

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103951/5001

Trade Name: Aranesp

Generic Name: darbepoetin alfa

Sponsor: Amgen, Incorporated

Approval Date: July 19, 2002

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

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

103951/5001

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 103951/5001

JUL 19 2002

Jeffrey N. Fellows
Director, Regulatory Affairs
Amgen, Incorporated
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Fellows:

Your request to supplement your biologics license application (BLA) for Darbepoetin alfa to include a new indication, for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy, has been approved. In addition, three new dosage strengths (150 µg, 300 µg and 500 µg) in the Albumin (Human) formulation have been approved for this indication.

The dating period for the new Darbepoetin alfa containing Albumin (Human) dosage strengths shall be 36 months from the date of manufacture when stored at 2 to 8°C. Results of ongoing stability studies should be submitted throughout the dating period, as they become available. The revised stability protocol to include these new dosage strengths is considered approved for the purpose of extending the expiration dating period of your drug product as specified in 21 CFR 601.12.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (21 CFR 601.27). On the basis of your commitment described in item 3 below, we are deferring the submission of your pediatric studies, under 21 CFR 601.27(b), until January 2003.

We acknowledge your written commitments of July 18, 2002 to provide the following:

Chemistry Manufacturing and Controls:

1. To establish a specification for the amount of oxidized Darbepoetin alfa in the Albumin (Human) formulation of the final product. The (b) (4) Darbepoetin alfa species will be detected by (b) (4) in accordance with analytical method (b) (4).
 - a. To set an initial specification for lot release and stability at $\leq \frac{(b) (4)}{(4)}\%$ and submit a copy of the Certificate of Analysis with the specification by August 30, 2002.

- b. To submit revised release specifications for the amount of oxidized Darbepoetin alfa in the final Albumin (Human) formulated product based upon the analysis of data obtained from 30 commercial lots of final material by July 30, 2003.

Clinical:

- 2. To perform immunogenicity testing on serum samples obtained from approximately 2000 patients with chemotherapy induced anemia (CIA), evenly distributed between those receiving either the Albumin (Human) or the Polysorbate 80 formulation of Darbepoetin alfa. The data will be obtained from the studies specified in your letter of July 18, 2002. Immunogenicity testing will be performed using the more sensitive assays developed under your commitment to the original BLA (STN103951/0), for studies that are ongoing, not yet initiated, and where retention serum samples are available. The results will be analyzed to establish the overall incidence of immune responses with additional exploratory analyses to identify associations between immune responses and various clinical factors. The analytic plan for analysis of these data will be submitted by December 30, 2002. You commit to completing the antibody testing, submitting the results, and filing revised draft labeling by July 31, 2004.
- 3. To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of Darbepoetin alfa in pediatric patients in an ongoing study conducted under BB-IND 8223, Study 20000126, entitled, "An Open-label Pharmacokinetic (PK) Study of Novel Erythropoiesis Stimulating Protein (NESP) Administered by Subcutaneous (SC) Injection for the Treatment of Anemia in Pediatric Subjects With Nonmyeloid Malignancies Receiving Multicycle Chemotherapy," initiated in April 2001.
 - a. The study will be completed (last patient exited) by September 2002, and the final clinical study report will be submitted to CBER in January 2003.
 - b. Following our evaluation of the PK and PD data, you have agreed to meet with us to discuss and evaluate the appropriateness of an additional pediatric study to identify a safe and effective dose for the use of Darbepoetin alfa in pediatric patients. If agreement is reached that an additional study is warranted, you commit to developing a protocol, obtaining our agreement on the study design and initiating this study by September 2003.

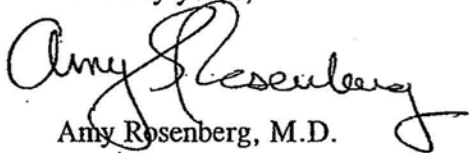
Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling materials with FDA Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448.

Final printed advertising and promotional labeling materials should be submitted at the time of initial dissemination, accompanied by FDA Form 2253.

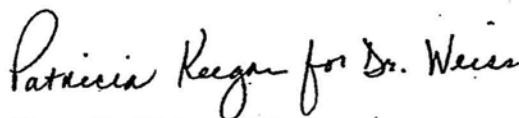
All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

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

Sincerely yours,



Amy Rosenberg, M.D.
Director
Division of Therapeutic Proteins
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research



Karen D. Weiss, M.D.
Director
Division of Clinical Trial
Design and Analysis
Office of Therapeutics
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Center for Biologics
Evaluation and Research

CONCURRENCE PAGE

cc: STN 103951/5001
HFM-500/J.Siegel (with final draft PI)
HFM-500/S.Risso
HFM-500/P. Bishop
HFM-570/K.Weiss
HFM-570/P. Keegan
HFM-570/P.Lincoln-Smith
HFM-585/G.Jones
HFM-585/E. Dye
HFM-672/D.Parshall
HFM-588/L.Burbank
HFM-670/J.McGuire
HFM-110/RIMS
HFM-4/QAS
HFM-535/A.Rosenberg
HFM-536/B.Cherney
HFM-515/P.Hughes
HFM-589/J.Delasko
HFM-541/F. Mills
HFM-541/D. Pluznik
HFM-573/S. Litwin
HFM-579/D. Green
HFM-579/M. Serabian
HFM-215/C. Chu
HFM-650/B. Kannan
HFM-220/S. Gershon
HFM-602/M. Gallagher (with final draft PI)
HFM-215/P. Lachenbruch
HFM-670/J. Eltermann
HFM-670/M. Malarkey
HFM-220/M. Miles Braun (with final draft PI)
HFM-1/K. Zoon
HFM-2/M. Elengold
HFM-45/J. McKeough
HFM-45/M. Myers (with final draft PI)
HFM-20/L. Gelb
PIB, HFM-604
DMPQ Blue file, HFM-670

PREPARED BY:HFM-589:JMDelasko:6/11-12/02:MGHarlow:7/17-18/02:JMDelasko
Revised:7/18-19/02:Townsend:7.19.2002:dixon:7.19.2002
(S:/Delasko/Amgen[Aranesp]/103951.5001/LetterAP001)

COMMUNICATION TYPE:

LETTER: Approval (AP)

Summary Text: Clinical Supplmt. Efficacy - New/Expanded Indication

REVIEW COMPLETION REQUIRED BY: RIS

SS Data Check:

- Place copy of Approval Ltr. with original signature concurrence page in Archival package behind the "Approval Materials" Tab after LAR (Licensing Action Recommendation).

RIS Data Check:

- Verify short summary - Ltr. & Submission screen should match.
- Check Letter for PMCs (if PMCs - add "PMCs - Approved With" special characteristic code.)
- Check if Major Approval - if so - add code.
- Perform Review Completion Process
- Milestone: Confirm Approved Status

Division	Name/Signature	Date
DARP	JMDelasko	7-19-02
DARP	Schneider	7-19-02
DARP	Dye L Jones	7-19-02
DTP	A Rosenberg	7/19/02
DCTDA	P. Kegan	7-19-2002
DARP	K. Townsend	7-22-02

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:

103951/5001

LABELING

ARANESP™ (darbepoetin alfa) For Injection

DESCRIPTION

Aranesp™ is an erythropoiesis stimulating protein, closely related to erythropoietin, that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Aranesp™ is a 165-amino acid protein that differs from recombinant human erythropoietin in containing 5 N-linked oligosaccharide chains, whereas recombinant human erythropoietin contains 3 chains (Egrie 2001). The 2 additional N-glycosylation sites result from amino acid substitutions in the erythropoietin peptide backbone. The additional carbohydrate chains increase the approximate molecular weight of the glycoprotein from 30,000 to 37,000 daltons. Aranesp™ is formulated as a sterile, colorless, preservative-free protein solution for intravenous (IV) or subcutaneous (SC) administration.

Single-dose vials are available containing 25, 40, 60, 100, 150, 200, 300, or 500 mcg of Aranesp™. Two formulations contain excipients as follows:

Polysorbate solution contains 0.05 mg polysorbate 80, 2.12 mg sodium phosphate monobasic monohydrate, 0.66 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in Water for Injection, USP (per 1 mL) at pH 6.2 ± 0.2.

Albumin solution contains 2.5 mg albumin (human), 2.23 mg sodium phosphate monobasic monohydrate, 0.53 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in Water for Injection, USP (per 1 mL) at pH 6.0 ± 0.3.

CLINICAL PHARMACOLOGY

Mechanism of Action

Aranesp™ stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. A primary growth factor for erythroid development, erythropoietin is produced in the kidney and released into the bloodstream in response to hypoxia. In responding to hypoxia, erythropoietin interacts with progenitor stem cells to increase red cell production. Production of endogenous erythropoietin is impaired in patients with chronic renal failure (CRF), and erythropoietin deficiency is the primary cause of their anemia. Increased hemoglobin levels are not generally observed until 2 to 6 weeks after initiating treatment with Aranesp™ (see *DOSAGE AND ADMINISTRATION: Dose Adjustment*). In patients with cancer receiving concomitant chemotherapy, the etiology of anemia is multifactorial.

Pharmacokinetics

The pharmacokinetics of Aranesp™ were studied in patients with chronic renal failure and cancer patients receiving chemotherapy.

Over the therapeutic range of 0.45 to 4.5 mcg/kg, pharmacokinetic measures (C_{max}, half-life, AUC) were linear with respect to dose and no evidence of accumulation was observed beyond an expected < 2-fold increase in blood levels when compared to the initial dose.

Following subcutaneous (SC) administration, absorption is slow and rate limiting. The observed half-life in CRF patients, which reflected the rate of absorption, was 49 hours (range: 27 to 89 hours). Following IV administration to these patients, Aranesp™ serum concentration-time profiles are biphasic, with a distribution half-life of approximately 1.4 hours and the mean terminal half-life of 21 hours. Post SC administration, CRF patients' peak concentrations occur at 34 hours (range: 24 to 72 hours) whereas cancer patients' peak concentrations are at 90 hours (range: 71 to 123 hours).

When administered by IV administration, the terminal half-life of Aranesp™ is approximately 3-fold longer than Epoetin alfa. The bioavailability of Aranesp™ as measured in CRF patients after SC administration is 37% (range: 30% to 50%).

CLINICAL STUDIES

Throughout this section of the package insert, the Aranesp™ study numbers associated with the nephrology and cancer clinical programs are designated with the letters "N" and "C", respectively.

Chronic Renal Failure Patients

The safety and effectiveness of Aranesp™ have been assessed in multicenter studies. Two studies evaluated the safety and efficacy of Aranesp™ for the correction of anemia in adult patients with CRF, and 2 studies assessed the ability of Aranesp™ to maintain hemoglobin concentrations in adult patients with CRF who had been receiving other recombinant erythropoietins.

De Novo Use of Aranesp™

In 2 open-label studies, Aranesp™ or Epoetin alfa were administered for the correction of anemia in CRF patients who had not been receiving prior treatment with exogenous erythropoietin. Study N1 evaluated CRF patients receiving dialysis; Study N2 evaluated patients not requiring dialysis (predialysis patients). In both studies, the starting dose of Aranesp™ was 0.45 mcg/kg administered once weekly. The starting dose of Epoetin alfa was 50 U/kg 3 times weekly in Study N1 and 50 U/kg twice weekly in Study N2. When necessary, dosage adjustments were instituted to maintain hemoglobin in the study target range of 11 to 13 g/dL. (Note: The recommended hemoglobin target is lower than the target range of these studies. See *DOSAGE AND ADMINISTRATION: General* for

recommended clinical hemoglobin target.) The primary efficacy endpoint was the proportion of patients who experienced at least a 1.0 g/dL increase in hemoglobin concentration to a level of at least 11.0 g/dL by 20 weeks (Study N1) or 24 weeks (Study N2). The studies were designed to assess the safety and effectiveness of Aranesp™, but not to support conclusions regarding comparisons between the two products.

In Study N1, the hemoglobin target was achieved by 72% (95% CI: 62%, 81%) of the 90 patients treated with Aranesp™ and 84% (95% CI: 66%, 95%) of the 31 patients treated with Epoetin alfa. The mean increase in hemoglobin over the initial 4 weeks of Aranesp™ treatment was 1.10 g/dL (95% CI: 0.82 g/dL, 1.37 g/dL).

In Study N2, the primary efficacy endpoint was achieved by 93% (95% CI: 87%, 97%) of the 129 patients treated with Aranesp™ and 92% (95% CI: 78%, 98%) of the 37 patients treated with Epoetin alfa. The mean increase in hemoglobin from baseline through the initial 4 weeks of Aranesp™ treatment was 1.38 g/dL (95% CI: 1.21 g/dL, 1.55 g/dL).

Conversion From Other Recombinant Erythropoietins

Two studies (Studies N3 and N4) were conducted in adult patients with CRF who had been receiving other recombinant erythropoietins and compared the abilities of Aranesp™ and other erythropoietins to maintain hemoglobin concentrations within a study target range of 9 to 13 g/dL. (Note: The recommended hemoglobin target is lower than the target range of these studies. See *DOSAGE AND ADMINISTRATION: General* for recommended clinical hemoglobin target.) CRF patients who had been receiving stable doses of other recombinant erythropoietins were randomized to Aranesp™, or to continue with their prior erythropoietin at the previous dose and schedule. For patients randomized to Aranesp™, the initial weekly dose was determined on the basis of the previous total weekly dose of recombinant erythropoietin. Study N3 was a double-blind study conducted in North America, in which 169 hemodialysis patients were randomized to treatment with Aranesp™ and 338 patients continued on Epoetin alfa. Study N4 was an open-label study conducted in Europe and Australia in which 347 patients were randomized to treatment with Aranesp™ and 175 patients were randomized to continue on Epoetin alfa or Epoetin beta. Of the 347 patients randomized to Aranesp™, 92% were receiving hemodialysis and 8% were receiving peritoneal dialysis.

In Study N3, a median weekly dose of 0.53 mcg/kg Aranesp™ (25th, 75th percentiles: 0.30, 0.93 mcg/kg) was required to maintain hemoglobin in the study target range. In Study N4, a median weekly dose of 0.41 mcg/kg Aranesp™ (25th, 75th percentiles: 0.26, 0.65 mcg/kg) was required to maintain hemoglobin in the study target range.

Cancer Patients Receiving Chemotherapy

The safety and effectiveness of Aranesp™ in reducing the requirement for red blood cell (RBC) transfusions in patients undergoing chemotherapy were assessed in a randomized, placebo-controlled, double-blind, multinational study (C1). This study was conducted in anemic (Hgb = 11 g/dL) patients with advanced, small cell or non-small cell lung cancer, who received a platinum-containing chemotherapy regimen. Patients were randomized to receive Aranesp™ 2.25 mcg/kg (n = 156) or placebo (n = 158) administered as a single weekly SC injection for up to 12 weeks. The dose was escalated to 4.5 mcg/kg/week at week six, in subjects with an inadequate response to treatment, defined as less than 1 g/dL hemoglobin increase. There were 67 patients in the Aranesp™ arm who had their dose increased from 2.25 to 4.5 mcg/kg/week, at any time during the treatment period.

Efficacy was determined by a reduction in the proportion of patients who were transfused over the 12 week treatment period. A significantly lower proportion of patients in the Aranesp™ arm, 26% (95% CI: 20, 33) required transfusion compared to 60% (95% CI: 52, 68) in the placebo arm (Kaplan-Meier estimate of proportion; $p < 0.001$ by Cochran - Mantel - Haenszel test). Of the 67 patients who received a dose increase, 28% had a 2 g/dL increase in hemoglobin over baseline, generally occurring between weeks 8 to 13. Of the 89 patients who did not receive a dose increase, 69% had a 2 g/dL increase in hemoglobin over baseline, generally occurring between weeks 6 to 13.

Studies were conducted that evaluated doses of Aranesp™ ranging from 0.5 mcg/kg to 8.0 mcg/kg administered weekly. Data from these studies indicate that there is a dose response relationship with respect to hemoglobin response. The minimally effective starting dose with respect to reducing transfusion requirements was 1.5 mcg/kg/week with a plateau observed at 4.5 mcg/kg/week.

INDICATIONS AND USAGE

Aranesp™ is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis, and for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.

CONTRAINDICATIONS

Aranesp™ is contraindicated in patients with:

- Uncontrolled hypertension
- Known hypersensitivity to the active substance or any of the excipients

WARNINGS

Cardiovascular Events, Hemoglobin, and Rate of Rise of Hemoglobin

Aranesp™ and other erythropoietic therapies may increase the risk of cardiovascular events, including death. The higher risk of cardiovascular events may be associated with higher hemoglobin and/or higher rates of rise of hemoglobin. The hemoglobin level should be managed carefully to avoid exceeding a target level of 12 g/dL.

In a clinical trial of Epoetin alfa (rHuEPO) treatment in hemodialysis patients with clinically evident cardiac disease, patients were randomized to a target hemoglobin of either 14 ± 1 g/dL or 10 ± 1 g/dL (Besarab 1998). Higher mortality (35% versus 29%) was observed in the 634 patients randomized to a target hemoglobin of 14 g/dL than in the 631 patients assigned a target hemoglobin of 10 g/dL. The reason for the increased mortality observed in this study is unknown; however, the incidence of nonfatal myocardial infarction, vascular access thrombosis, and other thrombotic events was also higher in the group randomized to a target hemoglobin of 14 g/dL.

In patients treated with Aranesp™ or other recombinant erythropoietins in Aranesp™ clinical trials, increases in hemoglobin greater than approximately 1.0 g/dL during any 2-week period were associated with increased incidence of cardiac arrest, neurologic events (including seizures and stroke), exacerbations of hypertension, congestive heart failure, vascular thrombosis/ischemia/infarction, acute myocardial infarction, and fluid overload/edema. It is recommended that the dose of Aranesp™ be decreased if the hemoglobin increase exceeds 1.0 g/dL in any 2-week period, because of the association of excessive rate of rise of hemoglobin with these events.

Hypertension

Patients with uncontrolled hypertension should not be treated with Aranesp™; blood pressure should be controlled adequately before initiation of therapy. Blood pressure may rise during treatment of anemia with Aranesp™ or Epoetin alfa. In Aranesp™ clinical trials, approximately 40% of patients with CRF required initiation or intensification of antihypertensive therapy during the early phase of treatment when the hemoglobin was increasing. Hypertensive encephalopathy and seizures have been observed in patients with CRF treated with Aranesp™ or Epoetin alfa.

Special care should be taken to closely monitor and control blood pressure in patients treated with Aranesp™. During Aranesp™ therapy, patients should be advised of the importance of compliance with antihypertensive therapy and dietary restrictions. If blood pressure is difficult to control by pharmacologic or dietary measures, the dose of Aranesp™ should be reduced or withheld (see *DOSAGE AND ADMINISTRATION: Dose Adjustment*). A clinically significant decrease in hemoglobin may not be observed for several weeks.

Seizures

Seizures have occurred in patients with CRF participating in clinical trials of Aranesp™ and Epoetin alfa. During the first several months of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. While the relationship between seizures and the rate of rise of hemoglobin is uncertain, it is recommended that the dose of Aranesp™ be decreased if the hemoglobin increase exceeds 1.0 g/dL in any 2-week period.

Thrombotic Events

An increased incidence of thrombotic events has been observed in patients treated with erythropoietic agents. In patients with cancer who received Aranesp™, pulmonary emboli, thrombophlebitis and thrombosis occurred more frequently than in placebo controls (see *ADVERSE REACTIONS: Cancer Patients Receiving Chemotherapy, Table 4*).

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. This has been reported predominantly in patients with CRF. PRCA has been reported in a limited number of subjects exposed to other recombinant erythropoietin products prior to exposure to Aranesp™ therefore, the contribution of Aranesp™ to the development of PRCA is unclear. Any patient with loss of response to Aranesp™ should be evaluated for the etiology of loss of effect (See *PRECAUTIONS: General*). Aranesp™ should be discontinued in any patient with evidence of PRCA and the patient evaluated for the presence of binding and neutralizing antibodies to Aranesp™, native erythropoietin, and any other recombinant erythropoietin administered to the patient. Amgen may be contacted to assist in this evaluation. In patients with PRCA secondary to neutralizing antibodies to erythropoietin, Aranesp™ should not be administered.

Albumin (Human)

Aranesp™ is supplied in 2 formulations with different excipients, one containing polysorbate 80 and another containing albumin (human), a derivative of human blood (see *DESCRIPTION*). Based on effective donor screening and product manufacturing processes, Aranesp™ formulated with albumin 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.

PRECAUTIONS

General

The safety and efficacy of Aranesp™ therapy have not been established in patients with underlying hematologic diseases (e.g., hemolytic anemia, sickle cell anemia, thalassemia, porphyria).

Lack or Loss of Response to Aranesp™

A lack of response or failure to maintain a hemoglobin response with Aranesp™ doses within the recommended dosing range should prompt a search for causative factors. Deficiencies of folic acid or vitamin B₁₂ should be excluded or corrected. Depending on the clinical setting, intercurrent infections, inflammatory or malignant processes, osteofibrosis cystica, occult blood loss, hemolysis, severe aluminum toxicity, and bone marrow fibrosis may compromise an erythropoietic response. In the absence of another etiology, the patient should be evaluated for evidence of pure red cell aplasia and sera should be tested for the presence of antibody to recombinant erythropoietins.

Hematology

Sufficient time should be allowed to determine a patient's responsiveness to a dosage of Aranesp™ 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 prevent the hemoglobin from exceeding the recommended target (12 g/dL) or rising too rapidly (greater than 1.0 g/dL in 2 weeks), the guidelines for dose and frequency of dose adjustments should be followed (see *WARNINGS, DOSAGE AND ADMINISTRATION: Dose Adjustment*).

Allergic Reactions

There have been rare reports of potentially serious allergic reactions including skin rash and urticaria associated with Aranesp™. Symptoms have recurred with rechallenge, suggesting a causal relationship exists in some instances. If a serious allergic or anaphylactic reaction occurs, Aranesp™ should be immediately and permanently discontinued and appropriate therapy should be administered.

Patients With CRF Not Requiring Dialysis

Patients with CRF not yet requiring dialysis may require lower maintenance doses of Aranesp™ than patients receiving dialysis. Though predialysis patients generally receive less frequent monitoring of blood pressure and laboratory parameters than dialysis patients, predialysis patients may be more responsive to the effects of Aranesp™, and

require judicious monitoring of blood pressure and hemoglobin. Renal function and fluid and electrolyte balance should also be closely monitored.

Dialysis Management

Therapy with Aranesp™ results in an increase in RBCs and a decrease in plasma volume, which could reduce dialysis efficiency; patients who are marginally dialyzed may require adjustments in their dialysis prescription.

Growth Factor Potential

Aranesp™ is a growth factor that primarily stimulates RBC production. The possibility that Aranesp™ can act as a growth factor for any tumor type, particularly myeloid malignancies, has not been evaluated. In the randomized, placebo-controlled study in 314 subjects with advanced lung cancer, there were no statistically significant differences in time-to-progression (TTP) or overall survival (OS) observed, however the study was not designed to detect or exclude clinically meaningful differences in either TTP or OS.

Laboratory Tests

After initiation of Aranesp™ therapy, the hemoglobin should be determined weekly until it has stabilized and the maintenance dose has been established (see *DOSAGE AND ADMINISTRATION*). After a dose adjustment, the hemoglobin should be determined weekly for at least 4 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.

In order to ensure effective erythropoiesis, iron status should be evaluated for all patients before and during treatment, as the majority of patients will eventually require supplemental iron therapy. Supplemental iron therapy is recommended for all patients whose serum ferritin is below 100 mcg/L or whose serum transferrin saturation is below 20%.

Information for Patients

Patients should be informed of the possible side effects of Aranesp™ and be instructed to report them to the prescribing physician. Patients should be informed of the signs and symptoms of allergic drug reactions and be advised of appropriate actions. Patients should be counseled on the importance of compliance with their Aranesp™ treatment, dietary and dialysis prescriptions, and the importance of judicious monitoring of blood pressure and hemoglobin concentration should be stressed.

If it is determined that a patient can safely and effectively administer Aranesp™ at home, appropriate instruction on the proper use of Aranesp™ should be provided for patients and their caregivers, including careful review of the "Information for Patients and Caregivers" insert. Patients and caregivers should also be cautioned against the reuse of needles, syringes, or drug product, and be thoroughly instructed in their proper disposal.

A puncture-resistant container for the disposal of used syringes and needles should be made available to the patient.

Drug Interactions

No formal drug interaction studies of Aranesp™ have been performed.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenicity: The carcinogenic potential of Aranesp™ has not been evaluated in long-term animal studies. Aranesp™ did not alter the proliferative response of non-hematological cells *in vitro* or *in vivo*. In toxicity studies of approximately 6 months duration in rats and dogs, no tumorigenic or unexpected mitogenic responses were observed in any tissue type. Using a panel of human tissues, the *in vitro* tissue binding profile of Aranesp™ was identical to Epoetin alfa. Neither molecule bound to human tissues other than those expressing the erythropoietin receptor.

Mutagenicity: Aranesp™ was negative in the *in vitro* bacterial and CHO cell assays to detect mutagenicity and in the *in vivo* mouse micronucleus assay to detect clastogenicity.

Impairment of Fertility: When administered intravenously to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected at any doses evaluated (up to 10 mcg/kg/dose, administered 3 times weekly). An increase in post implantation fetal loss was seen at doses equal to or greater than 0.5 mcg/kg/dose, administered 3 times weekly.

Pregnancy Category C

When Aranesp™ was administered intravenously to rats and rabbits during gestation, no evidence of a direct embryotoxic, fetotoxic, or teratogenic outcome was observed at doses up to 20 mcg/kg/day. The only adverse effect observed was a slight reduction in fetal weight, which occurred at doses causing exaggerated pharmacological effects in the dams (1 mcg/kg/day and higher). No deleterious effects on uterine implantation were seen in either species. No significant placental transfer of Aranesp™ was observed in rats. An increase in post implantation fetal loss was observed in studies assessing fertility (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility: Impairment of Fertility**).

Intravenous injection of Aranesp™ to female rats every other day from day 6 of gestation through day 23 of lactation at doses of 2.5 mcg/kg/dose and higher resulted in offspring (F1 generation) with decreased body weights, which correlated with a low incidence of deaths, as well as delayed eye opening and delayed preputial separation. No adverse effects were seen in the F2 offspring.

There are no adequate and well-controlled studies in pregnant women. Aranesp™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

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

Pediatric Use

The safety and efficacy of Aranesp™ in pediatric patients have not been established.

Geriatric Use

Of the 1598 CRF patients in clinical studies of Aranesp™, 42% were age 65 and over, while 15% were 75 and over. Of the 873 cancer patients in clinical studies receiving Aranesp™ and concomitant chemotherapy, 45% were age 65 and over, while 14% were 75 and over. No overall differences in safety or efficacy were observed between older and younger patients.

ADVERSE REACTIONS

General

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of Aranesp™ cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

Chronic Renal Failure Patients

In all studies, the most frequently reported serious adverse reactions with Aranesp™ were vascular access thrombosis, congestive heart failure, sepsis, and cardiac arrhythmia. The most commonly reported adverse reactions were infection, hypertension, hypotension, myalgia, headache and diarrhea, (see *WARNINGS: Cardiovascular Events, Hemoglobin, and Rate of Rise of Hemoglobin/Hypertension*). The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Aranesp™, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were hypotension, hypertension, fever, myalgia, nausea, and chest pain.

The data described below reflect exposure to Aranesp™ in 1598 CRF patients, including 675 exposed for at least 6 months, of whom 185 were exposed for greater than 1 year. Aranesp™ was evaluated in active-controlled (n = 823) and uncontrolled studies (n = 775).

The rates of adverse events and association with Aranesp™ are best assessed in the results from studies in which Aranesp™ was used to stimulate erythropoiesis in patients anemic at study baseline (n = 348), and, in particular, the subset of these patients in randomized controlled trials (n = 276). Because there were no substantive differences in

the rates of adverse reactions between these subpopulations, or between these subpopulations and the entire population of patients treated with Aranesp™, data from all 1598 patients were pooled.

The population encompassed an age range from 18 to 91 years. Fifty-seven percent of the patients were male. The percentages of Caucasian, Black, Asian, and Hispanic patients were 83%, 11%, 3%, and 1%, respectively. The median weekly dose of Aranesp™ was 0.45 mcg/kg (25th, 75th percentiles: 0.29, 0.66 mcg/kg).

