drug-Drug Interactions

The sponsor has not provided data on drug-drug interactions in this application.

1.3.6 Special Populations

The sponsor has requested a deferral for Pediatric studies. There were no gender or age specific findings related to the safety and efficacy of Epogen/Procrit in this application.

2.0 Background

2.1 Clinical Context of Application

EPOGEN/PROCRIT (epoetin alfa) when used three times/week is currently indicated for the treatment of anemia in cancer patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. It decreases the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of 2 months.

The current Biologic License Application (sBLA) is to obtain a dosing-regimen alternative to that which is currently approved for the indication described above. The current U.S. labeling recommends a starting dose of 150 Units/kg of EPOGEN/PROCRIT subcutaneously administered 3 times per week (t.i.w.), with an increase in dose up to 300 Units/kg t.i.w if the response is not satisfactory in terms of reducing transfusion requirements or increasing hematocrit after 8 weeks of therapy. In the alternative dosing regimen, the starting dose would be 40,000 IU subcutaneously (s.c.) administered once a week (q.w.), with an increase to 60,000 IU q.w. if hemoglobin has not increased by at least 1g/dL after 4 weeks of therapy.

The rationale for developing the weekly dosing schedule is the ease of administration of the product compared to the current three times a week regimen and subsequent reduction of visits by the sick cancer patients to their health care providers.

In addition to providing the pharmcokinetic/pharmacodynamic and clinical studies included with this application, the sponsor has provided extensive literature references of studies in cancer patients and in patients without cancer that show effectiveness and safety of this weekly dosing approach.

2.2 Pre-submission Activity

The sponsor sought FDA guidance and agreement on the clinical development plan for this submission which included the two types of studies to support once-weekly epoetin alfa dosing in anemic cancer patients receiving chemotherapy. Agreement on the design of the Phase 1 pharmacokinetic/ pharmacodynamic study, comparing once-weekly and three-times weekly dosing in anemic cancer patients as well as in healthy volunteers was reached between the FDA and the sponsor in a teleconference on January 31, 2001.

At a teleconference on September 18, 2001, the Company sought guidance from the Agency on the use of a double-blind, placebo-controlled study conducted by [redacted] as the pivotal Phase III study. The protocol number assigned to that trial by the Company was PR98-27-008. This study was originally designed as a Quality of Life (QoL) study; however, a secondary objective of the protocol was to assess transfusion requirements during treatment. Therefore, it was possible that the transfusion data, together with other data from the study, could reveal if a single weekly s.c. dose of epoetin alfa (40,000 IU with the potential for dose escalation to 60,000 IU) is effective in treating anemia in cancer patients receiving chemotherapy. As a result of discussions between the sponsor and the FDA, data from the [redacted] Study PR98-27-008 were deemed potentially acceptable to support a change in the EPOGEN/PROCRIT prescribing label to allow for an alternative regimen of epoetin alfa utilizing 40,000 IU once-a-week dosing in anemic cancer patients. For purposes of the submission, the primary endpoint would be the transfusion rate following 28 days of treatment, while QoL and other objectives in the [redacted] protocol would be considered secondary endpoints.

A statistical analysis plan, with the primary endpoint of transfusion rate after Day 28, prepared by the sponsor in collaboration with [redacted] investigators, was submitted to the FDA on February 27, 2002. On April 11, 2002, the sponsor, the [redacted] research team, and the FDA discussed and finalized the statistical analysis plan. After several clarifications, the plan was found acceptable to the Agency on April 16, 2002. The final statistical analysis plan was sent to the Agency on August 16, 2002.

A pre-BLA meeting was conducted between the sponsor and the FDA on May 20,2003 during which the details on the contents and format of the current sBLA submission were discussed and agreed upon.

3 Integrated Review of Clinical Data

3.1 Data Sources and Review Method

The data regarding safety and efficacy of alternative once weekly dosing are derived from [redacted] Study PR98-27-008, which was a Phase 3 placebo-controlled trial in 344 cancer patients receiving chemotherapy and has been reviewed in detail.

The submission also includes another clinical study EPO-CA-480 which is listed as supportive study. This study, discontinued due to slow enrollment, was an open label study that compared no treatment (control group, n=11) with epoetin alfa for 12 weeks administered in the following regimens: 150 IU/kg t.i.w (n=9), 300 IU/kg q.w.(n=5), 450 IU/kg q.w.(n=10), 600 IU/kg q.w. (n=9), and 900 IU/kg q.w. (n=10), in subjects with cancer who were receiving platinum-containing chemotherapy for the treatment of solid tumors. Because of the small sample size, data analysis was relegated to descriptive statistics and no meaningful conclusions can be drawn from this study.

The pharmacokinetics/pharmacodynamic data are derived from study EPO-PHI-377, which was a Phase 1 pharmacokinetic/pharmacodynamic study to compare once-weekly and three-times weekly dosing in anemic cancer patients as well as in healthy volunteers. Safety data in this small population of patients in the study were also provided which have been included in this review in section 6.1. A supportive pharmacokinetic/pharmacodynamic study (EPO-PHI-370) was also included in the submission. In depth review of both these PK/PD studies can be found in Dr. Hong Zhao's clinical pharmacology review.

3.2 Clinical Pharmacology

Please see Dr. Hong Zhao's detailed review of the PK/PD studies. The following is the relevant summary conclusions from her detailed review:
The results of Phase 1 studies EPO-PHI-377 and EPO-PHI-370 indicate that, although serum levels of erythropoietin were higher with the 40,000 IU q.w. dosing regimen as compared to the 150 IU/kg t.i.w. regimen, the two regimens produced similar pharmacodynamic responses, i.e., changes in percent reticulocytes, hemoglobin, and RBCs.

3.3 Integrated Review of Efficacy

3.3.1 Approach to Review of the Efficacy

For discussion on data sources, please see section 3.1

The efficacy data to support the use of alternative weekly regimen of Epogen/Procrit in anemic cancer patients on chemotherapy was derived from a single Phase III placebo controlled trial PR-98-008.

The primary objective of the study, as stated in the protocol, was to assess the effect of a single weekly dose of epoetin alfa on the quality of life (QOL) in cancer patients undergoing chemotherapy. The study, which was double-blind and placebo-controlled, utilized a single weekly s.c. dose of 40,000 IU of PROCRIT® epoetin alfa, which could be increased to 60,000 IU in subjects who did not show an adequate hemoglobin response. The maximum duration of treatment was 16 weeks.

Although originally designed by the [redacted] research group as a QoL study; a secondary objective of the protocol was to assess transfusion requirements during treatment. Hence, it was possible that that the transfusion data, together with other data from the study, could reveal if a single weekly s.c. dose of epoetin alfa, at 40,000 to 60,000 IU, is effective in treating anemia in cancer patients receiving chemotherapy. Therefore, prior to completion of the study, discussions were held between the FDA and the sponsor concerning the feasibility of using results from Study PR98-27-008 to support a change in epoetin alfa labeling to allow once-a-week dosing in cancer patients. For purposes of the submission, the primary endpoint was considered to be the transfusion rate following 28 days of treatment, while QoL and other objectives in the [redacted] protocol were considered as secondary endpoints.

Measuring the efficacy of erythropoietin in terms of reduction in transfusion rate is appropriate since it measures a tangible benefit to the cancer patient receiving chemotherapy. Following exogenous erythropoietin administration, a clinically significant increase in hemoglobin is usually not observed in less than 2 weeks and may require up to 6 weeks because of the length of time required for erythropoiesis- several days for erythroid progenitors to mature and be released in the circulation. Hence the endpoint of measuring transfusion requirement after 28 days is also appropriate. The registration trials of currently approved three times per week dosing schedule of Epogen/Procrit also used assessment of proportion of patients transfused during month 2 and 3 in comparison to placebo as an end point.

The secondary end points for the purposes of this submission included number of

units transfused, change in hemoglobin concentrations from baseline, hemoglobin over time, incidence of hemoglobin concentrations below 9.0 g/dL, predictors of response to Epoetin alfa treatment, incidence of nephrotoxicity in subjects receiving chemotherapy containing cis-platinum, overall survival, tumor response, and quality of life measurements.

3.3.2 Review of Trials by Indication

The efficacy evaluation for the alternative weekly dosing of EPOGEN/PROCRIT was based on the pivotal Phase III placebo controlled trial (Study PR-98-27-008). Detailed description of the trial is provided in section 6.1 of this document. What follows is a brief description of this trial and a detailed description and analysis of the efficacy endpoints.

Study PR-98-27-008 was a multi-center, randomized, double-blinded, placebo-controlled study conducted [redacted] in the North Central United States and Saskatchewan, Canada. The planned enrolment was 330 subjects with anemia who were receiving myelosuppressive cytotoxic chemotherapy for advanced cancer. Eligible patients were randomized in a 1:1 ratio to Epoetin alfa or placebo treatment, with stratification by center (investigator), type of primary cancer (lung, breast, or other), planned concurrent radiation therapy (yes vs. no), and degree of anemia (hemoglobin < 9 g/dL vs. ≥ 9 g/dL). The double-blind treatment was administered for a maximum of 16 weeks, after which the subjects were followed for one year from the time of randomization for event monitoring (death, new primary malignancies, and long-term toxicities). The dose of double-blind study medication (40,000 IU of Epoetin alfa or corresponding placebo) was to be administered by s.c. injection, once weekly. If after 4 weeks of therapy hemoglobin (Hgb) concentrations had not increased by > 1 g/dL or if the subject had received a transfusion during the first 4 weeks of therapy, the weekly dose of study drug was to be increased to 60,000 IU once weekly. If, at any time during the study, the Hgb concentration exceeded 15 g/dL, Hgb was to be determined one week later. If the Hgb exceeded 15 g/dL, study drug was to be witheld and Hgb was to be determined weekly until it fell below 13 g/dL. Study drug was then to be restarted at a dose level 25% less than that previously administered. During double-blind treatment, subjects were to receive a daily oral iron supplement. All subjects could receive RBC transfusions at the discretion of the physician. A Hgb determination was to be obtained at the time of transfusion. Subjects who discontinued chemotherapy during the double-blind period were to continue the study treatment through 16 weeks.

Analyses Planned

Primary Efficacy Endpoint

The primary efficacy endpoint was the transfusion rate, defined as the proportion of subjects who required transfusions after 28 days from randomization, i.e., those occurring on or after Day 29 to individual study end. All subjects who withdrew prior to Week 16 without receiving a transfusion would be considered as transfused. The primary statistical inference for the transfusion rate was to be based on logistic regression analysis adjusted for the stratification factors (size of center, type of primary cancer, planned concurrent radiation therapy, and degree of anemia). Treatment effect was to be compared using the adjusted odds ratio obtained from the model along with the 95% confidence interval and the p-value. Unadjusted Chi-square tests based on crude transfusion rates and the difference in crude rates along with the 95% confidence interval would also be presented. In addition, exploratory analyses for the transfusion rate would be performed using logistic regression models.

Description of Secondary Variables:

Change in Hemoglobin (Hgb) Concentration from Baseline: The mean change in Hgb concentration from baseline to the last value was to be presented for the two treatment groups. Treatment effect was to be estimated by the difference in the means along with the 95% CI. Student's t-test was to be used to test the equality of the means between the two treatment groups. ANCOVA adjusting for other prognostic factors was to be performed also. The main analysis on change in Hgb was based on available data. Sensitivity analysis on change in Hgb from the baseline to last value was conducted by imputing missing values via the following methods: last-value-carry-forward (LOCF), minimum-value-carry forward (MVCF), and average-value-carry-forward (AVCF).

Hemoglobin (Hgb) over Time: Hgb concentrations over time were to be analyzed using a mixed effects linear model for repeated measures. Terms in the model included treatment, time, covariates for demographic and baseline characteristics, and the time-by-treatment interaction term. The focus of this analysis was to be the slope parameter of the time variable that quantifies the rate of Hgb rise over time. Slope estimates for the two treatment groups, the difference in the slopes, the 95% CI of the difference, and the p-value were to be reported.

Incidence of Hemoglobin (Hgb) Concentration below 9.0 g/dL: The proportions of subjects with a Hgb concentration below 9.0 g/dL were to be presented for each treatment group. Treatment effect was to be estimated by the difference in proportions along with the 95% CI. A Chi-square test was used to test for equality of the proportions between the two treatment groups.

Number of Transfusion Units per Day Alive in the Study: For each of the two treatment groups, the number of transfusion units per day alive during the entire study would be calculated. This variable is a ratio-type estimate, i.e., both its numerator and denominator are random variables. Hence, an approximation based on relative variances to the standard error of a ratio would be used to calculate the standard error of this estimate for each treatment group. Normal approximation would be used to conduct the statistical test on the difference of the estimates and to obtain the 95% CI.

Incidence of Nephrotoxicity: The relative incidence of nephrotoxicity was ascertained by the investigators' CTC rating of serum creatinine determined in the subset of subjects receiving cis-platinum-based chemotherapy. The incidence was to be presented for the two treatment groups and tested using Fisher's exact test. The maximum reported toxicity grade over the course of the study was to be compared between the two treatment groups using the Wilcoxon rank-sum test.

Overall Survival: For this time-to-event variable, a survival analysis was conducted which included a Kaplan-Meier plot and the comparison of the two treatment groups via the logrank test. Median survival time was reported along with logrank test results.

Tumor Response: A descriptive summary of the number and percentage of subjects in each of the tumor response categories would be provided for the two treatment groups.

Quality of Life (QOL): A number of QOL scales were used, e.g., FACT-Anemia, SDS (symptom distress scale), and the UNISCALE. Scores for these scales were to be standardized by transforming them to a range of 0 – 100, with 0 representing the lowest QOL and 100 representing the highest QOL. The scores would be summarized using descriptive statistics. Inferential statistical analyses were to be performed on the AUC of the transformed scales for all QOL endpoints. QOL assessment dates were to be used to calculate the AUC. For [redacted] primary QOL endpoint, FACT-AN Fatigue Scale. Treatment difference would be tested via the Wilcoxon Rank Sum test or the t-

test depending upon the veracity of normality assumptions as determined by the Shapiro-Wilk test. O'Brien's multiple endpoint test statistic would be applied to the numerous secondary QOL endpoints. ANCOVA on each QOL endpoint would be performed with and without treatment-by-covariate interaction terms. If significant treatment-by-covariate interaction was found to be present, further exploratory analyses on the corresponding subgroups would be conducted. Sensitivity analyses for each QOL scale would be conducted on the AUC endpoint, with missing data values imputed using the last-value-carried-forward (LVCF), the average-value-carried-forward (AVCF), and the minimum-value-carried-forward (MVCF) methods. A fourth sensitivity analysis would be conducted using the LVCF, but imputing a score of 0 when subjects died. In addition, an exploratory analysis of the correlation between changes in QOL and changes in Hgb would be presented using the Pearson correlation coefficient. Change in QOL was defined as the change from baseline to the last available assessment. The change in Hgb value used was the one most closely associated in time with the last available QOL assessment. The two change scores would be analyzed for correlation if any difference in day of measurement represented no more than a 15-day window. This analysis was to be based on combined data from the two treatment groups.

Determination of Sample Size: This study was powered originally for the QOL analyses and not for the transfusion rate analysis. Based on the QOL calculations, it was determined that a sample size of 300 (i.e., 150 subjects/treatment group) was required. Assuming a 10% attrition rate, a total of 330 subjects (165 per group) was planned. In terms of the transfusion rate, a sample size of 300 (150 per group) would provide 80% power to detect a difference of 16% or more between the two treatment groups. Standard two-sided binomial testing was assumed with a type I error rate of $\alpha = 0.05$.

Study Populations: The number of subjects actually enrolled was 344. In accord with [redacted] definitions, any subject who did not receive any study treatment before removal from the study was designated a "cancellation." However, these subjects were included in the ITT (intent-to-treat) population, which was the primary efficacy population. The QOL population consisted of all ITT subjects having a baseline and at least one follow-up QOL assessment. Selected efficacy analyses were also performed on the evaluable-for-efficacy population that included all treated subjects, excluding subjects classified as ineligible or as having major protocol violations. In addition to analyses with formal statistical inferences provided for the two treatment comparisons, descriptive statistics for specified efficacy variables were to be provided for the subgroups defined by the following variables: type of primary cancer, planned concurrent radiation therapy, degree of anemia, and planned chemotherapy type (cis-platinum based or non-cis-platinum based). All statistical tests were 2-sided. Main effects were tested at the.05 significance level; interaction terms were tested at the 0.10 significance level.

Efficacy Results:

Patient Disposition:

A total of 344 subjects were registered and randomized into the study at 14 [redacted] study centers (13 in the United States and 1 in Canada); these subjects comprise the ITT population. The first subject was enrolled on December 4, 1998, and the study was closed to further enrollment on September 28, 2001. Enrollment by center is presented in the table below. Enrollment at the "large" centers (see definition in Table 3) ranged from 8 to 72 subjects while enrollment at the "small" centers ranged from 2 to 42 subjects.

Table 1: Subject Enrollment by Center [redacted]

[redacted]nters[a]	Placebo (n=170)	Epoetin alfa (n=174)	Total (n=344)
[redacted]arge Centers, n (%)			
[redacted]	6 (4%)	5 (3%)	11 (3%)
[redacted]	28 (16%)	27 (16%)	55 (16%)
[redacted]	14 (8%)	13 (7%)	27 (8%)
[redacted]	9 (5%)	12 (7%)	21 (6%)
[redacted]	22 (13%)	21 (12%)	43 (13%)
[redacted]	36 (21%)	36 (21%)	72 (21%)
[redacted]	5 (3%)	3 (2%)	8 (2%)
Small Centers, n (%)			
[redacted]	20 (12%)	22 (13%)	42 (12%)
[redacted]	12 (7%)	12 (7%)	24 (7%)
[redacted]	5 (3%)	5 (3%)	10 (3%)
[redacted]	3 (2%)	6 (3%)	9 (3%)
[redacted]	5 (3%)	6 (3%)	11 (3%)
[redacted]	5 (3%)	4 (2%)	9 (3%)
[redacted]	0 (0%)	2 (1%)	2 (1%)

[a] Large centers were defined as [redacted] centers that entered at least 15 patients per month on all [redacted] studies over the 2-year period from April 2000 to April 2002

As can be seen in the table, the treatment assignment was balanced among study sites.

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Table 2: Demographic and Baseline Characteristics
(Study PR98-27-008: Intent-to-Treat Population)

	Placebo (N=170)	Epoetin Alfa (N=174)	Total (N=344)
Age (years)			
N	170	174	344
Mean (SD)	63.7	63.5 (11.80)	63.6 (12.43)
Median	66	64	66
Range	(24-86)	(20-88)	(20-88)
Sex, n (%)			
Female	96(56%)	96(55%)	192(56%)
Male	74(44%)	78(45%)	152(44%)
Race, n (%)			
Black	18(11%)	10(6%)	28(8%)
Hispanic	1(1%)	0(0%)	1(0%)
White	151(89%)	164(94%)	315(92%)
Weight (kg)			
N	161	161	322
Mean (SD)	73.6	75.0 (17.20)	74.3 (16.72)
Median	71.9	74.0	72.6
Range	(41.8 - 127.0)	(36.6 - 136.1)	(36.6 - 136.1)
Previous chemotherapy, n (%)			
No	82(48%)	79(45%)	161(47%)
Yes	88(52%)	95(55%)	183(53%)
Previous radiotherapy, n (%)			
No	108(64%)	109(63%)	217(63%)
Yes	62(36%)	65(37%)	127(37%)
Type of malignant disease, n (%)			
Lung	49(29%)	48(28%)	97(28%)
Breast	28(16%)	28(16%)	56(16%)
Other[1]	93(55%)	98(56%)	191(56%)
Planned concurrent radiation therapy, n (%)	17(10%)	18(10%)	35(10%)
No	153(90%)	156(90%)	309(90%)
Degree of anemia, n (%)			
Mild (Hb >-9.0 g/dL)	117(69%)	119(68%)	236(69%)
Severe (Hb <9.0 g/dL)	53(31%)	55(32%)	108(31%)
Baseline tumor response, n (%)			
Missing	1(1%)	1(1%)	2(1%)
Complete response	5(3%)	4(2%)	9(3%)
Partial response (measurable disease only)	19(11%)	22(13%)	41(12%)
Regression	19(11%)	26(15%)	45(13%)
Stable	93(55%)	93(53%)	186(54%)
Progression	4(2%)	7(4%)	11 (3%)
Not Applicable/Unknown	29(17%)	21(12%)	50(15%)
ECOG status, n (%)			
0	46(27%)	37(21%)	83(24%)
1	124(73%)	137(79%)	261(76%)
Iron supplement, n (%)			
Missing	3(2%)	1 (1%)	4(1%)
Yes	143(84%)	153(88%)	296(86%)
No	24(14%)	20(11%)	44(13%)

1 'The most common other cancer sites were gastrointestinal (60/344 subjects, 17%), myeloma (30/344 subjects,9%), and gynecological (29/344 subjects, 8%) see table below.

Table 3: Other Cancer Sites
(Study PR98-27-008: Intent-to-Treat Population)

	Placebo (N=170)	Epoetin Alfa (N=174)	Total (N=344)
Other Cancer Sites	n (%)[a]	n (%)[a]	n (%)[a]
CNS	2(2%)	0(0%)	2(1%)
GI	34(37%)	26(27%)	60(31%)
GU	5(5%)	12(12%)	17(9%)
GYN	15(16%)	14(14%)	29(15%)
Head and Neck	4(4%)	3(3%)	7(4%)
Lymph nodes	3(3%)	5(5%)	8(4%)
Myeloma	11(12%)	19(19%)	30(16%)
Other	14(15%)	10(10%)	24(13%)
Other endocrine glands	0(0%)	1 (1%)	1 (1%)
Respiratory/Other	0(0%)	1 (1%)	1 (1%)
Unknown/ill-defined sites	5(5%)	7(7%)	12(6%)

[a] Percentages shown are based on the number of subjects in this category (other cancer sites) and not on all subjects in the group.

The following table describes the baseline laboratory values:

Table 4: Baseline Laboratory Values
(Study PR98-27-008: Intent-to-Treat Population)

	Placebo (N=170)	Epoetin Alfa (N=174)	Total (N=344)
Hemoglobin (g/dL)			
N	170	174	344
Mean (SD)	9.4 (0.93)	9.5 (0.94)	9.4 (0.93)
Median	9.5	9.6	9.6
Range	(6.9-11.4)	(6.0-11.4)	(6.0-11.4)
White Blood Cell Count (xIO^9/L)			
N	169	173	342
Mean (SD)	5.6 (4.35)	6.3 (8.71)	6.0 (6.91)
Median	4.5	4.7	4.6
Range	(0.8-34.7)	(0.7 - 103.5)	(0.7 - 103.5)
Platelet Count (xIO^9/L)			
N	169	173	342
Mean (SD)	257.4 (168.36)	254.8 (160.60)	256.1 (164.24)
Median	228.0	234.0	228.5
Range	(18.0-1234.0)	(28.0-1038.0)	(18.0-1234.0)
Creatinine (mg/dL)			
N	168	173	341
Mean (SD)	1.0 (0.40)	1.0 (0.30)	1.0 (0.35)
Median	0.9	0.9	0.9
Range	(0.4-3.7)	(0.4-2.1)	(0.4-3.7)
Ferritin (µg/L)			
N	168	173	341
Mean (SD)	505.8 (427.04)	560.7 (474.09)	533.6 (451.70)
Median	390.5	413.0	400.0
Range	(11.0[a]- 2216.0)	(37.0-2463.0)	(11.0-463.0)
Serum erythropoietin (mIU/mL)			
N	154	159	313
Mean (SD)	99.9 (172.34)	100.8 (131.43)	100.3 (152.69)
Median	55.3	64.5	59.8
Range	(1.4 - 1576.2)	(6.5 - 1181.0)	(1.4 - 1576.2)

[a] Subjects 78809 and 77890 had baseline ferritin values of 11 and 18 µg/L, respectively. These values were within the normal range for the local laboratories where they were determined.

The hemoglobin values at baseline were comparable between the two treatment groups. With comparable median WBC counts at baseline, and wider range in the Epoetin arm, the difference in the mean between the two arms is likely from outliers with leukemoid reactions.

The following table shows the prestudy transfusion data (transfusions within 3 months of study entry).

Table 5: Prestudy Transfusion Data
(Study PR98-27-008: Intent-to-Treat Population)

	Placebo (N=170)	Epoetin Alfa (N=174)	Total (N=344)
Transfused pretreatment,[a] n (%)			
No	143(84%)	142(82%)	285(83%)
Yes	27(16%)	32(18%)	59(17%)
Units transfused for subjects receiving prestudy transfusions			
N	27	32	59
Mean (SD)	2.6(1.01)	2.9(1.91)	2.7(1.56)
Median	2.0	2.0	2.0
Range	(1.0-5.0)	(1.0-9.0)	(1.0-9.0)
Hemoglobin concentration at time of prestudy transfusion (g/dL)			
N	27	32	59
Mean (SD)	8.2 (0.75)	8.1 (0.76)	8.1 (0.75)
Median	8.1	8.0	8.0
Range	(7.0-10.7)	(6.9-9.8)	(6.9-10.7)

a Within 3 months prior to baseline. Note that the protocol specified no transfusion within 2 weeks prior to entry into the study.

As can be seen in the table above, the pre-study mean hemoglobin levels were comparable in the two groups. Likewise, the summary of daily oral iron supplements shown below shows comparibility between the two groups.

Table 6: Summary of Daily Oral Iron Supplementation
(Study PR98-27-008: Intent-to-Treat Population)

	Placebo (N=170)	Epoetin Alfa (N=174)	Total (N=344)
Oral Iron Supplement at Baseline, n (%)			
Missing	3(2%)	1(1%)	4(1%)
Yes	143(84%)	153(88%)	296(86%)
No	24(14%)	20(11%)	44(13%)
Oral Iron Supplement in Cycle 1, n (%)			
Missing	5(3%)	8(5%)	13(4%)
Yes	161(95%)	161(93%)	322(94%)
No	4(2%)	5(3%)	9(3%)
Oral Iron Supplement in Cycle 2, n (%)			
Missing	21(12%)	23(13%)	44(13%)
Yes	135(79%)	139(80%)	274(80%)
No	14(8%)	12(7%)	26(8%)
Oral Iron Supplement in Cycle 3, n (%)			
Missing	39(23%)	39(22%)	78(23%)
Yes	117(69%)	118(68%)	235(68%)
No	14(8%)	17(10%)	31(9%)
Oral Iron Supplement in Cycle 4, n (%)			
Missing	51(30%)	58(33%)	109(32%)
Yes	101(59%)	102(59%)	203(59%)
No	18(11%)	14(8%)	32(9%)

The following tables describe the most frequently used chemotherapy agents and changes in chemotherapy during the study period, both of which were similar.

Table 7: The Ten Most Frequently Used Chemotherapy Agents
(Study PR98-27-008: Intent-to-Treat Population)

	Placebo (N=170)	Epoetin Alfa (N=174)
Chemotherapy agent, n (%)a		
Paclitaxel	47(28%)	55(32%)
Carboplatin	36(21%)	43(25%)
Cisplatin	35(21%)	26(15%)
Gemcitabine	29(17%)	31(18%)
Cyclophosphamide	26(15%)	25(14%)
5-Fluorouracil	22(13%)	19(11%)
Prednisone	25(15%)	18(10%)
Doxorubicin	21(12%)	21(12%)
Vincristine	20(12%)	18(10%)
Etoposide	14(8%)	20(11%)

[a] Subjects may be included in more than one category.

Table 8: Change in Chemotherapy
(Study PR98-27-008: Intent-to-Treat Population)

	Placebo (N=170)	Epoetin Alfa (N=174)	Total (N=344)
Change in Chemotherapy, n (%)			
Missing	3(2%)	4(2%)	7(2%)
Yes	117(69%)	110(63%)	227(66%)
No	50(29%)	60(34%)	110(32%)

For subjects in this study, the mean duration of treatment was 91.4 days in the placebo group and 89.6 days in the epoetin alfa group. The median duration of treatment was 106 days in each group.

The following table describes the percent of patients who received 40,000 units only and those who were escalated to 60,000 units per treatment cycle. Dose escalation occurred most frequently in cycle 2; in 75% subjects in the placebo group and 45% of subjects in the epoetin alfa group.

Table 9: Percent of Subjects Who Received 40,000 IU q.w. Only and Percent of Subjects Who Received at Least One Dose of 60,000 IU q.w., by Cycle (Study PR98-27-008: Intent-to-Treat Population)

	Placebo (N=170)			Epoetin Alfa (N=174)		
		40,000 IU only	40,000/ 60,000 IU		40,000 IU only	40,000/ 60,000IU
	N	n (%)	n (%)	N	n(%)	n(%)
Cycle 1	164	152(93%)	12[a] (7%)	167[b]	164(98%)	3 (2%)
Cycle 2	150	37(25%)	113(75%)	149	82(55%)	67(45%)
Cycle 3	131	31(24%)	100(76%)	130	68(52%)	62(48%)
Cycle 4	121	28(23%)	93(77%)	110	58(53%)	52(47%)
Overall	165	46(28%)	119(72%)	167	95(57%)	72(43%)

[a] This number includes one placebo-treated subject who was started at a dose of 60,000 IU

[b] One subject in the epoetin alfa group is not included because the subject's total dose was not recorded for the cycle. The subject started at a dose of 40,000 IU and discontinued in Cycle 1.

All dose modifications and the reasons of dose modifications are summarized in the following table. Modifications were made for 125 (74%) of subjects in the placebo group and 106 (61%) in the epoetin alfa group. The most frequent reason was lack of hemoglobin response. The dose was withheld for more subjects in the epoetin alfa group (n=54, 31%) than in the placebo group (n=25, 15%). Hemoglobin >15 was the reason given for withholding the dose in 27 of the 54 subjects in the active treatment arm but none in the placebo arm. 14 of the 16 patient sin the epoetin arm had reduction in dose due to hemoglobin > 115 gm/dL, compared to none in the placebo arm.