Some of the adverse events reported are typically associated with CRF, or recognized complications of dialysis, and may not necessarily be attributable to Aranesp™ therapy. No important differences in adverse event rates between treatment groups were observed in controlled studies in which patients received Aranesp™ or other recombinant erythropoietins.

The data in *Table 1* reflect those adverse events occurring in at least 5% of patients treated with Aranesp™.

Table 1. Adverse Events Occurring in $\geq 5\%$ of CRF Patients

Event	Patients Treated With Aranesp™ (n = 1598)
APPLICATION SITE	
Injection Site Pain	7%
BODY AS A WHOLE	
Peripheral Edema	11%
Fatigue	9%
Fever	9%
Death	7%
Chest Pain, Unspecified	6%
Fluid Overload	6%
Access Infection	6%
Influenza-like Symptoms	6%
Access Hemorrhage	6%
Asthenia	5%
CARDIOVASCULAR	
Hypertension	23%
Hypotension	22%
Cardiac Arrhythmias/Cardiac Arrest	10%
Angina Pectoris/Cardiac Chest Pain	8%
Thrombosis Vascular Access	8%
Congestive Heart Failure	6%
CNS/PNS	
Headache	16%
Dizziness	8%
GASTROINTESTINAL	
Diarrhea	16%
Vomiting	15%
Nausea	14%
Abdominal Pain	12%
Constipation	5%
MUSCULO-SKELETAL	
Myalgia	21%
Arthralgia	11%
Limb Pain	10%
Back Pain	8%

(Continued)

Table 1. Adverse Events Occurring in $\geq 5\%$ of CRF Patients (Continued)

Event	Patients Treated With Aranesp™ (n = 1598)
RESISTANCE MECHANISM	
Infection ^a	27%
RESPIRATORY	
Upper Respiratory Infection	14%
Dyspnea	12%
Cough	10%
Bronchitis	6%
SKIN AND APPENDAGES	
Pruritus	8%

^a Infection includes sepsis, bacteremia, pneumonia, peritonitis, and abscess.

The incidence rates for other clinically significant events are shown in *Table 2*.

Table 2. Percent Incidence of Other Clinically Significant Events in CRF Patients

Event	Patients Treated With Aranesp™ (n = 1598)
Acute Myocardial Infarction	2%
Seizure	1%
Stroke	1%
Transient Ischemic Attack	1%

Thrombotic Events

Vascular access thrombosis in hemodialysis patients occurred in clinical trials at an annualized rate of 0.22 events per patient year of Aranesp™ therapy. Rates of thrombotic events (e.g., vascular access thrombosis, venous thrombosis, and pulmonary emboli) with Aranesp™ therapy were similar to those observed with other recombinant erythropoietins in these trials; the median duration of exposure was 12 weeks.

Cancer Patients Receiving Chemotherapy

The data described below reflect the exposure to Aranesp™ in 873 cancer patients. Aranesp™ was evaluated in seven studies that were active-controlled and/or placebo-controlled studies of up to 6 months duration. The Aranesp™ treated patient demographics were as follows: median age of 63 years (range of 20 to 91 years);

40% male; 88% Caucasian, 5% Hispanic, 4% Black, and 3% Asian. Over 90% of patients had locally advanced or metastatic cancer, with the remainder having early stage disease. Patients with solid tumors (e.g., lung, breast, colon, ovarian cancers), and lymphoproliferative malignancies (e.g., lymphoma, multiple myeloma) were enrolled in the clinical studies. All of the 873 AranespTM treated subjects also received concomitant cyclic chemotherapy.

The most frequently reported serious adverse events included death (10%), fever (4%), pneumonia (3 %), dehydration (3%), vomiting (2%), and dyspnea (2%). The most commonly reported adverse events were fatigue, edema, nausea, vomiting, diarrhea, fever and dyspnea (see *Table 3*). Except for those events listed in *Tables 3 and 4*, the incidence of adverse events in clinical studies occurred at a similar rate compared with patients who received placebo and were generally consistent with the underlying disease and its treatment with chemotherapy. The most frequently reported reasons for discontinuation of AranespTM were progressive disease, death, discontinuation of the chemotherapy, asthenia, dyspnea, pneumonia, and gastrointestinal hemorrhage. No important differences in adverse event rates between treatment groups were observed in controlled studies in which patients received AranespTM or other recombinant erythropoietins.

Table 3. Adverse Events Occurring in $\geq 5\%$ of Patients Receiving Chemotherapy

Event	Aranesp™ (n = 873)	Placebo (n = 221)
BODY AS A WHOLE		
Fatigue	33%	30%
Edema	21%	10%
Fever	19%	16%
CNS/PNS		
Dizziness	14%	8%
Headache	12%	9%
GASTROINTESTINAL		
Diarrhea	22%	12%
Constipation	18%	17%
METABOLIC/NUTRITION		
Dehydration	5%	3%
MUSCULO-SKELETAL		
Arthralgia	13%	6%
Myalgia	8%	5%
SKIN AND APPENDAGES		
Rash	7%	3%

Table 4. Incidence of Other Clinically Significant Adverse Events in Patients Receiving Chemotherapy

Event	All Aranesp™ (n = 873)	Placebo (n = 221)
Hypertension	3.7%	3.2%
Seizures/Convulsions	0.6%	0.5%
Thrombotic Events	6.2%	4.1%
Pulmonary Embolism	1.3%	0.0%
Thrombosis	5.6%	4.1%

Seizures/Convulsions include the preferred terms: Convulsions, Convulsions Grand Mal, and Convulsions Local.

Thrombosis includes: Thrombophlebitis, Thrombophlebitis Deep, Thrombosis Venous, Thrombosis Venous Deep, Thromboembolism, and Thrombosis

Thrombotic and Cardiovascular Events

Overall, the incidence of thrombotic events was 6.2% for Aranesp™ and 4.1% for placebo. However, the following events were reported more frequently in Aranesp-treated patients than in placebo-controls: pulmonary embolism, thromboembolism, thrombosis, and thrombophlebitis (deep and/or superficial). In addition, edema of any type was more frequently reported in Aranesp-treated (21%) patients than in patients who received placebo (10%).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Aranesp™ has not been adequately determined. Radioimmunoprecipitation assays were performed on sera from 1534 CRF and 833 cancer patients treated with Aranesp™ in clinical studies. High-titer antibodies were not detected in patients with CRF, but assay sensitivity may be inadequate to reliably detect lower titers. Antibodies were detected by radioimmunoprecipitation in sera from three cancer patients; neutralizing activity, possibly related to antibodies, was detected in one of these three patients. There was no evidence of PRCA in that patient. (see *WARNINGS: Pure Red Cell Aplasia*).

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the

incidence of antibodies to Aranesp™, with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

The maximum amount of Aranesp™ that can be safely administered in single or multiple doses has not been determined. Doses over 3.0 mcg/kg/week for up to 28 weeks have been administered to CRF patients. Doses up to 8.0 mcg/kg every week and 15.0 mcg/kg every 3 weeks have been administered to cancer patients for up to 12-16 weeks.

Excessive rise and rate of rise in hemoglobin concentration, however, have been associated with adverse events (see *WARNINGS* and *DOSAGE AND ADMINISTRATION: Dose Adjustment*). In the event of polycythemia, Aranesp™ should be temporarily withheld (see *DOSAGE AND ADMINISTRATION: Dose Adjustment*). If clinically indicated, phlebotomy may be performed.

DOSAGE AND ADMINISTRATION

General

IMPORTANT: Aranesp™ dosing regimens are different for each of the indications described in this section of the package insert. Due to the longer serum half-life, Aranesp™ should be administered less frequently than Epoetin alfa (for example where Epoetin alfa is administered three times a week, Aranesp™ should be administered weekly). Aranesp™ should be administered under the supervision of a healthcare professional.

Chronic Renal Failure Patients

Aranesp™ is administered either IV or SC as a single weekly injection. The dose should be started and slowly adjusted as described below based on hemoglobin levels. If a patient fails to respond or maintain a response, other etiologies should be considered and evaluated (see *PRECAUTIONS: General/Laboratory Tests*). When Aranesp™ therapy is initiated or adjusted, the hemoglobin should be followed weekly until stabilized and monitored at least monthly thereafter.

For patients who respond to Aranesp™ with a rapid increase in hemoglobin (e.g., more than 1.0 g/dL in any 2-week period), the dose of Aranesp™ should be reduced (see *DOSAGE AND ADMINISTRATION: Dose Adjustment* because of the association of excessive rate of rise of hemoglobin with adverse events (see *WARNINGS: Cardiovascular Events, Hemoglobin, and Rate of Rise of Hemoglobin*).

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

Starting Dose***Correction of Anemia***

The recommended starting dose of Aranesp™ for the correction of anemia in CRF patients is 0.45 mcg/kg body weight, administered as a single IV or SC injection once weekly. Because of individual variability, doses should be titrated to not exceed a target hemoglobin concentration of 12 g/dL (see Dose Adjustment). For many patients, the appropriate maintenance dose will be lower than this starting dose. Predialysis patients, in particular, may require lower maintenance doses. Also, some patients have been treated successfully with a SC dose of Aranesp™ administered once every 2 weeks.

Conversion From Epoetin alfa to Aranesp™

The starting weekly dose of Aranesp™ should be estimated on the basis of the weekly Epoetin alfa dose at the time of substitution (see Table 5). Because of individual variability, doses should then be titrated to maintain the target hemoglobin. Due to the longer serum half-life, Aranesp™ should be administered less frequently than Epoetin alfa. Aranesp™ should be administered once a week if a patient was receiving Epoetin alfa 2 to 3 times weekly. Aranesp™ should be administered once every 2 weeks if a patient was receiving Epoetin alfa once per week. The route of administration (IV or SC) should be maintained.

**Table 5. Estimated Aranesp™ Starting Doses (mcg/week)
Based on Previous Epoetin alfa Dose (Units/week)**

Previous Weekly Epoetin alfa Dose (Units/week)	Weekly Aranesp™ Dose (mcg/week)
< 2500	6.25
2500 to 4999	12.5
5000 to 10,999	25
11,000 to 17,999	40
18,000 to 33,999	60
34,000 to 89,999	100
≥ 90,000	200

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, doses 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 1.0 g/dL in a 2-week period, the dose should be decreased by approximately 25%.

If the increase in hemoglobin is less than 1.0 g/dL over 4 weeks and iron stores are adequate (see *PRECAUTIONS: Laboratory Tests*), the dose of Aranesp™ 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

Aranesp™ dosage should be adjusted to maintain a target hemoglobin not to exceed 12 g/dL. If the hemoglobin exceeds 12 g/dL, the dose may be adjusted as described above. Doses must be individualized to ensure that hemoglobin is maintained at an appropriate level for each patient.

Cancer Patients Receiving Chemotherapy

The recommended starting dose for Aranesp™ is 2.25 mcg/kg administered as a weekly SC injection.

The dose should be adjusted for each patient to achieve and maintain a target hemoglobin. If there is less than a 1.0 g/dL increase in hemoglobin after 6 weeks of therapy, the dose of Aranesp™ should be increased up to 4.5 mcg/kg. If hemoglobin increases by more than 1.0 g/dL in a 2-week period or if the hemoglobin exceeds 12 g/dL, the dose should be reduced by approximately 25%. If the hemoglobin exceeds 13 g/dL, doses should be temporarily withheld until the hemoglobin falls to 12 g/dL. At this point, therapy should be reinitiated at a dose approximately 25% below the previous dose.

Preparation and Administration of Aranesp™

Do not shake Aranesp™. Vigorous shaking may denature Aranesp™, rendering it biologically inactive.

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.

Do not dilute Aranesp™.

Do not administer Aranesp™ in conjunction with other drug solutions.

Aranesp™ is packaged in single-use vials and contains no preservative. Discard any unused portion. **Do not pool unused portions.**

See the accompanying “Information for Patients and Caregivers” leaflet for complete instructions on the preparation and administration of Aranesp™ for patients.

HOW SUPPLIED

Aranesp™ is available in 2 solutions, an albumin solution and a polysorbate solution. The words “Albumin Free” appear on the polysorbate container labels and the package main panels as well as other panels as space permits. Aranesp™ is available in the following packages:

Single-dose Vial, Polysorbate Solution

1 Vial/Pack, 4 Packs/Case	4 Vials/Pack, 10 Packs/Case
200 mcg/1 mL (NDC 55513-006-01)	25 mcg/1 mL (NDC 55513-002-04)
	40 mcg/1 mL (NDC 55513-003-04)
	60 mcg/1 mL (NDC 55513-004-04)
	100 mcg/1 mL (NDC 55513-005-04)

Single-dose Vial, Albumin Solution

1 Vial/Pack, 4 Packs/Case	4 Vial/Pack, 4 Packs/Case	4 Vials/Pack, 10 Packs/Case
200 mcg/1 mL (NDC 55513-014-01)	200 mcg/1 mL (NDC 55513-014-04)	25 mcg/1 mL (NDC 55513-010-04)
300 mcg/1 mL (NDC 55513-015-01)	300 mcg/1 mL (NDC 55513-015-04)	40 mcg/1 mL (NDC 55513-011-04)
500 mcg/1 mL (NDC 55513-016-01)		60 mcg/1 mL (NDC 55513-012-04)
		100 mcg/1 mL (NDC 55513-013-04)
		150 mcg/0.75 mL (NDC 55513-054-04)

Storage

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

REFERENCES

1. Egrie JC and Browne JK. Development and characterization of novel erythropoiesis stimulating protein (NESP). *Brit J Cancer*. 2001;84(suppl 1):3-10.
2. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med*. 1998;339:584-90.

Rx only

This product, or its use, may be covered by one or more US Patents, including US Patent No. 5,618,698, in addition to others including patents pending.

Manufactured by:
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Aranesp™
(darbepoetin alfa)

Information for Patients and Caregivers

This patient package insert contains information and directions for patients who will be receiving injections of Aranesp™ and their caregivers. This patient package insert does not include all information about Aranesp™. You should discuss any questions about treatment with Aranesp™ with your doctor.

What is Aranesp™?

Aranesp™ (Air-uh-nesp) is a man made protein that acts like the natural protein human erythropoietin (ee-rith-row-po-eh-tin). Erythropoietin is a hormone, produced primarily by healthy kidneys, which stimulates the bone marrow to make oxygen-carrying red blood cells.

What is Aranesp™ used for?

Aranesp™ is used to treat anemia (a lower than normal number of red blood cells) in patients with kidney disease who may or may not be on dialysis and to treat anemia in patients with cancer where anemia is due to the effect of chemotherapy.

People with anemia may feel tired or lack energy. Some people may also have shortness of breath, chest pain, and feel cold much of the time.

How does Aranesp™ work?

When kidneys are not working properly, they cannot produce enough erythropoietin, so the body cannot make enough red blood cells. Patients with cancer receiving chemotherapy may not produce enough erythropoietin or may not respond adequately to the erythropoietin their bodies produce to overcome the effect of the chemotherapy on red blood cell counts.

Aranesp™ works by stimulating your bone marrow to make more red blood cells. An increase in the number of red blood cells may relieve the symptoms of anemia.

Your doctor will know when Aranesp™ is working because your blood tests will show an increase in the number of red blood cells. Your doctor may refer to the results of your blood tests as hemoglobin and/or hematocrit, and your doctor will be checking these tests while you are being treated with Aranesp™. The increase in the number of red blood cells is not immediate; it may take several weeks. The amount of time it takes to reach the red blood cell level that is right for you, and the dose of Aranesp™ needed to make the red blood cell level rise, is different for each person. You may need Aranesp™ dose adjustments before you reach your correct dose of Aranesp™ and the correct dose may change over time.

Who should not take Aranesp™?

- People with uncontrolled high blood pressure should not take Aranesp™.
- People who are allergic to Aranesp™, other erythropoietins, medicines made using mammalian cells, or any of the ingredients (for example, albumin or polysorbate 80) in Aranesp™ should not take Aranesp™.

Talk to your doctor if you have any questions about this information.

What are the possible or reasonably likely side effects of Aranesp™?

Your blood pressure may increase when the number of red blood cells rises, so your doctor or caregiver may monitor your blood pressure more frequently. Some people have also had infections, fevers, headaches, muscle aches or soreness, nausea, diarrhea, leg swelling, and chest pain. If you experience any of these symptoms, you should call your doctor.

If you are on hemodialysis, there is a risk of blood clots forming at your vascular access. Call your doctor if you think your access is blocked.

Patients with cancer may have an increased risk of blood clots in the veins (thrombophlebitis) or the lungs (pulmonary embolus). **Call your doctor if you experience pain and/or swelling in the legs or worsening in shortness of breath.**

Some people experience redness, swelling, or itching at the site of injection. This reaction may be an allergy to the ingredients in Aranesp™, or it may be a local irritation. If you notice any signs of redness, swelling, or itching at the site of injection, talk to your doctor.

Serious allergic reactions can also happen. These reactions can cause a rash over the whole body, shortness of breath, wheezing, a drop in blood pressure, swelling around the mouth or eyes, fast pulse, or sweating. If at any time a serious allergic reaction occurs, **stop using Aranesp™ and call your doctor or emergency medical personnel immediately (for example, call 911).**

What about pregnancy or breastfeeding?

Aranesp™ has not been studied in pregnant women and its effects on developing babies are not known. It is also not known if Aranesp™ can get into human breast milk. If you are pregnant, plan to become pregnant, or think you may be pregnant, or are breastfeeding, you should talk to your doctor before using Aranesp™.

What important information do I need to know about taking Aranesp™ at home?

In some cases, patients may be able to use Aranesp™ at home. If your doctor has determined that you can safely use Aranesp™ at home, you and/or your caregiver will receive instructions on how much Aranesp™ to use, how to inject it, how often it

should be injected, and how to dispose of the unused portions of each vial. **You should always follow your doctor's instructions.**

Too much Aranesp™ may cause your body to produce too many red blood cells too fast (lead to a hemoglobin that is too high). Producing too many red blood cells, or producing them too fast may cause serious problems. It is important that your blood pressure be monitored often and to report any changes outside of the guidelines that your doctor has given you, especially if you have heart disease. In addition, symptoms of temporary confusion or seizures should be reported to your doctor immediately. Certain laboratory tests, such as hemoglobin, hematocrit, or iron level measurements, may also need to be done more often and be reported to your doctor or dialysis center.

Over time, many kidney disease patients also need to take iron. Your doctor will know when or if you need an iron supplement from your laboratory test results.

Do not change the dose of Aranesp™. You should ask your doctor what to do if you miss a dose of Aranesp™.

Be sure to change the site for each injection to avoid soreness at any one site. Occasionally a problem may develop at the injection site. If there is a lump, swelling, or bruising at the injection site that does not go away, talk to your doctor.

If you have a hemodialysis vascular access, continue to check the access to make sure it is working. Call your doctor or dialysis center right away if you have any problems or questions.

Always call your doctor if you do not feel well while using Aranesp™.

What do you and/or your caregiver need to do to prepare and give an injection of Aranesp™?

When you receive your Aranesp™, always check to see that:

- The name Aranesp™ appears on the package and vial label.
- The expiration date on the vial label has not passed. **You should not use a vial after the date on the label.**
- The strength of the Aranesp™ vial (number of micrograms [mcg] in the colored dot on the package and on the vial) is the same as the doctor prescribed.
- The Aranesp™ liquid in the vial is clear and colorless. Do not use Aranesp™ if the liquid in the vial appears discolored or cloudy or if the liquid appears to contain lumps, flakes, or particles.
- Do not use Aranesp™ if the yellow cap on the vial has been removed or is missing when the package is opened.

Only use the syringe that your doctor prescribes.

The doctor or nurse will give you instructions on how to measure your dose of Aranesp™. This dose will be measured in milliliters. You should only use a syringe that is marked in tenths of milliliters, or mL (for example, 0.2 mL). The doctor or nurse may refer to an "mL" as a "cc" (1 mL = 1 cc). Using an unmarked syringe can lead to a mistake in the dose. If you do not use the correct syringe, you could inject too much or too little Aranesp™.

Only use disposable syringes and needles. Use the syringes and needles only once and dispose of them as instructed by your doctor or nurse.

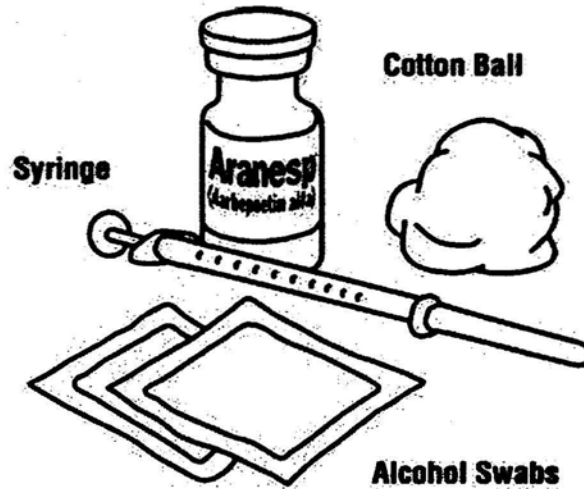
IMPORTANT: TO HELP AVOID POSSIBLE INFECTION, FOLLOW THESE INSTRUCTIONS.

Setting up for an injection

1. Find a clean, flat working surface such as a table.
2. Remove the vial of Aranesp™ from the refrigerator and place it on your flat working surface; allow it to reach room temperature. This should take about 30 minutes. Do not leave the vial in direct sunlight and do not use a vial that has been frozen.

You should use a vial only once. Do not put the needle through the rubber stopper more than once. **DO NOT SHAKE THE VIAL.** Shaking may damage the Aranesp™. If the Aranesp™ vial has been shaken vigorously, the solution may appear foamy and it should not be used.

3. Assemble the supplies you will need for an injection:
 - Aranesp™ vial
 - The correct disposable syringe and needle
 - Two alcohol swabs
 - One cotton ball or gauze
 - Puncture-proof disposable container

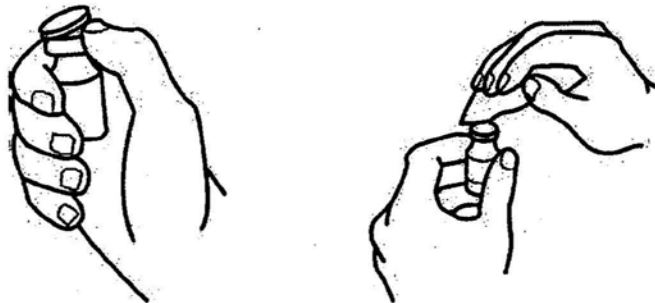


4. Wash your hands with soap and warm water.



How to prepare the dose of Aranesp™

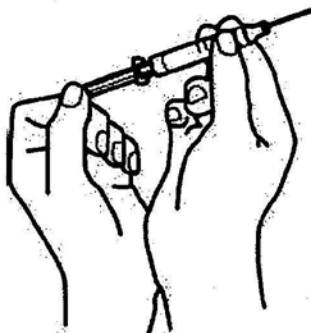
5. Take the yellow color cap off the vial. Clean the rubber stopper with one alcohol swab.



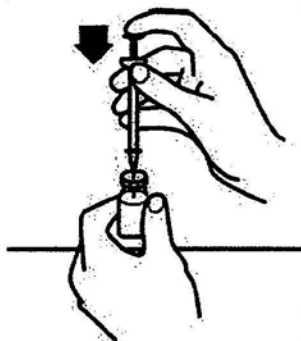
6. Check the package containing the syringe. If the package has been opened or damaged, do not use that syringe. You should dispose of that syringe in

the puncture-proof disposal container. If the syringe package is undamaged, open the package and remove the syringe.

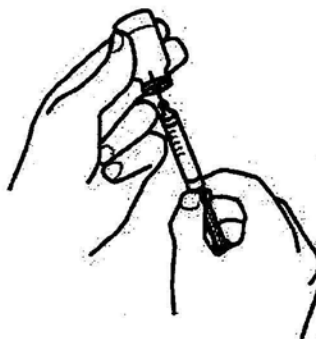
7. Pull the needle cover straight off the syringe. Then, pull back on the plunger to draw air into the syringe. The amount of air drawn into the syringe should be the same amount (mL or cc) as the dose of Aranesp™ that your doctor prescribed.



8. Keep the vial on your flat working surface and insert the needle straight down through the rubber stopper.
9. Push the plunger of the syringe down to inject the air from the syringe into the vial of Aranesp™.



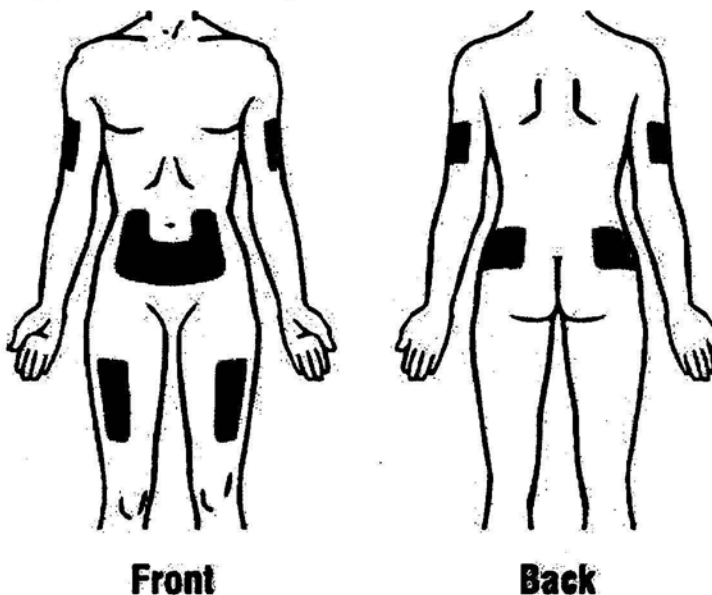
10. Keeping the needle inside the vial, turn the vial upside down. Make sure that the tip of the needle is in the Aranesp™ liquid.



11. Keeping the vial upside down, slowly pull back on the plunger to fill the syringe with Aranesp™ liquid to the number (mL or cc) that matches the dose your doctor prescribed.
12. Keeping the needle in the vial, check for air bubbles in the syringe. If there are air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. Then slowly push the plunger up to force the air bubbles out of the syringe. Keep the tip of the needle in the liquid and once again pull the plunger back to the number on the syringe that matches your dose. Check again for air bubbles. The air in the syringe will not hurt you, but too large an air bubble can reduce your dose of Aranesp™. If there are still air bubbles, repeat the steps above to remove them.
13. Check again to make sure that you have the correct dose in the syringe. It is important that you use the exact dose prescribed by your doctor.

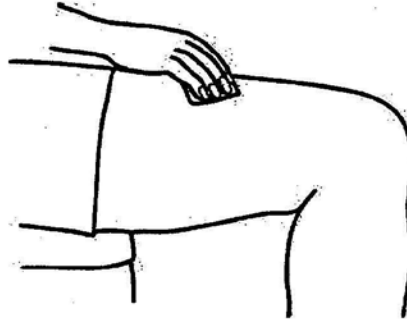
Selecting and preparing the injection site

14. Choose an injection site. Four recommended injection sites for Aranesp™ include:
 - The outer area of your upper arms
 - The abdomen (except for the two inch area around your navel)
 - The front of your middle thighs
 - The upper outer areas of your buttocks



Choose a new site each time you inject Aranesp™. Choosing a new site can help avoid soreness at any one site. Do not inject Aranesp™ into an area that is tender, red, bruised, or hard or that has scars or stretch marks.

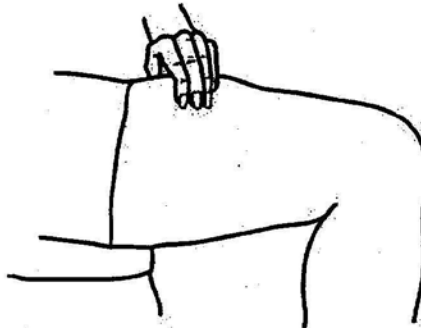
15. Clean the injection site with a new alcohol swab.



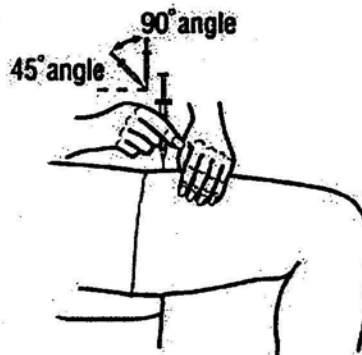
Injecting the dose of Aranesp™

For patients not on hemodialysis:

16. Remove the syringe and needle from the vial. Do not lay the syringe down or allow it to touch the surface.
17. Hold the syringe in the hand that you will use to inject Aranesp™. Use the other hand to pinch a fold of skin at the cleaned injection site.



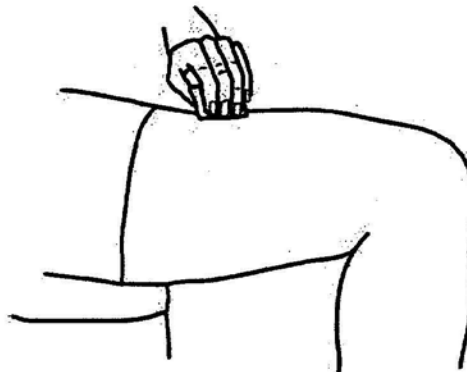
18. Holding the syringe like a pencil, use a quick "dart like" motion to insert the needle either straight up and down (90 degree angle) or at a slight angle (45 degrees) into the skin.



19. After the needle is inserted, let go of the skin. Pull the plunger back slightly. If no blood appears, slowly push the plunger all the way down, until all the Aranesp™ is injected. If blood comes into the syringe, do not inject Aranesp™ because the needle has entered a blood vessel. Withdraw the syringe and discard it in the puncture-proof container. Repeat the steps to choose and clean a new injection site and prepare a new syringe.



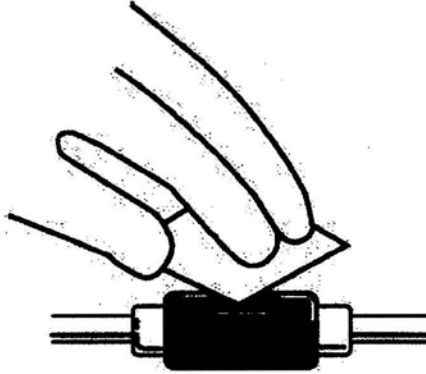
20. When the syringe is empty, pull the needle out of the skin and place a cotton ball or gauze over the injection site and press for several seconds.



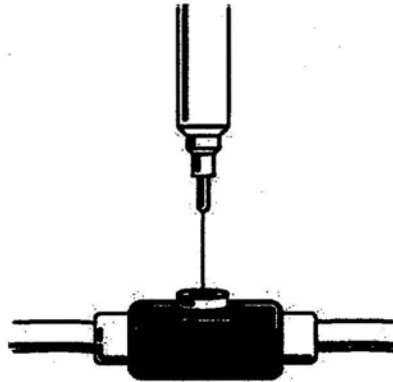
You should **ONLY** use a syringe and vial once. You should discard the vial with any remaining Aranesp™.

For patients on hemodialysis:

21. Clean the venous port of the hemodialysis tubing with a new alcohol swab.



22. Insert the needle of the syringe into the cleaned venous port and push the plunger all the way down to inject all the Aranesp™.



23. Remove the syringe from the venous port and discard the syringe and needle unit in the puncture-proof container (see Disposal of syringes and needles below).

Disposal of syringes and needles

24. Dispose of the syringe and needle as instructed by your doctor, nurse, or pharmacist, or by following these steps:
- Do not throw the needle or syringe in the household trash or recycle.

- DO NOT put the needle cover (the cap) back on the needle. Place the used needle, needle cover, and syringe in a hard plastic container with a screw-on cap or a metal container with a plastic lid, such as a coffee can, labeled "used syringes." If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard plastic container is used, always screw the cap on tightly after each use.
- Do not use glass or clear plastic containers.
- When the container is full, tape around the cap or lid to make sure the cap or lid does not come off.
- **Always** keep the container out of the reach of children.
- You should always first check with your doctor, nurse, or pharmacist for instructions on how to properly dispose of a filled container. There may be special state and local laws for disposal of used needles and syringes. **Do not throw the container in household trash. Do not recycle.**

How should Aranesp™ be stored?

Aranesp™ should be stored in the refrigerator at 2° to 8°C (36° to 46°F), but not in the freezer. Do not use a vial of Aranesp™ that has been frozen. Do not leave Aranesp™ in direct sunlight. Contact your doctor or nurse with any questions about storage. When traveling, transport Aranesp™ in its dispensing pack in an insulated container with a coolant such as blue ice. To avoid freezing, make sure no Aranesp™ vial touches the coolant.

[Amgen Logo]

Manufactured by Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

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Issue Date: 7/19/2002

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

103951/5001

SUMMARY REVIEW



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: July 19, 2002 *gms*
From: Jeanne M. Delasko, RN, MS
Regulatory Project Manager
Division of Application Review and Policy
To: STN 103951/5001
Subject: Summary Basis of Approval Equivalent for Amgen's BLS for Darbepoetin alfa [Aranesp™]

Indication

Aranesp™ is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis. This supplement is for a new indication for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. In addition, three new dosage strengths (150µg, 300µg and 500µg) in the Albumin (Human) formulation have been approved for this indication.

Dosage Form, Route of Administration, and Recommended Dosage

Aranesp™ is an erythropoiesis stimulating protein closely related to erythropoietin that is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Aranesp™ is formulated as a sterile, colorless, preservative-free protein solution for intravenous (IV) or subcutaneous (SC) administration.

Single-dose vials are available containing 25, 40, 60, 100, 150, 200, 300, or 500 mcg of Aranesp™.

For specific dosage and administration in cancer patients receiving chemotherapy, see package insert.

Basis for Approval

The following reviews, filed in the CBER correspondence section of the license application for STN 103951/5001 (under Tab 2 Approval Materials), comprise the SBA equivalent for this supplement:

<u>Discipline</u>	<u>Reviewer Name</u>	<u>Date</u>
Product	Fred Mills	July 18, 2002
Biostatistics	Clara Chu	July 1, 2002
Epidemiology	Sharon Gershon	June 27, 2002
Toxicology	Mercedes Serabian	June 20, 2002
BiMo	Bhanu Kannan	June 18, 2002

APPEARS THIS WAY ON ORIGINAL

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
103951/5001

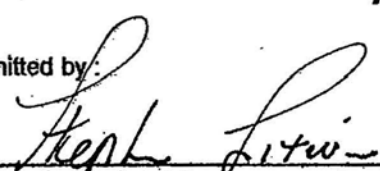
MEDICAL REVIEW(S)

SECTION A**MEDICAL OFFICER'S CLINICAL REVIEW**
STEPHEN D. LITWIN, M.D., CBER/OTRR/DCTDA**Revised August 2, 2002, Revised December 1, 2002**

Product
ARANESP™
Darbopoetin alfa
for oncologic patients

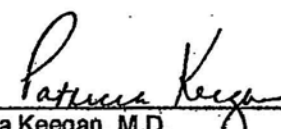
STN 103951\5001**DCC# 64165****CBER Receipt Date: 20-September-2001****AMGEN, INC.**

Submitted by:



Stephen D. Litwin M.D.
Medical Officer
Center for Biologic Research & Review
DCTDA, Oncology Branch
Office of Therapeutic Research & Review
FDA

1/8/03



Patricia Keegan, M.D.
Deputy Director, Division of Clinical Trial Design and Analysis
Center for Biologic Research and & Review
Office of Therapeutic Research and Review
FDA

Jan 15, 2003

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Section J Phase 3 pivotal trial 980297

**Placebo Controlled, Randomized Study of Novel Erythropoiesis
Stimulating Protein for the Treatment of Anemia in Lung Cancer
Subjects Receiving Multicycle Platinum Containing Chemotherapy**

36-48**Section K Integrated Summary of Safety [ISS]****49-59****Section L Attachments****Sponsor analyses requested by CBER****60**

1. Rapid ROR, exceeding maximum hgb threshold and
AE-"Special analysis"
1. High dose cohorts of Aranesp and AE
2. Transfusion triggers
3. Statistic analysis of nine subinvestigators with possible conflict of interest

ABBREVIATIONS AND TERMS USED

AE	adverse event
ca	cancer
CBER	Center for Biologic Evaluation and Research
chemorx	chemotherapy
CI	confidence interval
CRF	case report forms
CRT	case report tabulation
EOTP	end of treatment period
hgb	hemoglobin
hgb response	defined as a rise of hemoglobin of 2 g/dL or more compared to baseline in absence of transfusion for last 28 days
hgb correction	defined as reaching a hemoglobin of 12 g/dL or greater
ISS	Integrated Summary of Safety
IV	intravenous
K-M	Kaplan-Meier (analysis)
na	data not available
nm	non-myeloid (cancer)
Primary Analysis Dataset	a database which includes subjects who completed the first 4 weeks of treatment
NSCLC	non small cell lung cancer
PFS	progression free survival
PK	pharmacokinetics
Pt(s)	patient(s)
QW	once a week
Q2W	every two weeks
Q3W	every three weeks
ROR	rate of rise (of hgb)
SD	standard deviation
SC	subcutaneous
SCLC	small cell lung cancer
SC	subcutaneous
tfn	transfusion
TIW	three times a week
wk	week

REVIEW COMMITTEE

Clinical/Chair	Stephen D. Litwin, M.D.
Clinical Pharmacology	David Green, Ph.D.
Toxicology	Mercedes Serabian, M.S.
Product	Fred Mills, Ph.D.
Product	Dov Pluznik, Ph.D.
Statistical	Clara Chu, Ph.D.
Regulatory Coordinator	Jeanne Delasko, RN, MS
	Michael Harlow, B.S.

SOURCES REVIEW MATERIAL

The materials utilized in this review were submitted electronically to CBER and are found in the Electronic Document Retrieval (EDR) under STN 10351/5001. They include final reports on the six studies supporting registration, an interim report from an ongoing study (990174) from which safety data were used, an integrated safety section, Case Report Tabulations, Case Report Forms, 120 day safety update, a financial disclosure statement, and 3 special analyses requested by CBER from sponsor and reviewed by CBER (attachments 1, 2, and 3). Statistical information from CBER statistician Dr. Chu is included in this Clinical Review as well as in a separate report.

EDR

✓ Submitted Sept. 18, 2001	sBLA--major body of information
✓ Submitted Jan. 22, 2002	Proposed labeling
✓ Submitted March 1, 2002	120 day Safety update
✓ Submitted March 29, 2002	Analyses of safety requested by CBER
✓ Submitted May 1, 2002	Revised labeling
✓ Submitted May 10, 2002	Revised labeling
✓ Submitted May 20, 2002	Container labeling
✓ Submitted June 17, 2002	Information on labeling
✓ Submitted July 9, 2002	Information on labeling
✓ Submitted July 18 & 25, 2002	Post-marketing commitments

All patients in the study received human serum albumen (HSA)- containing formulation with the exception of 92 patients in protocol 20000174 who received an HSA-free formulation

SECTION B

The current submission of seven studies support a supplement to the present darbopoetin alfa license. The current indication is for treatment of chronic renal disease. The proposed additional indication is shown below. The information submitted includes 6 phase 1 or 2 studies, and pivotal study 980297. Two of the protocols (990146 and 980290) provided pharmacokinetic data.

Efficacy was established in the pivotal study protocol 980297: 320 subjects were enrolled and randomized; 314 received at least one dose of study agent. (156 Aranesp, 158 placebo). One Aranesp subject failed to receive erythropoiesis-stimulating agent and was retained in Aranesp arm for primary endpoint and secondary hgb response endpoint (156 Aranesp, 158 placebo) but placed in placebo arm for safety analyses (155 Aranesp, 159 placebo).

The numbers of patients who received the various study agents are shown in the table below. There were 975 patients who received Aranesp. The 975 included 873 patients who were on concomitant cyclic chemotherapy and 102 patients in study 990111 who were not on chemotherapy. The 873 chemotherapy patients included 92 in study 20000174 who only supplied safety data. There were 221 subjects who received placebo and 115 subjects who received rHuEPO for a total of 1311 patients studied. The list below includes patients who received a study agent and consequently the intent-to-treat number of enrolled patients is, in some studies, different from below; these differences are detailed under the individual study reports.

Amgen proposed additional/supplementary indication for Aranesp

"ARANESP™ (darbopoetin alfa) is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is associated with the effect of concomitantly administered chemotherapy".

"ARANESP™ (darbopoetin alfa)

(b) (4)

Study populations

NUMBERS OF STUDY PATIENTS BY PRODUCT, SCHEDULE & DOSE INTENSITY

	Placebo	rHuEPO	Aranesp schedule			Aranesp Dose/ mcg/kg/week			
			QW	Q2W	Q3W	<2	2-<3	>3	All Aranesp
990146	0	0	29	0	0	0	29	0	29
980290A	0	53	216	0	0	84	59	73	216
980290B	0	32	0	128	0	33	31	64	128
980291	51	0	0	0	198	32	17	149	198
990114	11	0	55	0	0	11	22	22	55
980297	159	0	155	0	0	0	155	0	155
20000174	0	30	92	0	0	0	0	92	92
990111	0	0	102	0	0	39	33	30	102
totals	221	115	649	128	198	199	346	430	975

STUDY POPULATION BY SCHEDULE AND DOSE

Study	Schedule	Initial Aranesp dose(s)	Later* Aranesp dose(s)
990146	SC QW	2.25 mcg/kg	4.5 mcg/kg
990114	SC QW	1.0, 2.25 & 4.5 mcg/kg	same
980290 pt A	SC QW	0.5 to 8.0 mcg/kg	same
980290 pt B	SC Q2W	3.0 to 9.0 mcg/kg	same
980291	SC Q3W	4.5 to 15.0 mcg/kg	same
20000174	SC QW	4.5 mcg/kg	1.5, 2.25, 3.0 mcg/kg
990111	SC QW	0.5 to 4.5 mcg/kg	same
980297	SC QW	2.25 mcg/kg	4.5 mcg/kg

* During the course of treatment doses were changed either because the patient did not respond and the dose was doubled or a different administration pattern was explored.

STUDY POPULATIONS AND TREATMENT ARMS

Study	Dose schedule & route	Study population	Number of patients by treatment		
PK			Aranesp Placebo EPO		
990146 part A	QW SC for 12 weeks	Non-myeloid cancer on cyclic chemorx	Aranesp	29	
part B	Same patients continued up to week 24 QW IV		[Aranesp	*	
Fixed dose PK study					
980290	see below	Non-myeloid cancer on cyclic chemorx	see below		
Dose ranging phase 2 study					
Phase 2 Dose-response of cancer patients			Aranesp Placebo EPO		
990114	QW SC QW SC	Lymphoma on cyclic chemorx	Aranesp	55	
			Placebo		11
980290 pt A	QW SC	Non-myeloid cancer on cyclic chemorx	Aranesp	216	
pt B	TIW SC		rHuEPO		53
	Q2W SC QW SC		Aranesp	128	
			rHuEPO		32
980291	Q3W SC Q3W SC	Non-myeloid cancer on cyclic chemorx	Aranesp	198	
			Placebo		51
20000174	QW SC QW SC	Non-myeloid cancer on cyclic chemorx	Aranesp	92	
			rHuEPO		30
990111	QW SC	Non-myeloid cancer... not on chemorx	Aranesp	102	
Phase 3 Pivotal/registration Study					
980297	QW SC	Lung cancer on cyclic chemorx	Aranesp	155	
			Placebo		159

* 15 of part A patients continued on part B

Section C OVERVIEW

The current supplement to the Aranesp™ license seeks to add an indication for the treatment of anemia of cancer patients on cyclic chemotherapy.

The clinical submission was provided in several major sections.

- The 9/18/01 submission to the EDR included six of seven studies reviewed:
 - two studies provided pharmacokinetic information (990146 and 980290);
 - there were four dose finding studies (990114, 980290, 980291 and 990111);
 - studies 990114, 980290, 980291, enrolled cancer patients receiving cyclic chemotherapy concomitant with the Aranesp;
 - protocol 990111 studied the anemia of cancer. Patients received no chemotherapy;
 - studies 990114, 980290 [part A] used QW SC dose schedules which were most relevant to the current license application;
 - there was a single, phase 3 protocol (980297) of 320 enrolled patients which compared Aranesp initial dose of 2.25 ug/kg SC QW to a blinded placebo;
- The 3/1/02 submission included an interim report from the ongoing protocol 990174 which provided further safety data. The 3/12/02 submission also updated safety information in the ISS.
- The 3/29/02 submission provided further analyses requested by CBER [Section L, Attachments].
- The 7/18/02 and 7/25/02 submissions detailed post-marketing commitments made by sponsor.

Phase 2 dose-finding studies explored the dose response of Aranesp to select a dose and schedule of dosing for the pivotal trial. Subcutaneous doses of 0.5 to 8.0 mcg/kg and dosing schedules of once a week [QW], once every two weeks [Q2W] and once every three weeks [Q3W] were explored by monitoring the effects of Aranesp on hemoglobin (hgb) responses, on hgb change from baseline and on the number of patients transfused during the treatment period. There were differences in the cancer populations studied as well as in their treatments. Studies 980290, 980291, 990146 and 20000174 enrolled patients with non-myeloid cancer who received concomitant Aranesp and cyclic chemotherapy. Study 990114 had a similar experimental design for lymphoma patients. Study 990111 enrolled patients with anemia of cancer not on chemotherapy

It was found that subcutaneous [SC] QW doses of Aranesp of 2.25 mcg/kg and 4.5 mcg/kg, Q2W doses of 3.0 to 9.0 mcg/kg, and Q3W doses of 6.75 to 15.0 mcg/kg all produced hgb responses in over 50% of patients [Hgb response was defined in this study as a 2.0 g/dL or larger increase in hgb over 28 days without transfusion]. In study 980290, in which the best information on weekly dosing was available, the following results were seen.

Dose mcg/kg	% subjects receiving transfusions week 5 to EOTP	Hgb response Kaplan-Meier proportion %
1.5	26	44
2.25	13	52
4.5	6	76

The minimal effective starting dose was 1.5 mcg/kg. A weekly starting dose of SC Aranesp 2.25 mcg/kg was selected for further study in pivotal trial 980297.

Study 980297 (Section J) was a phase 3, double blinded, multisite, multinational, treatment vs. placebo control- arm study. 320 subjects were randomized. Six patients failed to receive any study agent. The remaining 314 subjects were distributed as 156 to the treatment arm and 158 to the placebo arm (page 37-patient disposition). The study enrolled patients with either small cell

lung cancer (SCLC) or non small cell lung cancer (NSCLC) with a screening hemoglobin equal to or < 11.0 g/dL, and whom were scheduled for 12 weeks or more of cyclic platinum-containing chemotherapy regimens. The primary endpoint was a comparison between treatment and control arms of the proportion of subjects transfused from week 5 to end of treatment period. All patients withdrawn from study not due to death or progressive disease were imputed to be transfused (failure). Statistical analysis was by an estimate of the Kaplan-Meier proportion. There was equal randomization to study arms with stratification for type of lung cancer and region. The Aranesp dose was doubled after week 6 in subjects who did not increase their hgb by 1.0 g/dL. Analysis of the primary endpoint (Kaplan-Meier proportion) showed 51% of the control placebo arm patients and 21% of the Aranesp treatment arm subjects were transfused during the 8 week evaluation period (weeks 5 to 12). When the same analysis was conducted assessing the 12 week treatment period, weeks 0 to 12, the comparable figures were 60% and 26% (Section J, page 39). Differences between arms were statistically significant. Secondary endpoints (time to first transfusion, number of RBC units transfused, number of days RBC transfusions, hemoglobin response) consistently showed a lower RBC transfusion rate and higher- than- baseline hgb values (Section J) in the treatment group as compared to placebo.

Sensitivity analyses (Section J, page 41), which were designed to test the sturdiness of the primary endpoint with respect to withdrawal of subjects and transfusion policy, employed a number of strategies. Transfusion (failure) was imputed to all patients whose hemoglobin was below 8.0, and to all patients who withdrew after week 5 regardless of reason. An analysis was also conducted without imputation for withdrawn patients. The proportion of subjects transfused was also analyzed on the intent to treat population in a sensitivity analysis counting success/failure during the full 12 rather than the last 8 weeks of treatment period. All results were similar in significance and direction to the primary endpoint.

Factors which might influence endpoints in the registration study were examined. Transfusion triggers were analyzed in the two arms; they did not differ (see Section K, page 42 and attachment 3- Transfusion triggers). An imbalance was observed between the fraction of patients who had baseline hemoglobin values above 11.0 g/dL. This disparity was attributed to differences between screening and baseline hgb testing. An analysis which removed all subjects who at entry had hgb > 11.0 from the evaluation did not alter the primary endpoint as to direction or significance.

Covariates which impacted the treatment effect included both baseline hgb and baseline erythropoietin level (see pages 43-44).

Hgb response was compared between subjects who had their dose doubled from 2.25 to 4.5 mcg/kg at end of week 6, because they had failed to increase their hgb 1.0 g/dL or more over baseline, and those whose dose was maintained at the same level. Twenty eight % of the former were hgb responders while 69 % of the latter (dose not doubled) were responders. [Responders were defined as subjects who had their hgb values increased by 2.0 g/dL or more over baseline by end of treatment period] [page 43].

Serious AE observed were predominantly those consistent with the cancer diagnosis carried by the subjects. There were no serious allergic reactions at or around the time of injection of Aranesp. AE were usually mild (grade 1 and 2) constitutional and gastrointestinal AE and were similar to those encountered for epoetin alfa; they included fatigue, asthenia, fever, nausea and vomiting. The only AE in which there were disparities substantial enough to suggest agent-specific events and different from those observed with epoetin alfa were Thrombotic events and Edema (see Section K, ISS).

Both the rate of rise of hgb and the maximum-hgb value encountered at any point in the 12 week treatment period were viewed as possible factors in the etiology of AE of historical interest

(convulsions, hypertension, thrombotic events) and of AE of special interest (wider group of cardiovascular, thrombotic and cerebrovascular events). Maximum hgb value could not be shown to be related to AE (see page 54) except for hypertension.

The rate of rise of hgb greater than 0.5 g/dL/week was associated in the current studies with a spectrum of AE similar to those encountered earlier in the study of Aranesp in subjects with renal failure. However, there was a proclivity to cardiovascular, fluid load and cerebrovascular problems in the renal failure patients as opposed to the cancer patients who had an increased incidence of thrombotic events including pulmonary emboli (See Section K).

Certain AE analyses were reported as a group of related Preferred Terms rather than single Preferred terms; these were analyzed further. Under Thrombotic events the more numerous Preferred term venous thrombosis was relatively equally distributed between Aranesp and placebo patients while Preferred Terms pulmonary emboli, thrombophlebitis, thromboembolism and thrombosis were all higher in the Aranesp subjects. Eleven pulmonary emboli were reported among the Aranesp treated subjects 11/975 (1.1%) and an additional pulmonary embolus after week 16. No pulmonary emboli were reported in the placebo or rHuEPO arms. Edema and peripheral edema were higher with both erythropoiesis-stimulating agents (rHuEPO & Aranesp) than in the placebo group (see Section K, pages 55-57, CBER analysis of AE groupings).

CONCLUSIONS

1. Aranesp is used at higher doses for cancer patients to achieve a therapeutic effect than used in chronic renal failure (CRF) subjects. CRF doses start at 0.45 mcg/kg while the cancer patients receive from 2.25 to 4.5 mcg/kg. Doses of 2.25 and 4.5 had limited agent-associated toxicity in weekly dosing in the current studies. Higher doses than 4.5 mcg/kg doses of Aranesp were analyzed for adverse events; no differences between higher and lower doses were found but the numbers were limited and data came from different sources (Section K, page 50 and attachment two). There is incomplete information from the current trials or other controlled studies to determine if doses above 4.5 mcg/kg could have a different and more harmful AE pattern. Higher dosing at Q2W, Q3W and Q4W dose schedules are currently being explored by the sponsor. **This unresolved issue should be explored in future studies to support changes in the license if those future studies involve higher doses or substantially different patterns of administration.**
2. There is evidence to suggest that the pattern of response to erythropoiesis-stimulating agents could increase the risk of certain toxicities. Past information has been concerned with rate of rise of hgb and maximum level reached. Earlier chronic renal failure (CRF) patient studies showed trends to a higher risk of hypertension and a group of cardiovascular, cerebrovascular, thrombotic and fluid balance problems in subjects who had a rapid rate of rise of hgb (> 0.5 g/kg /week). The current study using the same rate of rise analysis shows a similar trend to higher risk but with less association with cardiac and fluid problems in the cancer subjects as opposed to the renal disease subjects. On the other hand the incidence of pulmonary emboli and related diagnoses at various doses were particularly striking. Analysis of the 11 pulmonary emboli patients demonstrated a trend toward a relationship between rapid rate of rise [ROR] and the embolic events, but was too limited however to permit conclusions to be drawn (Section K, pages 55-57). [Rapid rate of rise in the current studies was considered to be an increase of 0.5 or more grams of hgb in one week or 2 grams in 28 days.] **Future studies at higher Aranesp doses should consider this information and closely assess these AEs and the relationship to rapid rate of rise and adverse events.**
3. Antibody production to Aranesp was tested in the study population. However questions remain about the sensitivity and relevance of the available assays which Amgen is still refining and validating. Using available testing there were only three reactive sera in the cancer test population of 2392 patients. One of the 3 was both radioprecipitation and neutralizing antibody testing positive. Confirmatory Biacore antibody testing was negative (

Section K, page 57). It is unclear whether the sample which was positive in two tests contained antibody to the agent.

4. Erythropoiesis-stimulating agents are growth factors and the issue of acceleration of tumor growth during therapy has been raised. Within the one year follow up provided for the Aranesp patients in the pivotal study there is no evidence of increased mortality or lessened progression free survival. The effect of growth factors was not evaluated in myeloid tumors. The numbers of patients and limited study time duration were not powered sufficiently to resolve the issue of tumor stimulation by darbopoetin alfa.

SECTION D BACKGROUND

Epoetin alfa is the only US licensed erythropoiesis-stimulating agent. It is manufactured by Amgen. Epoetin alfa was licensed in 1989 for treatment of anemia associated with chronic renal failure. Later supplements added indications for treatment of the anemia in zidovudine-treated HIV patients, for the treatment of anemia of cancer patients receiving chemotherapy (b) (4)

Wording of current indication of Epoetin alfa in cancer patients is as follows:

Treatment of Anemia in Cancer Patients on Chemotherapy

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

There is a licensing agreement between Amgen and Ortho Biotech under which Amgen has the exclusive right to market epoetin alfa for treatment of anemia associated with chronic renal failure under the trade name EPOGEN while Ortho has the exclusive right to market epoetin alfa under the trade name PROCRIT for indications other than chronic renal failure in the US. The arrangement gives Ortho the right to manufacture, sell and distribute epoetin alfa outside of the US. [Ortho Biologics, another subsidiary of J & J, produces epoetin alfa under the trade name EPREX and manufactures it outside the US].

The current product darbopoetin alfa (Aranesp) has two more consensus N-linked carbohydrate addition sites in its primary structure than epoetin alfa or native erythropoietin. The latter have three N-linked primary sites while Aranesp has five. This permits additional glycosylation of Aranesp which is believed responsible for the 2-3 fold increase in the circulating half life of Darbopoetin alfa. The longer half life is the basis for the less frequent administration schedule proposed by the sponsor.

Darbopoetin alfa (Aranesp) is currently licensed for treatment of chronic renal disease.

SECTION E

GENERAL ELEMENTS OF DEVELOPMENT PLAN

FOR SEVEN STUDIES SUPPORTING SUPPLEMENTAL CHANGES IN LICENSURE OF ARANESP

- Multi-institutional and multi-national in both USA and abroad.
- Eligibility is similar in studies – 18 years or older, entry hgb 11 g/dL or less, subjects with non-myeloid lung, lymphoma or other tumors who are scheduled for at least 12 weeks of multicyle chemotherapy.
- Treatment period was similar in all studies; 12 weeks plus 4 weeks untreated follow up. The registration study has a 12 month follow-up period to provide estimates of tumor progression rates and survival times.
- The phase 2 dose escalation studies and the single phase 3 study are randomized against placebo in 3 cases (protocols 990114, 980291, 980297) and rHuEPO in two cases (protocols 980290, 20000174). The rHuEPO controlled studies are not designed to establish non-inferiority of Aranesp.
- Aranesp is given to patients with solid tumors who are beginning a minimum of 12 weeks of multicyle chemotherapy in order to reduce by approximately half the rate of RBC transfusions which ordinarily could be expected to be between 40-60% in such patients.
- A relatively high failure-to-complete study rate of 30-40% was encountered which is balanced between control and Aranesp arms (e.g. Protocol 297 shows dropout rate of 31% Aranesp arm and 32% placebo arm).