Table 10: Subjects With Dose Modifications (Study PR98-27-008: Intent-to-Treat Population)

	Placebo (N=170)	Epoetin Alfa (N=174)	Total (N=344)
	n (%)	n (%)	n (%)
Dose modifications,[1] any cycle[2]	125(74%)	106(61%)	231(67%)
Dose increase, any cycle			
Yes	119(70%)	72(41%)	191(56%)
Reason			
Hemoglobin Not Increased	103(61%)	61(35%)	164(48%)
Other[3]	12(7%)	9 (5%)	21(6%)
Unknown	4(2%)	3(2%)	7(2%)
Drug withheld, any cycle			
Yes	25(15%)	54(31%)	79(23%)
Reason			
Hemoglobin > 15 g/dL	0 (0%)	27(16%)	27(8%)
High blood pressure	2(1%)	1(1%)	3(1%)
Other[4]	24(14%)	29(17%)	53(15%)
Dose reduction, any cycle			
Yes	0 (0%)	16(9%)	16(5%)
Reason			
Hemoglobin > 15 g/dL	0 (0%)	14(8%)	14(4%)
Other	0(0%)	2(1%)	2(1%)

1 Dose modifications include dose increases, drug (dose) withheld, or dose reductions. Data for doses withheld were recorded on the case report forms, while dose increases and dose reductions were derived.

2 Individual subjects may be included in more than one category and may have had more than one dose modified.

3: Transfusion was the reason for dose increase for all 21 subjects.

4: Reason for dose withheld was refused injection (30 subjects), disease progression/declining health (10 subjects), dosing errors (7 subjects), and other (6 subjects).

Primary Efficacy Analysis

Percent of Subjects Transfused After Study Day 28:

The ITT population (i.e., all patients as randomized) was used as the primary population for efficacy analyses. According to the SAP, the primary efficacy endpoint was the percentage of subjects in the ITT population who were transfused after Day 28 (i.e., from Day 29 to end of study) using worst outcome imputation (i.e., subjects who withdrew from the study after Day 28, with no transfusion after Day 28, were imputed as transfused for purposes of analysis). The sponsor notes that when study data became available, it was clear that results based on non-responder imputation were not an appropriate representation of the clinical outcomes of this study. It is notable that withdrawn subjects in the Epoetin alfa group had greater Hgb improvements than withdrawn subjects in the placebo group, e.g., the 45 withdrawn subjects in the Epoetin alfa group had a mean change in Hgb from baseline to last value of 2.8 g/dL while the 42 withdrawn placebo subjects had a mean change of 0.6 g/dL. Among the subjects who did not complete the study and had "other" reasons for withdrawal, 6 subjects in the Epoetin alfa group were withdrawn with "high' Hgb concentrations (ranging from 13.5 to 15.5 g/dL) at the time of study discontinuation compared to 1 subject with "high" Hgb (11.2 g/dL) in the placebo group. *[Note: The protocol did not specify that subjects should be discontinued from the study when HGB was 'high", e.g., > 15 g/dL. Rather, the study drug was to be withheld. However, the seven subjects described were withdrawn from the study (at least as a partial reason) due to "high" Hgb or Hgb > 15 g/dL.]*

The following table shows Hgb values for subjects who withdrew early from study for "other" reasons or "other medical reasons" and had high Hgb values.

Table 11: Hgb Data for Early Withdrawals with High Hgb Values

Subject	Treatment	Withdrawal Reason	Last Cycle	Day of Last Evaluation	Tx after Day 28	Last Hgb
84788	Placebo	Removed for high Hgb	3	99	No	11.2
80286	Epo	Hgb > 15.0	4	107	No	15.2
84174	Epo	Hgb at 15.5	3	97	No	15.5
86642	Epo	4 weeks of greater/equal Hgb. At Cycle 3 Hgb was 15.2	4	107	No	13.5
91440	Epo	PI's decision[a]	3	78	No	14.9
92050	Epo	Hgb was 15.0	4	91	No	15.0
100852	Epo	Hgb > 15 for 4 weeks	2	61	No	15.3

[a] The reason given on the case evaluation form by the attending physician was that the patient would no longer benefit from continuing the study because all chemo- and radiotherapy had stopped and the patient did not want to come in. A note from the study chair on the case evaluation form indicated that the patient had Hgb > 15.

These data strongly suggest that had the withdrawn subjects completed the study, the number transfused after Day 28 would be lower in the Epoetin alfa group than in the placebo group. To use only the worst outcome imputation for transfusion status would produce bias against the efficacy of Epoetin alfa in reducing the need for transfusions. Therefore, in addition to this planned analysis, other plausible analyses were undertaken. Representatives of FDA/CBER agreed to these additional plausible analyses, allowing assessment of consistency of results at a pre-BLA meeting on May 20, 2003. These methods have been previously described in the **'Missing Data Handling' section**. Analytic findings based on the worst outcome imputation and these other plausible methods are described in the next section.

Analysis as Planned in the Statistical Analysis Plan, Kaplan-Meier Analysis, and Analysis of Crude Rate Using LOCF: Results of the primary analysis as planned in the SAP (i.e., all withdrawn subjects considered transfused) are presented in the following table (Analysis 1). It also shows the results of a Kaplan-Meier analysis (Analysis 2) and a LOCF analysis of crude transfusion rates (Analysis 3). Here, LOCF means imputing a patient's last known transfusion status at the time of dropout.

Table 12: Percent of Subjects Transfused After Day 28 (ITT)

Imputation Analysis Type:	Placebo (n = 170)	Δ and CI for Δ	Epoetin alfa (n = 174)	p-value
(1) Worst Outcome – Crude Rate:				
Subjects transfused, n (%)	84 (49.4%)		69 (39.7%)	0.0687[a]
Δ in % (Epo – Placebo)		-9.8%		
95% CI for Δ		-20.2%, 0.7%		
Adjusted Odds Ratio (Epo / Placebo)		0.668		0.0706[b]
95% CI for Odds Ratio		0.43, 1.03		
(2) LOCF – Kaplan-Meier:				
Subjects transfused (%)	32.7%		16.3%	0.0011[c]
Δ in % (Epo – Placebo)		-16.4%		
95% CI for Δ		-26.2%, -6.5%		
(3) LOCF – Crude Rate:				
Subjects transfused, n (%)	48 (28.2%)		25 (14.4%)	0.0017[a]
Δ in % (Epo – Placebo)		-13.9%		
95% CI for Δ		-22.4%, -5.3%		
Adjusted Odds Ratio (Epo / Placebo)		0.388		0.0010[b]
95% CI for Odds Ratio		0.22, 0.68		

[a] Based on Chi-square test

[b] The primary statistical inference, based on logistic regression analysis adjusting for the following randomization balancing variables: size of institution (≥ 15 or < 15 subjects accrued per month over the 2-year period from April 2000 to April 2002, type of primary cancer (lung, breast, other), planned radiation therapy (yes or no), and degree of anemia (≥ 9 or < 9 g/dL, i.e., mild or severe).

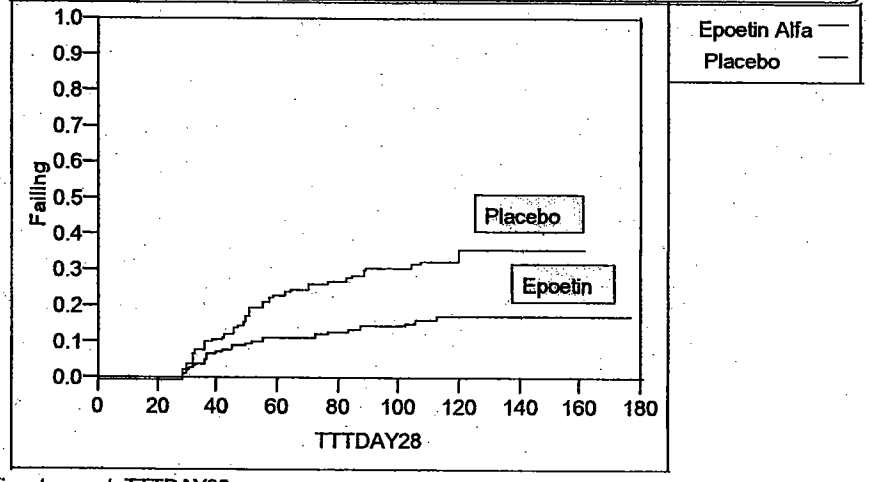
[c] Greenwood's method.

The Kaplan-Meier plot below presents time to first transfusion after Day 28. The time-to event comparison revealed a statistically significantly delayed finding for the Epoetin alfa group compared to the placebo group (p=0.0016, logrank test).

Figure 1: Study PR98-27-008 ITT population: Time to First Transfusion After Day 28 (From Day 29 to End of Treatment)

Product Limit Survival Fit

Failure Plot



Time to event: TTTDAY28
Censored by T2N
Grouped by NEWARM

Summary

Group	N Failed	N Censored	Mean	Std Error
Epoetin Alfa	25	149	103.303 Biased	1.98558
Placebo	48	122	98.4225 Biased	2.77186
Combined	73	271	103.806 Biased	1.77398

Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
Epoetin Alfa	.	.	.	.	.
Placebo	.	.	.	71	.
Combined	.	.	.	113	.

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	9.9345	1	0.0016
Wilcoxon	9.1177	1	0.0025

This time-to-event analysis as well as all of the efficacy analyses summarized were confirmed by the FDA statistical reviewer (Dr. Gnecco).

Sensitivity Analyses for the Primary Efficacy Endpoint: Three additional analyses were performed using other plausible imputations for the transfusion status of withdrawn subjects as follows:

Analysis (4): Subjects who withdrew from the study after Day 28 would be considered not transfused if they 1) withdrew from the study because they had a successful Hgb response, as indicated by the investigators, and 2) were not transfused after Day 28. This approach was used when it was noticed that a number of subjects withdrew for reasons related to the effectiveness of the study drug in raising Hgb concentrations (Table 8).

Analysis (5): Subjects who withdrew from the study after Day 28 would not be considered transfused if they 1) withdrew after having completed all 4 planned cycles but were not identified as completers by the investigators, and 2) were not transfused after Day 28. This imputation was used because the protocol specified that transfusion data were to be collected for a total of 4 evaluation cycles during the 16-week treatment phase.

Analysis (6): Subjects who withdrew from the study after Day 28 would not be considered transfused if they 1) withdrew due to disease progression, and 2) were not transfused after Day 28. The analysis was appropriately used in this study given that the numbers of subjects who withdrew due to disease progression were comparable in the two treatment arms, indicating that withdrawals for this reason were not treatment related.

In Analyses (4) – (6), crude transfusion rates ranged from 43.5% to 48.8% in the placebo group and from 32.8% to 36.2% in the Epoetin alfa group. Across these three analyses, differences for the two groups in transfusion rates ranged from –10.8% to –12.6% and were statistically significant for each analysis. A summary of the analysis of the difference in transfusion rates between the two treatment groups utilizing these three methods is presented in the table below.

Table 13: Sensitivity Analyses for % Subjects Transfused After Day 28

(Study PR98-27-008 ITT population)

Imputation Analysis Type[a]:	Placebo (n = 170)	Δ and CI for Δ	Epoetin alfa (n = 174)	p-value
(4) Subjects with successful Hgb response considered not transfused – Crude Rate				
Subjects transfused, n (%)	83 (48.8%)		63 (36.2%)	0.0179[b]
Δ in % (Epo – Placebo)		-12.6%		
95% CI for Δ		-23.0%, -2.3%		
Adjusted Odds ratio (Epo / Placebo)		0.584		
95% CI for Odds Ratio		0.38, 0.91		0.0169[c]
(5) Subjects who completed 4 cycles considered not transfused – Crude Rate				
Subjects Transfused, n (%)	82 (48.2%)		62 (35.6%)	0.0178[b]
Δ in %		-12.6%		
95% CI for Δ		-23.0%, -2.3%		
Adjusted Odds Ratio (Epo / Placebo)		0.589		
95% CI for Odds Ratio		0.38, 0.91		0.0181[c]
(6) Subjects with disease progression considered not transfused – Crude Rate				
Subjects transfused, n (%)	74 (43.5%)		57 (32.8%)	0.0397[b]
Δ in %		-10.8%		
95% CI for Δ		-21.0%, -0.6%		
Adjusted Odds Ratio (Epo / Placebo)		0.625		
95 % CI for Odds Ratio		0.40, 0.98		0.0394[c]

[a] In each analysis, withdrawn subjects considered not transfused were also required, while still on study, not to have been transfused after Day 28 in the study.

[b] Based on Chi-square test

[c] The primary statistical inference, based on logistic regression analysis adjusting for the following randomization balancing variables: size of institution (≥ 15 or < 15 subjects accrued per month over the 2-year period from April 2000 to April 2002), type of primary cancer (lung, breast, or other), planned radiation therapy (yes or no), and degree of anemia (≥ 9 or < 9 g/dL, i.e., mild or severe).

By all of these various analyses, the percentages of subjects transfused after Day 28 was consistently lower in the Epoetin alfa group, within the range of –10% to –16% of treated subjects. The sponsor claims that six different analyses, including 5 with differing imputations for the transfusion status of withdrawn subjects, provide evidence of the efficacy of Epoetin alfa, administered once weekly, in reducing the numbers of subjects requiring transfusions after Day 28 of treatment.

The statistical reviewer (Dr. Gnecco) confirmed the sponsor's statistical finding for these 6 imputation analyses. Since informative missing data was a major concern, she also performed an in-depth descriptive analysis of missing hemoglobin data patterns by cycle and treatment arm for the ITT population. Her findings showed that on the placebo arm there were 57 patients with missing values or 33.5%. On the Epoetin alfa arm there were 60 patients with missing values or 34.5%. Hemoglobin missing values patterns by treatment arm are remarkably similar. There is no indication of differential dropout pattern by treatment arm.

Regarding dropouts for progressive disease (PD), 26 patients were withdrawn with PD given as the reason. There were 13 such patients in each treatment arm. Dr. Gnaco's descriptive Kaplan-Meier analysis revealed very similar patterns; the curves are almost super-imposable.

These analyses support the sponsor's claim of superior efficacy of Epoetin alfa, administered once weekly, in reducing the numbers of subjects requiring transfusions after Day 28 of treatment.

Transfusion Results by Subgroups: The percentages of subjects transfused after Day 28, using their actual transfusion status at the time of withdrawal (LOCF), are presented by treatment group and specific subgroups (i.e., those subgroups that were balancing factors for the randomization) in table below:

Table 14: Proportion of Subjects Transfused After Day 28
(From Day 29 to Last Evaluation, Using Transfusion Status at Time of Withdrawal) for Key Subgroups (ITT)

Subgroup:	Placebo (N = 170)			Epoetin alfa (N = 174)		
	N	n	%	N	n	%
Primary tumor type:						
Lung	49	12	24%	48	6	13%
Breast	28	1	4%	28	2	7%
Other	93	35	38%	98	17	17%
Planned concurrent radio-therapy:						
Yes	17	3	18%	18	1	6%
No	153	45	29%	156	24	15%
Baseline anemia:						
Mild (≥ 9 g/dL)	117	26	22%	119	12	10%
Severe (< 9 g/dL)	53	22	42%	55	13	24%
Chemotherapy:						
Cis-Platinum based	33	13	39%	26	4	15%
Non-Cis-Platinum based	137	35	26%	148	21	14%

In the breast cancer subgroup the percentage of subjects transfused in the Epoetin alfa group was higher than in the placebo group using LOCF imputation. The sponsor suggests that this is an anomalous finding probably due to the small sample size and low transfusion rate. The second largest disease subgroup comprises those patients with gastro-intestinal (GI) tumors. There were a total of 63 patients (18.3%) classified as having GI disease. There were 28 (44.4%) on the Epoetin alfa arm and 35 (55.6%) on the placebo arm. Using LOCF imputation, the proportions transfused were 5/28 (17.9%) for the Epoetin alfa arm versus 7/35 (20%) for the placebo arm. As previously discussed, worst outcome imputation is the least tenable approach for this particular situation. Looking into the distribution of disease types within the GI subgroup, there were no esophageal disease patients in the placebo group and 3 in the Epoetin alfa group (12.5%). Only one of these was transfused, however. 44.1% of placebo patients had colon cancer compared to 33.3% Epoetin alfa

patients. There were 23.5 % placebo patients with pancreatic cancer compared to 12.5% Epoetin alfa patients. When the GI subgroup is excluded from the main by treatment arm comparison of transfusion rates, the Epoetin alfa group has consistently lower transfusion rates than the placebo group via all imputation methods. For worst outcome imputation, estimated transfusion rates are 57% for Epoetin alfa versus 54% for placebo. For LOCF imputation, estimated transfusion rates are 13.7% for Epoetin alfa and 30.4% for placebo. These are consistent with estimated transfusion rates for the entire ITT population.

Thus, once weekly treatment with Epoetin alfa reduced the number of subjects needing transfusions after Day 28 of the study. Across 6 analyses, the percentage of subjects transfused in the Epoetin alfa group was lower than in the placebo group. These differences between groups ranged from –10% to –16%.

Data Related to the Primary Endpoint – Percent of Subjects Transfused Overall: The percentages of subjects transfused at any time on study, including prior to Day 28 in Cycle 1, are presented by evaluation cycle in Table below. The percentage of subjects transfused was greater during each cycle in the placebo group than in the Epoetin alfa group. During the entire study, 39% of treated placebo subjects received one or more transfusions compared to 26% of Epoetin alfa treated subjects.

Table 15: Percent of Subjects Transfused by Evaluation Cycle and Overall

	Placebo (n = 170)		**Epoetin alfa (n = 174)**	
	N	**n (%)**	**N**	**n (%)**
Cycle 1	165	41 (25%)	166	31 (19%)
Cycle 2	150	34 (23%)	152	14 (9%)
Cycle 3	131	19 (15%)	137	8 (6%)
Cycle 4	119	13 (11%)	118	6 (5%)
Overall (any cycle)	165	65 (39%)	167	43 (26%)

The hemoglobin concentrations measured at the time of first transfusion on study are summarized for each treatment group in table below. Hemoglobin concentrations leading to first transfusion showed similar mean values and the same median value.

Table 16: *Pre-transfusion Hemoglobin for First Transfusion on Study (ITT)*

	Placebo (n = 170)	**Epoetin alfa (n = 174)**
Subjects Transfused, n (%)	65 (38%)	43 (25%)
Pre-transfusion Hgb (g/dL) for First Transfusion		
N	64	42
Mean (SD)	7.8 (0.99)	7.9 (0.97)
Median	7.8	7.8
Range	(4.8 – 10.2)	(6.5 – 10.7)
Pre-transfusion Hgb (g/dL) for First Transfusion	**n (%)***	**n (%)***
< 7.1	8 (12%)	9 (21%)
7.1 – 7.5	14 (22%)	7 (16%)
7.6 – 8.0	21 (32%)	10 (23%)
8.1 – 8.5	11 (17%)	5 (12%)
8.6 - 9.0	5 (8%)	6 (14%)
9.1 – 9.5	1 (2%)	3 (7%)
9.6 – 10.0	2 (3%)	1 (2%)
> 10.0	2 (3%)	1 (2%)
Missing	1 (2%)	1 (2%)

* Percents are based on subjects transfused.

Secondary Efficacy Analyses

mber of RBC Units Transfused: Table below presents red blood cell (RBC) units transfused per ubject and units transfused per 100 subject-days for the ITT population of the [redacted] study. As the table indicates, over the entire study the total number of RBC transfusions administered in the placebo group (256 units) was approximately twice the total number administered in the Epoetin alfa group (129 units). The mean number of cumulative RBC units transfused per subject in the placebo group (1.5 units) was also approximately twice the mean number in the Epoetin alfa group (0.7 units). Adjusted for each subject's time on study, the mean number of RBC units transfused per 100 subject-days was significantly higher in the placebo group vs. the Epoetin alfa group (1.52 vs. 0.76; $p < 0.0001$). The difference in the number of units transfused per 100 subject-days was –0.78 units, representing a reduction in the transfusion burden by approximately 50% for the Epoetin alfa group compared to the placebo group.

Table 17: *RBC Units Transfused/Subject and Units Transfused/100 Subject-Days (ITT)*

	Placebo (n = 170)	**Epoetin alfa (n = 174)**	**p-value**
Total Units /Subject:			
N	170	174	
Mean (SD)	1.5 (2.65)	0.7 (1.59)	
Median	0.0	0.0	
Range	(0.0 – 14.0)	(0.0 – 10.0)	
Total Days on Study:			
N	170	174	
Mean (SD)	97.7 (35.27)	97.0 (35.06)	
Median	112.0	111.5	
ange	(0 – 162)	(0 – 177)	
ransfusion Rate:			
Total No. of Study Days	16606	16884	
Total No. of Units Transfused	256	129	
Units Transfused per 100 Subject-Days (SE)	1.54 (0.0094)	0.76 (0.0161)	< 0.0001[a]
Effect Estimate (95% CI):			
Difference in Transfusion Rates (Epoetin alfa – Placebo)	-0.78 (-0.783, -0.777)		

[a] Test based on normal distribution.

Change in Hemoglobin Concentrations from Baseline: Values for Hgb concentrations at baseline and at last measurement, and changes in Hgb from baseline to last value, are summarized by treatment arm in the following table. The mean change in Hgb from baseline was 0.9 g/dL in the placebo group and 2.8 g/dL in the Epoetin alfa group; the difference between groups was statistically significant ($p < 0.0001$). The study days on which the last Hgb value was obtained were similar in the two treatment groups, with the mean study day being Day 91.8 for the placebo group and Day 91.9 for the Epoetin alfa group. Because the transfusion rate was higher in the placebo group than in the Epoetin alfa group, the effect of transfusions would contribute to Hgb increase to a greater degree in the placebo group than in the Epoetin alfa group.

Table 18: *Change in Hgb from Baseline to Last Value (ITT)*

	Placebo (n = 170)	Epoetin alfa (n = 174)	p-value
Baseline Value (g/dL):			
N	170	174	
Mean (SD)	9.4 (0.93)	9.5 (0.94)	
Median	9.5	9.6	
Range	(6.9 – 11.4)	(6.0 – 11.4)	
Last Value (g/dL):			
N	164	166	
Mean (SD)	10.3 (1.44)	12.2 (2.12)	
Median	10.4	12.3	
Range	(6.0 – 13.4)	(7.9 – 17.3)	
Δ in Hgb to Last Value (g/dL):			
N	164	166	
Mean (SD)	0.9 (1.49)	2.8 (2.05)	< 0.0001
Median	0.9	2.8	
Range	(-3.8 – 5.3)	(-2.2 – 7.5)	
Δ (95% CI) (Epo – Placebo):	1.9 (1.5, 2.3)		
Study Day Last Hgb Obtained:			
N	170	174	
Mean (SD)	91.8 (36.64)	91.9 (35.73)	
Median	110.0	106.5	
Range	(-4.0 – 161.0)	(-3.0 – 175.0)	

Changes in Hgb within specific subgroups are presented in Table below. Within each subgroup, a greater Hgb change was noted for subjects treated with Epoetin alfa than for subjects receiving placebo. The greatest difference in subgroups was found for the degree of anemia in the placebo group, where subjects with mild anemia showed a much smaller Hgb change than subjects with severe anemia. This might have been expected, however, since subjects with mild anemia would have required fewer transfusions.

Table 19: *Mean Change in Hgb Within Subgroups (ITT)*

	Placebo (n=170)		Epoetin Alfa (n=174)	
Subgroup:	**N**	**Mean Δ (SD)**	**N**	**Mean Δ (SD)**
Primary Malignant Disease				
Lung	49	1.1 (1.50)	48	2.5 (1.90)
Breast	28	1.2 (1.74)	28	3.6 (1.60)
Other	93	0.7 (1.41)	98	2.7 (2.19)
Planned Concurrent RT				
Yes	17	0.7 (1.39)	18	2.4 (2.18)
No	153	0.9 (1.51)	156	2.8 (2.04)
Degree of anemia				
Mild (Hgb ≥ 9 g/dL)	117	0.6 (1.30)	119	2.7 (2.09)
Severe (Hgb < 9 g/dL)	53	1.5 (1.69)	55	2.9 (1.96)
Chemotherapy Regimen				
Cis-platinum	33	1.0 (1.25)	26	2.9 (2.01)
Non-cis-platinum	137	0.9 (1.55)	148	2.7 (2.06)

The percentages of subjects with an increase in Hgb of ≥ 2 g/dL are summarized in table below. The percent of subjects with a ≥ 2 g/dL increase in Hgb was smaller at each cycle in the Placebo group

than in the Epoetin alfa group. Over all cycles, 32% of subjects in the placebo group compared to 73% of subjects in the Epoetin alfa group had a Hgb increase of ≥ 2 g/dL. The sponsor notes that any contribution of transfusion to these results would be greater in the placebo group than in the Epoetin alfa group due to the higher transfusion rate in the placebo group.

Table 20: *Percent of Subjects with a ≥ 2 g/dL Increase in Hgb (ITT)*

	Placebo (n=170)		Epoetin Alfa (n=174)	
	N	n(%)	N	n(%)
Cycle 1	164	10 (6%)	166	52 (31%)
Cycle 2	147	25 (17%)	152	82 (54%)
Cycle 3	129	23 (18%)	134	90 (67%)
Cycle 4	114	31 (27%)	115	81 (70%)
Overall (any cycle)	164	52 (32%)	166	122 (73%)

Hemoglobin Over Time: Results of the sponsor's longitudinal analysis of Hgb increase over time are presented in the table below. The rate of Hgb increase (i.e., the slope estimate) was 0.064 g/dL per week in the placebo group as compared to 0.201 g/dL per week in the epoetin alfa group. The difference between treatment groups was highly statistically significant ($p < 0.0001$).

Table 21: *Hemoglobin Over Time / Longitudinal Analysis (ITT)*

Estimated Effect	Placebo (n=170)		Epoetin Alfa (n=174)	p-value
Slope (g/dL/week)	0.064		0.201	
95% CI	(0.04, 0.08)		(0.18, 0.22)	
Δ (Epo – Placebo)		0.137		< 0.0001
95% CI		(0.11, 0.17)		

Longitudinal assessment of Hgb over the study period was analyzed via a mixed-effect model with the intercept and study day treated as random effects and controlling for study center size, age, gender, baseline body weight, type of primary cancer, concurrent radiation therapy, degree of anemia, baseline transfusion status, and chemotherapy type.

Incidence of Hgb Concentrations Below 9.0 g/dL: After Cycle 1, 29.5% of subjects treated with placebo had Hgb values of < 9 g/dL compared to 11.1% treated with Epoetin alfa. The p-value for this difference was statistically significant ($p < 0.0001$). These results are summarized in table below.

Table 22: *Number and Proportion of Subjects with Hgb < 9 g/dL After Cycle 1 to Individual Study End (ITT)*

	Placebo (n=170)		Epoetin alfa (n=174)	p-value
Hgb < 9 g/dL, n(%):				
N	149		153	
No	105 (70.5%)		136 (88.9%)	
Yes	44 (29.5%)		17 (11.1%)	<0.0001[a]
Δ (Epo – Placebo)		-18.4		
95% CI for Δ		(-27.3, -9.6)		

[a] Based on two-sided Chi-square test

Incidence of Nephrotoxicity in Subjects Receiving Chemotherapies Containing cis-Platinum: The incidence of nephrotoxicity (i.e., creatinine Grade ≥ 1) in subjects who were identified at study entry as receiving chemotherapies containing cis-platinum are tabulated by creatinine toxicity grade in the following table. Five subjects (16%) in the placebo group and 4 subjects (16%) in the epoetin

alfa group had signs of Grade 1 (mild) nephrotoxicity. Four subjects (13%) in the placebo group and 2 subjects (8%) in the epoetin alfa group had signs of Grade 2 (moderate) nephrotoxicity. The difference between groups was not statistically significant for creatininte grade or for incidence of phrotoxicity.

Table 23: Incidence of Nephrotoxicity in Subjects Receiving cis-Platinum-Based Chemotherapy

	Placebo (n=31)	Epoetin alfa (n=25)	p-value
Creatinine			
Maximum CTC Grade, n (%)			0.6404[a]
0	22 (71%)	19 (76%)	
1	5 (16%)	4 (16%)	
2	4 (13%)	2 (8%)	
Incidence, n (%)			0.7667[b]
No	22 (71%)	19 (76%)	
Yes	9 (29%)	6 (24%)	

[a] p-value for grade based on Wilcoxon rank sum test
[b] p-value for incidence based on Fisher's exact test
Note: The summary only includes those subjects identified on the study eligibility criteria form as receiving cis-platinum containing chemotherapies

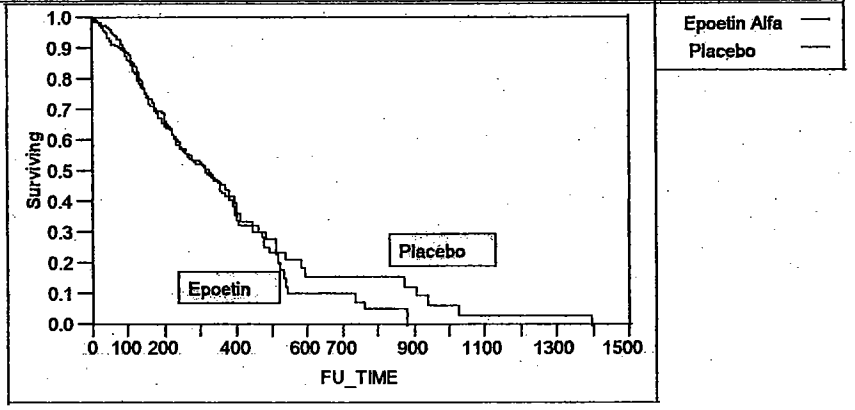
The statistical reviewer (Dr. Gnecco) performed univariate Fisher's exact test analysis on the primary efficacy endpoint of proportion transfused for the subgroup of patients who received cis-platinum chemotherapy as well as for the subgroup who received non-cisplatinum containing regimens. In both cases the proportion transfused was higher on the placebo arm relative to the poetin alfa arm. These differences did not reach statistical significance.

Survival: Univariate analytic findings for survival data, available at the time of the s-BLA submission, are presented for each treatment group in the following figure.