SUMMARIES OF THE SEVEN STUDIES

- ✓ Numbers (n) given are those patients who received study agent; further information on disposition is found in individual study summaries
- ✓ Hgb response is defined as an increase in hgb of 2 g/dL or more without transfusion for 28 days

Protocol 990146- Phase 2				
Title: An Open-label Pharmacokinetic Study of NESP Administered SC or IV in Subjects with Non-myeloid Malignancy Receiving Multicycle Chemotherapy				
Experimental design: Multicenter, open label, pharmacokinetic study using Aranesp doses of 2.25 mcg/kg initially and doubling after week 6 to 4.5 mcg/kg if response was inadequate (i.e. <1 gram of hgb). Part A studied SC QW dose schedule using sampling at baseline and hours 6, 24, 32, 72, 96, 120 and 168. Patients who had a hgb response could enter arm B where IV QW dose schedule was similarly sampled and analyzed.				
Period of study	Sites	Study arms and number patients	Study Objective(s)	Study Results
9/15/99 to 1/8/01	8 in Europe	Single arm 29 SC QW dose schedule (part A) followed by IV dose schedule (part B)	PK data for SC route (part A) and IV route (part B)	After SC injection, peak concentrations reached in 94.5 hrs. No unexpected dose accumulation after 7-9 wks. Dose -linear effect seen.

Protocol 980290-Phase 2				
Title: A Randomized Dose-Finding Study of NESP Administered by Subcutaneous Injection for the Treatment of Anemia in Subjects with Solid Tumors Receiving Multicycle Chemotherapy				
Experimental design: Multicenter, open label, escalating dose cohorts each randomized 4:1 Aranesp to rHuEPO. Part A used a weekly SC dose of Aranesp ranging from 0.5 to 4.5 mcg/kg or Procrit 150 U/kg TIW. Part B employed a Q2W SC dose of Aranesp ranging from 3.0 to 9.0 mcg/kg or Procrit 40,000 U QW SC.				
Period of study	Sites	Study arms/cohorts, dose and number patients	Study Objective (s)	Study Results
4/14/99 to 10/23/00	32 in USA	<u>Part A-QW</u> Aranesp 0.5 mcg/kg 13 Aranesp 1.0 mcg/kg 36 Aranesp 1.5 mcg/kg 35 Aranesp 2.25 mcg/kg 59 Aranesp 4.5 mcg/kg 29 Aranesp 6.0 mcg/kg 30 Aranesp 8.0 mcg/kg 14 EPO 150 U/kg TIW 53 <u>Part B-Q2W</u> Aranesp 3.0 mcg/kg 33 Aranesp 5.0 mcg/kg 31 Aranesp 7.0 mcg/kg 32 Aranesp 9.0 mcg/kg 32 EPO 40000 U/wk 32	Safety and dose-response to Aranesp	Part A: Hgb response > 50% at Aranesp SC QW 2.25 mcg/kg or 4.5 mcg/kg Part B: Hgb response > 50% at Aranesp doses from 3-9 mcg/kg Q2W.

Protocol 990114-Phase 2				
Title: A Multicenter, Blinded, Placebo-Controlled, Randomized, Dose-finding Study of NESP administered by Subcutaneous Injection for the Treatment of the Anemia in Subjects with Lymphoproliferative Malignancies Receiving Chemotherapy				
Experimental design: Multicenter, blinded, randomized trial. Aranesp was given weekly by SC route in doses of 1.0, 2.25, 4.5 mcg/kg of Aranesp or placebo.				
Period of study	Sites	Study arms/cohorts & number patients	Study Objective(s)	Study Results
11/99 to 7/00	15 in Eur. & Aus.	4 arms 1.0 mcg/kg Aranesp 11 2.25 mcg/kg Aranesp 22 4.5 mcg/kg Aranesp 22 Placebo 11	Safety and dose response to Aranesp in Lymphoma patients	No dose effect seen. Maximum hgb response at 4.5 mcg/kg Aranesp.

Protocol 980291-Phase 2				
Title: A Randomized, Double-blind, Placebo-controlled, Dose-finding Study of NESP Administered Once Every Three Weeks by SC Injection for the Treatment of Anemia in Subjects with Solid Tumors Receiving Multicycle Chemotherapy				
Experimental design: Double-blind, multicenter, dose-ranging study of Aranesp SC Q3W given to cancer patients undergoing cyclic chemotherapy. Patients randomized 4:1 to receive one of the doses of Aranesp or placebo.				
Period of study	Sites	Study arms and number patients	Study Objective(s)	Study Results
6/6/99-ongoing	26 in Aus., Canada, Costa Rico, Europe	Aranesp 4.5 mcg/kg 33 Aranesp 6.75 mcg/kg 19 Aranesp 9.0 mcg/kg 47 Aranesp 12.0 mcg/kg 28 Aranesp 13.5 mcg/kg 36 Aranesp 15.0 mcg/kg 45 Placebo 51	Safety of Aranesp given every 3 weeks in non-myeloid cancer subjects	A wide dose range, 9.0 mcg/kg to 15.0 mcg/kg, had hgb response > 50%.

Protocol 980297-Phase 3				
Title: A double-blind, Placebo Controlled , Randomized Study of NESP for the Treatment of Anemia in Lung Cancer Subjects Receiving Multicycle Platinum Containing Chemotherapy				
Experimental design: Phase 3 , placebo controlled, randomized, double-blinded, multicenter,multinational study. The Aranesp dose was 2.25 mcg/kg with doubling of dose at 6 weeks if response inadequate. Treatment period was 12 weeks with a 4 week untreated follow-up and later follow-up for a year. Stratification was for treatment center and for tumor type (NSCLC vs. SCLC).				
Period of study	Sites	Study arms and number patients	Study Objective(s)	Study Results
9/14/99 to 11/8/00	70 sites in Australia, Canada & Europe	<u>Two arm</u> Aranesp 155 Placebo 159	Determine if Aranesp is superior to placebo in reducing RBC transfusions during cyclic chemotherapy.	Transfusions reduced in Aranesp vs. placebo patients (60 % to 26 % in the ITT dataset) .

Protocol 990111-Phase 2				
Title: An Open-label, Dose-finding Study of NESP Administered by SC injection for the Treatment of Anemia in Subjects With Chronic Anemia of Cancer				
Experimental design: Multicenter, open label, dose escalation study of 4 successive cohorts of Aranesp				
Period of study	Sites	Study arms and number patients	Study Objective(s)	Study Results
4/30/99 to 1/4/01	19 in USA	<u>4 dose cohorts</u> Aranesp 0.5 mcg/kg 7 Aranesp 1.0 mcg/kg 33 Aranesp 2.25 mcg/kg 33 Aranesp 4.5 mcg/kg 30	Safety and response to Aranesp in series of doses given weekly in a group of non-myeloid cancer patients <i>not receiving chemotherapy</i>	Hgb responses noted at 1.0, 2.25 and 4.5 mcg/kg

Protocol 990174				
Title: A Dose-and Schedule-Finding Study of NESP for the Treatment of Anemia in Subjects with Solid Tumors Receiving Chemotherapy				
Experimental design: Randomized, active control study of four different dose and administration schedule cohorts of SC Aranesp. This study was only analyzed for safety data.				
Period of study	Sites	Study arms/cohorts & dose	Study Objective(s)	Study Results
Ongoing	Multiple	<u>Study arms*</u> Aranesp 4.5 mcg/kg/wk to hgb 12; then 1.5 mcg/kg/wk to wk 12 Aranesp 4.5 mcg/kg/wk x 4 wks; then 2.2.5 mcg/kg/wk x 8 wks Aranesp 4.5 mcg/kg/wk x 4 wks; then 3.0 mcg/kg/Q2W x 8 wks Procrit 40000 U/wk x 12 wks	Safety of Aranesp at different schedules/doses	Ongoing study

* There were 30 patients who received Procrit and 92 who received Aranesp with approximately equal numbers in the three Aranesp arms.

SECTION F FINANCIAL DISCLOSURE

Amgen considered "covered clinical studies" to be protocols

(b) (6)

They certified/signed that there was a lack of direct financial arrangements or payments between themselves and investigators which could affect the outcome of study. They sent a Certification/Disclosure form to clinical investigators and sub-investigators on the above studies. Each investigator was asked to indicate whether financial arrangements of concern to FDA did or did not exist during the study period. Second notices were sent if needed. Table 3 of the Financial Disclosure submission listed approximately 135 investigators and a larger number of sub-investigators each of whom indicated that they had no financial interest in the outcome of the study and no financial conflict existed. There were seven subinvestigators who failed to respond; they are listed under table 2 of the sponsor submission.

Nine investigators responded that they had an interest in Amgen in that they owned Amgen shares (> \$50,000). The nine investigators listed below were in study (b) (6). The involved investigators' patients were removed from the study groups and the results recalculated. The data are shown below. The time to hgb response at 2.25 mcg/kg and time to transfusion were both measured in both studies. The outcomes were not significantly altered. More detailed data on the complete analysis is included as attachment four.

LIST OF SUB INVESTIGATORS WITH POSSIBLE CONFLICT OF INTEREST

Sub-Investigator	Location
(b) (6)	

STATISTICAL ANALYSIS OF OUTCOMES AFTER REMOVAL OF POTENTIAL CONFLICT OF INTEREST STAFF IN (b) (6) STUDIES

	(b) (6)		(b) (6)	
	Full study group	Potential conflict of interest invest. removed	Full study group	Potential conflict of interest invest. removed
Hgb response at 2.25 mcg/kg				
n	59	42	33	24
K-m proportion resp. in %	52	55	66	67
95% CI	39, 66	40, 71	49, 84	46, 87
RBC transfusions at 2.25 mcg/kg				
n	58	41	30	22
K-m proportion resp. in %	13	11	92	87
95% CI	4, 23	1, 21	80, 100	71, 100
Hgb response at 4.5 mcg/kg				
n	29	23	30	21
K-m proportion resp. in %	76	71	14	14
95% CI	59, 94	51, 91	1, 26	0, 29
RBC transfusions 4.5 mcg/kg				
n	26	22	29	21
K-m proportion resp. in %	6	8	7	10
95% CI	0, 18	0, 22	0, 17	0, 23

Hgb response on ITT analysis set while RBC on primary analysis set

Section G Pharmacokinetics-Phase 1 Studies (Protocols 990146 and 980290)

PROTOCOL 990146

- ✓ Phase 1 study
- ✓ Pharmacokinetics of weekly SC followed by weekly IV Aranesp dosing
- ✓ 29 subjects with non-myeloid malignancies

Protocol 990146				
Title: An Open-label Pharmacokinetic Study of NESP Administered SC or IV in (the same) Subjects with Non-myeloid Malignancy Receiving Multicycle Chemotherapy				
Experimental design: Multicenter, open label, pharmacokinetic study using Aranesp doses of 2.25 mcg/kg initially and doubling after week 6 to 4.5 mcg/kg if response was inadequate (i.e. <1 gram of hgb). Part A studied SC QW dose schedule with sampling at baseline and hours 6, 24, 32, 72, 96, 120 and 168. Fifteen patients who had a hgb response in arm A were enrolled in arm B where an IV QW dose schedule was similarly sampled and analyzed.				
Period of study	Sites	Study arms and number patients	Study Objective(s)	Study Results
9/15/99 to 1/8/01	6 in Europe	Single arm 29 SC QW dose schedule followed by IV dose schedule	PK data for SC route (part A) and IV route (part B)	After SC injection, peak concentrations reached in 94.5 hrs. No unexpected dose accumulation after 7-9 wks. Dose -linear effect seen.

Objectives and overview: The goal was to obtain PK data on weekly SC dosing (part A) by weekly intravenous dosing (part B) in the same subjects.

Clinical population: The study enrolled patients with non-myeloid malignancies on chemotherapy. Eligibility criteria were similar to other studies.

Study design: Part A employed a QW dose schedule starting at 2.25 mg of Aranesp which was doubled after week 6 if hgb had not increased to at least 12.0 g/dL or the subject did not have a 1.0 g/dL rise in hgb from baseline. Weekly trough samples were collected during the first 168 hours of the first week of the first and third chemotherapy cycles. Treatment period was 12 weeks with a 4 week follow up. Fifteen patients who had a hgb response entered arm B and received a similar QW IV dose schedule for up to week 24.

The mean subject age was 63 years; race distribution was 28 white and one Asian; sex distribution was 12 men and 17 women. The primary pharmacokinetic endpoints were relative clearance, terminal half life and C max while secondary endpoints included the area under the curve (AUC), time of Cmax, terminal phase volume. Safety and response data were also collected.

Results: Peak concentrations after SC administration were reached slowly – approx. 95 hours after a single dose. Mean peak serum concentrations after single and multiple dosing were 10.6 ng/ml and 11.0 ng/ml respectively. Trough concentrations rose to a peak during the second week of the chemotherapy cycle and fell at week 3 suggesting some possible interaction with chemotherapy. No differences in Aranesp blood levels were apparent after multiple dosing; no evidence for accumulation over time was found. Pharmacokinetics were time-linear.

PROTOCOL 980290-PK data

- ✓ PK profiles in QW and Q2W Aranesp-dosed subjects
- ✓ Non-myeloid malignancies

This study is more fully described in Section H. The objective of the PK segment of the study was to collect a PK profile and to study time dependencies of the PK data. Both arm A [QW] and arm B [Q2W] subjects were studied using SC route of administration. There were 211 patients in arm A and 119 patients in arm B in the PK analysis set. Patients had non-myeloid malignancies, were receiving or about to receive cyclic chemotherapy, and were enrolled with the same inclusion criteria as in other studies.

Results showed that Aranesp given subcutaneously has a slow absorption reaching peak concentrations 72 hours after dosing. Multiple dosing produced less than 2 fold increases in Aranesp serum concentrations. PK was in general dose-linear. The sponsor concluded that the PK data could support either QW or Q2W dosing.

Section H Phase 2 Studies

PROTOCOL 990114

- ✓ Phase 2 study of Aranesp vs placebo
- ✓ Weekly SC dosing
- ✓ Lymphoma subjects

Protocol 990114-Phase 2				
Title: A Multicenter, Blinded, Placebo-Controlled, Randomized, Dose-finding Study of NESP administered by Subcutaneous Injection for the Treatment of the Anemia in Subjects with Lymphoproliferative Malignancies Receiving Chemotherapy				
Experimental design: Multicenter, blinded, randomized, placebo controlled, dose-ranging trial. Patients were randomized 4:1 to receive either one of Aranesp doses (1.0, 2.25, 4.5 mcg/kg) SC or placebo SC weekly.				
Period of study	Sites	Study arms/cohorts & number patients	Study Objective(s)	Study Results
11/99 to 7/00	15 in Eur. & Aus.	<u>4 arms</u> 1.0 mcg/kg Aranesp 11 2.25 mcg/kg Aranesp 22 4.5 mcg/kg Aranesp 22 Placebo 11	Safety and dose response to Aranesp in Lymphoma patients	No dose effect seen. Maximum hgb response at 4.5 mcg/kg Aranesp.

Objectives and Overview: Once a week SC doses of Aranesp were studied in patients with lymphoid malignancies. The purpose was to determine safe and effective dose and schedule for Aranesp. Secondary objectives included effect of Aranesp on number of RBC transfusions, safety, & HRQOL.

Clinical population: Patients had to be of legal age for consent and carry a histologic diagnosis of multiple myeloma, low or intermediate grade NHL, Waldenstrom's Macroglobulinemia, Hodgkin's disease or Chronic lymphocytic leukemia [CLL]. Screening hgb values had to be 11.0 g/dL or less; and patients had to be scheduled to receive chemotherapy for 12 or more weeks. Other requirements were an ECOG performance status 0-2, life expectancy of six or more months, adequate organ function on liver and renal testing. Anemia had to be primarily due to cancer or to chemotherapy (serum folate equal to or > than 4.5 ng/mL, vitamin B12 >148 pmol/L, no hemolysis, no gastrointestinal bleeding, no bleeding attributable to recent surgery).

Study design: Patients who were scheduled to begin cyclic chemotherapy were randomized 1:2:2:1 to receive Aranesp 1 mcg/kg (n=11), or Aranesp 2.25 mcg/kg (n=22), or Aranesp 4.5 mcg/kg (n=22) or placebo (n=11) once a week subcutaneously. The study was double blinded. Randomization assignments were designed to maximize exposure to 2.25 and 4.5 mcg/kg doses which were considered most closely related to rHuEPO dose of 150 U/kg TIW. The study period was 12 weeks. Patients were stratified to balance between myeloma and lymphoma subjects. Placebo subjects received matched placebo volumes. Efficacy endpoints were hgb response/ hgb correction.

Definitions: Hgb response was defined as an increase in hgb of equal to or > 2g/L of hgb from baseline. Hgb sustained correction was defined as a hgb equal to or > 12 g/L sustained for 28 days or until the end period of treatment in absence of any RBC transfusion.

Conduct of the study**PATIENT DISPOSITION:**

Subjects screened	78
Subjects enrolled	66
Aranesp cohorts	55
Placebo	11
Aranesp cohorts	55
Completed study	53
Failed to complete	2
Placebo cohort	
Completed study	10
Failed to complete	1

PROTOCOL COMPLIANCE/VIOLATIONS:

	Aranesp	Placebo
	Number pts	Number pts
Lacked folate or B12 screening	4	1
Unstable angina at entry	1	0
Delayed study drug by 4 or more days	1	1
Missed dose due to SAE (see drug exposure)	2	0
Reduced dose in violation of protocol	3	0
Overdose/incorrect dose	6	0
Missed antibody sample	2	1

Demographics: Minimal differences between Aranesp and placebo in age and sex were attributable to variation due to small patient numbers. The numbers of RBC transfusions preceding enrollment or baseline erythropoietin values did not differ between Aranesp and placebo patients. Number of patients with each diagnosis were CLL 12; Hodgkin's disease 11; Multiple Myeloma 18; NHL 14; Macroglobulinemia 11. The majority of patients had grade III/IV disease (62%); only 2 % had hepatic metastases and 62% had BM involvement. The majority of subjects were ECOG I. There was no substantial difference in the distribution of disease type by dose or disease feature.

DISEASE BY DOSE AND DISEASE FEATURES

Study group	Placebo	Aranesp 1.0 mcg/kg	Aranesp 2.25/mcg/kg	Aranesp 4.5 mcg/kg	All Aranesp	Total
Number	11	11	22	22	55	66
Tumor type in number of patients						
CLL	2	2	1	7	10	12
Hodgkin's disease	3	3	4	1	8	11
Multiple Myeloma	3	3	6	6	15	18
NHL	3	2	5	4	11	14
Macroglob.	0	1	6	4	11	11
Disease Stage in number of patients						
III	4	5	6	7	18	22
IV	3	5	5	6	16	19
BM involvement in % patients	45	45	55	82	64	61

ECOG in % of patients						
ECOG 0	45	9	32	36	29	32
ECOG 1	55	64	59	55	58	58
ECOG 2	0	27	9	9	13	11

NHL is non-Hodgkin's lymphoma; Macro is Waldenstrom's macroglobulinemia

Efficacy results: A higher proportion of Aranesp subjects than placebo subjects achieved a sustained correction. No dose linear response was seen. No hgb response to Aranesp except 4.5 mcg/kg was > than the 50%. There were some differences between response rates for the various clinical entities as listed below; Amgen emphasized the higher response rate in multiple myeloma.

Clinical dx	Hgb responders (%)
o Multiple Myeloma	11/18 (61%)
o Non-Hodgkin's lymphoma	4/14 (29%)
o Chronic lymphocytic leukemia	5/12 (45%)
o Hodgkin's lymphoma	4/11 (36%)

HEMOGLOBIN RESPONSE

		Hgb response	Patients transfused			Sustained correction
	n	K-M % proportion (95% CI)	K-M proportion %			Number pts hgb corrected /number tested
			Wk5-12	wk9-12	wk1-12	
All Aranesp	55	41 (27,54)				18/52
Aranesp 1 mcg/kg	11	45 (16,75)	27	18	36	4/11
Aranesp 2.25 mcg/kg	22	23 (5,40)	27	14	41	3/22
Aranesp 4.5 mcg/kg	22	57 (36, 79)	15	15	28	11/19
Placebo	11	0	45	40	55	2/10

Safety:

Aranesp and placebo had similar safety profiles. There were no deaths during or 30 days after the study and no dropouts due to adverse events. Among AE of historical interest [hypertension, convulsions and thrombotic events], and among cardiovascular, neurologic, vascular (thrombosis and hypertension) events, there were no differences observed between Aranesp and placebo patients.

Drug exposure:

- The median duration of Aranesp in the 55 patients was 12 weeks.
- Two male patients at 4.5 mcg/kg dose had drug withheld and not restarted because hgb > 15 g/uL. Neither had an associated AE within 14 days. One patient at 2.25 mcg/kg missed a dose at week 10 because of chest pain. Dose was restarted without problems on week 11. One subject receiving 1.0 mcg/kg missed the week 12 dose because of severe gastroenteritis and 4 patients missed doses because of non-compliance.
- Dose reductions were noted in 3 patients in the 1.0 mcg/kg dose group, 5 patients in the 2.25 mcg/kg dose group and 9 patients in the 4.5 mcg/kg dose group.

SUMMARY:

1. No linear dose effect found for endpoint of sustained hgb correction or for K-M fraction of transfused patients or hgb response. However the 4.5 mcg/kg dose showed a trend to an advantage over 2.25 mcg/kg.
2. Sponsor analysis of covariates concluded that the malignancy type and red cell transfusions prior to randomization were related to hgb response..
3. Aranesp & placebo patients had similar AE profiles.

Protocol 980291

- ✓ Phase 2 study of Aranesp vs placebo
- ✓ Aranesp given SC every three weeks
- ✓ Solid tumor patients receiving cyclic chemotherapy

Protocol 980291-Phase 2				
Title: A Randomized, Double-blind, Placebo-controlled, Dose-finding Study of NESP Administered Once Every Three Weeks by SC Injection for the Treatment of Anemia in Subjects with Solid Tumors Receiving Multicycle Chemotherapy				
Experimental design: Double-blind, multicenter, dose-ranging study of Aranesp SC Q3W given to cancer patients undergoing cyclic chemotherapy. Patients randomized 4:1 to receive one of the doses of Aranesp or placebo.				
Period of study	Sites	Study arms and number patients	Study Objective(s)	Study Results
6/6/99-ongoing	26 in Aus., Canada, Costa Rico, Europe	Aranesp 4.5 mcg/kg 33 Aranesp 6.75 mcg/kg 19 Aranesp 9.0 mcg/kg 47 Aranesp 12.0 mcg/kg 28 Aranesp 13.5 mcg/kg 36 Aranesp 15.0 mcg/kg 45 Placebo 51	Safety of Aranesp given every 3 weeks in non-myeloid cancer subjects	A wide dose range showed hgb responses. 9.0 mcg/kg to 15.0 mcg/kg had hgb response > 50%.

Objectives and Overview: The primary objective was the assessment of the safety and hgb response in patients placed on an every 3 week SC Aranesp schedule.

Clinical population: Patients were required to have solid tumors and to be receiving cyclic chemotherapy; all subjects had to be age 18 or older. Hgb screening values had to be 11.0 g/dL of hgb or less, and patients had to be scheduled to receive chemotherapy for 12 or more weeks. Other requirements were an ECOG performance status 0-2; life expectancy of six or more months, & adequate organ function on liver and renal function testing. Anemia had to be primarily due to cancer or to chemotherapy (serum folate equal to or > than 4.5 ng/mL, vitamin B12 >148 pmol/L, no hemolysis, no gastrointestinal bleeding, no bleeding attributable to recent surgery).

Study design: This was a dose ranging, placebo controlled study in anemic patients with solid tumors receiving cyclic chemotherapy. Subcutaneous injections were given once every 3 weeks for the 12 week study period. Randomization allocation was 4 (experimental): 1 (placebo). Aranesp doses were 4.5, 6.75, 9.0, 12.0, 13.5, 15.0 mcg/kg. Efficacy was based on part A; part B was unblinded continuation on the same dose of agent and was optional for patients who had completed part A. After the last dose of Aranesp all subjects were followed for an additional 8 weeks to monitor later safety events and study the maintenance of agent effect.

Demographics: There were 361 patients screened. Two hundred and fifty-nine patients (208 Aranesp and 51 placebo) were in the initial ITT analysis set. Ten patients failed to receive drug leaving 198 in the Aranesp and 51 in the placebo (n=24) arms.

DEMOGRAPHIC AND CLINICAL FEATURES

Men/women	%	29/71
Age <65 yrs	%	67
= to or >65 yrs	%	33
> 75 yrs	%	8
Tumor type	in %	
Breast		30
Gyn.		22
GI		19
Lung		17
GU		7
Other		5
Disease stage	in %	
I		3
II		8
III		19
IV		70
Bone Marrow involvement	%	6
ECOG 0	%	35
ECOG 1	%	55
ECOG 2	%	10

Definitions: The clinically effective dose [CED] was the primary endpoint. It was defined as the dose at which 50% or more of patients had a hgb response (2 or more g/dL of increase of hgb), and at which 20% or less of patients exceeded the upper acceptable hgb limit (> 14 g/uL for women and 15 g/uL for men) and 20% or less subjects had a DLT.

Conduct of the study: There were 259 patients enrolled (51 placebo and 208 Aranesp patients) and 249 received the designated study agent.

Enrollment by Aranesp dose level

	Number enrolled drug	Number received study
Subjects enrolled	208	198
Aranesp 4.5 mcg/kg	33	32
Aranesp 6.75 mcg/kg	19	17
Aranesp 9.0 mcg/kg	47	46
Aranesp 12.0 mcg/kg	28	28
Aranesp 13.5 mcg/kg	36	35
Aranesp 15 mcg/kg	45	40

Withdrawal from study: In the placebo group, 14 patients failed to complete the study. The reasons were consent withdrawn (1), death (3), and chemotherapy delay or discontinuation or failure to complete part A at time of report (10). In the Aranesp group there were 58 patients who did not complete study. The major reasons included failure to receive study drug (10), ineligibility (8), one protocol violation [non-compliance] and one AE each, consent withdrawn (9), disease progression (6), administrative decision (1), lost to follow up (2), death (7) and chemotherapy delay or change.

PATIENT VIOLATIONS

	Aranesp	placebo
Lacked folate or B12 screening	4	1
Unstable angina at entry	1	0
Delayed study drug by 4 or more days	1	1
Missed dose due to SAE (see drug exposure)	2	0
Reduced dose in violation protocol	3	0
Overdose/incorrect dose	6	0
Missed antibody sample	2	1

Efficacy : Primary endpoint: Doses from 9.0 to 15 mcg/kg met the criteria of the clinically effective dose (CED).

HGB RESPONSE AND TRANSFUSIONS AT DIFFERENT DOSE SCHEDULES

		Aranesp in mcg/kg given every 3 weeks SC					
	placebo	4.5	6.75	9.0	12.0	13.5	15.0
Number subjects	51	32	17	46	28	35	40
Hgb response Kaplan-Meier prop. % (95% CI)	14 (3,24)	24 (8,39)	48 (22,74)	51 (35,67)	62 (41,82)	69 (42, 75)	52 (35,69)
Change hgb BL to wk 13 Mean g/dL	0.08	0.64	1.18	1.27	2.64	1.47	1.38
Transfusions wk 5 -EOTP Kaplan-Meier prop.% (95% CI)	46 (32,61)	25 (9, 41)	28 (4, 51)	30 (16, 44)	24 (7, 41)	26 (11, 40)	19 (6,32)

Safety: There were 14 deaths on study [4 patients receiving placebo (8%) and 10 patients receiving Aranesp (5%)]; most were associated with progressive disease. There were 8 patients who withdrew from the study prematurely due to AE ; all had received Aranesp. In 7/8 instances the reason given was progressive disease; in one the reason was a venous thrombosis. The most frequent AE were gastrointestinal and systemic. There was one grade 3 or 4 AE (pulmonary embolism) observed in an Aranesp subject. In 13 women (9%) and one man (2%) receiving Aranesp, the hgb exceeded the maximum concentrations (14 g/dL for women and 15 g/dL for men).

Amendments

- ✓ Allowed investigation of incremental doses of Aranesp between defined doses
- ✓ Clarified planned analyses

Summary

A three week SC dose schedule at higher doses than used in one or two week schedules was active in increasing hgb values above baseline and decreasing the proportion of subjects transfused to less than anticipated from historical information . At 9.0 mcg/kg of Aranesp and higher the number of hgb responders was over 50% and met the prospectively set criteria for clinically effective dose; the reduction in transfusion requirements was less clear.

PROTOCOL 980290

- ✓ Phase 2 study of Aranesp vs. rHuEPO
- ✓ Parts A and B: part A is SC QW, sequential, dose escalation study; part B is SC Q2W, sequential, dose escalation study
- ✓ Subjects are cancer patients scheduled for cyclic chemotherapy.

Protocol 980290-Phase 2				
Title: A Randomized Dose-Finding Study of NESP Administered by Subcutaneous Injection for the Treatment of Anemia in Subjects with Solid Tumors Receiving Multicycle Chemotherapy				
Experimental design: Multicenter, open label, escalating dose cohorts each randomized 4:1 Aranesp to rHuEPO. Part A used a weekly SC dose of Aranesp ranging from 0.5 to 4.5 mcg/kg or Procrit 150 U/kg TIW. Part B employed a Q2W SC dose of Aranesp ranging from 3.0 to 9.0 mcg/kg or Procrit 40,000 U QW SC.				
Period of study	Sites	Study arms/cohorts, dose and number patients	Study Objective (s)	Study Results
4/14/99 to 10/23/00	32 in USA	<u>Part A -QW</u>	Safety and dose-response to Aranesp	Part A: Hgb response > 50% at Aranesp SC QW 2.25 mcg/kg or 4.5 mcg/kg Part B: Hgb response > 50% at Aranesp doses from 3-9 mcg/kg Q2W.
		Aranesp 0.5 mcg/kg 13		
		Aranesp 1.0 mcg/kg 36		
		Aranesp 1.5 mcg/kg 35		
		Aranesp 2.25 mcg/kg 59		
		Aranesp 4.5 mcg/kg 29		
		Aranesp 6.0 mcg/kg 30		
		Aranesp 8.0 mcg/kg 14		
		EPO 150 U/kg TIW 53		
		<u>Part B-Q2W</u>		
		Aranesp 3.0 mcg/kg 33		
		Aranesp 5.0 mcg/kg 31		
		Aranesp 7.0 mcg/kg 32		
		Aranesp 9.0 mcg/kg 32		
		EPO 40000 U/wk 32		

Overview and objectives: Two different administration schedules, QW (Part A) and Q2W (Part B), both SC, were explored for safety and hgb response.

Clinical population: Patients had to be 18 years of age or older and have a diagnosis of non-myeloid cancer. Hgb screening values had to be 11.0 g/dL of hgb or less, and patients had to be scheduled to receive chemotherapy for 12 or more weeks. Other requirements were an ECOG performance status 0-2; life expectancy of six or more months, & adequate organ function on liver and renal function testing. Anemia had to be primarily due to cancer or to chemotherapy (serum folate equal to or > than 4.5 ng/mL, vitamin B12 >148 pmol/L, no hemolysis, no gastrointestinal bleeding, no bleeding attributable to recent surgery).

Study design: Part A patients who were scheduled to begin cyclic chemotherapy were randomized to sequential, escalating dose cohorts of Aranesp at either 0.5, 1.0, 1.5, 2.25, 4.5, 6.0 or 8.0 mcg/kg SC QW or to rHuEPO. Within each Aranesp cohort there was a 4:1 randomization for Aranesp; rHuEPO. Control rHuEPO subjects were given rHuEPO at 150 ug/kg TIW and were permitted to double the dose at week 6 if hgb response was inadequate (< 1 g hgb/dL) while Aranesp patients remained on the same dose until the end of treatment at 12 weeks. A four week observation period followed the last dose.

Part B enrolled separate subjects who were also scheduled for cyclic chemotherapy. They were randomized 4:1 to one of the doses of Aranesp [3.0, 5.0, 7.0, or 9.0 ug/kg] and given Q2W or

rHuEPO 40000U given weekly. rHuEPO patients who failed to show a hgb increase of at least 1 g/dL by 6 weeks were permitted to increase their dose to 60000 /Q2W. The treatment period was 12 weeks followed by 4 weeks of follow-up.

Study drug was withheld from patients whose hgb increased to > 15 g/dL (men) or 14 g/dL for women.

Evaluation: The primary endpoint was incidence of AE and antibody to Aranesp [parts A and B]. Dose response for each dose cohort was evaluated for: Hgb response (increase hgb > 2 g/dL without transfusion); Hgb correction (hgb value 12.0 or >); Proportion of subjects transfused; Number days with one or > transfusions; Number units transfused; Time to first RBC transfusion; HRQOL.

Amendments

- ✓ Entry hgb changed from 10 to 11.0 g/dL hgb
- ✓ RBC transfusion policy changed from mandatory to a set of guidelines/recommendations
- ✓ NCI-CTC added as toxicity grading scale
- ✓ Dose adjustments and stopping rules further detailed
- ✓ Permit inclusion of subjects receiving cyclic chemotherapy of any cycle length
- ✓ Eligibility changed to include ANC equal to or > $1000 \times 10^9 /L$ and platelets equal to or > $75 \times 10^9 /L$
- ✓ Allowed local laboratory determinations
- ✓ Allowed subjects to have up to 30 Gy pelvic radiation therapy during study
- ✓ Removed minimum cohort sample size requirement
- ✓ Reduced screening period to 7 days

Disposition of patients: The major reason for failing to complete the study was delay or cessation of chemotherapy and withdrawal of consent for study.

Study arm patients screened and study arm patients who received drugs

	Part A		Part B	
	RHuEPO	Aranesp	RHuEPO	Aranesp
Screened	60	228	141	35
Received study agent	53	216	128	32

Demography and medical history: The table below lists selected pertinent demographic and clinical data. Demography was reported by dose in the sponsor submitted report; no significant differences were observed between doses or between Aranesp and rHuEPO.

Demographic and clinical data at baseline

	number	rHuEPO	Aranesp all doses
Age % of patients		53	216
< 65 years		66	54
Equal to or > age 65 years		34	46
Equal to or > 75 years		13	14
Men in %		28	32
Women in %		72	68
Primary tumor type in %			
Breast		28	30
Gastrointestinal		23	19
Lung		21	19
Gynecologic		11	13
GU		6	6
Other		11	14
Disease stage III %		21	21
Disease stage IV %		64	68
Bone marrow involvement in %		2	2

Efficacy results

Responses at different doses of Aranesp

	Study agent	Number of patients enrolled	Hgb response K-M prop. %	Increase in Hgb in g/dL mean	Subjects transfused week 5 to EOTP K-M prop. %
Part A Aranesp in mcg/kg QW SC	Aranesp 0.5	13	23	0.49	15
	Aranesp 1.0	36	43	0.62	10
	Aranesp 1.5	35	44	1.07	26
	Aranesp 2.25	59	52	1.31	13
	Aranesp 4.5	29	76	1.87	6
	Aranesp 6.0	30	73	1.85	16
	Aranesp 8.0	14	62	2.17	0
	rHuEPO 150 U/kg TIW	53	72	1.14	30
Part B Aranesp in mcg/dL Q2W SC	Aranesp 3.0	33	60	1.23	4
	Aranesp 5.0	31	79	1.46	22
	Aranesp 7.0	32	54	1.42	23
	Aranesp 9.0	32	67	1.51	11
	rHuEPO 40000u/wk	32	53	1.84	36

In part A there were 53 patients treated with rHuEPO 150 U/kg TIW which was doubled at week 6 if hgb was not 1 g/dL or more than that at the baseline.

In part B there were 32 patients treated with rHuEPO 40,000U QW which was increased to 60,000 U/kg if hgb was not 1 g/dL or more higher than that of baseline.

AE and immunogenicity are part of ISS report..

Deaths: 6/53 (11%) of rHuEPO patients and 17/216 (8%) of Aranesp patients died during the study. There were 3 deaths from infectious complications and the remaining were due to progressive malignant disease. None were considered drug related. Numbers are given below.

Deaths during study in study arms by dose

	Number patients	Number deaths
rHuEPO	53	6 (11%)
Aranesp 0.5 mcg/kg	13	1
Aranesp 1.0 mcg/kg	36	0
Aranesp 1.5 mcg/kg	35	5
Aranesp 2.25 mcg/kg	59	1
Aranesp 4.5 mcg/kg	29	4
Aranesp 6.0 mcg/kg	30	3
Aranesp 8.0 mcg/kg	14	3
All Aranesp	216	17 (8%)

Withdrawals from study due to AE: There were 2/53 (4%) withdrawals from the rHuEPO arm and 10/216 (5%) withdrawals from the Aranesp arm. The two rHuEPO withdrawals were due to a left chest wall hemorrhage at week 6 and progression of a uterine malignancy. The reasons for withdrawals from the Aranesp group were as follows: 3-disease progression; 1- increased blood pressure (160/88); 2- gastrointestinal bleeds; 2- pneumonia at weeks 11 and 12; one pulmonary embolus and one due to cellulitis. Discontinuations were found at different dose levels.

EXPLORATORY STUDIES OF ALTERNATIVE Q2W & Q3W DOSE SCHEDULES

Different weekly subcutaneous dosing schedules were explored in phase two studies 980291 (Q3W) and 980290 (one and two week schedules). Protocol 980290 permitted comparison of weekly and Q2W schedule within the same study. Three of the relevant dose results are seen below; responses to all doses utilized in the protocol can be found on page 31. Controls differed and no comparison of darbopoetin alfa with epoetin alfa was part of the development plan. In protocol 980291 (Q3W dosing) the control was placebo; in protocol 980290 part A the control was epoetin alfa SC 150 mcg/kg T1W and part B epoetin alfa a 40,000 unit fixed weekly dose SC. The main evaluation was the hgb response; data on number of patients receiving transfusions were collected. There were limited numbers of subjects in many cases [number of patients shown in brackets after hgb values]. The last column (incr hgb g/dL mean[n] , EOTP) counted all patients while week 4, 8, and 13 column values did not count missing/censored patients. The Q2W and Q3W data were not regarded by CBER as sufficient to support alternative Q2W or Q3W doses because the data were limited in number and developed in a phase two study in which the primary endpoint was not a clinical endpoint.

PHASE 2 STUDIES	Aranesp	Hgb response	Incr. Hgb g/dL mean [n]	Incr hgb g/dL mean [n]	Incr hgb g/dL mean [n]	Incr. Hgb g/dL mean [n]	Transfused w5-EOTP
Protocol	ug/kg SC (n)	K-M prop. in %	WEEK 4	WEEK 8	WEEK 13	EOTP	K-M prop. in %
291 Q3W	4.5 (33)	24	na	na	0.64 [14]	0.54 [32]	25
Q3W	6.75 (19)	48	na	na	1.18 [9]	0.86 [17]	28
Q3W	9.0 (47)	51	na	na	1.27 [26]	0.90 [46]	30
Q3W	12.0 (28)	62	na	na	2.64 [8]	1.63 [28]	24
Q3W	13.5 (36)	59	na	na	1.47 [26]	1.45 [35]	26
Q3W	15.0 (45)	52	na	na	1.38 [16]	1.21 [40]	19
Q3W	placebo (51)	14	na	na	0.08 [19]	0.02 [51]	46
290 QW	A 1.5 (35)	44	0.47 [35]	1.06 [21]	1.56 [16]	1.07 [35]	26
QW	A 2.25 (59)	52	0.70 [49]	1.16 [49]	1.45 [35]	1.31 [59]	13
QW	A 4.5 (29)	76	0.98 [22]	1.54 [19]	2.81 [8]	1.87 [29]	6
290 Q2W	B 3.0 (33)	60	0.61 [23]	0.81 [24]	1.61 [15]	1.23 [33]	na
Q2W	B 5.0 (31)	79	0.58 [25]	1.26 [21]	2.36 [14]	1.46 [31]	4
Q2W	B 7.0 (32)	54	0.61 [23]	0.87 [20]	2.35 [11]	1.42 [32]	22
Q2W	B 9.0 (32)	67	1.23 [24]	1.51 [25]	2.39 [15]	1.51 [32]	23

Hgb response was defined as an increase of hgb from baseline value of 2 grams or more with no transfusion within the last 28 days.

291 is protocol 990291 and 290 is protocol 980290.

In protocol 290 the letters A and B refer to part A and part B of the study:

na -no information available.

SECTION I

PROTOCOL 990111

- ✓ Phase 2 study
- ✓ QW SC Aranesp dose escalation study in patients with anemia associated with non-myeloid cancer
- ✓ Subjects are not receiving chemotherapy

Protocol 990111-Phase 2				
Title: An Open-label, Dose-finding Study of NESP Administered by SC injection for the Treatment of Anemia in Subjects With Chronic Anemia of Cancer				
Experimental design: Multicenter, open label, dose escalation study of 4 successive cohorts of Aranesp.				
Period of study	Sites	Study arms and number patients	Study Objective(s)	Study Results
4/30/99 to 1/4/01	19 in USA	<u>4 dose cohorts</u> Aranesp 0.5 mcg/kg 6 Aranesp 1.0 mcg/kg 33 Aranesp 2.25 mcg/kg 33 Aranesp 4.5 mcg/kg 30 102	Safety and response to Aranesp in series of doses given weekly in a group of non-myeloid cancer patients <i>not receiving chemotherapy</i>	Hgb responses noted at 1.0, 2.25 and 4.5 mcg/kg of Aranesp.

Objectives and overview : Dose-response to Aranesp SC QW in subjects with anemia of cancer not on chemotherapy.

Clinical population: Subjects were age 18 yrs or >; had a hgb 11 g/dL or less; had anemia attributable to non-myeloid malignancies and were not scheduled for nor had received chemotherapy or radiotherapy within last 16 weeks. Other requirements were an ECOG performance status 0-2; life expectancy of six or more months, & adequate organ function on liver and renal function testing. Anemia had to be primarily due to cancer (serum folate equal to or > than 4.5 ng/mL, vitamin B12 >148 pmol/L, no hemolysis, no gastrointestinal bleeding, no bleeding attributable to recent surgery).

Experimental design- This was an open label, dose escalation trial performed at multiple centers. Aranesp doses were 0.5, 1.0, 2.25 and 4.5 mcg/kg QW SC. The study period was 12 weeks followed by a 4 week untreated follow-up. Safety endpoints were incidences of AE and antibody to Aranesp. Response to different doses of Aranesp was measured by hgb response [2 or > g/dL of hgb increase over baseline without transfusion last 28 days], hgb correction, change in hgb concentration, and proportion of patients transfused.

Results

Demographics: The 102 enrolled patients included 54 men and 48 women with a mean age of 70; races were 81 % white, 16 % black, 2 % Asian, 2 % Hispanic and 1 other subject. Aside from the chronic effects of cancer, there were no other obvious other reasons for the anemia. Inclusion criteria required that serum folate ≥ 2.0 ng/mL, vitamin B12 ≥ 180 pg/mL, and that there be no hemolysis, no gastrointestinal bleeding, adequate renal function, as evidenced by a serum creatinine concentration of ≤ 2 mg/dL (≤ 176.8 μ mol/L) and adequate liver function, as evidenced by a serum bilirubin ≤ 1.5 times the central laboratory normal range. The distribution of baseline hgb endogenous erythropoietin levels, total Fe binding capacity and transferrin saturation are shown below. Patients in the lower quartile of transferrin values could include some patients with iron deficiency which was not clinically evident.

Baseline laboratory values

Laboratory findings	
Hgb at baseline in g/dL in % patients	
< 8 g/dL	7
8 to < 9 g/dL	15
9 to < 10 g/dL	27
10 to < 11 g/dL	42
11 or > g/dL	9
Total Fe binding capacity micromoles/L	
N	101
Median	53.2
Q1,Q3	46.2,58.6
Transferrin saturation in %	
N	101
Median	21
Q1,Q3	13,28

Efficacy: Data shown below suggest that there were responses to Aranesp in anemia of cancer patients not receiving chemotherapy. The change in hgb from baseline is within the same order of magnitude as noted in the cyclo chemotherapy study groups.

Responses to Aranesp at three different doses

Dose of Aranesp in mcg/kg	n	Hgb responders.	Change in hgb baseline to EOTP	Pts transfused Week 5-EOTP
		% K- M proportion (95% CI)	Mean hgb g/dL	K-M proportion (95% CI)
1.0	33	68 (50,86)	1.66 g/dL	36(10,32)
2.25	33	66 (49,84)	2.07 g/dL	14(1,26)
4.5	30	92 (80,100)	2.91 g/dL	7 (0,17)

Safety: The safety profile encountered was similar to that of the other Aranesp studies.

Comments and summary: This study does not provide support the current indication since the subjects were not receiving chemotherapy.

APPEARS THIS WAY ON ORIGINAL

SECTION J PIVOTAL TRIAL 980297

- ✓ Phase 3, randomized, pivotal trial
- ✓ Aranesp vs placebo compared in lung cancer patients given platinum containing chemotherapy

Protocol 980297-Phase 3				
Title: A double-blind, Placebo Controlled, Randomized Study of NESP for the Treatment of Anemia in Lung Cancer Subjects Receiving Multicycle Platinum Containing Chemotherapy				
Experimental design: Phase 3, double-blinded, multicenter, multinational, placebo-controlled, randomized, balanced study. The Aranesp dose utilized was 2.25 mcg/kg QW with doubling of dose at 6 weeks if hgb response was inadequate. Treatment period was 12 weeks with a 4 week untreated follow-up and more extended follow-up for a year. Stratification was for treatment center and for tumor type (NSCLC vs. SCLC).				
Period of study	Sites	Study arms and number patients	Study Objective(s)	Study Results
9/14/99 to 11/8/00	70 sites in Australia, Canada & Europe	Two arm Aranesp 155 Placebo 159	Determine if Aranesp is superior to placebo in reducing RBC transfusions during cyclic chemotherapy.	Transfusions reduced in Aranesp vs. placebo patients (60 % to 26 % in the ITT dataset) .

Overview and Objective(s) The study was designed to support licensure by comparing the effectiveness and safety of Aranesp to placebo in treating anemia in lung cancer patients receiving multicycle platinum-containing chemotherapy. The primary endpoint was the proportion of subjects who received RBC transfusions during the fifth to 12th week of treatment. Secondary objectives included increase in hgb from baseline and HRQOL after Aranesp therapy [HRQOL was later removed from proposed package insert by sponsor].

Patient population:

Inclusion criteria (verbatim from submitted protocol)

- o lung cancer (either SCLC or NSCLC)
- o at least 12 additional weeks of platinum-containing cyclic chemotherapy planned, regardless of cycle length
- o anemia (hemoglobin ≤ 11.0 g/dL), as assessed by a local or central laboratory result within 7 days before study day 1 (the first scheduled day of on-study chemotherapy and the first day of study-drug administration)
- o life expectancy of at least 6 months and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
- o anemia predominantly due to the cancer or chemotherapy (ie, serum folate equal to or less than 4.5 nmol/L [≥ 2.0 ng/mL] and vitamin B12 ≥ 148 pmol/L, no overt hemolysis, and no overt gastrointestinal bleeding or bleeding due to recent surgery), adequate renal function and adequate hepatic function (bilirubin ≤ 1.5 times the central laboratory's upper limit of normal range)
- o available for 4 weeks after administration of the last dose of study drug
- o legal age for informed consent and written informed consent obtained

Exclusion criteria are not verbatim from protocol but rather are summarized relevant points. Excluded were patients with a primary hematologic disorder associated with anemia; uncontrolled hypertension; a history of seizures; uncontrolled angina or congestive heart failure NY Heart Association > class II or a known ejection fraction < than 40%; central nervous system

malignancy. Also excluded were patients with iron deficiency (transferrin saturation < 15% and ferritin < 10 ng/ml); patients who received a RBC transfusion within 4 weeks or epoetin alfa within 8 weeks; anyone who received prior therapy with Aranesp.

Study design Protocol 980297 was a phase 3, multicenter, multi-national, randomized, placebo controlled, double blinded trial. Three hundred and twenty patients were enrolled & randomized equally (see patient disposition below) to receive either the 2.25 mcg/kg dose of Aranesp [treatment arm] or placebo SC. The first dose of study drug was given on the first day of the next cycle of chemotherapy after randomization whenever possible and re-administered weekly on the same day of the week. Each patient was treated for the 12 weeks (treatment phase). If a subject had not achieved a 1.0 gram/dL or > rise in hgb by week 6, the dose was doubled to 4.5 mcg/kg. After the conclusion of the treatment phase (EOTP) there was a four week follow-up without treatment. This was followed by a 12 month long term follow-up period. Transfusion of RBC was determined by study guidelines (non-mandatory) but the final decision was based on medical judgment. No information provided on transfusion practices of the 70 participating centers. Analysis of transfusion indications are found on page 42 of this Section.

Evaluation and endpoints: The primary endpoint was the estimated Kaplan-Meier proportion of subjects who received RBC transfusions from week 5 to EOTP stratified by tumor type and region. It was evaluated in the primary analysis dataset which considered evaluable all subjects who remained on study until week 5 of the treatment period as stipulated in the prospective development plan. The use of a "guarantee period" of the first 4 weeks of drug exposure as a prerequisite for evaluation is consistent with the knowledge that the response to epoetin alfa and darbopoetin alfa occurred after 3-6 weeks of therapy. Subjects who withdrew/discontinued from study after week 4 for death or disease progression were censored while those who withdrew for any other reason were imputed to be transfused (treatment failures for primary endpoint).

Stratification was by geographic region & by tumor type (SCLC vs NSCLC). There were three centers in Australia, 5 in Canada, 25 in Central and Eastern Europe, 37 in Western Europe.

Other endpoints were determined in the intent to treat population which included all randomized patients who received at least one dose of drug. As stated above, in the primary analysis, transfusions were imputed to any subject who withdrew from study before end of treatment phase (12 weeks) for reasons other than death or progressive disease. The same imputation was applied to statistical evaluation of the secondary endpoints.

Secondary endpoints included the time to first RBC transfusion week 5 to EOTP, the proportion of subjects receiving RBC transfusions week 1 to EOTP and weeks 1-4, the number of standard units RBCs transfused week 5 to EOTP, the number of days receiving RBC transfusions week 5 to EOTP, the proportion of subjects with hgb response (see definitions), the proportion subjects with hgb correction (see definitions), the time to hgb response after start treatment, the time to hgb correction after start treatment, the change in hgb from baseline to EOTP

Safety endpoints included the incidence of death, the incidence of AE and serious AE, the proportion of subjects with hgb > 15 g/dL for men and > 14 g/dL for women, the rate of rise of hgb, the changes in laboratory variables from baseline, the proportion subjects with antibody formation to NESP, the incidence of use of concomitant medications, the number days hospitalized. Tumor progression and survival data were collected for up to one year.

Definitions

Hgb response was defined as an increase in hgb equal to or > 2 g/dL over the baseline in absence of RBC transfusions during the preceding 28 days.

Hgb correction was defined as a hgb equal to or > than 12 g/dL in absence RBC transfusions during the preceding 28 days

EOTP is end of treatment period. It is usually day 1 of week 13. For subjects who withdrew, the treatment phase ended after last dose of study drug.

Primary analysis dataset included subjects on study up to the first day of week 5 and had received one or more doses of Aranesp.

Intent to treat (ITT) analysis dataset included all patients who were randomized and received one dose of study agent.

Guarantee period is the period of time (weeks 1-4) during which a patient had to be on study to be evaluated for primary endpoint.

Major amendments:

- ✓ Eligibility criteria
 - Cyclic chemotherapy can be other than 3 or 4 week cycles
 - Platelet and neutrophil entry criteria removed
 - Iron deficiency exclusion emended to transferrin saturation of 15% and serum ferritin < 10 ug/L
- ✓ Antibody assessments Q4 weeks to conform to other determinations
- ✓ RBC transfusion policy changed from requirement to a recommendation
- ✓ Primary endpoint changed from proportion of subjects achieving a hemoglobin response to proportion of subjects receiving a RBC transfusion weeks 5 to 12 (CBER request).
- ✓ Added collection of long-term, follow up data on survival and disease progression (CBER request).

Conduct of the study

Patient disposition: One hundred and one patients withdrew from study (32%). The protocol anticipated this level of withdrawal. Withdrawal numbers were balanced between arms.

Approximately half of the withdrawals were directly due to death or progression of disease. Changes in chemotherapy accounted for 18 withdrawals.

PATIENT DISPOSITION

DISPOSITION	Placebo arm # subjects	Aranesp arm # subjects	total # subjects
Subjects screened		413	
Subjects enrolled & randomized	161	159	320
dc'd before 1 st dose	-3	-3	-6
Subjects who received drug (ITT analysis set)	158 ³	156 ³	314 ³
dc'd bet. weeks 1-4	-9	-8	-17
Primary analysis set	149	148	297
RANDOMIZED SUBJ.	161	159	320
ON STUDY ¹	109	110	219
OFF STUDY ²	52	49	101
Adverse event	5	2	7
Consent withdrawn	5	5	10
Disease progression	9	9	18
Administrative decision	2	2	4
Lost to follow up	3	6	9
Death	19	14	33
Study specific reason	0	6	6
Chemorx delayed/discontinued	8	10	18
Other	1	1	2

¹ completed full course of study ² failed to complete full course of study

³ Because one Aranesp patients did not receive drug, the n of Aranesp 156, placebo 158 was used for the primary endpoint/efficacy and Aranesp 155, placebo 159 for safety and other analyses.

Demographic and clinical features: The two study arms appear balanced,

DEMOGRAPHIC AND CLINICAL FEATURES OF THE STUDY POPULATION

	Placebo	Aranesp	Total
n=	158	156	314
Male/female number	116/42	111/45	227
Race-white number	158	156	314
Age median yrs	61	62.5	62
Subjects 65 or> number	66	59	125
NSCLC number	114	108	222
Stage I	2	2	4
II	2	2	4
III	48	29	77
IV	62	75	137
SCLC number	44	48	92
Limited disease	19	16	35
Extensive disease	25	32	57
Bone marrow involvement %	4	6	5
ECOG %			
0	15	14	14
1	62	70	66
2	23	15	19
>2	0	1	0
Hepatic metastases %	20	20	20

Baseline hemoglobin:

Baseline hgb affected the proportion of subjects who received a RBC transfusion. Using the < 9.0 g/dL group as the reference group there was an independent effect using both the Cox proportional hazards regression and logistic regression (3 indicator variables). The Kaplan-Meier proportion of patients transfused weeks 5 to EOTP for groups with baseline hgb 9-<10, 10 to < 11, > 11 were 0.59, 0.47 and 0.21 respectively (data source was Amgen) [page 44 for further discussion baseline hgb as covariate).

The percentage of subjects in each of four ranges of hgb values are relatively comparable but there is an imbalance in the number of patients who had baseline hgb values above 11.0 grams/dL in violation of eligibility requirements. *Sponsor explanation is that the screening values met eligibility standards of hgb <11.0 g/dL but that later baseline determinations disclosed that 20 placebo and 42 Aranesp patients had hgb levels > 11.0* leaving the fraction of subjects with baseline hgb > 11.0 unbalanced between arms. To determine if the imbalance introduced a bias, Amgen included a sensitivity analysis in which they recalculated endpoints after removing > 11.0 subjects from both test groups; the endpoint was not substantially affected. CBER statistical analysis concurred with the Amgen analysis.

BASELINE HGB VALUES IN TWO STUDY ARMS

	Placebo	Aranesp
n	159	155
Hgb (g/dL)	#	#
< 8 g/dL	6	4
8 to < 9 g/dL	23	15
9 to <10 g/dL	41	31
10 to < 11 g/dL	69	63
11 or> g/dL	20	42

Baseline erythropoietin : The values reflect the relatively low and unresponsive serum erythropoietin levels observed in studies of cancer patients. Analysis of RBC transfusions and responders by baseline serum EPO distribution is seen on page 44.

ENDOGENOUS (BASELINE) ERYTHROPOIETIN VALUES

	Placebo	Aranesp	Total
Number tested	151	145	296
Baseline erythropoietin median mU/mL	36	36	36
Q1, Q3 mU/mL	24,62	22,52	23,59

Total Iron-binding capacity, ferritin, serum iron and transferrin saturation were balanced between study arms.

Efficacy

Primary endpoint: Study 980297 served as the pivotal study in support of licensure with supportive data from studies 990114, 980291, 990146, 980290, 20000174. The primary endpoint was a comparison between the two study arms, of the fraction of patients transfused between week 5 to end of the 12 week treatment period. The 95% confidence intervals [CIs] shown below do not overlap and the p value is < 0.001 . The primary endpoint was based on the primary analysis set (see Evaluation and Definitions in this Section)) which was restricted to data from patients who had completed the first 4 weeks of study; the Kaplan-Meier proportion of patients transfused was 51% for the patients in the placebo arm vs. 21% in the Aranesp arm. The same analysis was also performed on the intention to treat dataset which includes patients during all 12 study weeks. The comparable figures were 60% for the K-M proportion of patients in the placebo arm vs. 26% in the Aranesp arm. The two stratification variables, tumor type and the region, did not change the results. The platinum containing chemotherapy employed likewise did not affect results substantially (see table below).