Figure 2: Study PR98-27-008 / Overall Survival

Product-Limit Survival Fit

Survival Plot



Time to event: FU_TIME
Censored by fu_stjmp
Grouped by NEWARM

Summary

Group	N Failed	N Censored	Mean	Std Error
Epoetin Alfa	117	57	344.969	21.4164
Placebo	115	55	400.238	34.4882
Combined	232	112	372.27	20.6996

Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
Epoetin Alfa	319	248	371	157	515
Placebo	328	250	385	154	495
Combined	327	268	360	155	511

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.6253	1	0.4291
Wilcoxon	0.0626	1	0.8024

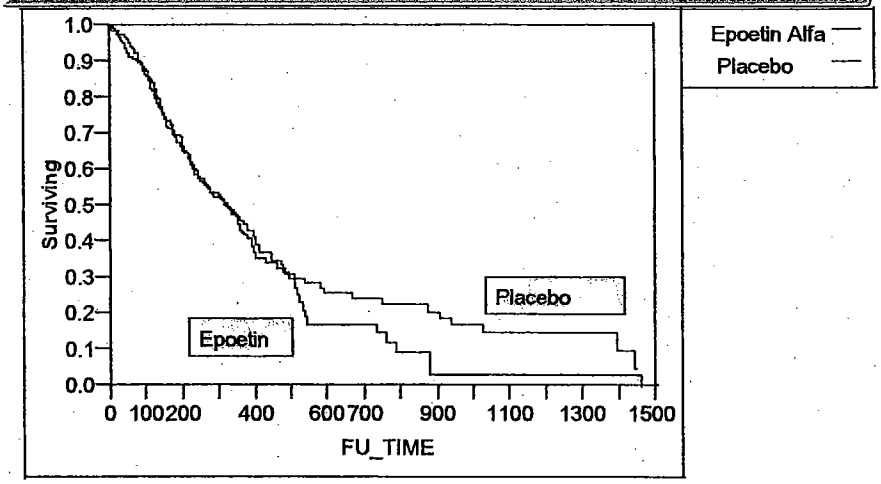
The survival curves are similar, with median survival times of 10.9 months (where 1 month = 30 days) in the placebo group and 10.6 months in the Epoetin alfa group. The difference between groups was not statistically significant via the logrank test (p=0.429).

An updated survival analysis was performed when the 4-month safety data became available. This is presented in the following figure.

Figure 3: Study PR98-27-008/ Overall Survival (4-Month Safety Update)

Product-Limit Survival Fit

Survival Plot



Time to event: FU_TIME
Censored by fu_stjmp
Grouped by NEWARM

Summary

Group	N Failed	N Censored	Mean	Std Error
Epoetin Alfa	121	53	387.472	32.2787
Placebo	119	51	495.729 Biased	42.7112
Combined	240	104	452.26	28.9151

Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
Epoetin Alfa	325	248	369	157	527
Placebo	328	250	397	154	673
Combined	327	268	362	155	542

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.8650	1	0.3524
Wilcoxon	0.1085	1	0.7418

Overall, 119 subjects (70%) in the placebo group and 121 subjects (70%) in the Epoetin alfa group died. The median survival times were similar between the placebo and Epoetin alfa groups (10.9 months and 10.8 months, respectively). The survival curves were similar up to 12 months, the protocol specified end point. The apparent separation of the curves after 17 months (approximately 550 days on the plot) could be due to the disparity in the number of censored subjects during Months 12 to 17 (360 – 510 days). The difference in overall survival times between the two groups was not statistically significant (p = 0.352 via the logrank test). A large proportion of the deaths in both treatment groups were due to disease progression. Table below presents the breakdown for cause of death.

Table 24: *Study PR98-27-008 / Cause of Death for Deaths that Occurred On Study and After the Study (During the Follow-Up Phase) for the ITT Population*

	Placebo (n = 170)	Epoetin alfa (n = 174)
Cause of Death (n, %)[a]		
Total deaths, n	119	121
Disease Progression	100 (84%)	102 (84%)
Other[b]	6 (5%)	8 (7%)
Unknown	13 (11%)	11 (9%)

Note: Deaths during the follow-up phase include those that occurred within 30 days following the last dose of study drug and those that occurred after 30 days following the last dose of study drug.

[a] Percentage is based on total deaths

[b] "Other" included the following: ischemia/infarction; pneumonitis; respiratory failure due to pulmonary metastases; pneumonia/ARDS; cerebral hemorrhage; necrosis of bowel; ischemic stroke, subarachnoid hemorrhage; coronary artery disease (CAD); congestive heart failure (CHF) exacerbation, chronic obstructive pulmonary disease (COPD); gastrointestinal (GI) bleed and anemia; stroke; renal failure; and unknown – chose to see another oncologist.

Tumor Response: Tumor response to chemotherapy at study completion, as estimated by the investigators, was comparable between the two treatment arms and is presented in table below. Tumor progression was reported for 29% of subjects in the placebo group and 32% of subjects in the Epoetin alfa group.

Table 25: *Study PR98-27-008 / Tumor Response to Chemotherapy at Study Completion (ITT)*

	Placebo (n = 170)	Epoetin alfa (n = 174)
Objective Status of Tumor Response, n (%)		
Missing	4 (2%)	6 (3%)
mplete response (CR)	13 (8%)	14 (8%)
tial response (measureable disease only) (PR)	19 (11%)	14 (8%)
Regression	15 (9%)	13 (7%)
Stable	70 (41%)	72 (41%)
Progression	49 (29%)	55 (32%)

QoL Analysis:

There were no differences in AUC-QoL scores between the subjects who received epoetin alfa treatment and the subjects who received placebo. An exploratory ANCOVA model confirmed this result.

3.3.3 Clinical Microbiology

Data regarding clinical microbiology were not provided in this submission (also not applicable).

3.3.4 Efficacy Conclusions

The randomized study PR-98-008 provides statistical support for the sponsor's efficacy claim. The primary efficacy analysis was based on the difference in proportions transfused in the ITT population. The pre-specified non-responder (worst outcome) imputation analysis of subjects receiving RBC transfusions after treatment Day 28 until individual study end (i.e., subjects who withdrew from the study after Day 28, with no transfusion after Day 28, were imputed as transfused for purposes of analysis) yielded an estimated difference of –9.8% favoring the Epoetin alfa group which reached borderline statistical significance (p =0.069, Chi square test; p =0.071, adjusted logistic regression

analysis). The sponsor presented a rationale that indicated that using non-responder imputation biased results against the Epoetin alfa treatment arm. This reviewer agrees with the sponsor's rationale described in section 3.3.2. Five additional imputation analyses, previously discussed with the FDA, ...ded estimated rate differences that consistently favored the Epoetin alfa group over the placebo ...oup (range: -10% to –16%); all of these differences were statistically significant ($p < 0.05$). In addition to the primary endpoint described above, the mean number of RBC units transfused/subject in the placebo group (1.5 units) was approximately twice that in the Epoetin alfa group (0.7 units). The mean number of units transfused/100 subject-days was statistically significantly lower in the Epoetin alfa group ($p < 0.0001$). There was a marked difference in hemoglobin response, favoring the Epoetin alfa group.

3.4 Integrated Review of Safety

3.4.1 Approach to Review of Safety

The safety information in support of this application was primarily derived from the pivotal Phase III double blinded placebo controlled trial PR98-27-008. The Safety population included all subjects who received at least 1 dose of study drug and had safety information available. The safety population included 165 subjects who received placebo and 168 subjects who received epoetin alfa

Additionally, safety information was also provided from the subjects in Phase I PK/PD study EPO-PHI-377, in which 18 of the 33 anemic cancer patients received epoetin alfa by a weekly schedule. Because of the limited number of patients exposed to the proposed regimen, safety information from this study is only included in section 6.1 and is not included in this section.

...2 Safety Findings

3.4.2.1 Exposure

The extent of exposure is summarized for the ITT population in Table 26. The mean duration of treatment was similar and the median duration of treatment was the same in the 2 treatment groups.

Table 26: Duration of Treatment
(Study PR98-27-008: Intent-to-Treat Population)

Placebo	(N=170)	Epoetin Alfa (N=174)
Never dosed, n (%)		
Yes	5(3)	6(3)
Duration of treatment (days)		
N	165	165[a]
Mean (SD)	91.4 (31.67)	89.8 (30.33)
Median	106.0	106.0
Range	(1.0-141.0)	(1.0-169.0)

a: One subject (99015) had no first dose date and 2 subjects (77445 and 78217) had no final dose date; these subjects are therefore not included in this total.

In the safety population, 115 (70%) of 165 subjects in the placebo group and 109 (65%) of 168 subjects in the epoetin alfa group completed treatment (a scheduled time of 16 weeks). The ...llowing table 27 shows the summary of average weekly dose of epoetin alfa or placebo by cycle. ...even patients were inadvertently unblinded after 5 cycles of treatment (4 in the placebo group and 3 in the epoetin alfa group). Adverse events information was collected on all these patients. Five of

these subjects had information on the study dose, hence are included in the following table.

Table 27: Average Weekly Dose Per Cycle
(Study PR98-27-008: Intent-to-Treat Population)

	Placebo (N=170)	Epoetin Alfa (N=174)
Never dosed, n (%)		
Yes	5(3)	6(3)
Average weekly dose		
Cycle 1		
N	164	167
Mean (SD)	40,563.0 (2,298.62)	40,024.0 (1,926.21)
Median	40,000.0	40,000.0
Range	(40,000.0-60,000.0)	(20,000.0-50,000.0)
Missing	1 (1%)	1 (1%)
No longer on study	5(3%)	6(3-/.)
Not Dosed	0	0
Cycle 2		
N	150	150
Mean (SD)	54,437.8 (8,657.55)	48,417.8 (9,896.72)
Median	60,000.0	40,000.0
Range	(40,000.0-60,000.0)	(26,666.7-60,000.0)
Missing	1 (1%)	2(1%)
No longer on study	19(11%)	21(12%)
Not Dosed	0	1 (1%)
Cycle 3		
N	131	130
Mean (SD)	55,267.2 (8,533.03)	49,538.5
Median	60,000.0	40,000.0
Range	(40,000.0-60,000.0)	(40,000.0-60,000.0)
Missing	0	2(1%)
No longer on study	39(23%)	36(21%)
Not Dosed	0	6(3%)
Cycle 4		
N	121	110
Mean (SD)	55,371.9 (8,469.68)	49,045.5
Median	60,000.0	40,000.0
Range	(40,000.0-60,000.0)	(30,000.0-60,000.0)
Missing	1 (1%)	1 (1%)
No longer on study	48(28%)	56(32%)
Not Dosed	0	7(4%)
Cycle 5		
N	4	1
Mean (SD)	55,000.0	60,000.0 (.)
Median	60,000.0	60,000.0
Range	(40,000.0-60,000.0)	(60,000.0-60,000.0)
No longer on study	166(98%)	173(99%)

Dose modifications for patients in the study have previously been described (please see table 10). As shown in that table the dose was withheld for more subjects in the epoetin alfa group (54 subjects, 31%) than in the placebo group (25 subjects, 15%). Among the reasons for withholding the dose, a hemoglobin value of >15 g/dL was given as the reason for 27 of the 54 subjects with doses withheld in the epoetin alfa group, but was not given as the reason for any subject in the placebo group. The dose was reduced for 16 subjects (9%) in the epoetin alfa group but was not reduced for any subject in the placebogroup. Among the subjects in the epoetin alfa group with dose

reductions, a hemoglobin value of >15 g/dL was given as the reason for 14 of the 16 subjects.

.4.2.2 Deaths

Table 28 describes the deaths that occurred in the subjects while on study. Twenty-one deaths occurred in subjects while on study (8 in the placebo and 13 in the epoetin alfa group). This difference was not statistically significant

Table 28: Deaths That Occurred On Study (Study PR98-27-008: Safety Population)

Treatment Arm	Subject	Sex	Age (Years)	Cause of Death	Study Day of Death	Severity	Drug Relationship
Placebo	79159	Male	52	Disease progression		NA[a]	NA[a]
	79429	Female	74	Disease progression		NA	NA
	79458	Male	50	Disease progression		NA	NA
	79927	Male	78	Disease progression		NA	NA
	80413	Male	66	Disease progression		NA	NA
	80838	Male	76	Disease progression		NA	NA
	84215	Male	79	Other ischemia/infarction[b]		5	Unlikely
	95473	Female	57	Disease progression		NA	NA
Epoetin Alfa	77358	Male	44	Disease progression		NA	NA
	77572	Female	66	Disease progression		NA	NA
	78767	Male	58	Disease progression		NA	NA
	78771	Male	66	Disease progression		NA	NA
	79647	Male	81	Disease progression		NA	NA
	86929	Female	74	Disease progression		NA	NA
	87516	Male	42	Disease progression		NA	NA
	87694	Male	58	Disease progression		NA	NA
	90646	Male	60	Disease progression		NA	NA
	92508	Male	68	Disease progression		NA	NA
	92730	Male	81	Disease progression		NA	NA
	94413	Male	72	Other\Pneumonitis		5	Not Related
	99015	Female	68	Disease progression		NA	NA

a NA (not applicable) is shown for deaths attributed to disease progression; under NCI criteria, such deaths are not reported or evaluated as adverse events.
[b] Myocardial infarction

Table 29 below describes the deaths that occurred within 30 days of the last dose of study medication. These include 15 in the placebo arm and 18 in the epoetin alfa arm.

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Table 29: Deaths That Occurred After the Study but Within 30 Days Following the Last Dose of Study Medication (Study PR98-27-008: Safety Population)

Treatment Arm	Subject	Sex	Age (Years)	Cause of Death	Days After Treatment
Placebo	77228	Male	34	Disease progression	
	78374	Male	60	Disease progression	
	78377	Female	56	Disease progression	
	79128 [a]	Male	70	Disease progression	
	79324	Male	78	Disease progression	
	84475	Female	63	Disease progression	
	88240[b]	Female	66	Disease progression	
	90996	Female	60	Disease progression	
	92162	Male	53	Disease progression	
	92405	Male	76	Disease progression	
	92573[b]	Female	43	Disease progression	
	97447	Female	42	Other\Respiratory failure	
	98957	Female	71	Other\Pneumonia/ARDS	
	99763	Male	63	Disease progression	
	100270	Male	67	Unknown	
Epoetin Alfa	77445'	Male	68	Other\pneumonitis	
	78085	Male	50	Disease progression	
	78217	Male	56	Disease progression	
	80039	Female	47	Disease progression	
	80306	Female	82	Disease progression	
	83490[b]	Male	58	Disease progression	
	83690	Female	64	Disease progression	
	83868	Female	69	Disease progression	
	84542	Male	46	Disease progression	
	84895	Male	61	Disease progression	
	84918	Male	88	Disease progression	
	85236	Female	67	Disease progression	
	86759	Male	42	Other\cerebral hemorrhage	
	88019	Female	42	Disease progression	
	91709[b]	Female	63	Disease progression	
	91880	Female	65	Disease progression	
	97060	Male	74	Disease progression	
	97313	Female	68	Disease progression	

In addition, the sponsor provided listings for all subjects who died in the follow up phase 30 days after the study. A total of 186 subjects died during this period and included 96 subjects in the placebo group and 90 subject in the epoetin alfa group. The following table 30 describes the cause of death in the subjects either on the study or in the follow-up period.

Table 30: Cause of Death for Deaths That Occurred On Study and After the Study (During the Follow-Up Phase)
(Study PR98-27-008: Intent-To-Treat Population)

Cause of Death (n, %)[a]	Placebo (N=170)	Epoetin Alfa (N=174)
Total Deaths, n	119	121
Disease progression	100(84)	102(84)
Other[b]	6(5)	8(7)
Unknown	13(11)	11(9)

Note: Deaths during the follow-up phase include those that occurred within 30 days following the last dose of study drug and those that occurred after 30 days following the last dose of study drug.

[a] Percentage is based on the total deaths

[b] "Other" included the following: ischemia/infarction; pneumonitis; respiratory failure due to pulmonary metastases; pneumonia/ARDS; cerebral hemorrhage; necrosis of bowel; ischemic stroke, subarachnoid hemorrhage; coronary artery disease (CAD); congestive heart failure (CHF) exacerbation, chronic obstructive pulmonary disease (COPD); gastrointestinal (GI) bleed and anemia; stroke; renal failure; and unknown - chose to see another oncologist.

3.4.2.3 Other Serious Adverse Events

Because the CTC criteria do not use the term "serious adverse event" as such, for this study, the Sponsor treated adverse events with toxicity Grade 3 (severe and undesirable) or Grade 4 (life-threatening or disabling) as serious adverse events. Overall, Grade 3 or 4 adverse events were reported for 73 subjects (44%) in the placebo group and 82 subjects (49%) in the epoetin alfa group. The grade 3 and 4 events that occurred in 5% or more subjects are described in table 31.

Table 31: Grade 3 and Grade 4 Adverse Events (SAEs) Reported for ≥5.0% of Subjects in Either Treatment Group

(Study PR98-27-008: Safety Population)

	Placebo (N=165)[a]			Epoetin Alfa (N=168)[a]		
CTC Catgeory	Grade 3	Grade 4		Grade 3		Grade 4
Adverse Event	n (%)	n	(%)	n	(%)	n (%)
Constitutional Symptoms						
Fatigue	12 (7%)	0	(0%)	12	(7%)	2 (1%)
Gastrointestinal						
Nausea	9 (5%)	0	(0%)	5	(3%)	0 (0%)
Hematology						
Anemia	8 (5%)	1	(1%)	3	(2%)	0 (0%)
Neutropenia[b]	3 (2%)	3	(2%)	3	(2%)	6 (4%)

[a] No subject appears in both categories 3 and 4.

[b] In addition to neutropenia, febrile neutropenia of Grade 3 was reported for 5 subjects (3%) in the placebo group and for 2 subjects (1%) in the epoetin alfa group.

The following table describes the attributions of Grade 3 and 4 adverse events according to study investigators.

Table 32: Drug Relationships of Grade 3 and 4 Adverse Events as Evaluated by Investigators (Study PR98-27-008: Safety Population)

	Placebo (N=165)	Epoetin Alfa (N=168)
Subjects with any Grade 3 or 4 adverse event (SAE), n (%)	73(44%)	82(49%)
Relationship of event to therapy,[a] n (%)		
Not Related	34(47 %)[b]	55(67%)
Unlikely	28(38%)	18(22%)
Possible	9(12%)	8(10%)
Probable	1 (1%)	1 (1%)
Definite	1 (1%)	0 (0%)

[a] If a subject had multiple reports of the same SAE with different drug-relationships,then the greatest relationship assigned to drug therapy was used.
[b] Percentages shown are based on the number of subjects with Grade 3 or 4 adverse events.

As can be seen, the majority of Grade 3 and Grade 4 adverse events were evaluated by the investigators as not related or as having an unlikely relationship to study therapy. The following table lists those that were reported as possibly, probably, or definitely drug-related.

Table 33: Listing of Subjects With Grade 3 or 4 Adverse Events Evaluated as Possibly, Probably, or Definitely Related to Study Drug
(Study PR98-27-008: Safety Population)

Treatment Arm	Subject	S	Age (years	Adverse Event	Initial Toxicity	Duration[1] (cycles)	Severity[2]	Drug Relation[3]
Placebo	77728	M	74	Fatigue	59	1	3	Possible
				Infection-no ANC	59	1	3	Possible
	79739	M	61	Thrombocytopenia	35	1	3	Possible
	83906	M	60	Neutropenia	44	1	4	Possible
	87943	M	71	Leukopenia	31	1	3	Possible
				Thrombocytopenia	31	2	3	Possible
	88240	F	66	Diarrhea-no colostomy	29	2	3	Probable
				Infection	29	2	3	Possible
				Nausea	29	1	3	Probable
				Pain-abdominal	60	1	3	Possible
				Vomiting	29	1	3	Probable
	92573	F	43	Constipation	127	1	3	Possible
				Thrombosis	34	1	4	Possible
	94050	F	73	Syncope	33	1	3	Possible
	94266	M	44	Myalgia	22	1	3	Possible
	94476	M	74	Anemia	35	1	3	Definite
	97819	F	68	Arrhythmia-SVT	57	1	3	Possible
	100492	F	52	Anemia	29	1	3	Possible
Epoetin	77358	M	44	Constipation	56	1	4	Possible
	83490	M	58	Dizziness	96	1	3	Possible
	86929	F	74	Hyponatremia	22	1	3	Possible
	88975	M	41	Thrombosis	57	1	4	Possible
	90060	M	71	Dyspnea	52	1	4	Probable
				Infection	52	1	3	Probable
	91709	F	63	Alkaline phosphatase	29	1	3	Possible
	92202	M	72	Hemolysis	58	1	3	Possible
	92730	M	81	Pain-abdominal	30	1	4	Possible
	95710	M	56	Myalgia	56	2	3	Possible

ANC=absolute neutrophil count; SVT=supraventricular tachycardia

1 Duration is the number of cycles where the toxicity was Grade 3 or higher.

2. In this table, severity is the maximum severity over all cycles.

3.In this table, drug relationship is the highest relationship overall cycles.

3.4.2.4 Dropouts and Other Significant Adverse Events

Three subjects withdrew from the study due to adverse events. These are summarized in the table below:

Table 34: Subjects Who Discontinued Due to Adverse Events
(Study PR98-27-008: Safety Population)

Treatment Arm	Subject	Sex	Age (Years)	Adverse Event	Evaluation Date	Drug Severity	Drug Relationship
Placebo	78495	Female	50	Nausea	27 May 1999	1	Unlikely
				Nausea	29 Jul 1999	2	Possible
				Pain-chest	29 Jul 1999	2	Unlikely
				Rash	29 Jul 1999	2	Unlikely
Epoetin Alfa	90060	Male	71	Dyspnea	31 Aug 2000	3	Not Related
				Dyspnea	29 Sep 2000	4	Probable
				Infection	29 Sep 2000	3	Probable
	90976	Female	75	Rash	27 Nov 2000	2	Possible

3.4.2.5 Other Search Strategies Applied to Clinical Safety Database

Other search strategies were not deemed necessary in the clinical safety database in this placebo controlled study. Sponsor provided narratives of deaths, grade 3 or 4 adverse events, TVEs and summary information on medwatch and hospital notification forms.

3.4.2.6 Common Adverse Events

Treatment emergent adverse events were reported in 142 patients in the placebo arm and 147 subjects in the Epoetin alfa arm. The following table lists those occurring in at least 5% in either study arms. There was no significant difference between the two study arms.

Table 35: Incidence of Treatment-Emergent Adverse Events Reported for 5% of Subjects in Either Treatment Group
(Study PR98-27-008: Safety Population)

CTC Category Adverse Event (Toxicity)	Placebo (N=165) n(%)	Epoetin Alfa (N=168) n(%)
Any adverse event	142 (86)	147 (88)
Cardiovascular		
Edema	14 (8)	14 (8)
Constitutional symptoms		
Fatigue	85 (52)	85 (51)
Fever-no ANC	10 (6)	7 (4)
Weight loss	9 (5)	15 (9)
Dermatology/skin		
Alopecia	48 (29)	42 (25)
Rash	7 (4)	11 (7)
Gastrointestinal		
Anorexia	31 (19)	31 (18)
Constipation	37 (22)	30 (18)
Diarrhea-no colostomy	36 (22)	33 (20)
Nausea	49 (30)	58 (35)
Stomatitis	12 (7)	16 (10)
Vomiting	27 (16)	33 (20)
Hematology		
Anemia	22 (13)	13 (8)
Leukopenia	11 (7)	14 (8)
Neutropenia	16 (10)	16 (10)
Thrombocytopenia	10 (6)	6 (4)
Infection/febrile neutropenia		
Infection	17 (10)	8 (5)
Metabolic/laboratory		
Hyperglycemia	6 (4)	10 (6)
Neurology		
Insomnia	4 (2)	10 (6)
Neuro-motor	12 (7)	11 (7)
Neuro-sensory	38 (23)	38 (23)
Pain		
Arthralgia	10 (6)	16 (10)
Myalgia	8 (5)	17 (10)
Pain	18 (11)	15 (9)
Pain-abdominal	17 (10)	11 (7)
Pain-bone	6 (4)	11 (7)
Pulmonary		
Cough	12 (7)	15 (9)
Dyspnea	36 (22)	27 (16)
Renal/genitourinary		
Creatinine	10 (6)	5 (3)

Key: ANC=absolute neutrophil count

3.4.2.7 Less Common Adverse Events

The incidence of less common adverse events was similar in both groups. The incidence of thrombovascular events is discussed in below in section 3.4.2.11. There were three incidences of

seizures (2 in placebo arm and 1 in epoetin alfa arm. All these patients had CNS pathology to account for the seizures.

4.2.8 Laboratory Findings

The following table lists the toxicity grade for all laboratory tests performed. As shown in the table below, there was higher incidence of anemia in placebo treated subjects than in those receiving active treatment.

Table 36: Toxicity Grade for All Laboratory Tests
(Study PR98-27-008: Safety Population)

	Placebo (N=165)	Epoetin Alfa (N=168)
WBC grade present, n (%)	164 (100)	165 (100)
WBC any incidence	*106(65)*	98(59)
WBC Grade 3,4[8]		
Grade 3	24(15)	37(22)
Grade 4	12(7)	7(4)
Hb grade present, n (%)	164 (100)	165 (100)
Hb any incidence	158(96)	141(85)
Hb Grade 3,4[8]		
Grade 3	34(21)	15(9)
Grade 4	4(2)	0
PLT grade present, n (%)	164 (100)	165 (100)
PLT any incidence	77(47)	75(45)
PLT Grade 3,4[8]		
Grade 3	18(11)	17(10)
Grade 4	2(1)	6(4)
Creatinine grade present, n (%)	163 (100)	163 (100)
Creatinine any incidence	43(26)	41(25)
Creatinine Grade 3,4[8]		
Grade 3	2(1)	0
Grade 4	0	1 (1)

Key: WBC=white blood count; Hb=hemoglobin; PLT=platelet There were no Grade 5 toxicities.

3.4.2.9 Vital Signs

The following table summarizes diastolic blood pressure values over time. Three subjects in the placebo group (2%) and 5 subject sin the epoetin alfa group were reported to have hypertension as an adverse event. All these events were Grade 1 or 2 except for 1 case of Grade 3 hypertension in the placebo group and 2 cases of Grade 3 hypertension in the epoetin alfa group.

Table 37: Summary of Diastolic Blood Pressure Values Over Time
(Study PR98-27-008: Safety Population)

	Placebo (N=165)	Epoetin Alfa (N=168)
Diastolic Blood Pressure (mmHg)		
Baseline		
N	162	166
Mean (SD)	70.4 (10.24)	71.8 (10.61)
Median	70	70
Range	(48-94)	(50-100)
Cycle 1		
N	161	161
Mean (SD)	70.8 (11.13)	71.1 (11.75)
Median	70	70
Range	(48-114)	(40-102)
Cycle 2		
N	143	144
Mean (SD)	70.9 (9.02)	72.0 (11.08)
Median	70	72
Range	(47-94)	(38-100)
Cycle 3		
N	125	128
Mean (SD)	71.2 (10.58)	71.5 (10.74)
Median	70	70
Range	(48-90)	(46-118)
Cycle 4		
N	114	107
Mean (SD)	72.4 (10.93)	74.2 (10.90)
Median	72	74
Range	(50-102)	(45-107)
Last Diastolic BP		
N	164	165
Mean (SD)	71.0 (11.18)	73.5 (11.16)
Median	70	72
Range	(48-102)	(38-107)
Change from baseline to last value		
N	161	163
Mean (SD)	0.6 (12.48)	1.7 (11.49)
Median	0	1
Range	(-40-34)	(-30-36)

3.4.2.10 ECGs

e sponsor of this application has not provided data on the ECGs of the study patients.

3.4.2.11 Special Safety Studies

Thrombovascular events: Because of the potential for increased thrombotic events in patients on epoetin alfa, particularly associated with a rapid rise in hematocrit, the sponsor was asked to provide narratives on all patients with thrombovascular events and explore the association of their occurrence with hemoglobin values. The following table lists the incidence of TVE.

Table 38: Listing of Thrombotic Vascular Events
(Study PR98-27-008: Safety Population)

Treatment Arm	Subject	Sex	Age (years)	Thrombotic Vascular Event	Cycle Reported	Toxicity Grade [a]	Drug Relationship
Placebo	78254	Male	46	Thrombosis	1	4	Not Related
	79953	Female	78	Thrombosis	2	3	Not Related
	84215	Male	79	Ischemia/infarction[b]	1	5	Unlikely
	89990	Female	60	Thrombotic microangiopathy	4	4	Not Related
	92573	Female	43	Thrombosis	1	4	Possible
	93897'	Female	70	Thrombosis	2	3	Not Related
				Thrombosis	3	3	Not Related
Epoetin Alfa	77068	Male	77	Thrombosis	3	3	Unlikely
	78492	Male	78	Thrombosis	1	3	Not Related
	79450	Male	70	Thrombosis	4	3	Not Related
	87694'	Male	58	Thrombosis	1	4	Not Related
				Thrombosis	3	4	Not Related
	88130	Male	69	Ischemia-cerebral	2	3	Not Related
	88975	Male	41	Thrombosis	2	4	Possible
	90123	Male	74	L ventricular failure	2	3	Not Related
	94611'	Female	54	Thrombosis	2	3	Not Related
				Thrombosis	4	3	Not Related
	96940	Female	79	Thrombosis	1	3	Unlikely
	97060[4]	Male	74	Thrombosis	3	3	Not Related

[a] CTC description of Grade 3 thrombosis: deep vein thrombosis requiring anticoagulant therapy. CTC description of Grade 4 thrombosis: embolic event including pulmonary embolism.

- Myocardial infarction
- It is unknown if the 2 reports of thrombosis for each of these subjects were for the same or separate occurrences.

Information from a MedWatch form indicated that this subject subsequently developed left hemiparesis and a CT scan showed an early infarct; however, no CTC toxicity term was assigned to this event.

The following table lists the TVEs by cycle, showing the change in hemoglobin from the previous cycle.

Table 39: Thrombotic Vascular Events by Cycle, Showing the Change in Hemoglobin From the Previous Cycle
(Study PR98-27-008: Safety Population)

	REPORTS OF TVE			SUBJECTS WITH NO TVE		
	Mean (SD) Baseline Hemoglobin = 9.4 (0.92) g/dL					
Placebo (N=165)						
Mean change from prior cycle:	Na (%)	n[b]	Mean Change in Hb (SD) g/dL	N (%)	n	Mean Change in Hb (SD) g/dL
at Cycle 1	3(2)	3	0.4(1.50)	161(98)	161	0.2(1.14)
at Cycle 2	2(1)	2	1.4 (0.14)	147(99)	145	0.4(1.41)
at Cycle 3	1 (1)	1	-0.7	129(99)	126	0.2(1.03)
at Cycle 4	1 (1)	0		114(99)	113	0.2(1.29)
Epoetin Alfa (N=168)	*Mean (SD) Baseline Hemoglobin = 9.4 (0.94) g/dL*					
Mean change from prior cycle:	N[a] (%)	n[b]	Mean Change in Hb (SD) g/dL	N (%)	n	Mean Change in Hb (SD) g/dL
at Cycle 1	3(2)	3	-0.3(1.82)	163(98)	163	1.2(1.50)
at Cycle 2	4(3)	4	0.4(1.64)	149(97)	148	1.1 (1.47)
at Cycle 3	3(2)	2	0.1 (0.64)	132(98)	131	0.6(1.39)
at Cycle 4	2(2)	2	0.9 (0.21)	113(98)	113	0.1 (1.53)

Note: Cycle 5 data are not included since none of the subjects who had TVEs had Cycle 5 data.
[a]N for this category is the number of TVE reports, i.e., across all cycles there were 7 reports (6 subjects) in the placebo group and 12 reports (10 subjects) in the epoetin alfa group.
[b]n is the number of subjects with a TVE for whom a hemoglobin measurement was available.