EFFICACY ENDPOINT OF PROPORTION OF SUBJECTS TRANSFUSED USING PRIMARY ANALYSIS DATASET*

		Placebo arm N= 149	Aranesp arm N=148
Subjects with RBC transfusions week 5 to EOTP	Number	74	39
	K-M proportion %	51 %	21 %
	95% CI	43,60	15,28

* The primary analysis data included subjects who had completed the first 4 weeks of the study (guarantee period).

EFFICACY ENDPOINT OF PROPORTION OF SUBJECTS TRANSFUSED USING ITT ANALYSIS DATASET*

		Placebo arm N= 158	NESP arm N=156
Subjects with RBC transfusions week 1 to EOTP	Number	89	53
	K-M proportion %	60 %	26 %
	95% CI	52,68	20,33

* The ITT analysis dataset included all subjects enrolled in the respective arms

Exploratory analysis: There is no correlation between the choice of platinum-containing regimen and the number of subjects transfused on chemotherapy with or without Aranesp.

Effect of platinum –containing chemotherapy on endpoint

		Placebo	Aranesp
Carboplatin	# subjects transfused /study group	43/83	15/56
	K-M proportion [95%CI]	54[43,65]	28[16,41]
Cisplatin	# subjects transfused /study group	31/66	24/92
	K-M proportion [95% CI]	50[37,62]	27[18,36]

Sensitivity analyses of primary endpoint: Sensitivity analyses were performed to assess the impact of withdrawal of subjects from study and the impact of transfusion policy on the primary endpoint. The primary endpoint stipulated that withdrawal from study due to progressive disease or death was legitimate but withdrawal for any other reason was assessed as a transfusion event. The sensitivity analysis of withdrawals performed the same calculation imputing transfusion for all withdrawn patients or using no imputation at all for withdrawn subjects. With respect to transfusion policy any subject with a hgb below 8.0 g/dL was considered transfused. For all sensitivity analyses performed, the proportion of patients transfused in the Aranesp arm was significantly less than in the placebo arm (see table).

SENSITIVITY ANALYSES

ANALYSIS	K-M proportion of patients transfused % (CI)	K-M proportion of patients transfused % (CI)	K-M proportions %
	Placebo	Aranesp	Aranesp minus placebo
Analyses which determine if withdrawals change efficacy endpoint			
N [primary analysis dataset]	149	148	
Impute transfusion to all patients who withdrew W5 to EOTP	56(48,64)	25(18,31)	-23
No imputation for any subject who withdrew W5 to EOTP	48(40,56)	16 (10,22)	-28
Analyses with determine effect transfusion policy on efficacy endpoint			
n	148	149	
Transfusion imputed for all subjects with hgb equal to or < 8.0 g/dL W5 to EOTP	62 (54,70)	29(21,36)	-30

EOTP is end of treatment period: Source of data was Amgen/re-analyzed by CBER.

Secondary endpoints : Secondary endpoints were consistent with the primary endpoint. The median time to the first transfusion for 25% of patients was 8 weeks in the placebo and not reached until week 12.7 by subjects in the treatment arm. The number of units transfused, the number of days of RBC transfusions were less for the Aranesp arm. hgb response, hgb correction and time to hgb response all were superior in the Aranesp study group trending in the same direction as the primary transfusion data [source-data reported by sponsor /re-analyzed by CBER].

SECONDARY ENDPOINTS

		Placebo	Aranesp
Number units Transfused			
Primary dataset	Mean +/-SE	1.92+/-0.27	0.67+/-0.14
ITT dataset	Mean +/-SE	2.64+/-0.32	1.14+/-0.19
Number days RBC Transfusions			
Primary analysis dataset	Mean +/-SE	0.9+/-0.1	0.3+/-0.1
ITT dataset	Mean +/-SE	1.2 +/-0.1	0.5+/-0.1
Hgb response	# patients/# in dataset	22/158	66/156
ITT dataset	K-M proportion [95%CI]	18 [11,24]	48 [39,56]
Hgb correction	# patients/# in dataset	20/158	78/156
ITT dataset	K-M proportion [95%CI]	10 [5,16]	59 [50,67]

Transfusion triggers: The primary endpoint depended on the decision to transfuse a subject. The basis for transfusion was, in the main, clinical judgment with a uniform set of sponsor-developed guidelines serving as recommendations. The study was double blinded; there is no information on how well the blind was maintained after start of study, to protect transfusion decisions from bias.

CBER requested the sponsor to compare the study arms for the different indications for transfusion as listed by the on-site investigators on case report forms. The reasons or indications for transfusion were divided into four categories of data. For each indication group the number of transfusions within past 7 days, the mean hgb at time of transfusion, Q1, Q3 and range are shown below. The indication, "study specific trigger reached", refers to hgb values below 8.0 g/dL of hgb. Medically indicated refers to signs, symptoms or medical conditions referable to the anemia. Prophylaxis for hemoglobin was rarely an indication for transfusion and presumably was in anticipation of further blood loss. Under other indications, the investigator verbatim terms were for radiotherapy; patients best interest; investigator decision; physicians decision; dyspnea. There was no ostensible difference noted between the placebo and Aranesp subjects.

Hemoglobin values at time of transfusion for different indications

	Placebo	Aranesp 2.25 mcg/kg/wk	Total
Number patients	158	156	314
Overall			
Number tfn last 7 days	192	84	276
Mean hgb at time tfn +/- S.D.	8.0 +/- 1.2	8.2 +/- 1.0	8.1 +/- 1.1
Median hgb at time tfn	7.9	8.1	8.0
Q1,Q3	7.3,8.8	7.6,8.9	7.4,8.8
Range	4.9-12.0	6.2-10.2	4.9 -12.0
Indication is "study specific trigger reached"			
Number tfn last 7 days	121	50	171
Mean hgb at time tfn +/- S.D.	7.5 +/- 1.0	7.6 +/- 0.7	7.6 +/- 0.9
Median hgb at time tfn	7.6	7.7	7.6
Q1,Q3	7.0,8.0	7.00,8.10	7.00, 8.00
Range	4.9-11.3	6.2,9.8	4.9, 11.3
Indication is "medically indicated"			
Number tfn last 7 days	65	29	94
Mean hgb at time tfn +/- S.D.	9.0 +/- 1.0	9.0 +/- 0.7	9.0 +/- 0.9
Median hgb at time tfn	8.9	9.0	9.0
Q1,Q3	8.30, 9.50	8.30, 9.50	8.30, 9.50
Range	7.0, 12.0	7.7, 10.2	7.0,12.0
Indication is "prophylactic for hgb"			
Number tfn last 7 days	2	0	2
Mean hgb at time tfn +/- S.D.	8.4 +/- 1.6	.	8.4 +/- 1.6
Median hgb at time tfn	8.4	.	8.4
Q1,Q3	7.30, 9.50	...	7.30, 9.50
Range	7.3, 9.5	...	7.3, 9.5
Indication is "other"			
Number tfn last 7 days	4	5	9
Mean hgb at time tfn +/- S.D.	8.6 +/- 0.5	8. +/- 0.6	8.7 +/- 0.5
Median	8.5	8.7	8.6
Q1,Q3	8.30, 8.95	8.30, 9.00	8.30, 9.00
Range	8.2, 9.3	8.2, 9.8	8.2, 9.8

Tfn is transfusion

See attachment 3 for data as provided by sponsor

Guidelines for transfusion from protocol-verbatim: " It is recommended that RBC transfusion be given in the event that the hgb decreased to less than or equal to 8.0 g/dL , providing there are signs and /or symptoms of anemia (e.g. lethargy, congestive heart failure, angina, or dyspnea). The reasons for administration of any RBC transfusion will be recorded in the CRF. Additionally , the reason for not administering a RBC transfusion when hgb is equal to or less than 8.0 g/dL , will also be recorded in the CRF. RBC transfusion when hgb is > 8.0 g/dL , in the absence of accompanying signs and / or symptoms, is not recommended".

"Responders" to Aranesp in registration protocol 980297; hgb increase and time sequence: Hemoglobin responders were defined in these studies as individuals who had a 2 gram/dL or more rise in hgb by the end of the treatment period. This is approximately similar to the change of 6 hematocrit units applied as a measure of response in epoetin alfa studies. Changes in hgb over baseline with time during treatment in 66 hgb responders in the Aranesp arm are shown in the table below. A 67th patient had a hgb response and is missing from the result. The missing values in weeks 4, 6, 8, and 13 were due to RBC transfusions that occurred within 28 days of a particular week and because of withdrawals as the study progressed . In contrast, the change in hgb from baseline to EOTP contains imputed values for all patients with last observation carried forward.

The initial dose in this protocol was 2.25 mcg/kg which was doubled in patients whose hgb had not increased 1.0 g/dL or more by week 6. Sixty seven of the 156 Aranesp-exposed patients had their dose doubled from 2.25 to 4.5 mcg/kg/ week. Twenty eight % of the 67 subjects who had their Aranesp dose doubled were responders i.e. they had a 2 g/dL or > rise in hgb over baseline, by the end of treatment period. Sixty nine % of 89 subjects who were not "doubled" were responders by the end of treatment period.

Changes in hgb compared to baseline in 66 of the 67 hgb responders in the Aranesp arm

Change from baseline	Week 4	Week 6	Week 8	Week 13	EOTP
N	45	48	57	43	66
Mean	0.42	1.12	1.63	2.54	2.43
SE	0.17	0.15	0.17	0.23	0.20
Median	0.40	1.15	1.70	2.40	2.45
Q1,Q3	-0.20,1.00	0.50,1.95	0.80,2.30	1.60,3.50	1.50,6.40
Range	-2.60,4.77	-2.40,3.10	-1.30,5.40	-1.10,6.40	-1.10,6.40

Covariates

Age: Covariates which might influence endpoints were examined. Age, tumor type, sex and race, lymphoproliferative vs. solid tumors did not interact with treatment effect (see table below for age- Source Sponsor).

Covariate analysis for age

	Test	< 65 yrs vs 65 or >	< 75 yrs vs 75 or >
Aranesp 2.25 mcg/kg SC QW	Hazard ratio for RBC transfusion w5-EOTP	0.5	0.5
	Hazard ratio for Hgb response	3.9	3.9
	Mean Incr. Hgb from baseline in grams/dL	0.8 vs. 1.2	1.0 vs. 1.1

Hgb and endogenous erythropoietin: Baseline hgb and baseline endogenous erythropoietin were examined for their relationship to hgb response and the number of transfusions received by a patient. The likelihood of transfusion was decreased with higher baseline hgb. The incidence of hgb response also fell but the inverse relationship was less marked. There were more transfusions in subjects with erythropoietin levels above 36 (median) or 59 (3rd quartile) [data from CBER analysis].

**RBC transfusions from week 5 to end of treatment by baseline hgb in
Aranesp and placebo arms**

Baseline Hgb g/dL	Aranesp		Placebo	
	n	Patients transfused K-M proportion %	n	Patients transfused K-M proportion %
< 9	18	0.50	26	0.58
9 to < 10	28	0.39	39	0.59
10 to < 11	72	0.19	70	0.47
> 11	30	0.17	14	0.21

**Hgb responders* from week 5 to end of treatment by baseline hgb in
Aranesp and placebo arms**

Hgb g/dL	Aranesp		Placebo	
	n	Hgb responders K-M proportion %	n	Hgb responders K-M proportion %
< 9	20	0.55	28	0.25
9 to < 10	31	0.52	41	0.20
10, to < 11	74	0.42	74	0.07
> 11	31	0.26	15	0.13

* Hgb response is defined as a 2 g/dL or > increase in hgb above baseline by end of treatment in absence of transfusion in last 28 days

**RBC transfusions from week 5 to 12 by baseline serum erythropoietin in
the Aranesp arm**

Serum EPO	Quartile	Total	# transfused	Transfused K-M proportion %
23	1	37	2	6%
>23-36	2	33	6	19%
36-59	3	36	12	34%
>59	4	31	14	46%

Safety

Adverse events: AE with a 5% or > incidence, regardless of relationship to study agent are shown in the table below. AE in bold have a 5% or more difference in incidence between arms. There is a trend to higher levels of nausea, vomiting, diarrhea, asthenia and fatigue in Aranesp arm. The dyspnea may be related to the underlying lung malignancies.

AE REGARDLESS OF RELATIONSHIP TO AGENT WITH A 5% OR HIGHER INCIDENCE

Preferred Terms	Placebo	Aranesp 2.25. mcg/kg/wk
	n= 159	n= 155
	% of patients	% of patients
# pts reporting AE	95%	95%
Nausea	38	43
Vomiting	29	34
Asthenia	19	24
Fatigue	26	21
Dyspnea	25	20
Fever	18	18
Constipation	14	17
Anorexia	18	15
Diarrhea	9	14
Dizziness	7	14
Granulocytopenia	13	12
Cough	15	11
Pulmonary carcinoma	14	11
Headache	8	10
Pain back	12	10
Pain limb	8	10
Alopecia	9	10
Pain abdominal	11	10
Paraesthesia	8	10
Pain chest	18	9

TREATMENT RELATED AE WITH AT LEAST A 1% INCIDENCE

Preferred terms	Placebo	Aranesp 2.5 mcg/kg/wk
n	159	155
	# pts reporting AE	# pts reporting AE
# pts reporting AE	5	8
Injection site pain	2	4
Nausea	1	2
Dizziness	0	1
Peripheral edema	1	1
Vomiting	1	1
Hypertension	1	1

Deaths: There were 22 deaths in the Aranesp and 19 in the placebo arm during the initial study period of 16 weeks. The causes are shown below by Body System and Preferred terms. Twenty five of the 41 deaths were attributable to progressive disease. No deaths were attributed [by site investigators) to epoetin or darbopoetin alfa.

CAUSES OF DEATH

	Placebo	Aranesp	total
N	159	155	314
Preferred term	Number of patients	Number of patients	Number of patients
Body as a whole	3	4	7
Metastatic neoplasm	1		
Sudden unexplained death	2		
Cardiovascular	2	1	3
Cardiac failure	1		
Circulatory failure	1		
Heart rate/ rhythm	1	0	1
Cardiac arrest	1		
Liver	0	1	1
Hepatic failure/hepatic neoplasm		1	
Myocardial	1	1	2
Coronary artery disorder		1	
Myocardial infarction	1		
Respiratory (tumor)	12	15	27
Cumulative	19	22	41

Withdrawals due to AE: Ten subjects withdrew from the Aranesp arm and 13 from the placebo due to AE; the most common reason was disease progression (11 of the 23).

Serious AE: There were 60 subjects or 39% of Aranesp arm and 58 subjects or 36% of the placebo arm who had serious AE. Only one subject, described below, had an SAE attributed to study drug.

- ✓ A 64 year old man with lower extremity ulcers related to heart disease noted a worsening of leg ulcers 8 days before study drug started. Fifteen days later he developed a rash and edema of extremities with a diagnosis of necrotic, ulcerative vasculitis. Symptoms/signs resolved in 7 days.

MOST FREQUENT SERIOUS AE

	Aranesp	Placebo
	% of subjects	% of subjects
Fever	7	6
Pulmonary carcinoma	7	8
Granulocytopenia	5	6
Metastatic neoplasm	6	3

All other SAE were below 1% incidence.

Antibody assays, biochemistry results and patients who exceeded either the maximum hgb value or the maximum rate of rise of hgb are discussed in the ISS.

Hypertension medications were initiated during the study in 19 (12%) of the patients in the Aranesp group and 13 (8%) of the placebo arm.

Hospitalization: In the placebo group 68% of patients were hospitalized; the mean number of hospital days was 19. Comparable data for the Aranesp treated patients were 66% hospitalized

with mean number of 15.7 hospitalized days. There were 291 hospitalization events listed (138 Aranesp and 153 placebo). The main causes of hospitalization events in order of frequency in the Aranesp arm were fever, granulocytopenia, metastatic disease, pulmonary carcinoma, dyspnea, pneumonia, confusion, fatigue, asthenia and anemia, and dizziness. Causes of hospitalization were essentially similar in the placebo arm.

Comments: The registration study shows a significant reduction in the number of subjects who needed transfusion of red blood cells compared to the placebo. Primary efficacy analysis showed 51% transfusion rate in the placebo arm vs 21 % in the Aranesp arm (Kaplan-Meier proportion) between week 5 and EOTP of study. Comparable figures for all 12 weeks of study were 60% and 26 % (see primary endpoint). There were consistent trends favoring Aranesp in supportive secondary endpoints such as hgb correction, time to hgb response, and change in hgb from baseline.

Problems within the study are the imbalance for subjects with hgb > 11.0 g/dL hgb and a relatively high dropout rate (Section L, ISS). These issues do not critically compromise the significance of the results.

APPEARS THIS WAY ON ORIGINAL

SECTION K

INTEGRATED SUMMARY OF SAFETY (ISS)

The initial submission in September 2001 included 781 patients in 5 major studies who received Aranesp and concomitant chemotherapy. A later update added another 92 patients to the safety database from protocol 20000174 for a total of 873 NESP- exposed, concomitant chemotherapy subjects plus another 102 patients from protocol 990111 who received Aranesp but were not on chemotherapy. The information presented in this section is all updated to the most recent safety dataset of 873 patients.

The mean observation period for the majority of subjects was 12 weeks on treatment plus 4 succeeding weeks off treatment. There was a longer term follow-up for survival and disease progression for 12 months on 314 patients in protocol 980297.

Initial submission 9/18/01	781 received Aranesp 85 received rHuEPO 221 received placebo	157 subject years
Update 3/3/02	873 received NESP 115 received rHuEPO 221 received placebo	177 subject years

Most patients had received several cycles of prior chemotherapy; for example in pivotal study 980297 the percent of patients with prior chemotherapy (mean # courses) was 91% (3.3 courses) & 94% (3.5 courses) for the placebo and Aranesp 2.25 mcg/kg patients respectively. All of the patients in the safety database were scheduled to receive at least 12 weeks of cyclic chemotherapy concomitant with the Aranesp except for those in protocol 990111 (anemia of cancer).

For all patients the maximum thresholds for hgb were 14 g/dL for women and 15 g/dL for men during the 12 week study period. Persons who exceeded those doses had drug withheld until the hgb was 13.0 g/dL hgb or less and then resumed at a decreased dose. The sponsor initially attempted to achieve a uniform policy with regards to transfusions and later changed to recommendations which are quoted from the 980297 pivotal study below. It is noted that one of the sensitivity analyses (ISE section) imputed transfusion to all patients who had a hgb at anytime below 8.0 g/dL; the comparative significance of the results did not change.

Sponsor recommendations for RBC transfusion

"RBC transfusions were recommended if a subject's hemoglobin concentration decreased to 8.0 g/dL. Subjects with hemoglobin concentrations > 8.0 g/dL could receive a RBC transfusion if signs or symptoms of anemia (eg, lethargy, congestive heart failure, angina, or dyspnea) were present".

Major safety review areas included:

- AE, deaths and withdrawals from study
- Serious adverse events (SAE)
- Adverse events of historical & special interest/higher risk
- Rate of rise of hgb and AE
- Maximum level of hgb and AE
- Antibody to Aranesp
- Relapse and survival in the protocol 980297 follow-up group
- Relationship/lack of between dose of Aranesp and toxicity

Demographics and clinical features: Forty percent of Aranesp-exposed patients (n= 873) were male. The female preponderance was probably related to the high number of breast cancer subjects. Race distribution was 88% Caucasian, 5% Hispanic, 4% Black. Sixty two percent of subjects had grade IV, 21 % grade III, 10% grade I or II disease and 7% were other or unclassified at entry to study. The major solid tumors were breast cancer 21%, ovarian cancer 10%, non-small cell lung cancer 23%.

Protocol 20000174 additional safety data : An interim report on safety was provided for protocol 20000174 which is a phase 2 study of 4 different dose-schedule combinations utilizing a fixed dose of rHuEPO as control arm. Only safety data was collected from this study. To be enrolled a patient had to have a hgb of 11.0 or less, and be receiving or about to received cyclic chemotherapy, ECOG had to be 0-2, and subjects had to have adequate organ function on laboratory studies. Approximately 30 subjects were randomized to each group. Treatment phase was 12 weeks followed by 4 weeks of follow up. [The endpoint was proportion of patients who had a hgb response (an increase in hgb of 2.0 g/dL or > in absence of transfusion. Transfusion was recommended if hgb < 8.0.]

Protocol 990174				
Title: A Dose-and Schedule-Finding Study of NESP for the Treatment of Anemia in Subjects with Solid Tumors Receiving Chemotherapy				
Experimental design: Randomized, active control study of four different dose and administration schedule cohorts of SC Aranesp. This study was only analyzed for safety data. There were 92 Aranesp patients randomized approximately equally between the 3 Aranesp arms and 30 active arm Procrit subjects.				
Period of study	Sites	Study arms/cohorts, dose and number patients	Study Objective(s)	Study Results
Ongoing	Multiple	<u>Study arms</u> Aranesp 4.5 mcg/kg/wk to hgb 12; then 1.5 mcg/kg/wk to wk 12 Aranesp 4.5 mcg/kg/wk x 4 wks; then 2.2.5 mcg/kg/wk x 8 wks Aranesp 4.5 mcg/kg/wk x 4 wks; then 3.0 mcg/kg/Q2W x 8 wks Procrit 40000 U/wk x 12 wks	Safety of Aranesp at different schedules/doses	Ongoing study

Overall incidence of AE, deaths and discontinuations from therapy because of AE at different doses: The incidence of AE (regardless of relationship to agent) was similar in the placebo (94%), rHuEPO (97%) and Aranesp (97%) populations. Deaths on study, defined as any death event within 30 days of a dose of study drug, were also similar [placebo 10%, rHuEPO 13% and Aranesp 9%].

There was no association between the Aranesp administration schedule (QW, Q2W, Q3W) and dose intensity with the incidence of the major events listed below (see Table below: Comparative Incidence of AE in ISS). The exception was the incidence of premature discontinuation of therapy observed for AE in the Aranesp 3.0 mcg/kg/wk or > subset (11%) as compared to patients receiving Aranesp at doses < 3.0 mcg/kg (see table below). The different protocol sources of the data of different dose intensity confounds interpretation of results (further comments on page 52).

Review of the reasons for discontinuation indicated the major causes were death and progression of malignant disease. Reasons other than disease progression/ death AE leading to premature discontinuation had an incidence of 1% or less for any single Preferred term.

COMPARATIVE INCIDENCE OF ADVERSE EVENTS IN ISS

	Placebo	RHuEPO	ARANESP in mcg/kg/week			
			< 2.0	2.0 to < 3.0	= to or > 3.0	All
Number	221	115	160	313	400	873
	Number (%)					
AE all ¹	208 [94]	112 [97]	158[99]	300 [96]	393 [98]	851 [97]
Severe AE ¹	90 [41]	53 [46]	66 [41]	143 [46]	195 [49]	404 [46]
Serious AE ¹	82 [37]	43 [37]	45 [28]	116 [37]	154 [39]	315 [36]
Treat AE ²	14 [8]	6 [5]	21[13]	30 [10]	47 [12]	98 [11]
Severe AE ²	2 [1]	0	1[1]	5 [2]	5 [1]	11 [8]
Serious AE ²	0	0	2 [1]	1 [0]	3 [1]	6 [1]
DCd-AE ³	12 [5]	8 [7]	9 [6]	17 [5]	43 [11]	69 [8]
Deaths	24 [11]	14[12]	13[8]	31[10]	44 [11]	88[10]

¹ regardless of relationship to study agent ² treatment related AE

³ Discontinuations due to AE

Severe AE are defined as severe or life threatening. Serious AE are as per FDA definition.

Source is Table 5-10, 120-day Safety Update, Amgen

AE of all grades: The table below lists adverse events of all grades in order of frequency regardless of relationship to study agent when found in greater than a 5% incidence. The majority of AE reported appeared to be related to the cancer study population. Those which could be agent related included fatigue, fever, anorexia, and possibly gastrointestinal complaints; they were all mild and have been observed with epoetin alfa. There was no evidence of serious allergic reactions on or close to the time of administration of Aranesp. The incidence of edema and diarrhea are higher in both EPO and Aranesp arms and may be related to erythropoiesis-stimulating agents.

AE REGARDLESS OF RELATIONSHIP TO STUDY AGENT AT INCIDENCE OF 5% OR MORE IN ISS POPULATION

	Placebo	rRHuEPO	All Aranesp*
n=	216	114	873
	%	%	%
All AE	94	98	98
Application site	3	3	6
Nausea	38	35	37
Fatigue	30	26	33
Vomiting	28	18	27
Diarrhea	12	23	22
Dyspnea	24	22	21
Edema, peripheral	8	18	16
Edema	1	0	5
Fever	16	20	19
Constipation	17	16	18
Anorexia	18	18	18
Pain abdominal	23	18	17
Asthenia	16	16	16
Pain back	14	14	15
Dizziness	8	12	14
Arthralgia	6	17	13
Headache	9	12	12

Insomnia	8	13	11
Pain chest	14	9	10
Upper resp. infection	7	7	9
Cough	13	15	9
Pain skeletal	10	8	9
Paraesthesia	7	4	7
Myalgia	5	6	8
Pain	5	12	8
Rash	3	7	7
Dehydration	3	12	5
Dyspepsia	4	9	6
Infection urinary tract	3	4	6

Source is table 5-10, 120-day Safety Update, Amgen, reviewed by CBER
 AE with 5% or > disparity between placebo and Aranesp were bolded

* Patients exposed to Aranesp who received concomitant chemorx.

Serious adverse events (SAE): The reported overall incidence of serious adverse events was not substantially different between Aranesp, placebo, and rHuEPO arms [see table. Comparative incidence of AE in ISS, above]. The most frequent SAE were death 10%, fever 4%, pneumonia 3%, dehydration 3%, vomiting 2%, dyspnea 2%. There were 5 possibly or probably treatment-related SAE reported in the Aranesp as opposed to none in placebo or rHuEPO groups; they included an allergic reaction, a cerebrovascular disorder, dyspnea, edema of the tongue, peripheral edema and skin ulceration and hypertension. Four of the five were in patients who received > 3.0 mcg/kg/wk who comprised 400 patients of the 873 Aranesp-treated chemotherapy patients. Among the treatment related AE, the hypertension, edema and cerebrovascular events could have been related to Aranesp in that they are consistent with the "historical AE (see below) and AE explored in the " special analysis" (see below) for erythropoiesis-stimulating agents..

Dose reductions: The protocol required dose reductions for rise of hgb equal to or > 2.0 g/dL in 28 days. These reductions were reported in 19 (12%) Aranesp subjects and 3 (2%) placebo subjects. Dose reductions for reasons not stated in protocol were found in 9 (6%) Aranesp subjects and in 6 (4%) placebo subjects.

Adverse events observed across erythropoietic –stimulating agents: Hypertension, seizures/convulsions and thrombotic events are the AE observed in the historical use of erythropoiesis-stimulating agents; they are listed as Warnings in the package insert for epoetin alfa and darbopoetin alfa. Data for the ISS and registration study showed limited numbers of these events. Convulsions were rare with an incidence below 1%. Fifteen reports of a Preferred term AE for hypertension are found in registration protocol 980297; the hypertension was severe in only 2 subjects with one subject from each study arm; neither was an SAE. Durations were 9 and 6 days respectively.

INCIDENCE OF HISTORICAL AE

	ISS			Protocol 980297	
	Aranesp	placebo	EPO	Aranesp	Placebo
N	862	217	113	155 ¹	159 ¹
	%	%	%	no. (%)	no. (%)
Hypertension+	3.7	3.2	2	9 (6%)	6 (4%)
Convulsions+	0.6	0.5	1	0	1 (1%)
Thrombotic +events	6.2	4.1	1	7 (5%)	5(3%)

+Hypertension included preferred terms Hypertension and Hypertension aggravated

Convulsions included the Preferred terms Convulsions, Convulsions Grand Mal and Convulsions Local

Thrombosis includes Preferred terms Thromboembolism, Thrombophlebitis Deep, Thrombosis, Thrombosis Venous, Thrombosis Venous Deep, and Pulmonary Embolism

Source was Table 5-15, 120-Day Safety Update, Amgen

¹ There were 314 protocol 980297 patients who received the study drug; 156 Aranesp and 158 placebo. A single patient enrolled on the Aranesp arm failed to receive the study drug. In the primary analysis he remained in the Aranesp arm to which he had been randomized but for Safety studies he was analyzed in the placebo arm explaining the n of 155 and 159.

Higher doses of Aranesp and AE: Inspection of data noted a trend to higher incidence of thrombotic events in Aranesp-treated subjects who received > 3 mcg/kg of Aranesp. The results were an incidence of 9% Thrombotic events in subjects who received over 3.0 mcg/kg of Aranesp (n= 394), 4 % in those who received 2- <3 mcg/kg (n= 311) and 3% in subjects who received below 2.0 mcg/kg of Aranesp (n= 157). When the > 3 mcg/kg population was further divided into progressive dose subsets, the very highest dose ranges did not show a dose effect (see attachment two-table 20) for incidence of hypertension, seizures or thrombotic events. Comparisons are confounded by the different dose administration patterns in different studies. The highest dose subsets were drawn largely from patients who received Aranesp or placebo every two or three weeks as opposed to the majority of the data which was from weekly dosed subjects. The question of the safety of doses of Aranesp above 3.0 mcg/kg for thrombotic events should be considered in greater detail if higher doses of Aranesp are considered for future licensing schedules.

Rate of Rise [ROR] of hgb:

In the initial licensing studies of Aranesp for chronic renal disease CBER performed analyses which calculated the incidence of AE as a function of the rate of rise of hgb/week. The results showed a higher risk of hypertension, pulmonary edema, vascular thrombosis, cardiac ischemia and infarction, cardiac arrest, and TVA (thrombovascular accidents) with rapid ROR of hgb. There was also increased risk in subjects for fluid overload, myocardial infarction [MI] and seizures. Prior to submission CBER and Amgen agreed to provide a similar "special analysis" in the cancer supplement—see attachment 1. CBER requested analysis for death, hypertension, cerebrovascular events (seizures, TIAs, "strokes"), cardiovascular events (MI, CAD, arrhythmia, angina, CHF, cardiac failure, cardiac arrest), thrombotic events related to vasculature, ischemic and peripheral vascular disease and pulmonary edema, pneumonia, infections and access infections as a function of ROR. Data from the same analysis of the relationship between ROR of hgb and AE in renal disease done earlier is seen below on the left and comparable figures from the current cancer patient analyses performed in the same manner are shown to the right.

In summary, the data show that the current cancer study group had a higher incidence of hypertension, vascular thrombosis, and ischemic infarction in patients correlated with a more rapid rate of rise of hgb in both chronic renal failure and cancer. No events were reported in the cancer subjects for cardiac arrest and myocardial infarction and the differences in rate of events for fluid overload as a function of ROR are not dramatic.

RATE OF RISE OF HGB AND AE /WEEK PER 1000 EVENTS

<i>AE grouping</i>	<i>Renal disease</i>			<i>Cancer indication</i>		
Rate of Rise in hgb/week	< 0.1	0.5 to 1.0	1.0 or >	< 0.1	0.5 to , 0.67	0.67 or >
Hypertension ³	7.5	19.9	13.1	2.1	1.8	5.2
Seizures ³	0.4	1.0	1.9	1.1	0	1.3
Vasc. Thrombosis,	1.7	3.8	7.5	1.1	7.1	3.9

ischemia, infarction ³						
Fluid overload ³	15.4	18.9	35.4	25.6	26.5	29.1
Cardiac arrest	0.0	1.0	1.9	No events reported		
MI, acute ³	0.4	0.3	1.9	No events reported		
Pulmonary edema ^{1,3}	1.5	3.1	7.5	No comparable category reported		

Source is Table 36 of Medical Officer Report on Aranesp for treatment of anemia associated with chronic renal failure and current submission

¹ Listed as CHF, abnormal ejection fraction, pulmonary edema: ² Listed as fluid overload; edema, dyspnea, orthopnea, pleural effusion

³ Data are Events/1000 weekly hgb observations

Other analyses of relationship between ROR of hgb and AE: In the first table the fraction of the study population who had a rapid ROR of hgb is shown. The second table shows the incidence of historical AE occurring within 14 days in those individuals who had a rapid ROR of hgb. No difference between the study arms was apparent. The third table below compares a wider group of selected AE in subjects with NO rapid ROR to subjects with YES, i.e. a rapid ROR. No differences of significance are noted.

RATE OF RISE OF HGB AND AE – AMGEN ANALYSIS (> 2 g/dL incr. Hgb in 28 days)

	Placebo	rHuEPO	NESP
n	221	115	873
Rapid ROR hgb Number pts [%]	45[20%]	52[45%]	378[43%]

**INCIDENCE OF HISTORICAL AE OCCURRING WITHIN 14 DAYS OF RAPID ROR OF HGB-
[Amgen analysis]**

	Number pts	Number pts	Number pts
n	221	115	873
Hypertension within 14 d	5	0	12
Convulsions within 14d	0	0	2
Thrombosis within 14d	5	2	14

**COMPARISON OF AE IN POPULATIONS WITH & WITHOUT RAPID ROR OF HGB
[Amgen analysis]**

	NO Rapid rate of rise of Hgb	YES Rapid rate of rise of Hgb
n	717	475
Hypertension	22[3%]	19[4%]
Arrhythmia	60[8%]	32[7%]
Coronary artery disease	14[2%]	7[1%]
CHF	16[2%]	5[1%]
Cerebrovascular, Accident	7[1%]	3[1%]
Cardiac arrest	1[<1%]	0[0%]
Fluid overload	270[38%]	159[33%]
Myocardial infarct	3[<1%]	2[<1%]
Siezuers	5[1%]	1[<1%]
Vascular thrombosis & ischemia/infarction	44[6%]	28[6%]

Maximum level of hgb and AE: The protocol used maximum hgb thresholds of 14.0 g/dL for women and 15.0 for men. The first table below presents the number and % of "historical" AE occurring in the each study population in patients who exceeded the maximum hgb threshold if the event happened within 14 days of the time threshold was exceeded. The second table examines the overall incidence during the treatment period of AE in subjects who did and did not exceed the maximum threshold. No major disparities are noted. It is noted that hypertension was higher in the Aranesp population (3rd table below) [source was Amgen report].

**INCIDENCE OF AE BY STUDY ARM IN PATIENTS > MAXIMUM HGB THRESHOLD
(Amgen analysis)**

	Placebo	rHuEPO	Aranesp
n	221	115	873
Number subjects exceeding max threshold [%]	4/221 (2%)	16/115 (14%)	114/873 (13%)
	Number pts	Number pts	Number pts
Hypertension within 14d*	0	0	4
Convulsions within 14d*	0	0	0
Thrombosis within 14d	1	0	3

Maximum threshold was 14 g/dL hgb for women and 15 g/dL hgb for men.

* Event occurring within 14 days + or - or exceeding maximum threshold

**INCIDENCE OF SPECIFIC AE IN PATIENTS EXCEEDING MAXIMUM HGB THRESHOLD
REGARDLESS OF STUDY ARM & REGARDLESS OF TIME OF OCCURRENCE
(Amgen analysis)**

	NO Max.threshold not reached	YES Max.threshold reached
N	1074	134
Hypertension	33[3%]	8[6%]
Arrhythmia	85[8%]	7[5%]
Coronary Artery Disease	18[2%]	3[2%]
CHF	22[2%]	2[1%]
Cerebrovasc. Accident	9[1%]	1[1%]
Cardiac arrest	2[<1%]	0
Fluid overload	388[36%]	42[31%]
MI	5[<1%]	0
Seizure	5[<1%]	1[1%]
Vascular thrombosis, ischemia, infarction	67[6%]	5[4%]

Exploratory analysis of AE groupings of Preferred Terms-CBER analysis

Amgen used groups of related preferred terms as shown in the table below for certain of their safety analyses for rapid rate ROR and patients who exceeded hgb threshold. The Preferred Terms for two groupings, thrombosis and fluid overload, were selected for further analysis by examining the incidence of AE for both the individual Preferred Terms and the group to ascertain if important disease relationships could be lost in the grouping pattern. The dataset used for the analysis by CBER was the updated ISS adverse event dataset submitted March 1, 2002.

AE GROUPS ANALYZED BY PREFERRED TERMS

Name of Group composed of related Preferred terms	Preferred terms in Group
Thrombosis	Embolism, pulmonary Thromboembolism Thrombophlebitis Thrombophlebitis, deep Thrombosis, venous Thrombosis, venous deep Thrombosis
Fluid Overload	Fluid overload Edema Dyspnea Orthopnea Pleural effusion Edema dependent Edema face Edema periorbital Edema peripheral Edema, circumoral Edema, genital Edema, tongue

Source ISS, 9/18/02, Appendix 3

When the individual Preferred terms for thrombosis were separately evaluated, sharp differences were noted. In the first table below the incidence of the combined Preferred Terms showed no major differences between study arms. This was attributable to the large number of venous events and their similar incidence in the study arms. In contrast, pulmonary emboli and related thromboembolism were restricted entirely to the Aranesp subjects. Thrombophlebitis, thrombophlebitis deep, and thrombosis showed a similar trend. It was concluded that pulmonary emboli in particular as well as related thrombophlebitis and the less clearly defined thrombosis could be at a higher risk in Aranesp subjects.

INCIDENCE OF PREFERRED TERMS IN THROMBOSIS GROUP

AE data are from all 7 studies including interim data from study 990174

Preferred term	All patients* N=1311 Number of patients (%)	rHuEPO N=115 Number of patients (%)	Aranesp N=975 Number of patients (%)	Placebo N=221 Number of patients (%)
Embolism, pulmonary	11 (0.8)	0	11 (1.1)	0
Thromboembolism	1 (0.1)	0	1 (0.1)	0
Thrombophlebitis	4 (0.3)	0	4 (0.4)	0
Thrombophlebitis, deep	3 (0.2)	0	2 (0.2)	1 (0.4)
Thrombosis, venous	12 (0.9)	2 (1.7)	9 (0.9)	3 (1.4)
Thrombosis, venous deep	44 (3.4)	4 (3.4)	27 (2.8)	11 (5.0)
Thrombosis	6 (0.5)	0	6 (0.6)	0
Total AE observed	81 (6.3)	6 (5.2)	60 (6.3)	15 (6.8)

CBER analysis of 11 Aranesp-exposed subjects with pulmonary emboli:

The incidence of pulmonary emboli was studied further. There were eleven patients with emboli during the treatment period and a 12th who reported a pulmonary embolus during the initial level of hgb at baseline, or malignant disease. The administrative pattern, ROR of hgb and the timing of the pulmonary emboli are shown in the table below. The data suggest that the rapid rise in hgb could be a contributory factor in at least three of the subjects (10101144, 12506009, and 16049012).

FURTHER ANALYSIS OF PULMONARY EMBOLI

Pulm.emboli Subjects	Dose schedule Aranesp	Dose ug/kg	Week of AE	Rapid ROR hgb	Week rapid ROR hgb	Max. incr. Hgb g/dL	Max. hgb ug/dL
10101144	QW	4.5	4	Yes	4	3.1	13.7
10116003	QW	1.0	3	No	na	2.8	13.9
12003012	Q3W	12.0	3	No	na	6.5	15.5
12502021	Q3W	9.0	1	Yes	11	4.4	14.2
12506009	Q3W	9.0	1	Yes	1	0.7	11.3
12609001	Q3W	4.5	11	Yes	17	4.5	12.6
12610013	Q3W	9.0	3	Yes	23	1.6	12.9
13035204	QW	2.25	16	Yes	10 on	6.3	14.3
13044102	QW	2.25	*	Yes	5 & 6	3.7	13.0
11109009	QW	2.25	9	Na	na	0.7	10.0
16049012	QW	2.25	5	Yes	5	2.9	12.0
12613008	Q3W	15.0	20	na	na	na	na

CBER analysis of fluid of fluid overload and AE: There was a higher incidence of edema and peripheral edema found for both Epoetin alfa and Darbopoetin alfa as compared to placebo. Analysis by individual Preferred term does differ from the combined group results. The two erythropoiesis –stimulating agents have a higher incidence than the the placebo arm.

ANALYSIS OF EDEMA AE BY PREFERRED TERM

Preferred term	All patients* N=1311	rHuEPO N=115	Aranesp N=975	Placebo N=221
	Number of patients (%)	Number of patients (%)	Number of patients (%)	Number of patients (%)
Edema peripheral	193 (14.7)	21(18.2)	151(15.5)	21(9.5)
Edema	51(3.9)	0	48(4.9)	3(1.4)
Edema circumoral	1(0.1)	0	1(0.1)	0
Edema face	8(0.6)	0	6(0.6)	2
Edema genital	2(0.2)	0	2(0.2)	0
Edema periorbital	10(0.8)	0	10(1.0)	0
Edema tongue	2(0.2)	0	2(0.2)	0
Fluid overload	3(0.2)	0	2(0.2)	1(0.5)
Pleural effusion	32(2.5)	0	28(2.9)	4(1.8)
Total AE	302(23)	21(18.2)	250 (25.6)	31((14.0)

Antibody testing: Serum for anti-Aranesp antibody testing was collected at baseline and at the end of study visit. The RIP screening assay used a rabbit polyclonal anti-Aranesp antibody. A

serum was considered positive if the assay counts per minute (cpm) were 2 or more times greater than the baseline value for the same subject. Sensitivity is given below when available.

- Radioimmunoprecipitation [RIP]—screening sensitivity 10 ng/ml
- Cell based bioassay—neutralizing/blocking- detection sensitivity 2.4 ug/ml
- Biacore confirmatory assay

Antibody testing of sera was by a radioimmunoprecipitation [RIP] assay and a bioassay. If a positive serology was detected, the sample was studied in the Biacore assay as a confirmatory test. There were three patients with positive serology by RIP. None of the three patients had a positive test by the Biacore assay and were considered by Amgen to be false positive reactions.

Patient 12610016 in protocol 980291 (Q3W administration of Aranesp) is of particular interest. At week 19 the patient had a positive result on RIP, a positive result (neutralizing antibodies) in the bioassay and a negative Biacore result. Hgb determinations in this patient were baseline 10.2 g/dL; week 19, 12.6 g/dL hgb; week 30 12.9 g/dL of hgb.

ANTIBODY TESTING

	Placebo	RHuEPO	Aranesp all
Assays	681	0	2392
Subj. tested	211	0	833
Subj. not tested	10 (5%)	115	38 (4%)
Positive on RIP	0	0	3

Disease progression and survival in the ISS study group:

The effect of darbopoetin on tumor biology and specifically tumor progression was evaluated in the ISS population at up to 30 days after the last dose of study agent. There were no significant differences observed between the placebo arm and epoetin or darbopoetin arms. It is noted that the rHuEPO pooled study group of 115 contained different rHuEPO regimens and must be interpreted with caution. In the Aranesp dose subsets of differing dose intensity there is no significant difference for either death or progression free survival.

DEATHS & DISEASE PROGRESSION IN ISS STUDY SUBJECTS

	Placebo	EPO	ARANESP			
			<2 mcg/kg/wk	2-<3 mcg/kg/wk	= to or >3 mcg/kg/wk	all
n	221	115	160	313	400	873*
Subjects who died by 30 days after last dose study agent [%]	24 [11%]	14 [12%]	13 [8%]	31 [10%]	44 [11%]	88 [10%]
Subjects with disease progression by 30 days after last dose study agent [%]	80 [36%]	42 [37%]	41 [26%]	82 [26%]	135 [34%]	258 [30%]

- Data from study 990111 was not included

Disease progress and survival in protocol 980297 with longer term follow-up: Follow up data (median one year) data was collected. There is no indication that Aranesp therapy increased the rate of tumor growth; the trend is in the opposite direction. When data was incomplete as to month, day or year data was imputed either by taking the midpoint between the two dates or the 15th for missing day.

DEATHS IN PIVOTAL PROTOCOL 980297 STUDY SUBJECTS

	Placebo	Aranesp
	N=159	N=155
Disease progression		
All subjects/# subjects in study arm (%)	129 (81%)	117 (75%)
Complete data	119	108
Imputed data	10	9
Death		
All subjects/# subjects in study arm (%)	109 (69%)	92 (59%)
Complete data	108	86
Imputed data	1	6
Disease Progression/death		
All subjects/# subjects in study arm (%)	129 (83%)	141 (89%)
Complete data	127	138
Imputed data	2	3

SECTION M

ATTACHMENTS

Analyses requested by CBER from Amgen

Attachment One - compilation of all AE of historical interest and special interest (cardiovascular, cerebrovascular, fluid balance, thrombotic events, hypertension) as a function of the rate of rise of hgb with particular interest in rates of rise of hgb > 0.5 g/dL/week. Source in EDR is submission of 9/18/01, Clnistat, ISS, pages 1004 to 1033.

Attachment Two - compilation of all AE of historical interest and special interest as a function of the dose of Aranesp with further division/breakdown of doses > 3 ug/kg. Source in EDR is submission of 3/29/02, Tables 18-21

Attachment Three – number of transfusions showing hemoglobin values within past 7 days of transfusion divided by study arms and the indication for transfusion stated by site physician on case report form.

Attachment Four- statistical analysis of nine subinvestigators with possible conflict of interest by recalculating data without those subjects in the study arms.

APPEARS THIS WAY ON ORIGINAL

Appendix 3. Preferred Terms Included in the Cardiovascular
and Thromboembolic Analyses

Adverse Event Category	Preferred Terms Included
Hypertension	Hypertension
Fluid Overload	Fluid Overload Edema Dyspnea Orthopnea Pleural Effusion Edema Dependent Edema Face Edema Periorbital Edema Peripheral Edema Circumoral Edema Genital Edema Tongue
CHF	Edema Pulmonary Cardiac Failure Ejection Fraction Abnormal Circulatory Failure Cardiomyopathy
CVA	Cerebrovascular Disorder Cerebral Ischemia Hemorrhage Intracranial Hemorrhage Cerebral Hemorrhage Subarachnoid Transient Ischemic Attack Carotid Stenosis
Seizure	Convulsions Convulsions Grand Mal Convulsions Local
Myocardial Infarction	Myocardial Infarction
Cardiac Arrest	Cardiac Arrest
Arrhythmia	Arrhythmia Any High Level Term = Arrhythmia
CAD	Angina Pectoris Coronary Artery Disorder Myocardial Ischemia Pain Chest (Myo/Endo/Pericardial) Arteriosclerosis Atherosclerosis

(continued)

Preferred Terms Included in the Cardiovascular
and Thromboembolic Analyses (Continued)

Adverse Event Category	Preferred Terms Included
Vascular Thrombosis/Ischemia/Infarction	Arterial Occlusion (1) Claudication (4) Gangrene (3) Necrosis Ischemia (3) Peripheral Ischemia (3) Embolism Arterial (2) Thrombophlebitis (1) Thrombosis Arterial (1) Thrombosis Venous (1) Thrombosis Venous Deep (1) Intestinal Ischemia (3) Embolism Pulmonary (1) Thrombophlebitis Deep (1) Thromboembolism (1)
(1) thrombosis of vasculature (2) emboli (originated from injured vasculature) (3) vascular ischemia (4) exacerbation of peripheral vascular disease	
Analyze as a group and as subgroups	

Appendix 4. Analyses Requested by CBER

The relationship between adverse event groups of concern (death, hypertension, cardiac events, cerebrovascular events, and thrombotic events) and both the rate of change in hemoglobin and hemoglobin concentrations were analyzed using the methodology requested by CBER in the Biologic License Application for the use of NESP in patients with chronic renal failure.

Adverse events were combined by common underlying pathophysiologic mechanisms into 10 event groups. The preferred terms that comprise each event group are listed in Appendix 3. In addition, all fatal events were combined into 1 event group. Weekly hemoglobin values were classified within 1-g/dL categories and by quintiles. The categories were defined as follows: ≤ 10 , > 10 to 11, > 11 to 12, > 12 to 13, > 13 to 14, and > 14 g/dL. Hemoglobin quintiles spanned the following ranges: < 9.4 , 9.4 to < 10.3 , 10.3 to < 11.1 , 11.1 to < 12.1 , and ≥ 12.1 g/dL. Mean hemoglobin was used for weeks with more than 1 measurement.

The slope of hemoglobin concentrations was calculated using hemoglobin values obtained over a 2-week period (ie, including 3 hemoglobin values) using a least-squares method (eg, hemoglobin values from weeks 5, 6, and 7 were used to calculate the slope at week 7). Missing hemoglobin values were not interpolated. When slopes could not be calculated over 2-week intervals, slopes were calculated over a 3-week period, if possible. Positive and negative slopes were classified separately; slopes of 0 were classified with the positive slopes. The positive slopes of hemoglobin were categorized into the following ranges: 0 to 0.1 g/dL/week, > 0.1 to 0.2 g/dL/week, > 0.2 to 0.25 g/dL/week, > 0.25 to 0.333 g/dL/week, > 0.333 to 0.5 g/dL/week, > 0.5 to 0.667 g/dL/week, and > 0.667 g/dL. The negative slopes were categorized in a similar manner.

Based on the study week of the onset for each adverse event, the adverse events were linked to their associated hemoglobin category, quintile, and slope.

Within each event group, incidences were tabulated for each hemoglobin category, quintile, and slope range. Event rates were calculated by dividing the number of events by the number of hemoglobin values in each category and were presented as number of events per 1000 hemoglobin values (or slopes).

In addition to these analyses, the subject incidence of pneumonia, pulmonary edema, congestive heart failure, infection, and access infection was compared between the NESP, placebo, and rHuEPO groups.

The results of the analyses are provided in Tables 1 to 7.

Table 1. Cardiovascular Event Rates by Slope of Hemoglobin Increase
(All Chemotherapy Studies Analysis Set)

		Slope Category (g/dL/wk)							
		Unknown	0 to 0.1	> 0.1 to 0.2	> 0.2 to 0.25	> 0.25 to 0.333	> 0.333 to 0.5	> 0.5 to 0.667	> 0.667
Number of Hemoglobin Slopes	Placebo	604	226	134	132	80	216	142	393
	rHuEPO	200	95	56	42	38	106	66	147
	NESP	1758	937	620	557	349	1021	565	1546
	Total	2562	1258	810	731	467	1343	773	2086
Arrhythmia	Placebo	5.0	4.4	0.0	0.0	12.5	4.6	0.0	5.1
	rHuEPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	11.4	1.1	6.5	3.6	0.0	1.0	7.1	3.9
	Total	9.0	1.6	4.9	2.7	2.1	1.5	5.2	3.8
CAD	Placebo	0.0	0.0	0.0	0.0	0.0	4.6	0.0	0.0
	rHuEPO	5.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	1.7	2.1	0.0	3.6	2.9	0.0	1.8	1.3
	Total	1.6	1.6	0.0	2.7	2.1	0.7	1.3	1.0
CHF	Placebo	5.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	rHuEPO	5.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.6	0.0	1.6	3.6	0.0	1.0	3.5	0.6
	Total	2.0	0.0	1.2	2.7	0.0	0.7	2.6	0.5

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The data collected for these subjects in the open-label portion have been excluded.

Note: Event rates are presented in number of events per 1000 Hemoglobin Slope Values

Program: /stat/nesp/oric/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_slopehbinc.sas
Output: t_ae_cv_by_slopehbinc_rate.rtf (Date Generated: 28JUN2001:10:35)

Table 1. Cardiovascular Event Rates by Slope of Hemoglobin Increase
(All Chemotherapy Studies Analysis Set)

		Slope Category (g/dL/wk)							
		Unknown	0 to 0.1	> 0.1 to 0.2	> 0.2 to 0.25	> 0.25 to 0.333	> 0.333 to 0.5	> 0.5 to 0.667	> 0.667
CVA	Placebo	0.0	0.0	0.0	0.0	0.0	0.0	7.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.6
	Total	0.0	0.0	0.0	0.0	0.0	0.0	1.3	0.5
Cardiac Arrest	Placebo	1.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	rHuEPO	5.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Death (Any Cause)	Placebo	11.6	4.4	7.5	15.2	12.5	0.0	7.0	10.2
	rHuEPO	35.0	0.0	0.0	0.0	0.0	0.0	0.0	13.6
	NESP	17.1	3.2	3.2	0.0	2.9	2.0	3.5	7.8
	Total	17.2	3.2	3.7	2.7	4.3	1.5	3.9	8.6
Fluid Overload	Placebo	28.1	26.5	14.9	7.6	37.5	13.9	35.2	38.2
	rHuEPO	45.0	42.1	0.0	0.0	26.3	9.4	0.0	47.6
	NESP	45.5	25.6	30.6	28.7	22.9	32.3	26.5	29.1
	Total	41.4	27.0	25.9	23.3	25.7	27.6	25.9	32.1

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The data collected for these subjects in the open-label portion have been excluded.

Note: Event rates are presented in number of events per 1000 Hemoglobin Slope Values.

Program: /stat/nesp/nc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_slopehbinc.sas

Output: t_ae_cv_by_slopehbinc_rate.rtf (Date Generated: 28JUN2001:10:35)

Table 1. Cardiovascular Event Rates by Slope of Hemoglobin Increase
(All Chemotherapy Studies Analysis Set)

		Slope Category (g/dL/wk)							
		Unknown	0 to 0.1	> 0.1 to 0.2	> 0.2 to 0.25	> 0.25 to 0.333	> 0.333 to 0.5	> 0.5 to 0.667	> 0.667
Hypertension	Placebo	1.7	0.0	7.5	0.0	0.0	4.6	0.0	5.1
	rHuEPO	5.0	0.0	0.0	0.0	0.0	0.0	15.2	0.0
	NESP	1.1	2.1	3.2	3.6	5.7	2.9	1.8	5.2
	Total	1.6	1.6	3.7	2.7	4.3	3.0	2.6	4.8
Myocardial Infarction	Placebo	1.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Seizure	Placebo	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.0	1.1	1.6	0.0	0.0	0.0	0.0	1.3
	Total	0.0	0.8	1.2	0.0	0.0	0.0	0.0	1.0
Vascular Thrombosis/Ischemia/ Infarction	Placebo	1.7	0.0	7.5	0.0	12.5	0.0	21.1	2.5
	rHuEPO	10.0	21.1	0.0	23.8	26.3	0.0	0.0	6.8
	NESP	6.8	1.1	8.1	0.0	0.0	2.9	7.1	3.9
	Total	5.9	2.4	7.4	1.4	4.3	2.2	9.1	3.8

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion. The data collected for these subjects in the open-label portion have been excluded.

Note: Event rates are presented in number of events per 1000 Hemoglobin Slope Values

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_slopehbinc.sas
Output: t_ae_cv_by_slopehbinc_rate.rtf (Date Generated: 28JUN2001:10:35)

Table 1. Cardiovascular Event Rates by Slope of Hemoglobin Increase
(All Chemotherapy Studies Analysis Set)

		Slope Category (g/dL/wk)						
		Unknown	0 to 0.1	> 0.1 to 0.2	> 0.2 to 0.25	> 0.25 to 0.333	> 0.333 to 0.5	> 0.5 to 0.667
Thrombosis of Vasculature	Placebo	1.7	0.0	0.0	0.0	12.5	0.0	2.5
	rHuEPO	5.0	0.0	0.0	0.0	26.3	0.0	6.8
	NESP	6.8	1.1	8.1	0.0	0.0	2.9	3.9
	Total	5.5	0.8	6.2	0.0	4.3	2.2	3.8
Emboli (Originated from Injured Vasculature)	Placebo	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Vascular Ischemia	Placebo	0.0	0.0	0.0	0.0	0.0	0.0	7.0
	rHuEPO	5.0	21.1	0.0	23.8	0.0	0.0	0.0
	NESP	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	0.4	1.6	0.0	1.4	0.0	0.0	1.3
Exacerbation of Peripheral Vascular Disease	Placebo	0.0	0.0	7.5	0.0	0.0	0.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	0.0	0.0	1.2	0.0	0.0	0.0	0.0

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion. The data collected for these subjects in the open-label portion have been excluded.
Note: Event rates are presented in number of events per 1000 Hemoglobin Slope Values

Program: /sta/nasp/onc/meta/ISS/analysis/statfiles/programs/tables/_ae_cv_by_slopehbinc.sas
Output: _ae_cv_by_slopehbinc_rate.rtf (Date Generated: 28JUN2001:10:35)

Table 2. Cardiovascular Events by Slope of Hemoglobin Increase
(All Chemotherapy Studies Analysis Set)

		Slope Category (g/dL/wk)							
		Unknown	0 to 0.1	> 0.1 to 0.2	> 0.2 to 0.25	> 0.25 to 0.333	> 0.333 to 0.5	> 0.5 to 0.667	> 0.667
Number of Hemoglobin Slopes	Placebo	604	226	134	132	80	216	142	393
	rHuEPO	200	95	56	42	38	106	66	147
	NESP	1758	937	620	557	349	1021	565	1546
	Total	2562	1258	810	731	467	1343	773	2086
Arrhythmia	Placebo	3	1	0	0	1	1	0	2
	rHuEPO	0	0	0	0	0	0	0	0
	NESP	20	1	4	2	0	1	4	6
	Total	23	2	4	2	1	2	4	8
CAD	Placebo	0	0	0	0	0	1	0	0
	rHuEPO	1	0	0	0	0	0	0	0
	NESP	3	2	0	2	1	0	1	2
	Total	4	2	0	2	1	1	1	2
CHF	Placebo	3	0	0	0	0	0	0	0
	rHuEPO	1	0	0	0	0	0	0	0
	NESP	1	0	1	2	0	1	2	1
	Total	5	0	1	2	0	1	2	1

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The data collected for these subjects in the open-label portion have been excluded.