Unfortunately, hemoglobin information was only available at the beginning of each cycle and not at the time of occurrence of TVE. Hence although it appears that there is no relationship between rate of Hb rise and occurrence of TVE, a definite conclusion can not be reached because of the limitation of available data.

3.4.2.12 Withdrawal Phenomena/Abuse Potential

Data regarding withdrawal phenomenon were not provided in this application. Data regarding abuse potential are described in the section of overdose experience.

3.4.2.13 Human Reproduction and Pregnancy Data

Data regarding Human Reproduction and Pregnancy were not provided in this application.

3.4.2.14 Overdose Experience

To comply with International Conference on Harmonization (ICH) Guidelines, and to capture all medically confirmed (non-consumer) cases of overdose and drug abuse including concomitant use of epoetin alfa, the sponsor conducted a search of the Johnson & Johnson Worldwide Pharmacovigilance and Safety (SCEPTRE) database using the Product Code for epoetin alfa to identify all formulations and dosage forms of EPREX and PROCRIT. The search included the MedDRA preferred terms "drug abuser NOS", "therapeutic response increased", "medication error", "accidental overdose", "nonaccidental overdose", "overdose NOS", "prescribed overdose", multiple drug overdose", "polysubstance abuse", "drug addict", "chemical abuser", and "maternal use of illicit drugs" to identify all reports including use of these medications received during the period between the International Birth Date, 03 June 1988, and 15 October 2003. Reports from clinical studies in which the study medication was blinded were not excluded from further analysis. All searches

included epoetin alfa identified as either a suspect or concomitant medication. The searches included all spontaneous, postmarketing studies, literature, registry, and health authority reports. All cases were retrieved independent of the reporter's relationship attribution.

When one excludes placebo cases, "no adverse drug effect" cases, and cases relating to medications other than epoetin alfa, a total of 451 reports (spontaneous and postmarketing study cases combined) involving epoetin alfa were identified that listed one of the following MedDRA adverse event terms: "drug abuser NOS", "therapeutic response increased", "medication error", "accidental overdose", "nonaccidental overdose", "overdose NOS", "prescribed overdose", "multiple drug overdose", "polysubstance abuse", "drug addict", "chemical abuser", and "maternal use of illicit drugs". Of these 451 cases, there were 434 PROCRIT cases (48 serious, 386 nonserious) and 17 EPREX cases (13 serious, 4 nonserious). The majority of PROCRIT cases (331) were related to possible counterfeit product.

There were a total of 31 deaths reported (6 EPREX, 25 PROCRIT). Of the 6 EPREX deaths, 3 were unrelated to EPREX, 1 was related to disease progression, 1 was related to postoperative complications, and 1 was not specified but occurred 2 months after EPREX was discontinued.

Of the 25 PROCRIT deaths, 15 were related to cancer progression, 2 to sepsis, 2 to renal failure, 1 to cardiac failure, 1 due to accidental injury, 1 due to methadone overdose, and 3 were not specified.

The cases identified in this review were heterogeneous and included events such as increased therapeutic response in addition to nonintentional events such as incorrect dose or route. A large number of PROCRIT cases were related to possible counterfeit product with little or no sequelae. No unusual trends were noted overall. No deaths were identified as direct outcomes of overdose or abuse.

3.4.2.15 Post-Marketing Experience in U.S. and Foreign Markets

To ascertain if once-weekly dosing of PROCRIT had a clinically different adverse event profile compared to dosing with any schedule, the sponsor submitted an initial report (dated 21 July 2003), summarizing the review of all PROCRIT adverse events reported in association with once-weekly dosing and compared them to all PROCRIT adverse events reported for all dosing schedules. This review, undertaken using a WHOART 97 dictionary-based database (Johnson & Johnson Worldwide Pharmacovigilance and Safety [JIPSy]), covered the period between Jan 1, 1991 and May 31, 2003. The sponsor then provided an update that covered the period between June 1, 2003 and November 15, 2003, using a MedDRA 5.1 dictionary-based database (SCEPTRE), due to a changeover of the Drug Safety & Surveillance database to MedDRA during the update interval.

Both these reviews showed that the most frequently reported adverse events for once-weekly PROCRIT are similar in type and relative numbers to those identified for any-dosing PROCRIT. No events were identified that were specifically associated with once-weekly dosing.

Other significant Information:

Since the submission of this application, safety concerns with erythropoietin product when using treatment strategies to raise the hemoglobin levels beyond those recommended in the current label emerged. These safety concerns have been addressed in a safety supplement that has been approved (STN 103234/5033). Briefly, these concerns were based on two clinical trials using different erythropoietin products. In one randomized, prospective trial conducted with another Epoetin alfa product, in 939 women with metastatic carcinoma of the breast who were receiving chemotherapy, patients were assigned to receive either Epoetin alfa or placebo for up to a year, in a weekly schedule, with the primary goal of showing improved survival and improved quality of life in the Epoetin alfa treatment arm. This study utilized a treatment strategy designed to maintain hemoglobin levels of 12 to14 g/dL (hematocrit 36 to 42%). Increased mortality in the first 4 months after randomization was observed among 469 patients who received the erythropoietin product [41 deaths (8.7% mortality)] compared to 470 patients who received placebo [16 deaths (3.4% mortality)]. In the first four months of the study, the incidence of fatal thrombotic vascular events (1.1% vs 0.2%) and death attributed to disease progression (6.0% vs 2.8%) were both higher in the group randomized to receive Epoetin alfa as compared to placebo. Based on Kaplan-Meier estimates, the proportion of subjects surviving at 12 months after randomization was lower in the Epoetin alfa group than in the placebo group (70% vs 76%), $p = 0.012$, log rank. In another randomized, placebo-controlled study using Epoetin beta, conducted in 351 patients with head and neck cancer, study drug was administered with the aim of achieving a hemoglobin level of 14 g/dL in women and 15 g/dL in men. (Henke, M, Laszig, R, Rübe, C, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomized, double-blind, placebo-controlled trial. *The Lancet.* 2003;362:1255-1260) Locoregional progression-free survival was significantly shorter (median PFS: 406 days Epoetin beta vs 745 days placebo, $p = 0.04$) in patients receiving Epoetin beta.

Since these data became available, the sponsor had additional ongoing studies, which also employed similar treatment strategy. The data safety monitoring committee of some of the studies also recommended closure of their respective studies based on increased incidence of thrombosis. The sponsor has provided details of all the literature in the supplement STN 103234/5033 that was recently approved. These issues were also discussed at the ODAC meeting on 5/4/04, and recommendations made to suggest that the sponsors perform additional studies to address the potential safety concerns. It should be noted that there is extensive experience in the use of erythropoietin products and there do not appear to be any safety concerns when used as described in the package insert in the indicated populations.

3.4.3 Adequacy of Safety Exposure and Safety Assessments

The safety exposure and assessments are adequate for approval of this supplement that is seeking an alternative dosing schedule for an already approved product.

3.4.4 Safety Conclusions

The safety findings in the pivotal trial PR98-008, which was a randomized double blinded placebo controlled trial, showed that the safety profile in the treatment arm was comparable to the placebo group. Specifically, the survival experience was similar in the two study arms. Although there were more subjects with thrombotic vascular events (TVE's) in the Epoetin alfa group than in the placebo group (i.e., 10 vs.6), examination of TVE occurrences in relation to hemoglobin increases did not reveal any suggestion of a relationship between the rate of hemoglobin rise and the occurrence of TVE's, although exploration of this relationship was hampered by the limited schedule of hemoglobin measurements in the study.

3.5 Other Clinical Issues

There were no other clinical issues identified during the review of this application.

3.5.1 Dosing, Regimen and Administration Issues

Epogen/ Procrit is already approved for three times/week dosing. Under this supplement, it can also be used in the following manner. The starting dose is 40,000 units per week. If after 4 weeks of therapy, the hemoglobin has not increased by ≥ 1 g/dL, in the absence of RBC transfusion, the Epogen/Procrit dose should be increased to 60,000 IU/week. If patients have not responded satisfactorily to a dose of 60,000 Units weekly after 4 weeks, it is unlikely that they will respond to higher doses. Epogen/Procrit should be withheld if the hemoglobin exceeds 13 g/dL and reinitiated with a 25% dose reduction when the hemoglobin is less than 12 g/dL. If Epogen/Procrit treatment produces a very rapid hemoglobin response (e.g., an increase of more than 1.3 g/dL in any 2-week period), the dose should be reduced by 25%.

3.5.2 Use in Special Populations

3.5.2.1 Demographic Worksheet

The following table describes the demographics as it pertains to the age, sex and race.

Table 40: Selected Demographics

	Placebo (N=170)	Epoetin Alfa (N=174)	Total (N=344)
Age (years)			
65 or greater	92 (54%)	86 (49%)	178 (52%)
less than 65	78 (46%)	88 (51%)	166 (48%)
Sex, n (%)			
Female	96(56%)	96(55%)	192(56%)
Male	74(44%)	78(45%)	152(44%)
Race, n (%)			
Black	18(11%)	10(6%)	28(8%)
Hispanic	1(1%)	0(0%)	1(0%)
White	151(89%)	164(94%)	315(92%)

3.5.2.2 Special Considerations based on Race

As seen above, 92% of study subjects were white. No definite difference in efficacy or safety was observed based on race.

3.5.2.3 Special Considerations based on Gender

There were 56% female and 44% males in the study population. Gender had no effect on efficacy or safety.

3.5.2.4 Special Considerations based on Age for Adults

Fifty-two percent of study participants were over the age of 65. No age related differences in safety or efficacy were seen.

3.5.2.5 Special Considerations based on Age for Pediatrics

The sponsor has sought deferral for studies in pediatric population in this application. The sponsor has suggested submitting study covering ages 5 to 16 years in second quarter of 2004 and requested indefinite deferral for the age group 0 to 5 years. For this age group the sponsor states that the need for, the timing of, the technical requirements of the study will be reviewed with the Agency following review of pediatric data from the ongoing study.

3.5.2.6 Other Special Considerations

- Renal or hepatic insufficiency
- Use in pregnancy or lactation

Erythropoietin is indicated in patients with renal failure. The sponsor has not provided data on its use in pregnancy, lactation or in patients with hepatic failure.

3.5.3 Outcome of Advisory Committee Meeting

Advice of the advisory committee was not sought for this supplemental BLA.

4.0 Mitigating Factors for Interpretation of Clinical Data

No mitigating factors for interpreting the data were identified.

4.1 Other Discipline Reviews

Please see statistical review by Dr. Gneco

4.1.1 CMC – including product microbiology, EA, EER

This supplement is simply to use an alternative weekly dosing strategy for the approved and marketed product. CMC review was not conducted for this application.

4.1.2 Pharmacology /Toxicology

Please see detailed review by Dr. Zhao

4.2 Auditing Functions

4.2.1 DSI Outcomes

The study sites were not audited by the FDA for this supplemental BLA, which employed an approved product but with a different dosing regimen.

4.2.2 Financial Disclosure

The sponsor has provided financial disclosure statements from studies PR98-27-008, EPO-PHI-370, EPO-PHI 377. None of the investigators/sub investigators from these studies reported having disclosable information.

4.3 Other Factors (as necessary)

No other factors were deemed necessary.

5.0 Summative Assessment

5.1 Conclusion on Available Data

The available data adequately supports the sponsor's contention that alternative weekly dosing of Epogen/Procrit is safe and effective as treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.

5.2 Recommendations for Regulatory Action

Approval

5.3 Review of Labeling

The label was agreed upon after discussions with the sponsor and is attached with this document.

5.4 Comments to Sponsor

None

5.4.1 Comments Regarding Labeling

None

5.4.2 Comments Regarding Need for Additional Data

None

5.4.3 Comments Regarding Other Topics

None

6.0 Individual Trial / Study Reports

6.1 Major Efficacy and Safety Trials

STUDY PR-98-27-008

OBJECTIVES:
For purposes of regulatory submission, the objective was to determine the proportion of subjects who required red blood cell (RBC) transfusions after 28 days from randomization, i.e., on or after Day 29 to individual study end.

METHODS
Overview of Study Design
This was a multicenter, randomized, double-blind, placebo-controlled, study conducted [redacted] in the North Central United States and Saskatchewan, Canada. Three hundred thirty subjects with anemia who were receiving myelosuppressive, cytotoxic chemotherapy for advanced cancer were to be enrolled. Eligible patients were randomized in a 1:1 ratio to epoetin alfa or placebo treatment, with stratification by center (investigator), type of primary cancer (lung, breast, or other), planned concurrent radiation therapy (yes or no), and degree of anemia (hemoglobin <9 g/dL or ≥9 g/dL). The double-blind treatment was administered for a maximum of 16 weeks, after which the subjects were followed for one year from the time of randomization for event monitoring (death, new primary malignancies, and long-term toxicities).
The dose of double-blind study medication (40,000 IU of epoetin alfa or corresponding placebo) was to be administered by s.c. injection, once weekly. If after 4 weeks of therapy hemoglobin concentrations had not increased by >lg/dL or if the subject had received a transfusion during the first 4 weeks of therapy, the weekly dose of study drug was to be increased to 60,000 IU once weekly. If, at any time during the study, the hemoglobin concentration exceeded 15 g/dL, the hemoglobin concentration was to be determined 1 week later. If the hemoglobin concentration exceeded 15 g/dL, study drug was to be withheld and the hemoglobin concentration was to be determined weekly until it fell below 13 g/dL. Study drug was then to be restarted at a dose level 25% less than that previously administered. Additional criteria for withholding, decreasing, or increasing the dose are given in the section on Dosage and Administration.

During double-blind treatment, subjects were to receive a daily oral iron supplement (ferrous sulfate 324 mg or equivalent commercially available supplement). All subjects could receive RBC transfusions at the discretion of the physician. A hemoglobin value was to be obtained at the time of transfusion and recorded on the subject's Concurrent Treatment Log. Subjects who discontinued chemotherapy during the double-blind period were to continue the study treatment through 16 weeks.
Safety evaluations included assessments of adverse events using National Cancer Institute (NCI) Common Toxicity Criteria (CTC), Version 2.0. Blood pressure measurements and 4 laboratory tests (white blood cell counts [WBC], hemoglobin,

platelets, and creatinine) were obtained at each evaluation.

Changes in Conduct of Trial:

There were 3 addenda (i.e., amendments) to the protocol. Addendum 1 on March 5, 1999, updated the [redacted] nurse contact. This addendum also specified that the submission of the Concurrent Treatment Log with the on-study materials was no longer required and added a question regarding oral iron supplementation to the On-Study form. Addendum 2 on May 11, 2001, updated the consent form to reflect current [redacted] ; IRB formatting guidelines. Addendum 3 on September 28, 2001, closed the study to subject accrual.

Study Population

Overview

Three hundred thirty subjects receiving myelosuppressive, cytotoxic chemotherapy for advanced cancer were to be enrolled in the study. The number of subjects actually enrolled was 344. Subjects were to be enrolled according to the inclusion and exclusion criteria summarized below.

Inclusion Criteria

- Age of 18 years or older
- Anemia: hemoglobin <11.5 g/dL in males and <10.5 g/dL in females
- Normal or elevated ferritin
- Currently receiving myelosuppressive, cytotoxic chemotherapy for advanced cancer. Patients receiving adjuvant therapy for cancers that had been surgically removed were not eligible.
- An Eastern Cooperative Oncology Group (ECOG) performance score of 0 (able to carry out all normal activity without restriction) or 1 (restricted in physically strenuous activity but ambulatory and able to do light work)
- A life expectancy of ≥ 6 months as assessed by the physician
- Able to reliably take oral medication
- Alert and mentally competent

Exclusion Criteria

- Anemia secondary to Vitamin B12, folic acid, or iron deficiency
- Anemia secondary to gastrointestinal bleed or hemolysis
- Anemia secondary to a primary or chemotherapy-induced myelodysplastic syndrome
- Uncontrolled hypertension (i.e., systolic blood pressure >180 mmHg or diastolic blood pressure >100 mmHg)
- Pregnant or lactating
- Known hypersensitivity to epoetin alfa
- Previous epoetin alfa therapy within the last year
- Unwilling or unable to undergo weekly subcutaneous injections
- Currently undergoing peripheral blood stem cell or bone marrow transplant
- Anemia secondary to acute lymphocytic or acute nonlymphocytic leukemia
- Red blood cell transfusions within the last 2 weeks before entry
- Unwilling or unable to fill out QOL forms

Removal of Subjects From Therapy or Assessment

Subjects could voluntarily withdraw from the study at any time for any reason. At the time of withdrawal, the study site completed an End of Active Treatment Form for the subject. The categories used on the End of Active Treatment Form for classification of treatment discontinuation were: 1) Completed treatment per protocol; 2) Refused further treatment; 3) Adverse reactions; 4) Disease progression; 5) Alternative treatment; 6) Other medical problems; 7) Died on study, and 8) Other.
In accord with [redacted] definitions, any subject who did not receive any study treatment before removal from the study was designated a "cancellation". These subjects were, however, included in the Intent-to-Treat (ITT) population, which was the primary efficacy population for the purpose of this report. Exclusion of subjects from other analysis populations is described in Section on Data Sets Analyzed.

Study Drug Information

Drug supplies (i.e., cartons containing vials of study drug and empty syringes for s.c. injection) were shipped from J&JPRD's clinical supplies facility to the [redacted]
Pharmacy to the study sites dispensed supplies.
Study drug was supplied in vials containing 1-mL of 20,000 IU/mL PROCRIT or placebo. Single doses of 40,000 IU and 60,000 IU would require the use of 2 or 3 vials, respectively.
Information on the study drug labels stated that the vials were to be used for subcutaneous injection only; that they should be used as directed by the protocol; and that they were to be stored in the refrigerator at 2-8°C (36-46°F) and should not be frozen or shaken. The vial labels also contained spaces for insertion of patient number, i.e., subject code number, and patient initials. The labels also contained a space for the date dispensed. Other information required by governmental regulations also appeared on the labels. Study drug vials for a single subject were provided in a carton which contained a space for the subject's code number.
Syringe labels were also provided which specified the protocol number and gave administration, storage, and handling information. The syringe labels also contained spaces for patient number, patient initials, and the date administered.
The J&JPRD batch numbers for epoetin alfa (FD No. 22512-000-Q-45) were R10630, R10052, R8967, R8614, and R7676. The batch numbers for placebo (FD No. 22512-000-QX-45) were R10784, R10053, R8968, R8615, and R7677.

Registration/Randomization and Blinding
Registration Procedures
IRB approval was required for each study site, and a signed 310 Form documenting IRB approval was to be on file at the [redacted] office before patient accrual. To register a patient as a study subject, the study site called or faxed a completed eligibility checklist to the [redacted] office, where a randomization specialist checked the patient's eligibility and verified the existence of a signed consent form. A randomization code was assigned as explained below. Study treatment could not begin prior to registration but was required to begin ≤7 days after registration.

Randomization and Double Blinding Procedures

Randomization was conducted in a 1:1 ratio using the dynamic allocation procedure of Pocock and Simon to balance the two treatment arms for the marginal distributions of the following stratification factors: center, type of primary cancer (lung vs. breast vs. other), planned concurrent radiation therapy (yes vs. no), and degree of anemia (Hgb level < 9 g/dL vs. ≥ 9 g/dL). The procedure was carried out centrally.

Blinding of the study drug vials was achieved by use of a 2-part label containing identical information. One part of the label was removed at the time drug was dispensed. The portion of the label remaining attached to the vial contained a hidden panel, which in the event of an emergency could be uncovered to reveal the identification of the study drug (PROCRIT 20,000 U/mL or placebo 20,000 U/mL).

Data Safety Monitoring and Interim Analyses

[redacted] reviews all Phase 3 cancer treatment and cancer control trials coordinated [redacted]. The primary functions of the [redacted] are to a) assure safety of the treatment regimens, b) examine efficacy results and determine whether or not the trial should be continued, modified, or discontinued, c) review changes in study design to promote the scientific integrity of the trial, d) review accrual information to assure that the trial will yield meaningful results, and e) review requests for release of data to investigators prior to general release as specified in the trial design.

The [redacted] meetings at which this study was reviewed took place on April 13, 1999, October 14, 1999, April 11, 2000, September 26, 2000, April 24, 2001, and October 24, 2001. The interim analyses reported to the [redacted] included differences between treatment arms for QOL, survival times, and toxicities (adverse events). Both the efficacy and toxicity data were blinded by treatment group (only the lead statistician and master's level statistician from the [redacted] were unblinded).

At the April 13 and October 14, 1999 meetings, the recommendation of the Committee was to continue the study per protocol. At the April 11, 2000 meeting, the submitted report showed a potential difference in survival between the 2 arms of the study based on a very small number of events and limited sample size. The [redacted] noted the result and requested a specific update on the survival endpoint at the next meeting; the Committee voted unanimously to continue the study per the protocol. At the September 26, 2000 [redacted] meeting, updated survival information showed that the previously observed preliminary potential survival difference had dissipated. The [redacted] voted unanimously to recommend that the study be continued.

At the April 24, 2001 meeting, the [redacted] voted unanimously to continue the study per the protocol. At the October 24, 2001 meeting, the Committee voted unanimously to release the data to the [redacted] study team and to terminate [redacted] monitoring in January 2002.

Dosage and Administration

The treatment schedule called for administering the study drug (epoetin alfa 40,000 IU or placebo) by subcutaneous injection once weekly, with modifications to the dose as specified below. Nursing guidelines concerning study drug handling and symptoms that can occur after study drug administration were provided in the study protocol. The

injections could be given by a patient or a family member trained in self-administration. The nurse instructed the patient or family member in subcutaneous injection techniques.

Dosage Modification

The dose of study drug could be changed based on subject response and toxicity findings as follows:

- After 4 weeks of therapy, if hemoglobin had not increased by >lg/dL independent of transfusional support, the study drug was to be increased to 60,000 IU s.c. per week.
- If a subject received transfusion(s) during the first 4 weeks of therapy, the study drug was to be increased to 60,000 IU s.c. per week (after the first 4 weeks of therapy).
- If hemoglobin was >15 g/dL, it was to be repeated one week later. If>15 g/dL, it was to be checked weekly and the treatment was to be withheld until hemoglobin dropped to <13.0 g/dL. The dose level of the study drug was to be decreased 25%.
- If the systolic blood pressure was >180 mmHg or the diastolic pressure was >110 mmHg, the dose was to be held until the hypertension was controlled, and the dose was to be resumed at the same dose level.

Treatment Compliance

Because this was [redacted] study, it was not monitored by the applicant sponsor. Therefore, information on study drug dispensed and returned by individual subjects was not available to the applicant. [redacted] was responsible for keeping records of investigational drug requests and out-going packing slips for proof of distribution and for drug accountability.

The following information on dosing was recorded on the subject's Evaluation/Treatment form at each cycle evaluation (terms in italics represent the wording on the forms): *Agent start date, Dose level this cycle* (this represented the first dose of the cycle). *Total dose this cycle. Was dose level adjusted this cycle?, and Reason for dose adjustment (Hb > 15 g/dL, Hb not increased, or Other* (with line for specifying the other reason), *Was the Study Drug Held? and Primary Reason (Hb >15 g/dL, Blood Pressure >180Systolic/>110 diastolic or Other* (with a line for specifying the other reason).

Ancillary Therapy

Ferrous Sulfate

An oral supplement of ferrous sulfate, 324 mg, or equivalent commercially available iron supplement, was to be taken by the study subject each day. If a subject was unable to tolerate 324 mg because of gastrointestinal intolerance (e.g., dyspepsia, diarrhea, constipation), the dose of ferrous sulfate was to be reduced to a tolerated dose. If the subject was unable to tolerate any dose of ferrous sulfate, the supplement was to be discontinued but the subject was to continue on the study.

The dose of the oral iron supplement was to be recorded on each subject's study forms at baseline and at each cycle evaluation. Any adjustments to the dose, together with the reason for adjustment (gastrointestinal intolerance or Other) were also to be recorded at each cycle evaluation.

Blood Transfusions

Subjects could receive RBC transfusions at the discretion of the physician. The hemoglobin value that led to the decision for transfusion was to be recorded on the

flow sheet. At each cycle evaluation, the administration of any RBC transfusion was to be indicated, together with the total number of units administered, on the Concurrent Treatment Log.

Chemotherapies

The regimen and start date of concurrent chemotherapy were to be recorded on the On-Study Form. Previous chemotherapy regimens were to be recorded also. The doses of regimens containing cis-platinum were to be provided. To allow a more complete presentation of the doses for all chemotherapy regimens, a new form "Concurrent & Previous Therapy;
Baseline Weight" was used after study completion to collect drug name, dose level, start and end dates for chemotherapies administered during the study and for chemotherapies administered in the 3 months prior to study entry; and the baseline body weight. The study was not to interfere with any treatment decision regarding antitumor therapy.

Radiotherapy

The use of previous radiotherapy or planned or concurrent radiotherapy was to be recorded on the On-Study Form, giving the site and total dose.

Study Evaluations

Time and Events Schedule

The scheduling of study procedures is shown below. While on study treatment, subjects were to be seen every 4 weeks for evaluation.

All evaluations were to be conducted by a [redacted] physician at a [redacted] institution.

The dates for study evaluations were to be scheduled as follows:

Cycle 1 evaluation to occur at Week 4 (Day 28) on study;
Cycle 2 evaluation to occur at Week 8 (Day 56) on study;
Cycle 3 evaluation to occur at Week 12 (Day 84) on study;
Cycle 4 evaluation to occur at Week 16 (Day 112) on study.

It should be noted that the term "Cycle" refers to the scheduled 4-week treatment periods and does not refer to chemotherapy cycles. Following the treatment period, there was an event-monitoring phase that extended for 12 months from the time the subject was registered for the study. Events monitored were deaths, new malignancies, and long-term toxicities. The sites were supplied with a Forms Packet for each subject which contained the case report forms to be completed for the study.

Efficacy Evaluations RBC Transfusions

Transfusion history was recorded at baseline for the prior 3 months, with dates of transfusion and number of units. Transfusions during study treatment (the total number of units for the cycle) were recorded at each cycle evaluation. Because specific dates of transfusions were not required on the study forms for the on-study transfusions, this information was obtained retrospectively to allow the determination of the number of transfusions administered before or after Day 28 of the study, i.e., on or after Day 29 to individual study end.

Hemoglobin Measurements
Hemoglobin concentrations were measured within 7 days prior to registering the subject and at each cycle evaluation. Hemoglobin was also measured prior to each RBC transfusion.

Serum Erythropoietin
Serum erythropoietin concentrations were measured within 30 days prior to subject registration and at the end of Cycle 1 of treatment. Erythropoietin measurements were performed at [redacted] Ferritin concentrations were measured within 7 days prior to subject registration in the study and at the end of Cycle 1.

Incidence of Nephrotoxicity
Evaluation of nephrotoxicity was based on investigators' reporting and toxicity grading of serum creatinine at each cycle evaluation.

Overall Survival
If death occurred, the study site was to submit an Event Monitoring Form to the [redacted] office, giving the date of death or last contact, and the cause of death, specifying the cancer or other cause of death.

Tumor Response to Concurrent Chemotherapy
Tumor response was estimated by investigators at baseline and at the end of therapy using the following terms: complete response, partial response (measurable disease only), regression (evaluable disease only), stable, or progression. At baseline, the tumor response was the response of the subject's advanced cancer to the chemotherapy being received at the time the subject entered the study. (Note: Actual tumor measurements were not recorded for this study.)

ECOG Performance Status:
The subject's ECOG performance grade was recorded at baseline (within <7 days prior to registration) and at each cycle evaluation.

Quality of Life Assessments
Quality of life questionnaires were completed by the study subjects at baseline, i.e., within 7 days of registration into the study, and at each cycle evaluation. The questionnaires, which required about 10 to 15 minutes to answer, were completed before the subjects were seen by the [redacted] physician. Subjects who discontinued study treatment were still to have QoL assessments completed though 16 weeks. The QoL measurements included
FACT-An Scale (from which FACT-An Fatigue subscale and FACT-G subscale were derived), UNISCALE and Symptom Distress Scale (SDS).

Safety Evaluations
Certain data collected for efficacy evaluations also contributed to safety evaluations. In addition, the following data were collected:

Adverse Events

Adverse events (toxicities) were recorded on an Adverse Event Log for each treatment cycle using the NCI Common Toxicity Criteria Manual, Version 2.0. The relationship of each toxicity to study drug was also recorded as 1 = not related, 2 = unlikely, 3 = possible, 4 = probable, 5 = definite. Adverse events were recorded by evaluation cycle; the onset date and duration of the adverse event were not recorded. In the NCI CTC system, adverse events due to the underlying disease were not to be graded.

Subjects discontinuing the study before the evaluation cycle visit were not required to have an additional completion/withdrawal visit; hence, some toxicities that occurred in the last incomplete evaluation cycle may not have been recorded on the study forms. However, any adverse event that led to withdrawal of a subject from the study was recorded on the forms.

An indication was also given on the Adverse Event Log if an Adverse Drug Reaction (ADR) report had been submitted for the cycle. The protocol specified that all unexpected Grade 4-5 ADRs or an increased incidence of a known ADR (i.e., an ADR that has been reported in the package insert or the literature) be reported on FDA Form 3500 (MedWatch form) to the [redacted] office and to the local IRB/IEC within 5 days. The [redacted] Office was also to fax a copy of the ADR to designated personnel at [redacted] was to route reportable ADRs.

For the purposes of this report, J&JPRD medical personnel [redacted] retrospectively adapted the CTC toxicity reporting system to approximate J&JPRD safety reporting requirements for serious adverse events (SAEs) by classifying all reported Grade 3 or 4 toxicities and all deaths as SAEs. Deaths not due to disease progression were reported as Grade 5 toxicities. All deaths were reported on Event Monitoring forms from the subjects' Forms Packet. In addition, safety information reported on MedWatch forms (as described above) and Hospitalization Notification forms was reviewed.

Blood Pressure

To evaluate the occurrence of hypertension, systolic and diastolic blood pressure readings were recorded at baseline and at each cycle evaluation. A subdictionary for thrombotic vascular events based on World Health Organization Adverse Reaction Terminology, 4th quarter, 1997, was developed previously by J&JPRD.

Clinical Laboratory Tests
Hematology (WBC, platelets, and hemoglobin) and serum creatinine tests were performed at baseline (<7 days prior to registration), and at each cycle evaluation. Measurements of total bilirubin, alkaline phosphatase, and SGOT were performed only within <30 days prior to registration to determine patient eligibility for the study. All clinical laboratory tests were performed by a local laboratory.

Data Quality Assurance
Database "snapshots" of this study were created by the [redacted] group while database cleaning was ongoing following study completion and unblinding to the [redacted] investigative team; this was consistent with [redacted] standard procedures. After the SAP was agreed upon [redacted], a series of summary tables and data listings were generated [redacted] and shared with J&JPRD. J&JPRD personnel reviewed these tables and listings to assist in identifying missing data required for regulatory submission. The study sites were then contacted by the [redacted] office, via written queries, to obtain missing data or clarifications. Data entry and control of the original database remained with [redacted]

The study population, statistical analysis plan, safety and efficacy conclusions for this study have all been described in detail in the safety and efficacy sections of this review.

6.2 Other Trials

EPO-PHI-377:

This was a Phase 1 pharmacokinetic/pharmacodynamic study to compare once-weekly and three-times weekly dosing in anemic cancer patients as well as in healthy volunteers. In depth review of both these PK/PD studies can be found in Dr. Hong Zhao's clinical pharmacology review and is not included here. Safety data in this small population of cancer patients in the study (n=15 Epoetin alfa 150 units/kg 3 times/week for six weeks; n=18 Epoetin alfa 40,000 units weekly for 6 weeks) were also provided.

The following table shows the demographics of the anemic cancer patients in the study:

Table 41: Demographic and Baseline Characteristics
(Study EPO-PHI-377: Anemic Cancer Subjects; Safety Population)

	Epoetin Alfa 150 IU/kg t.i.w (N=15)	Epoetin Alfa 40, 000 IU q.w. (N=18)	Total (N=33)
Age (year)			
Mean (SD)	62.1 (12.49)	56.7 (11.40)	59.2 (12.04)
Median	67.0	58.5	60.0
Range	(42-77)	(31-72)	(31-77)
Sex (n, %)			
Male	9(60)	2(11)	11(33)
Female	6(40)	16(89)	22(67)
Race (n, %)			
White	12(80)	11(61)	23(70)
Black	1(7)	3(17)	4(12)
Asian	0	0	0
Other[a]	2(13)	4(22)	6(18)
Weight (kg)			
Mean (SD)	73.9 (9.47)	68.1 (10.70)	70.8 (10.43)
Median	70.5	68.4	69.5
Range	(56.8- 90.6)	(50.9- 94.1)	(50.9- 94.1)
Height (cm)			
Mean (SD)	171.7 (8.89)	163.5 (7.71)	167.2 (9.12)
Median	172.7	165.1	167.6
Range	(160.0-185.4)	(143.5-177.8)	(143.5-185.4)
Diagnosis of malignancy			
Solid	13(87)	14(78)	27(82)
Breast	2(13)	7(39)	9(27)
Lung	6(40)	3(17)	9(27)
Small cell	4(27)	0	4(12)
Non-small cell	2(13)	3(17)	5(15)
Gastrointestinal	2(13)	1(6)	3(9)
Gynecologic	1(7)	2(11)	3(9)
Esophagus	1(7)	1(6)	2(6)
Pancreas	1(7)	0	1(3)
Bladder	0	0	0
Kidney	0	0	0
Hematological	0	0	0
Other[b]	2(13)	4(22)	6(18)
Chemotherapy stratification			
Platinum	8(53)	9(50)	17(52)
Nonplatinum	7(47)	9(50)	16(48)

[a] Other=Hispanic (1), Native American/Black (1) for the 150 IU/kg t.i.w. group; Hispanic (3), Puerto Rican (1) in the 40,000 IU q.w. group

[b] Other = melanoma (1), squamous cancer of left pharynx (1) for the 150 IU/kg t.i.w. group; malignant peripheral nerve sheath of high-grade variant with metastasis (1), melanoma (1), neuroendocrine carcinoma (1), prostate (1), for the 40,000 IU q.w. group The stratification was based on planned chemotherapy.

One patient died in the study from progression of non-small cell cancer 17 days after last dose of epoetin alfa at 150 units/kg and thought to be unrelated to the treatment. Other safety data showed that 88% of the anemic cancer subjects overall reported an adverse event (87% of the anemic cancer

subjects who received epoetin alfa 150 IU/kg t.i.w. and 89% of the anemic cancer subjects who received 40,000 IU q.w. The most frequently-reported adverse event among all anemic cancer subjects was nausea (6 [18%] subjects), followed by diarrhea, vomiting, and fever (each reported. for 5 [15%] subjects). The adverse event profiles for the 2 anemic cancer subject treatment groups were generally similar. The following table describes the incidence of treatment emergent adverse events in 10% or more of the study population.

Table 42: Incidence of Treatment-Emergent Adverse Events (≥ 10% in Either Treatment Group) by Preferred Term
(Study EPO-PHI-377: Anemic Cancer Subjects; Safety Population)

Body System Preferred Term	Epoetin Alfa 150IU/kg t.i.w. (N=15) n (%)	Epoetin Alfa 40,000 IU q.w. (N=18) n (%)	Total (N=33) n (%)
Any adverse event	**13(87)**	**16(89)**	**29(88)**
Gastro-intestinal system disorders	**11(73)**	**5(28)**	**16(48)**
Nausea	4(27)	2(11)	6(18)
Diarrhea	3(20)	2(11)	*5(15)*
Vomiting	3(20)	2(11)	*5(15)*
Abdominal pain	2(13)	1(6)	3(9)
Constipation	3(20)	0	3(9)
Body as a whole-general disorders	**7(47)**	**6(33)**	**13(39)**
Fever	1(7)	4(22)	*5(15)*
Fatigue	2(13)	2(11)	4(12)
Pain	3(20)	0	3(9)
Hot flushes	0	2(11)	2(6)
CNS disorders	**4(27)**	**5(28)**	**9(27)**
Headache	1(7)	2(11)	3(9)
Hypoaesthesia	2(13)	0	2(6)
Metabolic and nutritional disorders	**3(20)**	**4(22)**	**7(21)**
Dehydration	1(7)	2(11)	3(9)
Respiratory system disorders	**4(27)**	**3(17)**	**7(21)**
Pneumonia	2(13)	1(6)	3(9)
Coughing	0	2(11)	2(6)
Psychiatric disorders	**3(20)**	**3(17)**	**6(18)**
Insomnia	2(13)	1(6)	3(9)
Anorexia	0	2(11)	2(6)
Anxiety	0	2(11)	2(6)
Musculo-skeletal system disorders	**3(20)**	**2(11)**	**5(15)**
Myalgia	2(13)	1(6)	3(9)
Skin and appendages disorders	**2(13)**	**3(17)**	**5(15)**
Localized skin reaction	1(7)	2(11)	3(9)
Cardiovascular disorders, general	**2(13)**	**2(11)**	**4(12)**
Cardiac failure	2(13)	0	2(6)
Urinary system disorders	**3(20)**	**1(6)**	**4(12)**
White cell and RES disorders	**1(7)**	**3(17)**	**4(12)**
Leucopenia	0	3(17)	3(9)
Platelet, bleeding & clotting disorders	**2(13)**	**1(6)**	**3(9)**
Thrombocytopenia	2(13)	0	2(6)
Resistance mechanism disorders	**1(7)**	**2(11)**	**3(9)**
Moniliasis	0	2(11)	2(6)

Key: CNS=central nervous system; RES=reticulo-endothelial system

As can be seen, the adverse events profile in this small study showed comparability between the two study arms.

6.3 Literature Review and Other Relevant Materials

Review of Literature suggests frequent use of once weekly dosing in clinical practice. It is possible that a 3 times-per-week dosing regimen is inconvenient in many patient populations, including oncology patients, largely because of shift in medical practice towards outpatient management of patients. A major benefit of once-a-week dosing would be to reduce the frequency of injections and thereby improve compliance. The sponsor has provided a literature review of studies that employed a once a week dosing and are briefly summarized here. While these studies may not have the rigor of a registration trial, they do bolster the argument that once weekly dosing of epoetin alfa is safe and effective.

Studies in Cancer patients With Once weekly dosing of Epoetin Alfa:

Shasha et al (ref.1) conducted a multicenter study to evaluate the clinical outcomes, efficacy, and safety of once-weekly dosing of epoetin alfa (PROCRIT) in anemic cancer patients with nonmyeloid malignancies receiving radiotherapy either concomitantly or sequentially with chemotherapy. Subjects received an initial fixed dose (40,000 ill q.w.) of epoetin alfa with potential dose escalation (to 60,000 IU q.w.). The overall response rate to r-HuEPO was 73.7%; 29.9% of patients required a dose increase. Both hemoglobin levels and QOL (energy score, activity score, overall QOL score) improved significantly ($p<0.05$) and transfusion requirements were decreased. In sum, once-weekly dosing with epoetin alfa was well tolerated and effective in anemic patients with nonmyeloid malignancies receiving radiotherapy either concomitantly or sequentially with chemotherapy.

Gabrilove et al (ref. 2) conducted a large, prospective, community-based study to evaluate the impact of epoetin alfa (PROCRIT) on QOL, transfusion requirements, and hemoglobin levels in anemic cancer patients with nonmyeloid malignancies undergoing chemotherapy. Subjects received an initial fixed dose (40,000 IU q.w.) of epoetin alfa with potential dose escalation (to 60,000 IU q.w.). Patients whose hemoglobin level exceeded 13 g/dL had epoetin alfa therapy interrupted until their hemoglobin level fell to 12 g/dL. Treatment with epoetin alfa was resumed at 75% of the previous dose and titrated to maintain the desired hemoglobin level. A hematopoietic response to epoetin alfa therapy was defined as an increase in hemoglobin $\geq$2 g/dL or achieving a hemoglobin level of 12 g/dL at any point during the study, with no transfusions within the previous 30 days. Of the 2,869 assessable subjects with at least 2 hemoglobin

measurements, there was a significant ($p<0.001$) mean increase in hemoglobin of 1.8 ± 1.8 g/dL from baseline to mean final hemoglobin (11.3 ± 1.8 g/dL). The hematopoietic response rate to r-HuEPO 40,000 IU q.w. was 49.2%. A total of 33.4% of patients required dose escalation (to 60,000 IU) throughout the 16-week study period. When these latter patients were included, the overall response rate increased to 68%. With respect to transfusion requirements, the percentage of patients who required transfusions as well as the number of units of blood transfused per patient decreased by 8 weeks ($p<0.007$) and continued to decrease throughout the remainder of the study. With respect to QOL, once-weekly epoetin alfa therapy resulted in significant improvements in energy level, ability to perform daily tasks, and overall QOL (as assessed by LASA). Furthermore, improvements in QOL parameters correlated significantly ($p<0.001$) with increased hemoglobin levels (as assessed by the Functional Assessment of Cancer Therapy-Anemia [FACT-An] Questionnaire). This latter finding was maintained throughout the entire 16-week study period.

Samuel et al (ref. 3) conducted a retrospective review on anemic cancer patients with solid tumors and lymphomas receiving chemotherapy. Nineteen (86%) of 22 subjects had Stage IV disease. Subjects were evaluated for the effect of epoetin alfa (PROCRIT) on hemoglobin/hematocrit levels and QOL. Subjects received an initial fixed dose (40,000 IU q.w.) of epoetin alfa with potential dose escalation (to 60,000 IU q.w.). Treatment was discontinued if no response was observed after 8 weeks of treatment. If hematocrit levels reached 40% or greater, r-HuEPO therapy was withheld until the hematocrit declined to 36%. Iron supplementation was administered as needed. Results showed improvement in hemoglobin levels in 11 (50%) of 22 subjects at 4 weeks; no hemoglobin response was observed in 6 subjects. Five subjects required a higher r-HuEPO dose (i.e., 60,000 IU); 2 of these subjects showed no hemoglobin response. Improvement in QOL was also noted in 11 (50%) subjects at 4 weeks; 5 subjects did not show improvement in QOL.

A placebo-controlled pilot study was conducted by O'Shaughnessy et al (ref. 4) to study the impact of once weekly epoetin alfa therapy on hemoglobin, cognitive function, mood, asthenia, and QOL in anemic breast cancer patients receiving chemotherapy. Patients were randomly assigned to receive 40,000 IU epoetin alfa once weekly s.c. or placebo while receiving 4 cycles of chemotherapy over a 3-month period. Data were available for 65 out of 93 patients (36, epoetin alfa, 29, placebo). Mean hemoglobin changes from baseline through 4 cycles of chemotherapy were significantly improved in the group receiving epoetin alfa compared with placebo ($p<0.001$). Furthermore, results

indicated that epoetin alfa administered once weekly can significantly improve asthenia and mood symptoms, attenuate QOL decline, and may improve cognitive function (sample size too small to determine statistical significance) compared with patients receiving placebo.

In a phase II multicenter trial, the effect of once weekly epoetin alfa was evaluated by Rosen et al (ref 5) in anemic patients with head and neck cancers receiving a novel chemoradiotherapy regimen (i.e., I-hour paclitaxel infusion, fluorouracil, hydroxyurea and twice-daily radiation) Patients were randomly assigned to receive either 40,000 IU epoetin alfa s.c. or no epoetin therapy. The objective of epoetin alfa therapy was to maintain baseline hemoglobin levels or increase hemoglobin during chemoradiation and prevent or reduce transfusion requirements. Results of the study showed that grade 2/3 hemoglobin toxicity occurred less frequently in epoetin-treated patients than in those not receiving epoetin therapy (52% versus 77%; p=0.02). While there was a positive trend for fewer transfusions in epoetin-treated patients compared with patients who did not receive epoetin therapy (40% versus 56%; p=0.20), the difference was not statistically significant.

Two smaller open label piolot studies (Chap et al and Patten et al Ref. 6,7) that employed initial 60,000 IU epoetin alfa s.c. weekly in anemic cancer patients with nonmyeloid malignancies receiving chemotherapy showed that 60,000 IU epoetin alfa administered once weekly is effective in increasing hemoglobin levels in anemic cancer patients receiving chemotherapy.

Studies in patients without cancer With Once weekly dosing of Epoetin Alfa
Once weekly dosing of Epoetin Alfa has been used in several studies that showed its effectiveness and safety in increasing hemoglobin levels and reducing transfusion requirements in patients with chronic renal failure (predialysis and dialysis ref. 8-11), and in HIV-positive patients who are receiving ZDV therapy as well as those who are not receiving ZDV therapy (ref 12,13). This dosing regimen has also been shown to successfully reduce the use of allogeneic blood transfusions in the peri surgical setting (ref. 14-15).

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103234s5053

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	s-BLA STN # 103234 / 5053
Drug Name:	Recombinant Human Erytropoietin (Epoetin alfa) (Procrit)
Indication(s):	Alternative weekly dosing for the use of Epoetin alfa in anemic patients with non-myeloid malignancies, where anemia is due to chemotherapy
Applicant:	Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
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Keywords: TVE (thrombovascular event), Hgb (hemoglobin concentration), LOCF (last observation carried forward), MVCR (minimum value carried forward), AVCF (average value carried forward),

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1. EXECUTIVE SUMMARY

s-BLA STN #103234/5053 is a supplemental biologics application for the use of Epoetin alfa for the treatment of anemia via alternative weekly dosing in anemic patients with non-myeloid malignancies, where anemia is due to chemotherapy. Major evidence presented by the sponsor included one pivotal randomized controlled study, #PR98-27-008 [redacted] This study was conducted as a [redacted] with the [redacted] as the research base. Epoetin alfa is currently approved for the treatment of anemia in cancer patients on chemotherapy when administered subcutaneously (s.c.) 3 times a week at a recommended starting dose of 150 IU/kg.

1.1 Conclusions and Recommendations

The major statistical issue is that data on the primary efficacy endpoint of this trial (transfusion rate after 28 days of treatment) did not yield a statistically significant improvement when using the pre-specified non-responder (worst outcome) imputation method for dealing with missing data. The sponsor presented a rationale and several reasonable alternative imputation strategies, which indicated that using non-responder imputation biased results against the Epoetin alfa treatment arm. This reviewer's analyses of the major efficacy endpoints, based on the electronic database provided, confirm the sponsor's rationale and reported statistical findings.

1.2 Brief Overview of Clinical Studies

One clinical study constitutes the major evidence for this supplemental BLA submission. This is Study #PR98-27-008 [redacted]. The original primary objective of this study was to assess the effect of a single weekly dose of Epoetin alfa on health related quality of life (QOL) in cancer patients undergoing chemotherapy. However, because a secondary objective of the protocol was to assess transfusion requirements during treatment, it was apparent that the transfusion data, together with other data from the study, could reveal if a single weekly s.c. dose of Epoetin alfa, at 40,000 to 60,000 IU, is effective in treating anemia in cancer patients receiving chemotherapy. Agreement was reached with the Agency that for purposes of this submission, the primary endpoint would be the transfusion rate following 28 days of treatment, while QOL and other objectives in the [redacted] protocol would be secondary endpoints. A Statistical Analysis Plan (SAP), with the primary endpoint of transfusion rate after Day 28, was prepared in a collaboration between [redacted] and J&JPRD and was submitted to FDA. The plan was found acceptable to the FDA on April 16, 2002, after revisions were incorporated. All data for the study were entered into a [redacted] database, and all analyses were performed by [redacted] statisticians. The database was officially locked on March 10, 2003. The clinical study report (CSR) was prepared by J&JPRD for purposes of this regulatory submission. The CSR summarizes data from the 16-week, double-blind treatment period. However, survival data are summarized beyond that period, i.e., all survival data available at the time of report preparation are included. Additional follow-up safety and survival data were provided in a 4-month safety update to the supplemental BLA.

1.3 Statistical Issues and Findings

The primary efficacy analysis was based on the difference in proportions transfused in the ITT population. The pre-specified non-responder (worst outcome) imputation analysis of subjects receiving RBC transfusions after treatment Day 28 until individual study end yielded an estimated difference of –9.8% favoring the Epoetin alfa group which reached borderline statistical significance (p=0.069, Chi square test; p=0.071, adjusted logistic regression analysis). Five additional imputation analyses, previously discussed with the FDA, yielded estimated rate differences that consistently favored the Epoetin alfa group over the placebo group (range: -10% to –16%); all of these differences were statistically significant ($p < 0.05$). The mean number of RBC units transfused/subject in the placebo group (1.5 units) was approximately twice that in the Epoetin alfa group (0.7 units). The mean number of units transfused/100 subject-days was statistically significantly lower in the Epoetin alfa group ($p < 0.0001$). There was a marked difference in hemoglobin response, favoring the Epoetin alfa group. Survival experience, based on the 4 month safety update, was similar in the two treatment groups. The safety profiles for the two treatment groups appeared similar. Although there were more subjects with thrombotic vascular events (TVE's) in the Epoetin alfa group than in the placebo group (i.e., 8 vs. 5), examination of TVE occurrences in relation to hemoglobin increases did not reveal any consistent findings suggesting a relationship between the rate of hemoglobin rise and the occurrence of TVE's.

2. INTRODUCTION

2.1 Overview

General Background on Study Agent and Disease Indication: Patients with a malignancy commonly become anemic during the course of their disease. The causes of the anemia may be marrow replacement by tumor cells, suppression of marrow reticulocyte production by cytokines released or induced by malignant cells, blood loss, or the myelosuppressive effects of chemotherapy or radiotherapy. Patients with anemia frequently experience fatigue, which can reduce performance status and impair ability to work or perform daily activities. Blood transfusions can be given to correct anemia in cancer patients. However, transfusions are costly in terms of both time and resource requirements and may be associated with significant side effects. Side effects such as transfusion reactions and sensitization to future blood products are possible, and there is some risk that transmission of infectious agents, such as cytomegalovirus, hepatitis C virus, human immunodeficiency virus, and prions may occur. The drug Epoetin alfa is an alternative to blood transfusion for the treatment of anemia in cancer patients on chemotherapy. In clinical studies, the administration of Epoetin alfa has been demonstrated to raise the hemoglobin of patients with multiple myeloma and other cancers.

2.2 Data Sources

The relevant study report and supporting documenation were provided in paper format. The electronic data sets comprised raw and derived SAS transport data sets for the [redacted] study. SAS programs for the major efficacy analyses were also provided electronically. CD-ROM's were the media used.

3. STATISTICAL EVALUATION

The statistical analyses performed on the [redacted] study were initially specified in the study protocol. Further details of the planned statistical analyses were provided in the statistical analysis plan (SAP) that was approved by the FDA on April 16, 2003. Statistical analyses were performed by the [redacted] using a database lock date of March 10, 2003.

3.1 Evaluation of Efficacy

3.1.1 [redacted] Study

3.1.1.1 Design

This was a multi-center, randomized, double-blind, placebo-controlled study conducted by [redacted] in the North Central United States and Saskatchewan, Canada. The planned enrolment was 330 subjects with anemia who were receiving myelosuppressive cytotoxic chemotherapy for advanced cancer. Eligible patients were randomized in a 1:1 ratio to Epoetin alfa or placebo treatment, with stratification by center (investigator), type of primary cancer (lung, breast, or other), planned concurrent radiation therapy (yes vs. no), and degree of anemia (hemoglobin < 9 g/dL vs. ≥ 9 g/dL). The double-blind treatment was administered for a maximum of 16 weeks, after which the subjects were followed for one year from the time of randomization for event monitoring (death, new primary malignancies, and long-term toxicities). The dose of double-blind study medication (40,000 IU of Epoetin alfa or corresponding placebo) was to be administered by s.c. injection, once weekly. If after 4 weeks of therapy hemoglobin (Hgb) concentrations had not increased by > 1 g/dL or if the subject had received a transfusion during the first 4 weeks of therapy, the weekly dose of study drug was to be increased to 60,000 IU once weekly. If, at any time during the study, the Hgb concentration exceeded 15 g/dL, Hgb was to be determined one week later. If the Hgb exceeded 15 g/dL, study drug was to be witheld and Hgb was to be determined weekly until it fell below 13 g/dL. Study drug was then to be restarted at a dose level 25% less than that previously administered. During double-blind treatment, subjects were to receive a daily oral iron supplement. All subjects could receive RBC transfusions at the discretion of the physician. A Hgb determination was to be obtained at the time of transfusion. Subjects who discontinued chemotherapy during the double-blind period were to continue the study treatment through 16 weeks.

Amendments: There were 3 amendments to the protocol. Addendum 1 on March 5, 1999, updated the [redacted] nurse contact. This addendum also specified that the submission of the Concurrent Treatment Log with the on-study materials was no longer required and added a question regarding oral iron supplementation to the On-Study form. Addendum 2 on May 11, 2001, updated the consent from to reflect current [redacted] IRB formatting guidelines. Addendum 3 on September 28, 2001, closed the study to subject accrual.

Study Populations: The number of subjects actually enrolled was 344. In accord with [redacted] definitions, any subject who did not receive any study treatment before removal from the study was designated a "cancellation." However, these subjects were included in the ITT (intent-to-treat) population, which was the primary efficacy population. The QOL population consisted of all ITT subjects having a baseline and at least one follow-up QOL assessment. Selected efficacy analyses were also performed on the evaluable-for-efficacy population that included all treated

subjects, excluding subjects classified as ineligible or as having major protocol violations. In addition to analyses with formal statistical inferences provided for the two treatment comparisons, descriptive statistics for specified efficacy variables were to be provided for the subgroups defined by the following variables: type of primary cancer, planned concurrent radiation therapy, degree of anemia, and planned chemotherapy type (cis-platinum based or non-cis-platinum based). All statistical tests were 2-sided. Main effects were tested at the.05 significance level; interaction terms were tested at the 0.10 significance level.

Randomization: Study treatment could begin prior to registration but was required to begin ≤ 7 days after registration. Randomization was conducted in a 1:1 ratio using the dynamic allocation procedure of Pocock and Simon to balance the two treatment arms for the marginal distributions of the following stratification factors: center, type of primary cancer (lung vs. breast vs. other), planned concurrent radiation therapy (yes vs. no), and degree of anemia (Hgb level < 9 g/dL vs. ≥ 9 g/dL). The procedure was carried out centrally.

3.1.1.2 Endpoints and Results

Description of Primary Efficacy Variable:

The **primary efficacy endpoint** was the transfusion rate, defined as the proportion of subjects who required transfusions after 28 days from randomization, i.e., those occurring on or after Day 29 adjusted (via logistic regression) for the stratification factors (size of center, type of primary cancer, planned concurrent radiation therapy, and degree of anemia). Treatment effect was to be compared primarily using the adjusted odds ratio obtained from the model along with the 95% CI and the p-value. Unadjusted Chi-square tests based on crude transfusion rates and the difference in crude rates along with the 95% CI would also be presented. In addition, exploratory analyses for the transfusion rate would be performed using logistic regression models, adjusting for other prognostic factors specified in the SAP. Another analysis employed for the primary endpoint was time-to-event. Using transfusion status determined by LOCF (i.e., carrying forward a patient's last known transfusion status), the primary efficacy endpoint was further analyzed using the Kaplan-Meier method where subjects without transfusions after Day28, who either withdrew or completed the study, were considered as censored at the time of withdrawal or completion. The Kaplan-Meier estimate of the transfusion rate at Week 16 was obtained for each treatment group and Greenwood's method was used to calculate the corresponding standard error. The Normal approximation was then used to obtain the CI and p-value for the treatment comparison at Week 16. The time point of Week 16 was chosen because it was the end of the treatment duration planned in the protocol. Time to first transfusion after Day 28 was also compared for the two treatment arms via the logrank test.

Reviewer's Comment: Regarding the time to event analysis, Greenwood's formula provides a good estimate of the precision of a time-to-event curve when a reasonable number of subjects are still being followed up, but not in the tail of the curve, where misleading plateaux often occur. It is to be noted that the Statistical Analysis Plan (SAP) pre-specified the adjusted analysis utilizing logistic regression of transfusion status (yes/no) as the dependent variable, controlling for the

randomization stratification factors, as the primary analysis of the primary endpoint. The other analyses presented should be considered only supportive.

Description of Secondary Variables:

Change in Hemoglobin (Hgb) Concentration from Baseline: The mean change in Hgb concentration from baseline to the last value was to be presented for the two treatment groups. Treatment effect was to be estimated by the difference in the means along with the 95% CI. Student's t-test was to be used to test the equality of the means between the two treatment groups. ANCOVA adjusting for other prognostic factors was to be performed also. The main analysis on change in Hgb was based on available data. Sensitivity analysis on change in Hgb from the baseline to last value was conducted by imputing missing values via the following methods: last-value-carry-forward (LOCF), minimum-value-carry forward (MVCF), and average-value-carry-forward (AVCF).

Hemoglobin (Hgb) over Time: Hgb concentrations over time were to be analyzed using a mixed effects linear model for repeated measures. Terms in the model included treatment, time, covariates for demographic and baseline characteristics, and the time-by-treatment interaction term. The focus of this analysis was to be the slope parameter of the time variable that quantifies the rate of Hgb rise over time. Slope estimates for the two treatment groups, the difference in the slopes, the 95% CI of the difference, and the p-value were to be reported.

Incidence of Hemoglobin (Hgb) Concentration below 9.0 g/dL: The proportions of subjects with a Hgb concentration below 9.0 g/dL were to be presented for each treatment group. Treatment effect was to be estimated by the difference in proportions along with the 95% CI. A Chi-square test was used to test for equality of the proportions between the two treatment groups.

Number of Transfusion Units per Day Alive in the Study: For each of the two treatment groups, the number of transfusion units per day alive during the entire study would be calculated. This variable is a ratio-type estimate, i.e., both its numerator and denominator are random variables. Hence, an approximation based on relative variances to the standard error of a ratio would be used to calculate the standard error of this estimate for each treatment group. Normal approximation would be used to conduct the statistical test on the difference of the estimates and to obtain the 95% CI.

Incidence of Nephrotoxicity: The relative incidence of nephrotoxicity was ascertained by the investigators' CTC rating of serum creatinine determined in the subset of subjects receiving cis-platinum-based chemotherapy. The incidence was to be presented for the two treatment groups and tested using Fisher's exact test. The maximum reported toxicity grade over the course of the study was to be compared between the two treatment groups using the Wilcoxon rank-sum test.

Overall Survival: For this time-to-event variable, a survival analysis was conducted which included a Kaplan-Meier plot and the comparison of the two treatment groups via the logrank test. Median survival time was reported along with logrank test results.

Tumor Response: A descriptive summary of the number and percentage of subjects in each of the tumor response categories would be provided for the two treatment groups.

Quality of Life (QOL): A number of QOL scales were used, e.g., FACT-Anemia, SDS (symptom distress scale), and the UNISCALE. Scores for these scales were to be standardized by transforming them to a range of 0 – 100, with 0 representing the lowest QOL and 100 representing the highest QOL. The scores would be summarized using descriptive statistics. Inferential statistical analyses were to be performed on the AUC of the transformed scales for all QOL endpoints. QOL assessment dates were to be used to calculate the AUC. For the [redacted] primary QOL endpoint, FACT-AN Fatigue Scale, the treatment difference would be tested via the Wilcoxon Rank Sum test or the t-test depending upon the veracity of normality assumptions as determined by the Shapiro-Wilk test. O'Brien's multiple endpoint test statistic would be applied to the numerous secondary QOL endpoints. ANCOVA on each QOL endpoint would be performed with and without treatment-by-covariate interaction terms. If a significant treatment-by-covariate interaction was found to be present, further exploratory analyses on the corresponding subgroups would be conducted. Sensitivity analyses for each QOL scale would be conducted on the AUC endpoint, with missing data values imputed using the last-value-carried-forward (LVCF), the average-value-carried-forward (AVCF), and the minimum-value-carried-forward (MVCF) methods. A fourth sensitivity analysis would be conducted using the LVCF, but imputing a score of 0 when subjects died. In addition, an exploratory analysis of the correlation between changes in QOL and changes in Hgb would be presented using the Pearson correlation coefficient. Change in QOL was defined as the change from baseline to the last available assessment. The change in Hgb value used was the one most closely associated in time with the last available QOL assessment. The two change scores would be analyzed for correlation if any difference in day of measurement represented no more than a 15-day window. This analysis was to be based on combined data from the two treatment groups.

Reviewer's Comment on QOL Analyses: After extensive statistical analyses by [redacted] no QOL measure showed any statistical evidence of improvement. Thus, no further statistical review comments will be forthcoming on QOL endpoints.

Determination of Sample Size: This study was powered originally for the QOL analyses and not for the transfusion rate analysis. Based on the QOL calculations, it was determined that a sample size of 300 (i.e., 150 subjects/treatment group) was required. Assuming a 10% attrition rate, a total of 330 subjects (165 per group) was planned. In terms of the transfusion rate, a sample size of 300 (150 per group) would provide 80% power to detect a difference of 16% or more between the two treatment groups. Standard two-sided binomial testing was assumed with a type I error rate of $\alpha = 0.05$.

Pooling of Study Centers: For analysis purposes, sites were grouped by large or small (enrollment of ≥ 15 or < 15 subjects per month on all [redacted] studies over the two year period from April 2000 to April 2002).

Missing Data Handling: The following pre-specified imputations were applied **to handle missing transfusion data or dates that were not due to withdrawal.** Transfusion status after

Day 28, determined using these imputations, was used throughout the transfusion data analyses. These imputations were as follows:

- If a subject had a missing evaluation cycle, this subject was considered as transfused during that cycle, and the transfusion date was imputed using the date of the next cycle evaluation minus 1 day.
- If a subject had missing transfusion status for a non-missing evaluation cycle, this subject was considered as transfused during the cycle, and the transfusion date was imputed using the cycle evaluation date.
- If a subject was known transfused in an evaluation cycle but the transfusion date was missing, the missing date was imputed using the cycle evaluation date.

For handling missing transfusion data that were due to withdrawals, the following strategy was employed. As stated in the SAP, subjects withdrawn from the study with no transfusion after Day 28 would be assumed as transfused in the analysis of the primary efficacy endpoint. When such data became available, it became clear that the result based on this imputation method introduced serious bias against Epoetin alfa treated subjects. To present these data in a way that was more reflective of the clinical outcomes of the study, the sponsor further analyzed the primary efficacy endpoint data using **four other plausible imputation methods**. All five imputation methods for withdrawals are described below. It is noted that, per the SAP, subjects who died on study were considered to have completed the study. **The five imputations used were as follows:**

1. As specified in the SAP, subjects who withdrew from the study without receiving a transfusion after Day 28 were considered as transfused.
2. Transfusion status for each withdrawn subject was determined by the actual transfusion occurrence after Day 28 without imputation.
3. Withdrawn subjects were considered as not transfused if they (1) withdrew from the study due to having a successful Hgb response indicated by the investigators and (2) they were not transfused after Day 28.
4. Withdrawn subjects were considered as not transfused if they (1) withdrew after having completed all 4 planned cycles and (2) were not transfused after Day 28.
5. Withdrawn subjects were considered as not transfused if they (1) withdrew due to disease progression and (2) were not transfused after Day 28.

Method 2 is essentially the last-observation-carried-forward (LOCF) method, where the patient's last transfusion status is carried forward.

Sponsor's Note: Upon examination of the characteristics of the withdrawals, it was observed that withdrawn subjects in the Epoetin alfa group had greater Hgb improvements and fewer transfusions than the withdrawals in the placebo group. It was also noticed that a number of subjects withdrew due to a successful HGB response; none were transfused after Day 28. The data also indicated that a number of subjects withdrew after completing all 4 cycles of evaluation, despite the fact that 4 cycles was the maximum number of evaluations planned per protocol. These observations provided the basis for imputation methods (3) and (4). Method (5) was considered because it was used in similar clinical trials reported in the literature (e.g., randomized Phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy). One of the necessary assumptions needed for this imputation method to be valid is that withdrawals due to disease progression are not treatment related. This imputation could be

appropriately used for this study because the numbers of subjects who withdrew due to disease progression were comparable between the two treatment arms.

Reviewer's Comment: Twenty six patients were withdrawn with progressive disease given as the reason. There were 13 such patients in each treatment arm. This reviewer's descriptive Kaplan-Meier analysis of time to progression showed very similar patterns by treatment arm; the estimated curves were almost super-imposable.

Efficacy Results:

Patient Disposition: A total of 344 subjects were registered and randomized into the study at 14 [redacted] study centers (13 in the U.S. and 1 in Canada). These subjects comprise the ITT population. The first subject was enrolled on December 4, 1998, and the study was closed to further enrollment on September 28, 2001. Enrollment by study center is presented below in **Table 1**. Enrollment at the "large" centers (see definition in Table 1) ranged from 8 to 72 subjects while enrollment at the "small" centers ranged from 2 to 42 subjects.

Table 1: Subject Enrollment by Center / [redacted] Study

Centers[a]	Placebo (n=170)	Epoetin alfa (n=174)	Total (n=344)
Large Centers, n (%)			
[redacted]	6 (4%)	5 (3%)	11 (3%)
	28 (16%)	27 (16%)	55 (16%)
	14 (8%)	13 (7%)	27 (8%)
	9 (5%)	12 (7%)	21 (6%)
	22 (13%)	21 (12%)	43 (13%)
	36 (21%)	36 (21%)	72 (21%)
	5 (3%)	3 (2%)	8 (2%)
Small Centers, n (%)			
[redacted]	20 (12%)	22 (13%)	42 (12%)
	12 (7%)	12 (7%)	24 (7%)
	5 (3%)	5 (3%)	10 (3%)
	3 (2%)	6 (3%)	9 (3%)
	5 (3%)	6 (3%)	11 (3%)
	5 (3%)	4 (2%)	9 (3%)
	0 (0%)	2 (1%)	2 (1%)

[a] Large centers were defined as [redacted] centers that entered at least 15 patients per month on all [redacted] studies over the 2-year period from April 2000 to April 2002

Table 1 indicates that balanced treatment assignment was achieved within study sites. **Table 2** below presents the breakdown of major demographic characteristics by treatment arm.

Table 2: Demographics and Baseline Characteristics for [redacted] Study (ITT population)

	Placebo (n=170)	Epoetin alfa (n=174)	Total (n=344)
Age (years)			
N	170	174	344
Mean (SD)	63.7 (13.09)	63.5 (11.80)	63.6 (12.43)
Median	66	64	66
Range	24 - 86	20 - 88	20 - 88
Gender (%)			
Female	96 (56%)	96 (55%)	192 (65%)
Male	74 (44%)	78 (45%)	152 (44%)
Race, n (%)			
Black	18 (11%)	10 (6%)	28 (8%)
Hispanic	1 (1%)	0 (0%)	1 (0%)
White	151 (89%)	164 (94%)	315 (92%)
Weight (kg)			
N	161	161	322
Mean (SD)	73.6 (16.24)	75.0 (17.20)	74.3 (16.72)
Median	71.9	74.0	72.6
Range	41.8 – 127.0	36.6 – 136.1	36.6 – 136.1
Previous chemotherapy, n (%)			
No	82 (48%)	79 (45%)	161 (47%)
Yes	88 (52%)	95 (55%)	183 (53%)
Previous radiotherapy, n (%)			
No	108 (64%)	109 (63%)	217 (63%)
Yes	62 (36%)	65 (37%)	127 (37%)
Type of malignant disease, n (%)			
Lung	49 (29%)	48 (28%)	97 (28%)
Breast	28 (16%)	28 (16%)	56 (16%)
Other[a]	93 (55%)	98 (56%)	191 (56%)
Planned concurrent radiotherapy, n (%)			
Yes	17 (10%)	18 (10%)	35 (10%)
No	153 (90%)	156 (90%)	309 (90%)
Degree of anemia, n (%)			
Mild (Hgb ≥ 9.0 g/dL)	117 (69%)	119 (68%)	236 (69%)
Severe (Hgb < 9.0 g/dL)	53 (31%)	55 (32%)	108 (31%)
Baseline tumor response, n (%)			
Missing	1 (1%)	1 (1%)	2 (1%)
Complete response	5 (3%)	4 (2%)	9 (3%)
Partial response (measurable dis.only)	19 (11%)	22 (13%)	41 (12%)
Regression	19 (11%)	26 (15%)	45 (13%)
Stable	93 (55%)	93 (53%)	186 (54%)

Progression	4 (2%)	7 (4%)	11 (3%)
Not applicable/Unknown	29 (17%)	21 (12%)	50 (15%)
ECOG status, n (%)			
0[b]	46 (27%)	37 (21%)	83 (24%)
1	124 (73%)	137 (79%)	261 (76%)
Iron supplement, n (%)			
Missing	3 (2%)	1 (1%)	4 (1%)
Yes	143 (84%)	153 (88%)	296 (86%)
No	24 (14%)	20 (11%)	44 (13%)

[a] The most common other cancer sites were gastrointestinal (60/344 subjects, 17%), myeloma (30/344 subjects, 9%), and gynecological (29/344 subjects, 8%).
[b] ECOG performance status scores: 0 = able to carry out all normal activity without restriction and 1 = restricted in physical strenuous activity but ambulatory and able to do light work.

Overall, the percentages of subjects in the ITT population who had received previous chemotherapy, had received previous radiotherapy, or planned concurrent radiation therapy were similar in the two treatment arms. The two groups were also comparable with respect to baseline tumor response, degree of anemia, and use of iron supplement. Overall, 183 (53%) of the subjects had received previous chemotherapy and 127 (37%) had received previous radiotherapy. The baseline tumor response was "stable" for 186 (54%) of the subjects. Sixty-nine percent of the subjects had mild anemia (Hgb ≥ 9 g/dL) rather than severe anemia (Hgb < 9g/dL). Iron supplements were used by 296 (86%) of the subjects. The types of malignant disease listed in the table were similarly represented in each treatment group. Overall, 28% of the subjects had lung malignancies, 16% had breast tumors, and 56% had "other" malignancies. The most frequently occurring "other" malignancies were gastrointestinal for 34/170 (20%) of subjects in the placebo group and 26/174 (15%) of subjects in the Epoetin alfa group; myeloma for 11/170 (6%) of subjects in the placebo group and 19/174 (11%) of subjects in the Epoetin alfa group; and gynecologic for 15/170 (9%) of subjects in the placebo group and 14/174 (8%) of subjects in the Epoetin alfa group. The distribution of ECOG performance scores (0 or 1) were slightly different in the two groups at baseline: 73% of subjects in the placebo group had a baseline score of 1 compared with 79% of subjects in the Epoetin alfa group. Baseline hemoglobin (Hgb) values are present in Table 3.

Table 3: Baseline Hemoglobin Values for ▬ Study

Hemoglobin (g/dL)	Placebo (n=170)	Epoetin alfa (n=174)	Total (n=344)
N	170	174	344
Mean (SD)	9.4 (0.93)	9.5 (0.94)	9.4 (0.93)
Median	9.5	9.6	9.6
Range	6.9 – 11.4	6.0 – 11.4	6.0 – 11.4

Hemoglobin values at baseline were comparable between the two treatment groups, with mean values of 9.4 g/dL in the placebo group and 9.5 g/dL in the Epoetin alfa group.

Data for pre-study blood transfusions, i.e., transfusions received within 3 months prior to the start of the study, are summarized in **Table 4**.

Table 4: Pre-study Transfusion Data for ▬ Study

	Placebo (n = 170)	Epoetin alfa (n = 174)	Total (n = 344)
Transfused pre-treatment,[a] n (%)			
No	143 (84%)	142 (82%)	285 (83%)
Yes	27 (16%)	32 (18%)	59 (17%)
Units transfused for subjects			
receiving pre-study transfusion			
N	27	32	59
Mean (SD)	2.6 (1.01)	2.9 (1.91)	2.7 (1.56)
Median	2.0	2.0	2.0
Range	1.0 – 5.0	1.0 – 9.0	1.0 – 9.0
Hemoglobin concentration at time			
of pre-study transfusion (g/dL)			
N	27	32	59
Mean (SD)	8.2 (0.75)	8.1 (0.76)	8.1 (0.75)
Median	8.1	8.0	8.0
Range	7.0 – 10.7	6.9 – 9.8	6.9 – 10.7

[a] Within 3 months prior to baseline. Note that the protocol specified no transfusion within 2 weeks prior to entry into the study.

Pre-study transfusions were received by 16% of subjects in the placebo group and 18% of subjects in the Epoetin alfa group. Among subjects receiving pre-study transfusions, the mean number of RBC units received was 2.6 for subjects randomized to placebo and 2.9 for subjects randomized to Epoetin alfa. Mean Hgb values for these subjects at the time of pre-study transfusions were comparable between groups.

Protocol Deviations: The following two subjects were classified as ineligible for evaluation of response (i.e., ineligible for inclusion in the evaluable-for-efficacy population): Subjects 7745 and 78729, treated with Epoetin alfa, who received RBC transfusions within two weeks prior to randomization. A third subject, 92405 in the placebo group, was classified as a major protocol violator because the subject had not started iron supplementation as of Cycle 2.

Treatment Compliance: A general review by the sponsor of study drug administration data indicated that there was good compliance with the dosing schedule specified by the protocol. Known errors in study drug administration were the following (note: these errors did not exclude the subjects from any of the populations analyzed): Subject 88240 in the placebo group received one dose of 1,000 IU of commercial Procrit Epoetin alfa while in the hospital. Subject 79739 in the placebo group started the study at a dose of 60,000 IU rather than 40,000 IU. Subject 97819 in the placebo group missed a dose of study drug while hospitalized in Cycle 2; this was not noticed until she was off study. Subject 92202 in the Epoetin alfa group received study drug from the "wrong box"; however, the medication received by the subject was the correct one (Epoetin alfa).

Completion / Withdrawal: Completion and withdrawal information is presented by treatment group in Table 5 below. The percentages of subjects who completed the study were similar in the placebo and Epoetin alfa groups (i.e., 72% and 70% of subjects, respectively). Subjects who died on study (8 subjects in the placebo group and 13 subjects in the Epoetin alfa group) are classified as having completed the study. The percentage of subject withdrawals was similar overall in the placebo and Epoetin alfa groups (28% and 30%, espectively). However, the percentage of subjects who refused further treatment was somewhat higher in the placebo group (12%) than in the Epoetin alfa group (8%). Thirteen subjects in each group withdrew due to disease progression. Only 3 subjects (1 in the placebo group and 2 in the Epoetin alfa group) withdrew due to adverse events.

Table 5: [redacted] Study Completion / Withdrawal Information (Based on ITT Population)

	Placebo (n = 170)	Epoetin alfa (n = 174)	Total (n = 344)
Completion, n (%)			
Completed study	123 (72%)	122 (70%)	245 (71%)
Completion by category, n (%)			
Completed treatment	115 (68%)	109 (63%)	224 (65%)
Died on study	8 (5%)	13 (7%)	21 (6%)
Withdrawal, n (%)			
Yes	47 (28%)	52 (30%)	99 (29%)
Reason for withdrawal, n (%)			
Refused further treatment	20 (12%)[a]	14 (8%)[a]	34 10%)
Disease progression	13 (8%)	13 (7%)	26 (8%)
Other	6 (4%)	10 (6%)	16 (5%)
Other medical problems	2 (1%)	6 (3%)	8 (2%)
Reason missing	3 (2%)[b]	4 (2%)[b]	7 (2%)
Adverse event	1 (1%)	2 (1%)	3 (1%)
Ineligible	1 (1%)[a]	2 (1%)[a]	3 (1%)
Alternative treatment	1 (1%)	1 (1%)	2 (1%)

[a] One subject withdrew prior to receiving study treatment.
[b] All subjects withdrew prior to receiving study treatment.

The "other" reasons and "other" medical problems leading to withdrawal were balanced between the two groups and are summarized by treatment group in **Table 6** below.

Table 6: [redacted] Study / "Other" Reasons and "Other Medical Problems" Leading to Subject Withdrawal (Summarized from Investigators' Comments)

	Placebo (n = 170)	Epoetin alfa (n = 174)
Reason, n (%)		
Medical Reasons	4 (2%)	6 (3%)

Hemoglobin > 15 g/dL	0	4 (2%)
"High" hemoglobin	1 (1%)	2 (1%)
Subject ineligible	1 (1%)	0
Noncompliance	1	0
Subject treated elsewhere	1	1 (1%)
Chemo- or radiotherapy stopped	0	2 (1%)

In the 4 month Safety Update the sponsor updated these data. Their update is based on the safety population (N=333) rather than the ITT population (N=344). The 11 ITT subjects who withdrew prior to receiving study drug are not included. The results are essentially the same as those reported in the original ITT table.

Chemotherapies: The 10 most frequently used chemotherapy agents used during the study are summarized for the ITT population in **Table 7**. Specific types of chemotherapy agents were received by similar percentages of subjects in the two treatment arms.

Table 7: [redacted] Study / Ten Most Frequently Used Chemotherapy Agents

	Placebo (n = 170)	**Epoetin alfa (n = 174)**
Chemotherapy agent, n (%)[a]		
Paclitaxel	47 (28%)	55 (32%)
Carboplatin	36 (21%)	43 (25%)
Cisplatin	35 (21%)	26 (15%)
Gemcitabine	29 (17%)	31 (18%)
Cyclophosphamide	26 (15%)	25 (14%)
5-Fluorouracil	22 (13%)	19 (11%)
Prednisone	25 (15%)	18 (10%)
Doxorubicin	21 (12%)	21 (12%)
Vincristine	20 (12%)	18 (10%)
Etoposide	14 (8%)	20 (11%)

[a]Subjects may be included in more than one category.

Although there were some differences in doses of specific chemotherapies between groups, overall, the intensity of chemotherapy appeared to be similar in the two treatment arms. Also, the percentage of ITT subjects whose chemotherapy was known to have changed during the study was similar in the placebo group (69%) and the Epoetin alfa group (63%). Chemotherapy dosing issues are covered in more detail in the clinical review.

Dosage Modifications: This is discussed in detail in the clinical review. Overall, 72% of subjects in the placebo group and 43% of subjects in the Epoetin alfa group received dose escalations to the 60,000 IU of study drug. Dose escalation occurred most frequently in Cycle 2, with 75% of subjects in the placebo group and 45% of subjects in the Epoetin alfa group (with data available for Cycle 2) receiving a dose of 60,000 IU in Cycle 2. The percentages of subjects receiving a 60,000 IU remained fairly constant in Cycles 3 and 4. Dose modifications were made for 125 (74%) of subjects in the placebo group and 106 (61%) of subjects in the Epoetin

alfa group. For subjects with dose increases, the most frequent reason given for the increase in each treatment arm was that hemoglobin had not increased. The dose was withheld for more subjects in the Epoetin alfa group (54 subjects or 31%) than in the placebo group (25 subjects or 15%). Among the reasons for withholding the dose, a Hgb value of > 15 g/dL was given as the reason for 27 of the 54 subjects (50%) with doses withheld in the Epoetin alfa group, but was not given as the reason for any subject in the placebo group. The dose was reduced for 16 subjects (9%) in the Epoetin alfa group, but was not reduced for any subject in the placebo group. Among the subjects in the Epoetin alfa group with dose reductions, a Hgb value of > 15 g/dL was given for the reason for 14 of the 16 subjects.

Primary Efficacy Analysis

Percent of Subjects Transfused After Study Day 28:

The ITT population (i.e., all patients as randomized) was used as the primary population for efficacy analyses. Per the SAP, the **primary efficacy endpoint** was the percentage of subjects in the ITT population who were transfused after Day 28 (i.e., from Day 29 to end of study) using worst outcome imputation (i.e., subjects who withdrew from the study after Day 28, with no transfusion after Day 28, were imputed as transfused for purposes of analysis). The sponsor notes that when study data became available, it was clear that results based on non-responder imputation were not an appropriate representation of the clinical outcomes of this study. It is notable that withdrawn subjects in the Epoetin alfa group had greater Hgb improvements than withdrawn subjects in the placebo group, e.g., the 45 withdrawn subjects in the Epoetin alfa group had a mean change in Hgb from baseline to last value of 2.8 g/dL while the 42 withdrawn placebo subjects had a mean change of 0.6 g/dL. Among the subjects who did not complete the study and had "other" reasons for withdrawal, 6 subjects in the Epoetin alfa group were withdrawn with "high' Hgb concentrations (ranging from 13.5 to 15.5 g/dL) at the time of study discontinuation compared to 1 subject with "high" Hgb (11.2 g/dL) in the placebo group. *[Note: The protocol did not specify that subjects should be discontinued from the study when HGB was 'high", e.g., > 15 g/dL. Rather, the study drug was to be withheld. However, the seven subjects described were withdrawn from the study (at least as a partial reason) due to "high" Hgb or Hgb > 15 g/dL.]* **Table 8** below presents Hgb values for subjects who withdrew early from study for "other" reasons or "other medical reasons" and had high Hgb values.

Table 8: Hgb Data for Early Withdrawals with High Hgb Values

Subject	Treatment	Withdrawal Reason	Last Cycle	Day of Last Evaluation	Tx after Day 28	Last Hgb
84788	Placebo	Removed for high Hgb	3	99	No	11.2
80286	Epo	Hgb > 15.0	4	107	No	15.2
84174	Epo	Hgb at 15.5	3	97	No	15.5
86642	Epo	4 weeks of greater/equal Hgb. At Cycle 3 Hgb was 15.2	4	107	No	13.5
91440	Epo	PI's decision[a]	3	78	No	14.9

92050	Epo	Hgb was 15.0	4	91	No	15.0
100852	Epo	Hgb > 15 for 4 weeks	2	61	No	15.3

[a] The reason given on the case evaluation form by the attending physician was that the patient would no longer benefit from continuing the study because all chemo- and radiotherapy had stopped and the patient did not want to come in. A note from the study chair [redacted] on the case evaluation form indicated that the patient had Hgb > 15.

These data strongly suggest that had the withdrawn subjects completed the study, the number transfused after Day 28 would be lower in the Epoetin alfa group than in the placebo group. To use only the worst outcome imputation for transfusion status would produce bias against the efficacy of Epoetin alfa in reducing the need for transfusions. Therefore, in addition to this planned analysis, other plausible analyses were undertaken. Representatives of FDA/CBER agreed to these additional plausible analyses, allowing assessment of consistency of results at a pre-BLA meeting on May 20, 2003. These methods have been previously described in the **'Missing Data Handling' section**. Analytic findings based on the worst outcome imputation and these other plausible methods are described in the next section.

Analysis as Planned in the Statistical Analysis Plan, Kaplan-Meier Analysis, and Analysis of Crude Rate Using LOCF: Results of the primary analysis as planned in the SAP (i.e., all withdrawn subjects considered transfused) are presented in **Table 9** below (Analysis 1). **Table 9** also presents results of a Kaplan-Meier analysis (Analysis 2) and a LOCF analysis of crude transfusion rates (Analysis 3). Here, LOCF means imputing a patient's last known transfusion status at the time of dropout.

Table 9: [redacted] Study / % Subjects Transfused After Day 28 (ITT)

Imputation Analysis Type:	Placebo (n = 170)	Δ and CI for Δ	Epoetin alfa (n = 174)	p-value
(1) Worst Outcome – Crude Rate:				
Subjects transfused, n (%)	84 (49.4%)		69 (39.7%)	0.0687[a]
Δ in % (Epo – Placebo)		-9.8%		
95% CI for Δ		-20.2%, 0.7%		
Adjusted Odds Ratio (Epo / Placebo)		0.668		0.0706[b]
95% CI for Odds Ratio		0.43, 1.03		
(2) LOCF – Kaplan-Meier:				
Subjects transfused (%)	32.7%		16.3%	0.0011[c]
Δ in % (Epo – Placebo)		-16.4%		
95% CI for Δ		-26.2%, -6.5%		
(3) LOCF – Crude Rate:				
Subjects transfused, n (%)	48 (28.2%)		25 (14.4%)	0.0017[a]
Δ in % (Epo – Placebo)		-13.9%		
95% CI for Δ		-22.4%, -5.3%		
Adjusted Odds Ratio (Epo / Placebo)		0.388		0.0010[b]
95% CI for Odds Ratio		0.22, 0.68		

[a] Based on Chi-square test

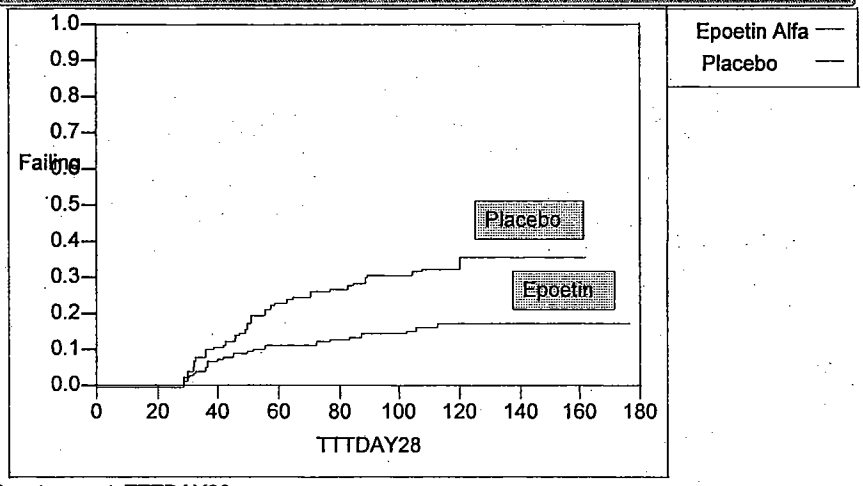
[b] The primary statistical inference, based on logistic regression analysis adjusting for the following randomization balancing variables: size of institution (≥ 15 or < 15 subjects accrued per month over the 2-year period from April 2000 to April 2002, type of primary cancer (lung, breast, other), planned radiation therapy (yes or no), and degree of anemia (≥ 9 or < 9 g/dL, i.e., mild or severe).

[c]Greenwood's method.

The Kaplan-Meier plot in **Figure 1** below presents time to first transfusion after Day 28. The time-to event comparison revealed a statistically significantly delayed finding for the Epoetin alfa group compared to the placebo group (p=0.0016, logrank test).

Figure 1: Product-Limit Survival Fit / Time to 1st Transfusion

Failure Plot



Time to event: TTTDAY28
Censored by T2N
Grouped by NEWARM

Summary

Group	N Failed	N Censored	Mean		Std Error
Epoetin Alfa	25	149	103.303	Biased	1.98558
Placebo	48	122	98.4225	Biased	2.77186
Combined	73	271	103.806	Biased	1.77398

Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
Epoetin Alfa	.	.	.	.	.
Placebo	.	.	.	71	.
Combined	.	.	.	113	.

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	9.9345	1	0.0016
Wilcoxon	9.1177	1	0.0025

Reviewer's Comment: This reviewer confirmed this time-to-event analysis as well as all of the efficacy analyses summarized in Table 9.

Sensitivity Analyses for the Primary Efficacy Endpoint: Three additional analyses were performed using other plausible imputations for the transfusion status of withdrawn subjects as follows:

Analysis (4): Subjects who withdrew from the study after Day 28 would be considered not transfused if they 1) withdrew from the study because they had a successful Hgb response, as indicated by the investigators, and 2) were not transfused after Day 28. This approach was used when it was noticed that a number of subjects withdrew for reasons related to the effectiveness of the study drug in raising Hgb concentrations (Table 8).

Analysis (5): Subjects who withdrew from the study after Day 28 would not be considered transfused if they 1) withdrew after having completed all 4 planned cycles but were not identified as completers by the investigators, and 2) were not transfused after Day 28. This imputation was used because the protocol specified that transfusion data were to be collected for a total of 4 evaluation cycles during the 16-week treatment phase.

Analysis (6): Subjects who withdrew from the study after Day 28 would not be considered transfused if they 1) withdrew due to disease progression, and 2) were not transfused after Day 28. The analysis was appropriately used in this study given that the numbers of subjects who withdrew due to disease progression were comparable in the two treatment arms, indicating that withdrawals for this reason were not treatment related.

In Analyses (4) – (6), crude transfusion rates ranged from 43.5% to 48.8% in the placebo group and from 32.8% to 36.2% in the Epoetin alfa group. Across these three analyses, differences for the two groups in transfusion rates ranged from –10.8% to –12.6% and were statistically significant for each analysis. A summary of the analysis of the difference in transfusion rates between the two treatment groups utilizing these three methods is presented in **Table 10** below.

Table 10: [redacted] Study / Sensitivity Analyses for % Subjects Transfused After Day 28 (ITT)

Imputation Analysis Type[a]:	Placebo (n = 170)	Δ and CI for Δ	Epoetin alfa (n = 174)	p-value
(4) Subjects with successful Hgb response considered not transfused – Crude Rate				
Subjects transfused, n (%)	83 (48.8%)		63 (36.2%)	0.0179[b]
Δ in % (Epo – Placebo)		-12.6%		
95% CI for Δ		-23.0%, -2.3%		
Adjusted Odds ratio (Epo / Placebo)		0.584		
95% CI for Odds Ratio		0.38, 0.91		0.0169[c]
(5) Subjects who completed 4 cycles considered not transfused – Crude Rate				
Subjects Transfused, n (%)	82 (48.2%)		62 (35.6%)	0.0178[b]

Δ in %		-12.6%		
95% CI for Δ		-23.0%, -2.3%		
Adjusted Odds Ratio (Epo / Placebo)		0.589		
95% CI for Odds Ratio		0.38, 0.91		0.0181[c]
(6) Subjects with disease progression considered not transfused – Crude Rate				
Subjects transfused, n (%)	74 (43.5%)		57 (32.8%)	0.0397[b]
Δ in %		-10.8%		
95% CI for Δ		-21.0%, -0.6%		
Adjusted Odds Ratio (Epo / Placebo)		0.625		
95 % CI for Odds Ratio		0.40, 0.98		0.0394[c]

[a] In each analysis, withdrawn subjects considered not transfused were also required, while still on study, not to have been transfused after Day 28 in the study.
[b] Based on Chi-square test
[c] The primary statistical inference, based on logistic regression analysis adjusting for the following randomization balancing variables: size of institution (≥ 15 or < 15 subjects accrued per month over the 2-year period from April 2000 to April 2002), type of primary cancer (lung, breast, or other), planned radiation therapy (yes or no), and degree of anemia (≥ 9 or < 9 g/dL, i.e., mild or severe).

By all of these various analyses, the percentages of subjects transfused after Day 28 was consistently lower in the Epoetin alfa group, within the range of –10% to –16% of treated subjects. The sponsor claims that six different analyses, including 5 with differing imputations for the transfusion status of withdrawn subjects, provide evidence of the efficacy of Epoetin alfa, administered once weekly, in reducing the numbers of subjects requiring transfusions after Day 28 of treatment.

Reviewer's Comment on Missing Data: This reviewer confirmed the sponsor's statistical finding for these 6 imputation analyses. Since informative missing data was a major concern, this reviewer performed an in-depth descriptive analysis of missing hemoglobin data patterns by cycle and treatment arm for the ITT population. Reviewer's findings are summarized as follows:

Table 11: Reviewer's Summary of Missing Hemoglobin Data Patterns

Hemoglobin Missing Value Pattern:	Placebo (n = 170)	Epoetin alfa (n = 174)
Baseline + All 4 Cycle Values (i.e., Complete Data)	113	114
Baseline, 1, 2, 3, **[a]	14	19
Baseline, 1, 2, **, **	19	18
Baseline, 1, **, **, **	15	14
Baseline, **, **, **, ** (i.e., Only Baseline)	6	8
Intermittent Missing[b]	3	1

[a] ** indicates a missing cycle value
[b] Intermittent patterns include all other possible patterns not listed

On the placebo arm there were 57 patients with missing values or 33.5%. On the Epoetin alfa arm there were 60 patients with missing values or 34.5%. Hemoglobin missing values patterns by treatment arm are remarkably similar. There is no indication of differential dropout pattern by treatment arm.

Regarding dropouts for progressive disease (PD), 26 patients were withdrawn with PD given as the reason. There were 13 such patients in each treatment arm. This reviewer's descriptive Kaplan-Meier analysis (not shown) reveals very similar patterns; the curves are almost super-imposable.

These analyses support the sponsor's claim of superior efficacy of Epoetin alfa, administered once weekly, in reducing the numbers of subjects requiring transfusions after Day 28 of treatment.

Transfusion Results by Subgroups: The percentages of subjects transfused after Day 28, using their actual transfusion status at the time of withdrawal (LOCF), are presented by treatment group and specific subgroups (i.e., those subgroups that were balancing factors for the randomization) in **Table 12** below:

Table 12: [redacted] Study / Proportion of Subjects Transfused After Day 28 (From Day 29 to Last Evaluation, Using Transfusion Status at Time of Withdrawal) for Key Subgroups (ITT)

Subgroup:	Placebo (N = 170)			Epoetin alfa (N = 174)		
	N	n	%	N	n	%
Primary tumor type:						
Lung	49	12	24%	48	6	13%
Breast	28	1	4%	28	2	7%
Other	93	35	38%	98	17	17%
Planned concurrent radio-therapy:						
Yes	17	3	18%	18	1	6%
No	153	45	29%	156	24	15%
Baseline anemia:						
Mild (≥ 9 g/dL)	117	26	22%	119	12	10%
Severe (< 9 g/dL)	53	22	42%	55	13	24%
Chemotherapy:						
Cis-Platinum based	33	13	39%	26	4	15%
Non-Cis-Platinum based	137	35	26%	148	21	14%

Reviewer's Comment: In the breast cancer subgroup the percentage of subjects transfused in the Epoetin alfa group was higher than in the placebo group using LOCF imputation. The sponsor suggests that this is an anomalous finding probably due to the small sample size and low transfusion rate. The second largest disease subgroup comprises those patients with **gastro-intestinal (GI) tumors**. There were a total of 63 patients (18.3%) classified as having GI disease. There were 28 (44.4%) on the Epoetin alfa arm and 35 (55.6%) on the placebo arm. Using LOCF imputation, the proportions transfused were 5/28 (17.9%) for the Epoetin alfa arm versus 7/35 (20%) for the placebo arm. As previously discussed, worst outcome imputation is the least tenable approach for this particular situation. Looking into the distribution of disease

types within the GI subgroup, there were no esophageal disease patients in the placebo group and 3 in the Epoetin alfa group (12.5%). Only one of these was transfused, however. 44.1% of placebo patients had colon cancer compared to 33.3% Epoetin alfa patients. There were 23.5 % placebo patients with pancreatic cancer compared to 12.5% Epoetin alfa patients. When the GI subgroup is excluded from the main by treatment arm comparison of transfusion rates, the Epoetin alfa group has consistently lower transfusion rates than the placebo group via all imputation methods. For worst outcome imputation, estimated transfusion rates are 37% for Epoetin alfa versus 54% for placebo. For LOCF imputation, estimated transfusion rates are 13.7% for Epoetin alfa and 30.4% for placebo. These are consistent with estimated transfusion rates for the entire ITT population.

Thus, once weekly treatment with Epoetin alfa reduced the number of subjects needing transfusions after Day 28 of the study. Across 6 analyses, the percentage of subjects transfused in the Epoetin alfa group was lower than in the placebo group. These differences between groups ranged from –10% to –16%.

Data Related to the Primary Endpoint – Percent of Subjects Transfused Overall: The percentages of subjects transfused at any time on study, including prior to Day 28 in Cycle 1, are presented by evaluation cycle in **Table 13**. The percentage of subjects transfused was greater during each cycle in the placebo group than in the Epoetin alfa group. During the entire study, 39% of treated placebo subjects received one or more transfusions compared to 26% of Epoetin alfa treated subjects.

Table 13: — Study / Percent of Subjects Transfused by Evaluation Cycle and Overall

	Placebo (n = 170)		Epoetin alfa (n = 174)	
	N	n (%)	N	n (%)
Cycle 1	165	41 (25%)	166	31 (19%)
Cycle 2	150	34 (23%)	152	14 (9%)
Cycle 3	131	19 (15%)	137	8 (6%)
Cycle 4	119	13 (11%)	118	6 (5%)
Overall (any cycle)	165	65 (39%)	167	43 (26%)

The hemoglobin concentrations measured at the time of first transfusion on study are summarized for each treatment group in **Table 14** below. Hemoglobin concentrations leading to first transfusion showed similar mean values and the same median value.

Table 14: — Study / Pre-transfusion Hemoglobin for First Transfusion on Study (ITT)

	Placebo (n = 170)	**Epoetin alfa (n = 174)**
Subjects Transfused, n (%)	65 (38%)	43 (25%)
Pre-transfusion Hgb (g/dL) for First Transfusion		
N	64	42
Mean (SD)	7.8 (0.99)	7.9 (0.97)
Median	7.8	7.8
Range	(4.8 – 10.2)	(6.5 – 10.7)

Pre-transfusion Hgb (g/dL) for First Transfusion	n (%)*	n (%)*
< 7.1	8 (12%)	9 (21%)
7.1 – 7.5	14 (22%)	7 (16%)
7.6 – 8.0	21 (32%)	10 (23%)
8.1 – 8.5	11 (17%)	5 (12%)
8.6 - 9.0	5 (8%)	6 (14%)
9.1 – 9.5	1 (2%)	3 (7%)
9.6 – 10.0	2 (3%)	1 (2%)
> 10.0	2 (3%)	1 (2%)
Missing	1 (2%)	1 (2%)

* Percents are based on subjects transfused.

Secondary Efficacy Analyses

Number of RBC Units Transfused: Table 15 below presents red blood cell (RBC) units transfused per subject and units transfused per 100 subject-days for the ITT population of the [redacted] study. As the table indicates, over the entire study the total number of RBC transfusions administered in the placebo group (256 units) was approximately twice the total number administered in the Epoetin alfa group (129 units). The mean number of cumulative RBC units transfused per subject in the placebo group (1.5 units) was also approximately twice the mean number in the Epoetin alfa group (0.7 units). Adjusted for each subject's time on study, the mean number of RBC units transfused per 100 subject-days was significantly higher in the placebo group vs. the Epoetin alfa group (1.54 vs. 0.76; $p < 0.0001$). The difference in the number of units transfused per 100 subject-days was –0.78 units, representing a reduction in the transfusion burden by approximately 50% for the Epoetin alfa group compared to the placebo group.

Table 15: [redacted] Study / RBC Units Transfused/Subject and Units Transfused/100 Subject-Days (ITT)

	Placebo (n = 170)	Epoetin alfa (n = 174)	p-value
Total Units /Subject:			
N	170	174	
Mean (SD)	1.5 (2.65)	0.7 (1.59)	
Median	0.0	0.0	
Range	(0.0 – 14.0)	(0.0 – 10.0)	
Total Days on Study:			
N	170	174	
Mean (SD)	97.7 (35.27)	97.0 (35.06)	
Median	112.0	111.5	
Range	(0 – 162)	(0 – 177)	

Transfusion Rate:			
Total No. of Study Days	16606	16884	
Total No. of Units Transfused	256	129	
Units Transfused per 100 Subject-Days (SE)	1.54 (0.0094)	0.76 (0.0161)	< 0.0001[a]
Effect Estimate (95% CI):			
Difference in Transfusion Rates (Epoetin alfa – Placebo)	-0.78 (-0.783, -0.777)		

[a] Test based on normal distribution.

Change in Hemoglobin Concentrations from Baseline: Values for Hgb concentrations at baseline and at last measurement, and changes in Hgb from baseline to last value, are summarized by treatment arm in **Table 16** below. The mean change in Hgb from baseline was 0.9 g/dL in the placebo group and 2.8 g/dL in the Epoetin alfa group; the difference between groups was statistically significant ($p < 0.0001$). The study days on which the last Hgb value was obtained were similar in the two treatment groups, with the mean study day being Day 91.8 for the placebo group and Day 91.9 for the Epoetin alfa group. Because the transfusion rate was higher in the placebo group than in the Epoetin alfa group, the effect of transfusions would contribute to Hgb increase to a greater degree in the placebo group than in the Epoetin alfa group.

Table 16: [redacted] Study / Change in Hgb from Baseline to Last Value (ITT)

	Placebo (n = 170)	**Epoetin alfa (n = 174)**	**p-value**
Baseline Value (g/dL):			
N	170	174	
Mean (SD)	9.4 (0.93)	9.5 (0.94)	
Median	9.5	9.6	
Range	(6.9 – 11.4)	(6.0 – 11.4)	
Last Value (g/dL):			
N	164	166	
Mean (SD)	10.3 (1.44)	12.2 (2.12)	
Median	10.4	12.3	
Range	(6.0 – 13.4)	(7.9 – 17.3)	
Δ in Hgb to Last Value (g/dL):			
N	164	166	
Mean (SD)	0.9 (1.49)	2.8 (2.05)	< 0.0001
Median	0.9	2.8	
Range	(-3.8 – 5.3)	(-2.2 – 7.5)	
Δ (95% CI) (Epo – Placebo):	1.9 (1.5, 2.3)		
Study Day Last Hgb Obtained:			
N	170	174	
Mean (SD)	91.8 (36.64)	91.9 (35.73)	
Median	110.0	106.5	

Range	(-4.0 – 161.0)	(-3.0 – 175.0)	

Changes in Hgb within specific subgroups are presented in **Table 17** below. Within each subgroup, a greater Hgb change was noted for subjects treated with Epoetin alfa than for subjects receiving placebo. The greatest difference in subgroups was found for the degree of anemia in the placebo group, where subjects with mild anemia showed a much smaller Hgb change than subjects with severe anemia. This might have been expected, however, since subjects with mild anemia would have required fewer transfusions.

Table 17: [redacted] Study / Mean Change in Hgb Within Subgroups (ITT)

	Placebo (n=170)		Epoetin Alfa (n=174)	
Subgroup:	**N**	**Mean Δ (SD)**	**N**	**Mean Δ (SD)**
Primary Malignant Disease				
Lung	49	1.1 (1.50)	48	2.5 (1.90)
Breast	28	1.2 (1.74)	28	3.6 (1.60)
Other	93	0.7 (1.41)	98	2.7 (2.19)
Planned Concurrent RT				
Yes	17	0.7 (1.39)	18	2.4 (2.18)
No	153	0.9 (1.51)	156	2.8 (2.04)
Degree of anemia				
Mild (Hgb ≥ 9 g/dL)	117	0.6 (1.30)	119	2.7 (2.09)
Severe (Hgb < 9 g/dL)	53	1.5 (1.69)	55	2.9 (1.96)
Chemotherapy Regimen				
Cis-platinum	33	1.0 (1.25)	26	2.9 (2.01)
Non-cis-platinum	137	0.9 (1.55)	148	2.7 (2.06)

The percentages of subjects with an increase in Hgb of ≥ 2 g/dL are summarized in **Table 18** below. The percent of subjects with a ≥ 2 g/dL increase in Hgb was smaller at each cycle in the Placebo group than in the Epoetin alfa group. Over all cycles, 32% of subjects in the placebo group compared to 73% of subjects in the Epoetin alfa group had a Hgb increase of ≥ 2 g/dL. The sponsor notes that any contribution of transfusion to these results would be greater in the placebo group than in the Epoetin alfa group due to the higher transfusion rate in the placebo group.

Table 18: [redacted] Study / Percent of Subjects with a ≥ 2 g/dL Increase in Hgb (ITT)

	Placebo (n=170)		Epoetin Alfa (n=174)	
	N	**n(%)**	**N**	**n(%)**
Cycle 1	164	10 (6%)	166	52 (31%)
Cycle 2	147	25 (17%)	152	82 (54%)
Cycle 3	129	23 (18%)	134	90 (67%)
Cycle 4	114	31 (27%)	115	81 (70%)

Overall (any cycle)	164	52 (32%)	166	122 (73%)

Hemoglobin Over Time: Results of the sponsor's longitudinal analysis of Hgb increase over time are presented in **Table 19** below. The rate of Hgb increase (i.e., the slope estimate) was 0.064 g/dL per week in the placebo group as compared to 0.201 g/dL per week in the epoetin alfa group. The difference between treatment groups was highly statistically significant ($p < 0.0001$).

Table 19: [redacted] Study / Hemoglobin Over Time / Longitudinal Analysis (ITT)

Estimated Effect	Placebo (n=170)		Epoetin Alfa (n=174)	p-value
Slope (g/dL/week)	0.064		0.201	
95% CI	(0.04, 0.08)		(0.18, 0.22)	
Δ (Epo – Placebo)		0.137		< 0.0001
95% CI		(0.11, 0.17)		

- Longitudinal assessment of Hgb over the study period was analyzed via a mixed-effect model with the intercept and study day treated as random effects and controlling for study center size, age, gender, baseline body weight, type of primary cancer, concurrent radiation therapy, degree of anemia, baseline transfusion status, and chemotherapy type.

Incidence of Hgb Concentrations Below 9.0 g/dL: After Cycle 1, 29.5% of subjects treated with placebo had Hgb values of < 9 g/dL compared to 11.1% treated with Epoetin alfa. The p-value for this difference was statistically significant ($p < 0.0001$). These results are summarized in **Table 20** below.

Table 20: [redacted] Study / Number and Proportion of Subjects with Hgb < 9 g/dL After Cycle 1 to Individual Study End (ITT)

	Placebo (n=170)		Epoetin alfa (n=174)	p-value
Hgb < 9 g/dL, n(%):				
N	149		153	
No	105 (70.5%)		136 (88.9%)	
Yes	44 (29.5%)		17 (11.1%)	<0.0001[a]
Δ (Epo – Placebo)		-18.4		
95% CI for Δ		(-27.3, -9.6)		

[a] Based on two-sided Chi-square test

Incidence of Nephrotoxicity in Subjects Receiving Chemotherapies Containing cis-Platinum: The incidence of nephrotoxicity (i.e., creatinine Grade ≥ 1) in subjects who were identified at study entry as receiving chemotherapies containing cis-platinum are tabulated by creatinine toxicity grade in **Table 21** below. Five subjects (16%) in the placebo group and 4 subjects (16%) in the epoetin alfa group had signs of Grade 1 (mild) nephrotoxicity. Four subjects (13%) in the placebo group and 2 subjects (8%) in the epoetin alfa group had signs of Grade 2 (moderate) nephrotoxicity. The difference between groups was not statistically significant for creatininte grade or for incidence of nephrotoxicity.

Table 21: [redacted] Study / Incidence of Nephrotoxicity in Subjects Receiving cis-Platinum-Based Chemotherapy

	Placebo (n=31)	Epoetin alfa (n=25)	p-value
Creatinine			
Maximum CTC Grade, n (%)			0.6404[a]
0	22 (71%)	19 (76%)	
1	5 (16%)	4 (16%)	
2	4 (13%)	2 (8%)	
Incidence, n (%)			0.7667[b]
No	22 (71%)	19 (76%)	
Yes	9 (29%)	6 (24%)	

[a] p-value for grade based on Wilcoxon rank sum test
[b] p-value for incidence based on Fisher's exact test
Note: The summary only includes those subjects identified on the study eligibility criteria form as receiving cis-platinum containing chemotherapies

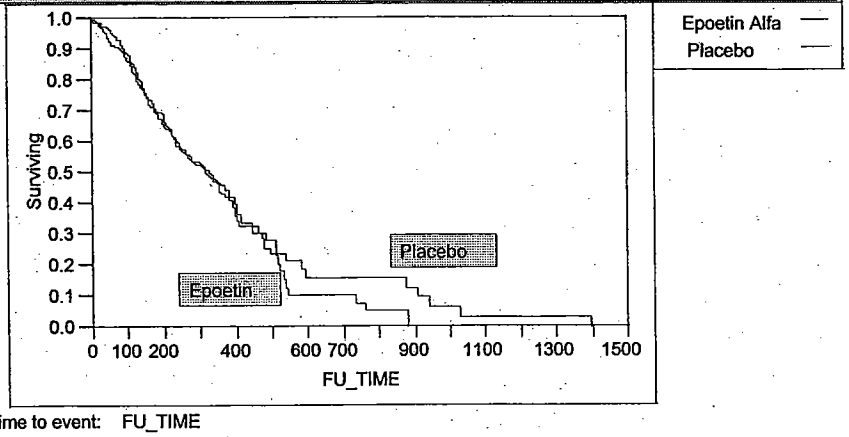
Reviewer's Comment: This reviewer performed univariate Fisher's exact test analysis on the primary efficacy endpoint of proportion transfused for the subgroup of patients who received cis-platinum chemotherapy as well as for the subgroup who received non-cisplatinum containing regimens. In both cases the proportion transfused was higher on the placebo arm relative to the Epoetin alfa arm. These differences did not reach statistical significance.

Survival: Univariate analytic findings for survival data, available at the time of the s-BLA submission, are presented for each treatment group in **Figure 2**.

Figure 2: [redacted] Study / Overall Survival

Product-Limit Survival Fit

Survival Plot



Time to event: FU_TIME
Censored by fu_stjmp
Grouped by NEWARM

Summary

Group	N Failed	N Censored	Mean	Std Error
Epoetin Alfa	117	57	344.969	21.4164
Placebo	115	55	400.238	34.4882
Combined	232	112	372.27	20.6996

Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
Epoetin Alfa	319	248	371	157	515
Placebo	328	250	385	154	495
Combined	327	268	360	155	511

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.6253	1	0.4291
Wilcoxon	0.0626	1	0.8024

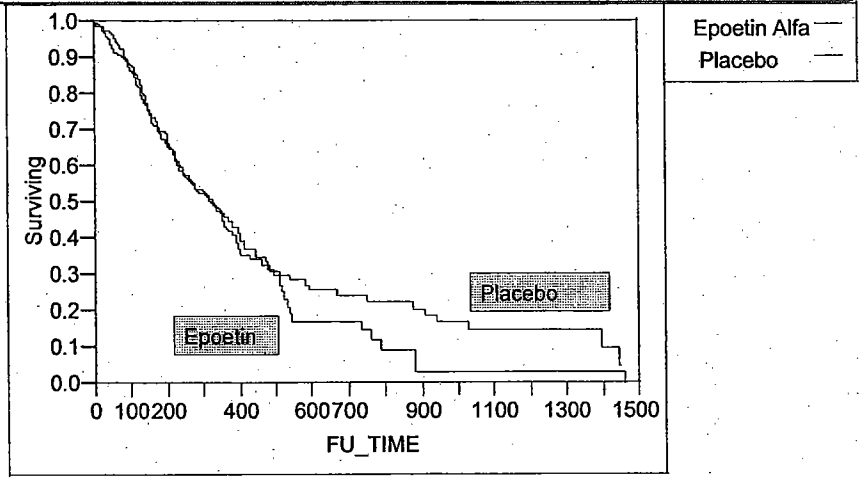
The survival curves are similar, with median survival times of 10.9 months (where 1 month = 30 days) in the placebo group and 10.6 months in the Epoetin alfa group. The difference between groups was not statistically significant via the logrank test (p=0.429). The estimated hazard ratio (Epoetin/Placebo) is 1.11 with associated 95% CI of [0.86, 1.44].

An updated survival analysis was performed when the 4-month safety data became available. This is presented in **Figure 3** below.

Figure 3: [redacted] Study / Overall Survival (4-Month Safety Update)

Product-Limit Survival Fit

Survival Plot



Time to event: FU_TIME
Censored by fu_stjmp
Grouped by NEWARM

Summary

Group	N Failed	N Censored	Mean	Std Error
Epoetin Alfa	121	53	387.472	32.2787
Placebo	119	51	495.729 Biased	42.7112
Combined	240	104	452.26	28.9151

Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
Epoetin Alfa	325	248	369	157	527
Placebo	328	250	397	154	673
Combined	327	268	362	155	542

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.8650	1	0.3524
Wilcoxon	0.1085	1	0.7418

Overall, 119 subjects (70%) in the placebo group and 121 subjects (70%) in the Epoetin alfa group died. The median survival times were similar between the placebo and Epoetin alfa groups (10.9 months and 10.8 months, respectively). The survival curves were similar up to 12 months, the protocol specified end point. The apparent separation of the curves after 17 months (approximately 550 days on the plot) could be due to the disparity in the number of censored subjects during Months 12 to 17 (360 – 510 days). The difference in overall survival times between the two groups was not statistically significant ($p = 0.352$ via the logrank test). The estimated hazard ratio (Epoetin/Placebo) is 1.13 with associated 95% CI of [0.87, 1.46]. A large proportion of the deaths in both treatment groups were due to disease progression. **Table 22** below presents the breakdown for cause of death.

Table 22: [redacted] Study / Cause of Death for Deaths that Occurred On Study and After the Study (During the Follow-Up Phase) for the ITT Population

	Placebo (n = 170)	Epoetin alfa (n = 174)
Cause of Death (n, %)[a]		
Total deaths, n	119	121
Disease Progression	100 (84%)	102 (84%)
Other[b]	6 (5%)	8 (7%)
Unknown	13 (11%)	11 (9%)

Note: Deaths during the follow-up phase include those that occurred within 30 days following the last dose of study drug and those that occurred after 30 days following the last dose of study drug.

[a] Percentage is based on total deaths

[b] "Other" included the following: ischemia/infarction; pneumonitis; respiratory failure due to pulmonary metastases; pneumonia/ARDS; cerebral hemorrhage; necrosis of bowel; ischemic stroke, subarachnoid hemorrhage; coronary artery disease (CAD); congestive heart failure (CHF) exacerbation, chronic obstructive pulmonary disease (COPD); gastrointestinal (GI) bleed and anemia; stroke; renal failure; and unknown – chose to see another oncologist.

Tumor Response: Tumor response to chemotherapy at study completion, as estimated by the investigators, was comparable between the two treatment arms and is presented in **Table 23** below. Tumor progression was reported for 29% of subjects in the placebo group and 32% of subjects in the Epoetin alfa group.

Table 23: [redacted] Study / Tumor Response to Chemotherapy at Study Completion (ITT)

	Placebo (n = 170)	Epoetin alfa (n = 174)
Objective Status of Tumor Response, n (%)		
Missing	4 (2%)	6 (3%)
Complete response (CR)	13 (8%)	14 (8%)
Partial response (measureable disease only) (PR)	19 (11%)	14 (8%)
Regression	15 (9%)	13 (7%)
Stable	70 (41%)	72 (41%)
Progression	49 (29%)	55 (32%)

3.2 Evaluation of Safety

The safety population included all subjects who received at least one dose of study drug and had safety information available. The safety population included 165 subjects who received placebo and 168 subjects who received Epoetin alfa. A full discussion of the survival experience was presented in the previous section. Only key safety variables, e.g., thrombovascular events, will be briefly discussed in this review. A comprehensive discussion of safety appears in the clinical review.

Thrombotic Vascular Events: Thrombotic vascular AE's that occurred during the study were reported for 5 subjects (3%) in the placebo group and 8 subjects (5%) in the Epoetin alfa group.

These are summarized in **Table 24** below. Based on these figures, the difference in the proportion of subjects with TVE's in each treatment group was not statistically significant by Fisher's exact test (p=0.574).

Table 24: [redacted] Study / Number of Subjects with Thrombotic Vascular Events / Safety Population

Body System	**Placebo (n=165)**	**Epoetin Alfa (n=168)**
Thrombotic Vascular Event	n (%)	n (%)
Any Thrombotic Vascular Event[a]	5 (3%)	8 (5%)
Cardiovascular:		
Ischemia/Infarction	1 (1%)	0 (0%)
Thrombosis, NOS	4 (2%)	7 (4%)
Neurology:		
Ischemia-cerebral	0 (0%)	1 (1%)

[a] Three subjects in this table (1 in the Placebo group and 2 in the Epoetin alfa group) had 2 reports each of thrombosis.

As indicated in the table, one subject in the placebo group and two subjects in the Epoetin alfa group had two reports each of thrombosis. It is unknown if the second report for each subject refers to the same or to a different occurrence of thrombosis. One subject in the placebo group had myocardial ischemia/infarction which resulted in death. One subject in the Epoetin alfa group had cerebral ischemia. All other TVE's were cases of thrombosis. The sponsor states that no case of TVE was evaluated as probably or definitely drug-related. Two cases of TVE's (one case of thrombosis in each treatment group) were evaluated as possibly drug related. The sponsor notes that one subject in the placebo group (#89990) and two subjects in the Epoetin alfa group (#90123 and #97060) had TVE occurrences that were not reported as AE's and hence are not included in the study database. If these 3 subjects are included in the number of subjects with TVE's (for a total of 6 subjects in the placebo group and 10 subjects in the Epoetin alfa group), the difference between groups for the proportion of subjects with TVE's does not reach statistical significance (p=0.444). Refer to the clinical review for a comprehensive review of TVE's and other adverse event experience.

Reviewer's Comment: The sponsor's counts were confirmed in the electronic database and the Fisher's exact test result was confirmed.

4. FINDINGS IN SPECIAL SUBGROUP POPULATIONS

4.1 Gender and Age Subgroups

Reviewer's analytic findings for the primary efficacy endpoint for gender and age (non-geriatric, geriatric) subgroups are presented in the following tables:

Table 25: Primary Endpoint Findings for Males (ITT)

	Transfused After Day 28		
	Yes	**No**	
Placebo	22 (30%)	53 (70%)	74
Epoetin alfa	11 (14%)	67 (86%)	78

Reviewer's Comment: The difference in transfusion rates for Epoetin alfa vs. placebo male patients (14% vs. 30%) was statistically significantly lower for the Epoetin alfa patients (Fisher's exact test p-value = 0.029).

Table 26: Primary Endpoint Findings for Females (ITT)

	Transfused After Day 28		
	Yes	**No**	
Placebo	26 (27%)	70 (73%)	96
Epoetin alfa	14 (14%)	82 (86%)	96

Reviewer's Comment: The difference in transfusion rates for Epeotin alfa vs. placebo female patients (14% vs. 27%) was statistically significantly lower for the Epoetin alfa patients (Fisher's exact test p-value = 0.049).

Table 27: Primary Endpoint Findings for Age ≤ 65 Years (ITT)

	Transfused After Day 28		
	Yes	**No**	
Placebo	18 (23%)	61 (77%)	79
Epoetin alfa	16 (18%)	74 (82%)	90

Reviewer's Comment: The difference in transfusion rates for Epoetin alfa vs. placebo patients (18% vs. 23%) was not statistically significantly lower for the Epeotin alfa patients ≤ 65 years (Fisher's exact test p-value = 0.447).

Table 28: Primary Endpoint Findings for Age > 65 Years (ITT)

	Transfused After Day 28		
	Yes	**No**	
Placebo	30 (33%)	61 (67%)	91
Epoetin alfa	9 (11%)	75 (89%)	84

Reviewer's Comment: The difference in transfusion rates for Epoetin alfa vs. placebo patients (11% vs. 33%) was statistically significantly lower for the Epoetin alfa patients > 65 years (Fisher's exact test p-value < 0.0001).

4.2 Other Special/Subgroup Populations:

Analytic finding for two other important subgroups (GI disease and cis-platinum/non-cisplatinum patients) have been previously discussed in the appropriate sections.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This application's source of major evidence consisted of one randomized pivotal study. This reviewer uncovered no problematic statistical issues and confirmed the sponsor's major efficacy analytical findings.

5.2 Conclusions and Recommendations

This reviewer confirmed the sponsor's major efficacy analyses for the pivotal [redacted] study. No problematic statistical issues were uncovered.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103234s5053

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review Worksheet

Submission Date: 8/29/03, 9/22/03
12/17/03, 1/29/04

STN Number:	103234/5053
Product Name:	Epogen®, Procrit® (Epoetin alfa, rHuEPO)
Dosage Form:	Injectable, IV, SC, 2,000; 3,000; 4,000; 10,000; 20,000; 40,000 Units/mL
Indication:	Treatment of anemia in patients receiving chemotherapy
Submission Type:	Labeling Supplement
Sponsor:	Amgen Inc., Thousand Oaks, CA
Reviewer:	Hong Zhao, Ph.D.

Overview

Epogen/Procrit epoetin alfa solution for injection is a biologic product containing the active substance epoetin alfa (recombinant human erythropoietin, r-HuEPO). The product is currently indicated for the treatment of anemia in cancer patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. Epogen/Procrit is indicated to decrease the need for transfusion in patients who will be receiving concomitant chemotherapy for a minimum of 2 months. The current labeling recommends a starting dose of 150 Units/kg of Epogen/Procrit subcutaneously administered 3 times per week (t.i.w.), with an increase in dose up to 300 Units/kg t.i.w. if the response is not satisfactory in terms of reducing transfusion requirements or increasing hematocrit after 8 weeks of therapy.

The purpose of the present submission is to obtain a dosing-regimen alternative to the currently approved regimen. In the proposed alternative dosing regimen, the starting dose would be 40,000 IU SC. administered once a week (q.w.), with an increase to 60,000 IU q.w. if hemoglobin has not increased by at least 1 g/dL. In support of once-weekly epoetin alfa dosing in anemic cancer patients receiving chemotherapy, 2 types of studies were conducted: (1) a Phase 1 pharmacokinetic/pharmacodynamic study to compare once-weekly and three-times weekly dosing in anemic cancer patients as well as in healthy volunteers (Study EPO-PHI-377), and (2) a Phase 3 placebo-controlled trial in cancer patients receiving chemotherapy ([redacted] Study PR98-27-008). This Phase 3 trial provides pivotal support for the proposed new dosing regimen.

In addition to the data for Study PR98-27-008 and Study EPO-PHI-377, this submission also includes data from 2 supportive studies: the Phase 1 Study EPO-PHI-370 in healthy volunteers, which compared the epoetin alfa 150 IU/kg t.i.w., and the proposed epoetin alfa 40,000 IU q.w. dosing regimens, and a discontinued (due to slow enrollment) Phase 3b study (Protocol EPO-CA-480) which compared no treatment (control group) with epoetin alfa for 12 weeks administered in the following regimens: 150 IU/kg t.i.w., 300 IU/kg q.w., 450 IU/kg q.w., 600 IU/kg q.w., and 900 IU/kg q.w., in subjects with cancer who were receiving platinum-containing chemotherapy for the treatment of solid tumors (as supportive for safety).

Also, submitted in the supplemental application is a request for deferral of pediatric study of children ages 0-<5 and 5-16. The sponsor answer to the question "Is the indication for a life-threatening condition that occurs in the pediatric population" is "No". Reasons for deferring pediatric study are as follows: Pediatric studies are on going but are not yet completed. The condition under study does occur in the pediatric population, but the number of children affected by this condition is much smaller and studies in children take longer for patient recruitment. General information on the ongoing weekly dosing pediatric study PR99-11-034/044 for children ages 5-18 is provided in this deferral. Suggested deferral date for submission of studies are: 2Q2004 for ages 5-16. For ages 0-<5 age group, the need for, timing of, and technical requirements for such a study will be reviewed with the Agency following review of pediatric data from the ongoing study. At this time, an indefinite deferral is requested.

Pediatric Clinical Studies (PR99-11-034/044): Efficacy and safety evaluation of QW dosing of Procrit in children with solid tumors, Hodgkin's disease, ALL, or NHL undergoing myelosuppressive chemotherapy. This is a randomized, placebo- controlled, double-blind, multi-center, 16-week treatment study in children 5-18 years of age. PK/PD data is to be obtained for 12 patients from PR99-11-034. A total of 224 patients enrolled, 169 patients have completed, and completion of study treatment for the final enrolled subjects is projected in approximately November 2003.

Review of Study EPO-PHI-377

This Phase 1 study was entitled "*Comparative Pharmacokinetics of Epoetin Alfa in Anemic Cancer Subjects Receiving Cyclic Chemotherapy and in Healthy Subjects after Subcutaneous Administration of Epoetin Alfa 150 IU/kg 3 Times Weekly or 40,000 IU Per Week for 6 Weeks*".

Study Design and Conduct: This was a randomized, open-label, parallel-design, multicenter study. Treatment period for healthy volunteers was 4 weeks instead of 6 weeks due to the possibility that excessive hemoglobin response might occur.

Dosing Schedule

Group	Treatment (Epoetin Alfa)	Day of Last dose	Other Treatment
A (patient)	150 IU/kg 3 times weekly x 6	Day 40	At least 1 cytotoxic chemotherapy agent
B (patient)	40,000 IU/week x 6	Day 36	Same as above
C (healthy)	150 IU/kg 3 times weekly x 4	Day 26	None
D (healthy)	40,000 IU/week x 4	Day22	None

Lots for 10,000 IU/ml were R11209, R11707, R12129; and for 40,000 IU/ml were R11210, 11706 and R12130.

Study Performance

Population	ITT	Dosed	Completed	PK-Evaluable	PD-Evaluable
Patient	n=36	33	29	32	27
Healthy	n=12	12	12	12	12

Demographic Characteristics

Group	Age (yr)	Sex (M/F, %)	Race (W/B/A/H, %)	Weight (kg)
A (patient, 150IU/kg x3)	62.1±12.5	9/6 (60/40%)	12/1/0/2 (80/7/0/13%)	73.9±9.5
B (patient, 40,000IU/week)	56.7±11.4	2/16 (11/89%)	11/3/0/4 (61/17/0/22%)	68.1±10.7
C (healthy, 150IU/kgx3)	35.8±14.1	3/3 (50/50%)	2/2/0/2 (33/33/0/33%)	77.7±19.0
D (healthy, 40,000IU/week)	36.2±15.9	3/3 (50/50%)	4/1/1/0 (67/17/17/0%)	71.7±8.6

PK Sampling Schedule

Treatment	PK sampling time
3-times-weekly dosing	Day 1 Predose, Day 5 predose, 3, 6, 9, 12, 24, 27, 36, 48, and 72 hours [predose on Day 8] postdose, and predose on Days 15, 22, 29, 36, and 43 Day 15 predose, 9, 12, and 24 hours post dose, Day 17 predose, 9, 12, and 24 hours postdose and Day 19 predose, 3, 6, 9, 12, 24, 27, 36, and 48 hours [Day 21] postdose
Once weekly dosing	Day 1 predose, and 3, 6, 9, 12, 24, 27, 36, 48, 72, 96, 120, and 144 hours [Day 7] postdose, and predose on Days 8, 15, 22, 29, 36, and 43. Day 15 predose and 3, 6, 9, 12, 24, 27, 36, 48, 72, 96, 120, and 144 hours [Day 21] postdose

Because chemotherapy may affect endogenous erythropoietin levels, extensive blood sampling was done for all subjects during Week 1 to describe the PK profile of epoetin alfa when anemic cancer patients were receiving chemotherapy. A second period of extensive PK blood sampling during Week 3 was optional for anemic cancer patients not scheduled to receive chemotherapy from Day 15 to Day 21.

Analytical Procedure: Serum concentrations of erythropoietin were measured by [redacted] using a validated enzyme-linked immunosorbent assay (ELISA) method. The quantification range was [redacted] mIU/ml. Since the method cannot distinguish endogenous erythropoietin and administered epoetin alfa, a procedure of [redacted] to estimate the PK of exogenous epoetin alfa by [redacted] the study period.

Study Results:

1. Baseline Endogenous Erythropoietin Levels

Table 1. Baseline Endogenous Erythropoietin Levels (mIU/ml) (Mean±SD)

Group	A (patient) 150 IU/kg x3	B (patient) 40,000IU/week	C (healthy) 150 IU/kg x3	D (healthy) 40,000IU/week
Prior first dose	29.4±19.5 (n=14)	33.4±25.8 (n=18)	10.1±3.3 (n=6)	9.8±2.4 (n=6)
Day 8 predose	131±140	86.9±90.2	39.9±18.3	21.3±5.8
Day 22 predose	82.4±51.4	46.9±53.8	36.2±9.5	17.6±8.6
All predose range	15.3-469	9.7-1910	23.3-76.1	8.7-30.1

Summary: In general, the baseline endogenous erythropoietin concentrations in anemic cancer patients were higher than in healthy volunteers. Predose serum erythropoietin levels in anemic cancer patients on Day 8 and Day 22 ranged from values near the upper range of physiological level (30 mIU/ml) to slightly below 500 mIU/ml, whereas in healthy volunteers the levels ranged from 30 mIU/ml to slightly below 100 mIU/ml. The

mean serum levels of erythropoietin were above the upper end of the physiological range throughout the dosing period in the 150 IU/kg t.i.w. groups, whereas the level returned to baseline prior to the next dose for subjects in the 40,000 IU/week groups. However, predose serum erythropoietin levels were substantially above 30 mIU/ml on Days 8 and 22 in most anemic cancer patients in the 40,000 IU/week group.

2. Pharmacokinetic Results in Healthy Volunteers

Table 2. Pharmacokinetic Parameters of Epoetin Alfa Administered 150 IU/kg t.i.w. or 40,000 IU q.w. in Healthy Subjects (Corrected from Baseline) – PK Evaluable Population (Mean±SD)

Parameter	C_{max} (mIU/ml)	C_{min} (mIU/ml)	T_{max} (h)	$AUC_{0\text{-}168h}$ (mIU.h/ml	$t_{1/2}$ (h)	CL/F (ml/h/kg)
N	6	6	6	6	4-6	6
150 t.i.w. (Day 5)	163±53.6	28.6±10.4	9.0±3.3	15708±4327	25.0±7.1	31.2±11.5
(Day 19)	125±31.9	---	15.0±9.9	12913±3249	26.0±8.6	36.9±10.0
40,000 q.w. (Day 1)	1036±238	9.2±5.7	21.0±7.1	47469±13301	28.8±8.1	12.6±3.1
(Day 15)	909±398	---	24.5±8.8	32969±7945	23.7±8.5	17.8±3.7

Table 3. Ratio of PK Parameter Means (40,000 IU/Week / 150 IU/kg t.i.w.) (Healthy Population)

Parameter	Uncorrected for baseline		Corrected for Baseline	
	First PK profile	Second PK profile	First PK profile	Second PK profile
C_{max} Ratio	6.05	6.80	6.37	7.27
$AUC_{0\text{-}168hr}$ Ratio	2.82	2.37	3.02	2.55
Relative Bioavailability	228%	191%	244%	206%

Bioavailability of the 40,000 IU/week dosing regimen relative to that obtained after the 150 IU/kg t.i.w. dosing regimen was calculated using the following formula:

($AUC_{0\text{-}168h}$ of 40,000 IU/week/$AUC_{0\text{-}168h}$ of 150 IU/kg t.i.w.)x(450xmean body weight/40,000) x100%
Where $AUC_{0\text{-}168h}$ for the 150 IU/kg t.i.w. regimen = $2xAUC_{0\text{-}48h} + AUC_{0\text{-}72h}$

Summary: The 40,000 IU/week dosing regimen resulted a 6- to 7-fold higher C_{max} and 2- to 3-fold higher AUC to serum erythropoietin than that for the 150 IU/kg t.i.w. dosing regimen in healthy subjects. The extent of exposure of the two dose regimens was similar to those reported in the previous studies of healthy subjects.

3. Pharmacokinetic Results in Anemic Cancer Patients

Table 4. Pharmacokinetic Parameters of Epoetin Alfa Administered 150 IU/kg t.i.w. or 40,000 IU q.w. in Anemic Cancer Subjects (Uncorrected from Baseline) – PK Evaluable Population (Mean±SD)

Parameter	C_{max} (mIU/ml)	C_{min} (mIU/ml)	$AUC_{0\text{-}168h}$ (mIU.h/ml)	T_{max} (h)	$t_{1/2}$ (h)	CL/F (ml/h/kg)
150 t.i.w. (Day5)	414±312	---	43014±37270	13.3±12.4	43.7±3.9	20.2±15.9
N	14		14	14	3	14
(Day 19)	178±58	90.4±41.4	21082±6909	14.2±6.7	41.9±14.8	23.6±9.5
N	4	14	4	4	2	4
40,000 q.w. (Day1)	1077±510	---	84205±46999	38.5±17.8	35.3±16.8	9.2±4.7
N	18		18	18	11	18
(Day 15)	897±322	116±230	48254±17658	22.3±4.5	38.8±11.0	13.9±7.6
N	7	18	7	7	7	7

Table 5. Ratio of PK Parameters Means (40,000 IU/Week / 150 IU/kg t.i.w.) (Patient Population)

Parameter	Uncorrected for baseline		Corrected for Baseline	
	First PK profile	Second PK profile	First PK profile	Second PK profile
C_{max} Ratio	2.60	5.04	2.71	6.12
$AUC_{0\text{-}168hr}$ Ratio	1.96	2.29	2.06	2.89
Relative Bioavailability	155%	199%	164%	251%

Summary: The ratio (40,000 IU/week /150 IU /kg t.i.w.) of the C_{max} during the first PK profile is much lower in the anemic cancer patients compared to that in healthy volunteers (2.6 vs. 6.1), reflecting the unusually high mean C_{max} in the 150 IU/kg t.i.w. regimen in anemic cancer patients. The extent of exposure of the 40,000 IU/week regimen relative to that of the 150 IU/kg t.i.w. regimen in anemic cancer patients was similar to that in healthy volunteers (in the order of 2- to 3-fold higher).

4. Pharmacodynamic Results in Healthy Subjects

Table 6. Pharmacodynamic Parameters Uncorrected for Baseline Value in Healthy Subjects (PD-Evaluable Population in Study EPO-PHI-377) (Mean±SD)

Treatment Group	N	AUC (RETI) (%.d)	Ratio*	AUC (HEMO) (g.d/dL)	Ratio	AUC (RBC) ($x10^{12}$.d/L)	Ratio
			0-4 week				
150 IU/kg t.i.w.	6	100±27.7	0.96	410±19.9	1.0	137±8.3	1.1
40,000 IU q.w.	6	96.1±33.4		417±35.9		146±18.0	
			0-6 week				
150 IU/kg t.i.w.	6	125±35.8	0.97	612±44.3	1.0	206±16.7	1.1
40,000 IU q.w.	6	121±37.9		625±56.0		221±29.9	

*Ratio of mean values for each parameter, calculated as (40,000 IU/week /150 IU/kg t.i.w.)

Summary: In healthy subjects, the PD responses, in terms of AUCs of the respective PD parameters (percent reticulocytes, hemoglobin concentration and total RBC counts), were similar between the 40,000 IU/week and 150 IU/kg t.i.w. treatment groups despite a larger exposure of the 40,000 IU/week dosing regimen than the 150 IU/kg t.i.w. dosing regimen (the ratio of mean AUC serum erythropoietin was approximately equal 3).

5. Pharmacodynamic Results in Anemic Cancer Patients

Table 7. Pharmacodynamic Parameters Uncorrected for Baseline Value in Anemic Cancer Subjects (PD-Evaluable Population in Study EPO-PHI-377) (Mean±SD)

Treatment Group	N	AUC (RETI) (%.d)	Ratio*	AUC (HEMO) (g.d/dL)	Ratio	AUC (RBC) ($x10^{12}$.d/L)	Ratio
			0-4 week				
150 IU/kg t.i.w.	11	76.4±24.6	1.3	313±43.4	1.0	104±11.8	0.98
40,000 IU q.w.	16	95.9±26.9		321±26.3		102±10.6	
			0-6 week				
150 IU/kg t.i.w.	11	112±32.6	1.2	479±70.4	1.0	160±18.8	0.98
40,000 IU q.w.	16	134±35.0		495±44.0		157±15.2	

*Ratio of mean values for each parameter, calculated as (40,000 IU/week /150 IU/kg t.i.w.)

Figure 1. Mean Change in Percent Reticulocytes from Baseline Anemic Cancer Patients: PD-Evaluable Population

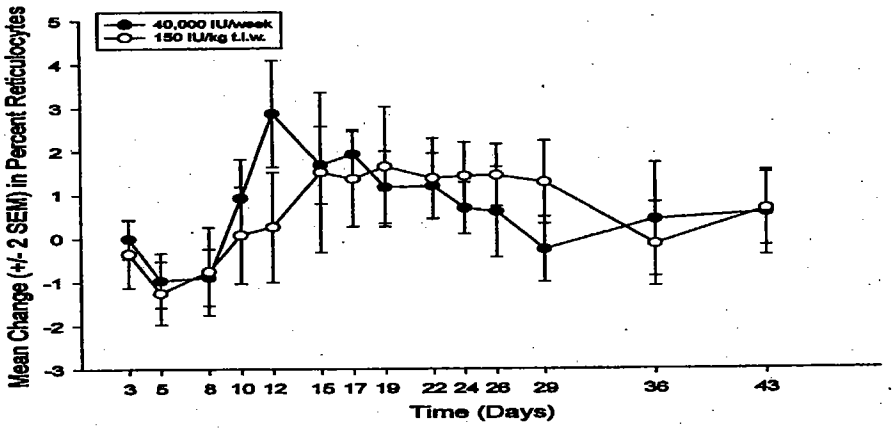


Figure 2. Mean Change in Hemoglobin from Baseline Anemic Cancer Patients: PD-Evaluable Population

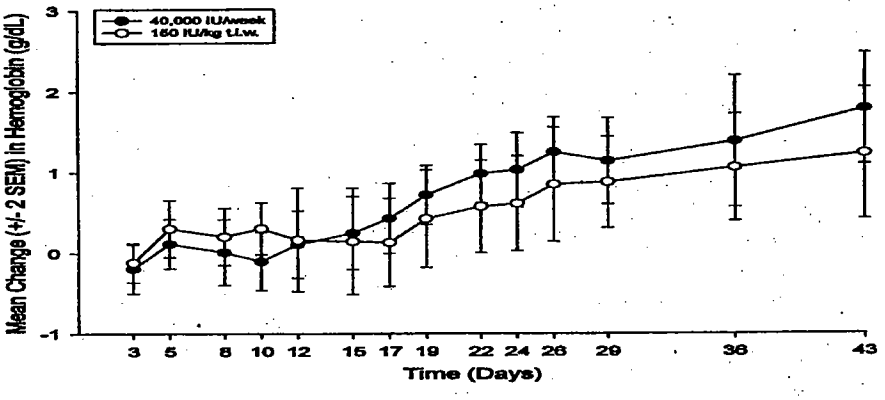
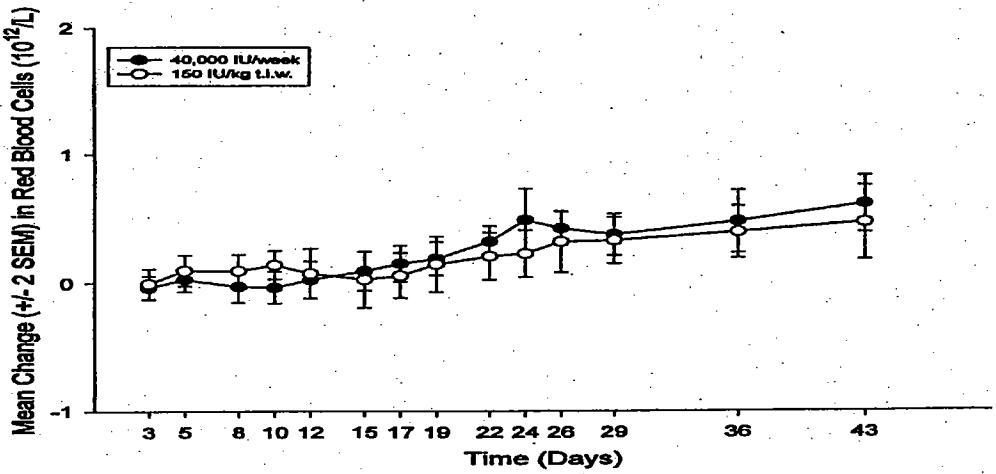


Figure 3. Mean Change in Red Blood Cells from Baseline Anemic Cancer Patients: PD-Evaluable Population



The above three figures were taken from the sponsor's submission.

Summary: The 40,000 IU/week and 150 IU/kg t.i.w. treatment groups had similar reticulocytes, hemoglobin concentration, and total RBC count responses in anemic cancer patients despite a larger exposure to erythropoietin in the 40,000 IU/week treatment group (the ratio of mean AUC serum erythropoietin was approximately equal 2).

6. Comparisons of PD between Healthy Subjects and Anemic Cancer Patients

Table 8. Ratio of AUC Means (40,000 IU q.w./150 IU/kg t.i.w.) (PD-Evaluable Population)

Population	AUC_{RETI} (%.d)		AUC_{HEMO} (g.d/dL)		AUC_{RBC} (#cellx10^{12}.d/L)	
	$AUC_{0\text{-}4wk}$	$AUC_{0\text{-}6wk}$	$AUC_{0\text{-}4wk}$	$AUC_{0\text{-}6wk}$	$AUC_{0\text{-}4wk}$	$AUC_{0\text{-}6wk}$
Uncorrected from Baseline						
Healthy Subjects	0.96	0.97	1.02	1.02	1.07	1.07
Cancer Subjects	1.26	1.20	1.03	1.03	0.98	0.98
Corrected from Baseline						
Healthy Subjects	0.91	0.95	1.09	1.14	1.10	1.12
Cancer Subjects	1.05	0.99	1.15	1.24	1.06	1.15

Table 9. Baseline and Mean Changes from Baseline in PD Parameters (PD-Evaluable Population) (Mean±SD)

Parameter	Healthy Subjects			Anemic Cancer Patients		
	Baseline	Day 10	Day 29	Baseline	Day 10	Day 29
RETI (%)						
150 IU/kg t.i.w.	1.7±0.8	2.1±1.2	2.0±1.5	2.2±1.0	0.1±1.8	1.3±1.6
40,000 IU/week	1.7±0.4	2.2±2.5	1.7±1.0	2.6±0.8	0.9±1.8	-0.3±1.4
Hemoglobin						
150 IU/kg t.i.w.	13.4±0.6	1.0±0.2	1.7±0.4	10.7±1.1	0.3±0.5	0.9±0.9
40,000 IU/week	13.6±1.6	0.9±0.9	2.0±1.0	10.9±0.9	-0.1±0.72	1.1±1.0
Total RBC						
150 IU/kg t.i.w.	4.4±0.2	0.4±0.1	0.8±0.1	3.5±0.3	0.1±0.2	0.3±0.3
40,000 IU/week	4.7±0.6	0.3±0.3	0.9±0.4	3.4±0.4	0.0±0.2	0.4±0.3

Table 10. Comparison of AUC of Pharmacodynamic Response between Healthy and Anemic Cancer Patients over 4-Week Period (PD-Evaluable Population) (Mean±SD)

Parameter	Uncorrected for Baseline			Corrected for Baseline		
(AUC)	Healthy	Anemic	Ratio	Healthy	Anemic	Ratio
Percent Reticulocyte (%.d)						
150 IU/kg t.i.w.	100±28	76±25	0.76	52±18	32±19	0.61
40,000 IU/week	96±33	96±27	1.00	47±26	33±16	0.70
Hemoglobin (g.d/dL)						
150 IU/kg t.i.w.	410±20	313±43	0.76	29±6.3	15±12	0.51
40,000 IU/week	417±36	321±26	0.77	31±16	17±11	0.54
Total RBC Count (x10^{12} cell.d/L)						
150 IU/kg t.i.w.	137±8.3	104±12	0.76	12.2±2.2	5.3±4.0	0.44
40,000 IU/week	146±18	102±11	0.70	13.4±6.1	5.7±3.0	0.42

Summary: In healthy subjects, and anemic cancer patients, the 150 IU/kg t.i.w. and 40,000 IU q.w. treatments produced similar changes in percent reticulocytes, similar changes in hemoglobin, and similar changes in RBC counts despite a larger exposure to erythropoietin in the 40,000 IU q.w. treatment group. These data suggest that total systemic exposure is not the sole determinant of the pharmacodynamic effects of epoetin

alfa. Other factors, e.g., pattern of exposure or duration of exposure above a critical threshold level, may also contribute to these effects.

Exploratory Analysis of 4-Week Responders
A 4-week responder was defined as a subject whose hemoglobin concentration increased from baseline by at least 1 g/dL on 2 occasions through Day 29, independent of transfusion.

Table 11. Proportion of 4-Week Responders (PD-Evaluable Population)

Treatment	150 IU/kg t.i.w. n/N (%)	40,000 IU/Week n/N (%)
Healthy Subjects	6/6 (100%)	5/6 (83%)
Anemic Cancer Patients	6/11 (55%)	12/16 (75%)

Summary: The proportion of anemic cancer patients who were 4-week responders in the ITT population was similar in the 2 treatment groups. All but 1 of the healthy subjects were 4-week responders.

Conclusions

- There was no accumulation of serum erythropoietin after the 2 dosing regimens in both healthy subjects and anemic cancer patients during the study period.

- In general, the concentration-time profiles and PK parameters of anemic cancer patients were different from those in healthy subjects during Week 1 but similar during Week 3. Most anemic cancer patients had higher C_{max}, lower CL/F, and longer T_{max} than the respective parameters in healthy subjects during Week 1.

- The 40,000 IU/week regimen had a higher C_{max}, higher exposure ($AUC_{0\text{-}168hr}$) of erythropoietin and lower CL/F than the 150 IU/kg t.i.w. regimen in both healthy subjects and anemic cancer patients.

- Despite difference in pharmacokinetic exposure between the 150 IU/kg t.i.w. and 40,000 IU/week treatment groups, results of this study indicate that the PD responses (percent reticulocytes, hemoglobin concentration, and total RBC counts) of epoetin alfa were similar between these two regimens in healthy subjects and in anemic cancer patients.

- Epoetin alfa was safe and tolerated by subjects in this study.

Review of Phase 1 Study EPO-PHI-370
This was a single-center, parallel group, open label, randomized study to evaluate the PK and PD profile of epoetin alfa (Procrit) after administration of 150 IU/kg t.i.w. or 40,000 IU q.w. Forty-nine (49) healthy adults were assigned by randomization to 2 groups and received study treatment for 4 weeks. There were some technical difficulties with the study, primarily a relatively high degree of variability in hemoglobin values between the screening and baseline measurements. The problem with fluctuating hemoglobin levels at screening and baseline resulted in a mean baseline hemoglobin in the 40,000 IU q.w.

group that was above protocol entry criteria. However, relative changes in hemoglobin in the 2 treatment groups were consistent with the changes in reticulocytes.

Table 1. Pharmacokinetic Parameters (mean with range)

Treatment Group	C_{max} (mIU/ml)	C_{min} (mIU/ml)	$t_{1/2}$ (hr)	F (Relative)
150 IU/kg t.i.w.	191 (78-447)	39 (7-88)	31.8	100%
40,000 IU q.w.	785	13 (<7.8-44)	39.3	176%

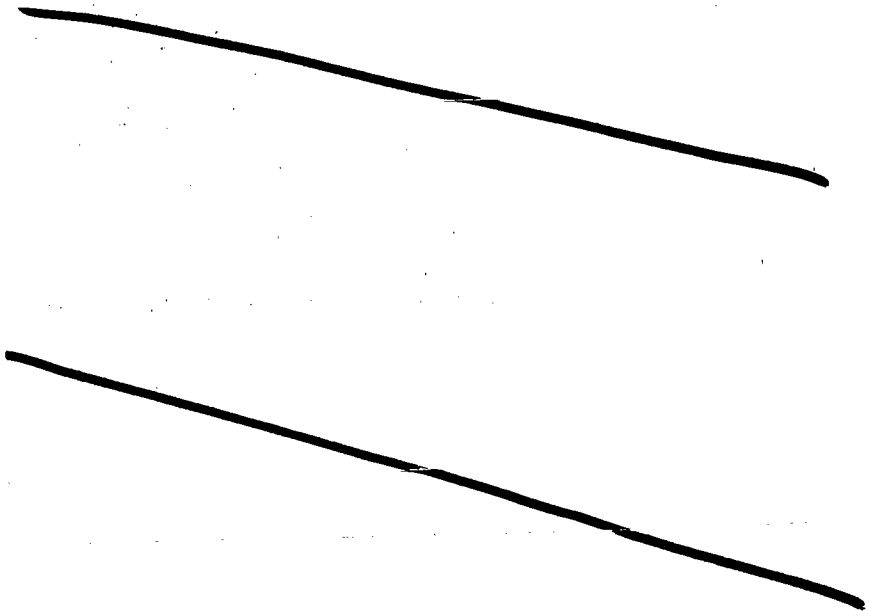
Table 2. Pharmacodynamic Parameters Corrected for Baseline Value (Efficacy Population in Study EPO-PHI-370) (Mean±SD) (% CV)

Treatment Group	N	AUC (RETI) (%.d)	AUC (HEMO) (g.d/dL)	AUC (RBC) ($x10^{12}$.d/L)
150 IU/kg t.i.w.	24	62.9±20.6 (32.7%)	27.9±16.1 (57.8%)	12.2±5.1 (41.7%)
40,000 IU q.w.	22	77.2±9.9 (12.8%)	31.0±12.5 (40.3%)	12.9±4.0 (31.1%)
Ratio (q.w. to the t.i.w.)		1.23	1.11	1.06

PK/PD Relationship

The results of Phase 1 studies EPO-PHI-377 and EPO-PHI-370 indicate that, although serum levels of erythropoietin were higher with the 40,000 IU q.w. dosing regimen as compared to the 150 IU/kg t.i.w. regimen, the two regimens produced similar pharmacodynamic responses, i.e., changes in percent reticulocytes, hemoglobin, and red blood cell counts.

Sponsor Proposed Clinical Pharmacology-related Labeling Changes



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✓ Draft Labeling

_____ Deliberative Process

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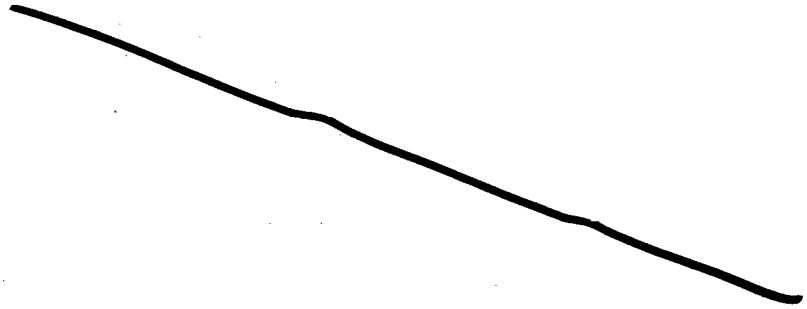

The sponsor has accepted the above labeling recommendations.

Hong Zhao 6/23/04

Hong Zhao, Ph.D.
Clinical Pharmacology Reviewer

Martin D. Green 6/23/04

Martin David Green, Ph.D.
Supervisor, Clinical Pharmacology and Toxicology

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103234s5053

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: Donna Peterson

From: Monica Hughes/DRMP/ODE-VI/CDER

Subject: Amgen Supplement 103234/5053, Revisions to Package Insert

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Donna,

Hello. Attached is the package insert for 103234/5053 with minor FDA revisions. Please note the following changes were made:

1. Line 108: FDA is removing "In Anemic Cancer Patients", Please begin this sentence with "The" as originally proposed. Including this in the statement would be incorrect as the data referred to covers both healthy and anemic cancer patients.

2. Inserted "the" on line 951.

3. Replaced "QW" with "Weekly" on lines 950, 1106, 1128, and 1129 for consistency.

4. Added "by" in line 1137

Please let me know if you have any questions.

Thank you,
Monica Hughes, M.S.
Regulatory Project Manager