Note: Number of actual events are presented.

Program: /sta/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/_ae_cv_by_slopehbinc.sas

Output: _ae_cv_by_slopehbinc_cnt.rtf (Date Generated: 28JUN2001:10:35)

Table 2. Cardiovascular Events by Slope of Hemoglobin Increase
(All Chemotherapy Studies Analysis Set)

		Slope Category (g/dL/wk)							
		Unknown	0 to 0.1	> 0.1 to 0.2	> 0.2 to 0.25	> 0.25 to 0.333	> 0.333 to 0.5	> 0.5 to 0.667	> 0.667
CVA	Placebo	0	0	0	0	0	0	1	0
	rHuEPO	0	0	0	0	0	0	0	0
	NESP	0	0	0	0	0	0	0	1
	Total	0	0	0	0	0	0	1	1
Cardiac Arrest	Placebo	1	0	0	0	0	0	0	0
	rHuEPO	1	0	0	0	0	0	0	0
	NESP	0	0	0	0	0	0	0	0
	Total	2	0	0	0	0	0	0	0
Death (Any Cause)	Placebo	7	1	1	2	1	0	1	4
	rHuEPO	7	0	0	0	0	0	0	2
	NESP	30	3	2	0	1	2	2	12
	Total	44	4	3	2	2	2	3	18
Fluid Overload	Placebo	17	6	2	1	3	3	5	15
	rHuEPO	9	4	0	0	1	1	0	7
	NESP	80	24	19	16	8	33	15	45
	Total	106	34	21	17	12	37	20	67

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The data collected for these subjects in the open-label portion have been excluded.

Note: Number of actual events are presented.

Program: /sta/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_slopehbinc.sas

Output: t_ae_cv_by_slopehbinc_cnt.rtf (Data Generated: 28JUN2001:10:35)

Table 2. Cardiovascular Events by Slope of Hemoglobin Increase
(All Chemotherapy Studies Analysis Set)

		Slope Category (g/dL/wk)							
		Unknown	0 to 0.1	> 0.1 to 0.2	> 0.2 to 0.25	> 0.25 to 0.333	> 0.333 to 0.5	> 0.5 to 0.667	> 0.667
Hypertension	Placebo	1	0	1	0	0	1	0	2
	rHuEPO	1	0	0	0	0	0	1	0
	NESP	2	2	2	2	2	3	1	8
	Total	4	2	3	2	2	4	2	10
Myocardial Infarction	Placebo	1	0	0	0	0	0	0	0
	rHuEPO	0	0	0	0	0	0	0	0
	NESP	0	0	0	0	0	0	0	0
	Total	1	0	0	0	0	0	0	0
Seizure	Placebo	0	0	0	0	0	0	0	0
	rHuEPO	0	0	0	0	0	0	0	0
	NESP	0	1	1	0	0	0	0	2
	Total	0	1	1	0	0	0	0	2
Vascular Thrombosis/Ischemia/ Infarction	Placebo	1	0	1	0	1	0	3	1
	rHuEPO	2	2	0	1	1	0	0	1
	NESP	12	1	5	0	0	3	4	6
	Total	15	3	6	1	2	3	7	8

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The data collected for these subjects in the open-label portion have been excluded.

Note: Number of actual events are presented.

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/_lae_cv_by_slopehbinc.sas
Output: _lae_cv_by_slopehbinc_cnt.rtf (Date Generated: 28JUN2001:10:35)

Table 2. Cardiovascular Events by Slope of Hemoglobin Increase
(All Chemotherapy Studies Analysis Set)

		Slope Category (g/dL/wk)							
		Unknown	0 to 0.1	> 0.1 to 0.2	> 0.2 to 0.25	> 0.25 to 0.333	> 0.333 to 0.5	> 0.5 to 0.667	> 0.667
Thrombosis of Vasculature	Placebo	1	0	0	0	1	0	2	1
	rHuEPO	1	0	0	0	1	0	0	1
	NESP	12	1	5	0	0	3	4	6
	Total	14	1	5	0	2	3	6	8
Emboli (Originated from Injured Vasculature)	Placebo	0	0	0	0	0	0	0	0
	rHuEPO	0	0	0	0	0	0	0	0
	NESP	0	0	0	0	0	0	0	0
	Total	0	0	0	0	0	0	0	0
Vascular Ischemia	Placebo	0	0	0	0	0	0	1	0
	rHuEPO	1	2	0	1	0	0	0	0
	NESP	0	0	0	0	0	0	0	0
	Total	1	2	0	1	0	0	1	0
Exacerbation of Peripheral Vascular Disease	Placebo	0	0	1	0	0	0	0	0
	rHuEPO	0	0	0	0	0	0	0	0
	NESP	0	0	0	0	0	0	0	0
	Total	0	0	1	0	0	0	0	0

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The data collected for these subjects in the open-label portion have been excluded.

Note: Number of actual events are presented.

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_slopehblnc.sas
Output: t_ae_cv_by_slopehblnc_cnt.rtf (Date Generated: 28JUN2001:10:35)

Table 3. Cardiovascular Event Rates by Slope of Hemoglobin Decrease
(All Chemotherapy Studies Analysis Set)

		Slope Category (g/dL/wk)							
		Unknown	-0.1 to < 0	-0.2 to < -0.1	-0.25 to < -0.2	-0.333 to < -0.25	-0.5 to < -0.333	-0.667 to < -0.5	< -0.667
Number of Hemoglobin Slopes	Placebo	604	153	134	120	76	257	165	346
	rHuEPO	200	71	57	43	27	67	39	85
	NESP	1758	513	534	503	312	835	434	996
	Total	2562	737	725	666	415	1159	638	1427
Arrhythmia	Placebo	5.0	6.5	0.0	8.3	13.2	7.8	12.1	5.8
	rHuEPO	0.0	0.0	0.0	0.0	37.0	29.9	0.0	0.0
	NESP	11.4	5.8	9.4	8.0	0.0	7.2	4.6	8.0
	Total	9.0	5.4	6.9	7.5	4.8	8.6	6.3	7.0
CAD	Placebo	0.0	0.0	0.0	0.0	0.0	3.9	6.1	0.0
	rHuEPO	5.0	0.0	0.0	0.0	0.0	14.9	0.0	0.0
	NESP	1.7	1.9	1.9	2.0	0.0	2.4	2.3	5.0
	Total	1.6	1.4	1.4	1.5	0.0	3.5	3.1	3.5
CHF	Placebo	5.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	rHuEPO	5.0	0.0	0.0	0.0	0.0	0.0	0.0	11.8
	NESP	0.6	0.0	1.9	2.0	3.2	3.6	2.3	2.0
	Total	2.0	0.0	1.4	1.5	2.4	2.6	1.6	2.1

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion. The data collected for these subjects in the open-label portion have been excluded.

Note: Event rates are presented in number of events per 1000 Hemoglobin Slope Values

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_slopehbdec.sas
Output: t_ae_cv_by_slopehbdec_rate.rtf (Date Generated: 28JUN2001:10:36)

Table 3. Cardiovascular Event Rates by Slope of Hemoglobin Decrease
(All Chemotherapy Studies Analysis Set)

		Slope Category (g/dL/wk)							
		Unknown	-0.1 to < 0	-0.2 to < -0.1	-0.25 to < -0.2	-0.333 to < -0.25	-0.5 to < -0.333	-0.667 to < -0.5	< -0.667
CVA	Placebo	0.0	0.0	0.0	0.0	0.0	0.0	6.1	0.0
	rHuEPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.0	0.0	1.9	0.0	0.0	1.2	2.3	1.0
	Total	0.0	0.0	1.4	0.0	0.0	0.9	3.1	0.7
Cardiac Arrest	Placebo	1.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	rHuEPO	5.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Death (Any Cause)	Placebo	11.6	0.0	7.5	0.0	0.0	3.9	0.0	11.6
	rHuEPO	35.0	14.1	0.0	0.0	37.0	0.0	0.0	0.0
	NESP	17.1	3.9	1.9	2.0	3.2	8.4	0.0	9.0
	Total	17.2	4.1	2.8	1.5	4.8	6.9	0.0	9.1
Fluid Overload	Placebo	28.1	52.3	29.9	25.0	52.6	19.5	36.4	40.5
	rHuEPO	45.0	56.3	52.6	0.0	74.1	44.8	25.6	23.5
	NESP	45.5	40.9	30.0	33.8	41.7	39.5	36.9	46.2
	Total	41.4	44.8	31.7	30.0	45.8	35.4	36.1	43.4

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The data collected for these subjects in the open-label portion have been excluded.

Note: Event rates are presented in number of events per 1000 Hemoglobin Slope Values

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_slopehbdec.sas

Output: t_ae_cv_by_slopehbdec_rate.rtf (Date Generated: 28JUN2001:10:36)

Table 3. Cardiovascular Event Rates by Slope of Hemoglobin Decrease
(All Chemotherapy Studies Analysis Set)

		Slope Category (g/dL/wk)							
		Unknown	-0.1 to < 0	-0.2 to < -0.1	-0.25 to < -0.2	-0.333 to < -0.25	-0.5 to < -0.333	-0.667 to < -0.5	< -0.667
Hypertension	Placebo	1.7	0.0	0.0	8.3	0.0	7.8	6.1	2.9
	rHuEPO	5.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	1.1	1.9	5.6	0.0	0.0	0.0	2.3	5.0
	Total	1.6	1.4	4.1	1.5	0.0	1.7	3.1	4.2
Myocardial Infarction	Placebo	1.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.0	0.0	1.9	0.0	0.0	1.2	0.0	0.0
	Total	0.4	0.0	1.4	0.0	0.0	0.9	0.0	0.0
Seizure	Placebo	0.0	0.0	0.0	0.0	0.0	3.9	0.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0
	Total	0.0	0.0	0.0	0.0	0.0	0.9	0.0	0.7
Vascular Thrombosis/Ischemia/ Infarction	Placebo	1.7	0.0	0.0	8.3	0.0	3.9	6.1	8.7
	rHuEPO	10.0	0.0	0.0	0.0	0.0	14.9	25.6	0.0
	NESP	6.8	1.9	3.7	6.0	9.6	6.0	0.0	4.0
	Total	5.9	1.4	2.8	6.0	7.2	6.0	3.1	4.9

Page 3 of 4

Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The data collected for these subjects in the open-label portion have been excluded.

Note: Event rates are presented in number of events per 1000 Hemoglobin Slope Values

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_slopehbdec.sas

Output: t_ae_cv_by_slopehbdec_rate.tif (Date Generated: 28JUN2001:10:36)

Table 3. Cardiovascular Event Rates by Slope of Hemoglobin Decrease
(All Chemotherapy Studies Analysis Set)

		Slope Category (g/dL/wk)							
		Unknown	-0.1 to < 0	-0.2 to < -0.1	-0.25 to < -0.2	-0.333 to < -0.25	-0.5 to < -0.333	-0.667 to < -0.5	< -0.667
Thrombosis of Vasculature	Placebo	1.7	0.0	0.0	8.3	0.0	3.9	0.0	5.8
	rHuEPO	5.0	0.0	0.0	0.0	0.0	14.9	25.6	0.0
	NESP	6.8	1.9	3.7	6.0	6.4	6.0	0.0	4.0
	Total	5.5	1.4	2.8	6.0	4.8	6.0	1.6	4.2
Emboli (Originated from Injured Vasculature)	Placebo	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Vascular Ischemia	Placebo	0.0	0.0	0.0	0.0	0.0	0.0	6.1	2.9
	rHuEPO	5.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.0	0.0	0.0	0.0	3.2	0.0	0.0	0.0
	Total	0.4	0.0	0.0	0.0	2.4	0.0	1.6	0.7
Exacerbation of Peripheral Vascular Disease	Placebo	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Page 4 of 4

Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The data collected for these subjects in the open-label portion have been excluded.

Note: Event rates are presented in number of events per 1000 Hemoglobin Slope Values

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_slopehbdec.sas
Output: t_ae_cv_by_slopehbdec_rate.rtf (Date Generated: 28JUN2001:10:36)

Table 4. Cardiovascular Events by Slope of Hemoglobin Decrease
(All Chemotherapy Studies Analysis Set)

		Slope Category (g/dL/wk)							
		Unknown	-0.1 to < 0	-0.2 to < -0.1	-0.25 to < -0.2	-0.333 to < -0.25	-0.5 to < -0.333	-0.667 to < -0.5	< -0.667
Number of Hemoglobin Slopes	Placebo	604	153	134	120	76	257	165	346
	rHuEPO	200	71	57	43	27	67	39	85
	NESP	1758	513	534	503	312	835	434	996
	Total	2562	737	725	666	415	1159	638	1427
Arrhythmia	Placebo	3	1	0	1	1	2	2	2
	rHuEPO	0	0	0	0	1	2	0	0
	NESP	20	3	5	4	0	6	2	8
	Total	23	4	5	5	2	10	4	10
CAD	Placebo	0	0	0	0	0	1	1	0
	rHuEPO	1	0	0	0	0	1	0	0
	NESP	3	1	1	1	0	2	1	5
	Total	4	1	1	1	0	4	2	5
CHF	Placebo	3	0	0	0	0	0	0	0
	rHuEPO	1	0	0	0	0	0	0	1
	NESP	1	0	1	1	1	3	1	2
	Total	5	0	1	1	1	3	1	3

Page 1 of 4

Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion. The data collected for these subjects in the open-label portion have been excluded.

Note: Number of actual events are presented.

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_slopehbdec.sas
Output: t_ae_cv_by_slopehbdec_cnt.rtf (Date Generated: 28JUN2001:10:36)

Table 4. Cardiovascular Events by Slope of Hemoglobin Decrease
(All Chemotherapy Studies Analysis Set)

		Slope Category (g/dL/wk)							
		Unknown	-0.1 to < 0	-0.2 to < -0.1	-0.25 to < -0.2	-0.333 to < -0.25	-0.5 to < -0.333	-0.667 to < -0.5	< -0.667
CVA	Placebo	0	0	0	0	0	0	1	0
	rHuEPO	0	0	0	0	0	0	0	0
	NESP	0	0	1	0	0	1	1	1
	Total	0	0	1	0	0	1	2	1
Cardiac Arrest	Placebo	1	0	0	0	0	0	0	0
	rHuEPO	1	0	0	0	0	0	0	0
	NESP	0	0	0	0	0	0	0	0
	Total	2	0	0	0	0	0	0	0
Death (Any Cause)	Placebo	7	0	1	0	0	1	0	4
	rHuEPO	7	1	0	0	1	0	0	0
	NESP	30	2	1	1	1	7	0	9
	Total	44	3	2	1	2	8	0	13
Fluid Overload	Placebo	17	8	4	3	4	5	6	14
	rHuEPO	9	4	3	0	2	3	1	2
	NESP	80	21	16	17	13	33	16	46
	Total	106	33	23	20	19	41	23	62

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion. The data collected for these subjects in the open-label portion have been excluded.

Note: Number of actual events are presented.

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_slopehbdec.sas
Output: t_ae_cv_by_slopehbdec_cnt.rtf (Date Generated: 28JUN2001:10:36)

Table 4. Cardiovascular Events by Slope of Hemoglobin Decrease
(All Chemotherapy Studies Analysis Set)

		Slope Category (g/dL/wk)							
		Unknown	-0.1 to < 0	-0.2 to < -0.1	-0.25 to < -0.2	-0.333 to < -0.25	-0.5 to < -0.333	-0.667 to < -0.5	< -0.667
Hypertension	Placebo	1	0	0	1	0	2	1	1
	rHuEPO	1	0	0	0	0	0	0	0
	NESP	2	1	3	0	0	0	1	5
	Total	4	1	3	1	0	2	2	6
Myocardial Infarction	Placebo	1	0	0	0	0	0	0	0
	rHuEPO	0	0	0	0	0	0	0	0
	NESP	0	0	1	0	0	1	0	0
	Total	1	0	1	0	0	1	0	0
Seizure	Placebo	0	0	0	0	0	1	0	0
	rHuEPO	0	0	0	0	0	0	0	0
	NESP	0	0	0	0	0	0	0	1
	Total	0	0	0	0	0	1	0	1
Vascular Thrombosis/Ischemia/ Infarction	Placebo	1	0	0	1	0	1	1	3
	rHuEPO	2	0	0	0	0	1	1	0
	NESP	12	1	2	3	3	5	0	4
	Total	15	1	2	4	3	7	2	7

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The data collected for these subjects in the open-label portion have been excluded.

Note: Number of actual events are presented.

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_slopehbdec.sas
Output: t_ae_cv_by_slopehbdec_cnt.rtf (Date Generated: 28JUN2001:10:36)

Table 4. Cardiovascular Events by Slope of Hemoglobin Decrease
(All Chemotherapy Studies Analysis Set)

		Slope Category (g/dL/wk)							
		Unknown	-0.1 to < 0	-0.2 to < -0.1	-0.25 to < -0.2	-0.333 to < -0.25	-0.5 to < -0.333	-0.667 to < -0.5	< -0.667
Thrombosis of Vasculature	Placebo	1	0	0	1	0	1	0	2
	rHuEPO	1	0	0	0	0	1	1	0
	NESP	12	1	2	3	2	5	0	4
	Total	14	1	2	4	2	7	1	6
Emboli (Originated from Injured Vasculature)	Placebo	0	0	0	0	0	0	0	0
	rHuEPO	0	0	0	0	0	0	0	0
	NESP	0	0	0	0	0	0	0	0
	Total	0	0	0	0	0	0	0	0
Vascular Ischemia	Placebo	0	0	0	0	0	0	1	1
	rHuEPO	1	0	0	0	0	0	0	0
	NESP	0	0	0	0	1	0	0	0
	Total	1	0	0	0	1	0	1	1
Exacerbation of Peripheral Vascular Disease	Placebo	0	0	0	0	0	0	0	0
	rHuEPO	0	0	0	0	0	0	0	0
	NESP	0	0	0	0	0	0	0	0
	Total	0	0	0	0	0	0	0	0

Page 4 of 4

Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.
The data collected for these subjects in the open-label portion have been excluded.

Note: Number of actual events are presented.

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_slopehbdec.sas
Output: t_ae_cv_by_slopehbdec_cnt.rtf (Date Generated: 28JUN2001:10:36)

Table 5. Cardiovascular Event Rates By Treatment Group by Hemoglobin Value
(All Chemotherapy Studies Analysis Set)

		Hemoglobin Quintile (g/dL)						Hemoglobin Category (g/dL)					
		Unknown	< 9.4	9.4 to < 10.3	10.3 to < 11.1	11.1 to < 12.1	≥ 12.1	≤ 10	> 10 to 11	> 11 to 12	> 12 to 13	> 13 to 14	> 14
Number of Hb Values	Placebo	418	973	743	538	363	143	1562	687	368	110	23	10
	rHuEPO	155	147	186	184	225	242	270	246	225	140	74	29
	NESP	1287	1746	1951	2033	2191	2272	3255	2470	2194	1234	687	353
	Total	1860	2866	2880	2755	2779	2657	5087	3403	2787	1484	784	392
Arrhythmia	Placebo	0.0	7.2	4.0	11.2	2.8	0.0	5.8	10.2	2.7	0.0	0.0	0.0
	rHuEPO	6.5	13.6	0.0	0.0	0.0	0.0	7.4	0.0	0.0	0.0	0.0	0.0
	NESP	5.4	11.5	6.2	4.4	4.6	3.5	9.8	3.6	4.6	5.7	1.5	0.0
	Total	4.3	10.1	5.2	5.4	4.0	3.0	8.5	4.7	3.9	4.7	1.3	0.0
CAD	Placebo	2.4	1.0	0.0	0.0	2.8	0.0	0.6	0.0	2.7	0.0	0.0	0.0
	rHuEPO	0.0	6.8	5.4	0.0	0.0	0.0	7.4	0.0	0.0	0.0	0.0	0.0
	NESP	1.6	2.3	4.1	1.0	2.3	0.4	3.4	1.2	2.3	0.8	0.0	0.0
	Total	1.6	2.1	3.1	0.7	2.2	0.4	2.8	0.9	2.2	0.7	0.0	0.0
CHF	Placebo	0.0	2.1	0.0	1.9	0.0	0.0	1.3	1.5	0.0	0.0	0.0	0.0
	rHuEPO	0.0	0.0	0.0	5.4	4.4	0.0	0.0	4.1	4.4	0.0	0.0	0.0
	NESP	2.3	2.3	2.1	1.5	1.4	0.0	2.5	1.2	1.4	0.0	0.0	0.0
	Total	1.6	2.1	1.4	1.8	1.4	0.0	2.0	1.5	1.4	0.0	0.0	0.0

Page 1 of 4

Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The data collected for these subjects in the open-label portion have been excluded.

Note: Event rates are presented in number of events per 1000 hemoglobin values

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_hbquint.sas
Output: t_ae_cv_by_hbquint_rate.rtf (Date Generated: 28JUN2001:10:25)

Table 5. Cardiovascular Event Rates By Treatment Group by Hemoglobin Value
(All Chemotherapy Studies Analysis Set)

		Hemoglobin Quintile (g/dL)						Hemoglobin Category (g/dL)					
		Unknown	< 9.4	9.4 to < 10.3	10.3 to < 11.1	11.1 to < 12.1	≥ 12.1	≤ 10	> 10 to 11	> 11 to 12	> 12 to 13	> 13 to 14	> 14
CVA	Placebo	0.0	1.0	1.3	0.0	0.0	0.0	1.3	0.0	0.0	0.0	0.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.8	0.0	0.5	0.0	0.9	0.4	0.3	0.0	0.9	0.0	1.5	0.0
	Total	0.5	0.3	0.7	0.0	0.7	0.4	0.6	0.0	0.7	0.0	1.3	0.0
Cardiac Arrest	Placebo	0.0	1.0	0.0	0.0	0.0	0.0	0.6	0.0	0.0	0.0	0.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	0.0	4.1	0.0	0.0	0.0	7.1	0.0	0.0
	NESP	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	0.0	0.3	0.0	0.0	0.0	0.4	0.2	0.0	0.0	0.7	0.0	0.0
Death (Any Cause)	Placebo	31.1	5.1	1.3	0.0	2.8	21.0	3.8	0.0	2.7	18.2	43.5	0.0
	rHuEPO	45.2	13.6	0.0	0.0	0.0	8.3	7.4	0.0	0.0	14.3	0.0	0.0
	NESP	41.2	4.0	2.6	0.5	0.5	2.6	3.4	0.8	0.5	2.4	1.5	5.7
	Total	39.2	4.9	2.1	0.4	0.7	4.1	3.7	0.6	0.7	4.7	2.6	5.1
Fluid Overload	Placebo	16.7	52.4	25.6	26.0	8.3	14.0	41.6	27.7	8.2	9.1	43.5	0.0
	rHuEPO	19.4	47.6	64.5	16.3	17.8	33.1	51.9	32.5	17.8	57.1	0.0	0.0
	NESP	30.3	51.0	38.4	40.8	28.3	23.8	44.2	41.7	28.3	27.6	14.6	28.3
	Total	26.3	51.3	36.8	36.3	24.8	24.1	43.8	38.2	24.8	29.0	14.0	25.5

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.
The data collected for these subjects in the open-label portion have been excluded.
Note: Event rates are presented in number of events per 1000 hemoglobin values

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_hbquint.sas
Output: t_ae_cv_by_hbquint_rate.rtf (Date Generated: 28JUN2001:10:25)

Table 5. Cardiovascular Event Rates By Treatment Group by Hemoglobin Value
(All Chemotherapy Studies Analysis Set)

		Hemoglobin Quintile (g/dL)						Hemoglobin Category (g/dL)					
		Unknown	< 9.4	9.4 to < 10.3	10.3 to < 11.1	11.1 to < 12.1	≥ 12.1	≤ 10	> 10 to 11	> 11 to 12	> 12 to 13	> 13 to 14	> 14
Hypertension	Placebo	0.0	2.1	8.1	1.9	2.8	0.0	3.8	4.4	2.7	0.0	0.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	8.9	0.0	0.0	0.0	8.9	0.0	0.0	0.0
	NESP	1.6	0.6	2.1	3.0	2.7	5.7	1.5	2.4	2.7	5.7	7.3	2.8
	Total	1.1	1.0	3.5	2.5	3.2	4.9	2.2	2.6	3.2	4.7	6.4	2.6
Myocardial Infarction	Placebo	0.0	1.0	0.0	0.0	0.0	0.0	0.6	0.0	0.0	0.0	0.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.8	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.8	0.0	0.0
	Total	0.5	0.3	0.0	0.0	0.0	0.4	0.2	0.0	0.0	0.7	0.0	0.0
Seizure	Placebo	0.0	1.0	0.0	0.0	0.0	0.0	0.6	0.0	0.0	0.0	0.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	1.6	0.0	0.0	0.0	0.9	0.4	0.0	0.0	0.9	0.8	0.0	0.0
	Total	1.1	0.3	0.0	0.0	0.7	0.4	0.2	0.0	0.7	0.7	0.0	0.0
Vascular Thrombosis/ Ischemia/Infarction	Placebo	0.0	6.2	8.1	1.9	0.0	0.0	6.4	4.4	0.0	0.0	0.0	0.0
	rHuEPO	6.5	6.8	0.0	5.4	13.3	12.4	3.7	4.1	13.3	21.4	0.0	0.0
	NESP	8.5	1.1	5.6	4.9	3.7	3.1	3.4	4.9	3.6	1.6	2.9	8.5
	Total	6.5	3.1	5.9	4.4	4.0	3.8	4.3	4.7	3.9	3.4	2.6	7.7

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The data collected for these subjects in the open-label portion have been excluded.

Note: Event rates are presented in number of events per 1000 hemoglobin values

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_hbquint.sas

Output: t_ae_cv_by_hbquint_rate.rtf (Date Generated: 28JUN2001:10:25)

Table 5. Cardiovascular Event Rates By Treatment Group by Hemoglobin Value
(All Chemotherapy Studies Analysis Set)

		Hemoglobin Quintile (g/dL)						Hemoglobin Category (g/dL)					
		Unknown	< 9.4	9.4 to < 10.3	10.3 to < 11.1	11.1 to < 12.1	≥ 12.1	≤ 10	> 10 to 11	> 11 to 12	> 12 to 13	> 13 to 14	> 14
Thrombosis of Vasculature	Placebo	0.0	4.1	5.4	1.9	0.0	0.0	4.5	2.9	0.0	0.0	0.0	0.0
	rHuEPO	6.5	6.8	0.0	5.4	4.4	4.1	3.7	4.1	4.4	7.1	0.0	0.0
	NESP	7.8	1.1	5.6	4.9	3.7	3.1	3.4	4.9	3.6	1.6	2.9	8.5
	Total	5.9	2.4	5.2	4.4	3.2	3.0	3.7	4.4	3.2	2.0	2.6	7.7
Emboli (Originated from Injured Vasculature)	Placebo	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Vascular Ischemia	Placebo	0.0	2.1	1.3	0.0	0.0	0.0	1.9	0.0	0.0	0.0	0.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	8.9	8.3	0.0	0.0	8.9	14.3	0.0	0.0
	NESP	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	0.5	0.7	0.3	0.0	0.7	0.8	0.6	0.0	0.7	1.3	0.0	0.0
Exacerbation of Peripheral Vascular Disease	Placebo	0.0	0.0	1.3	0.0	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0
	rHuEPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NESP	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.0

Page 4 of 4

Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.
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Note: Event rates are presented in number of events per 1000 hemoglobin values

Program: /stat/nesp/nc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_hbquint.sas
Output: t_ae_cv_by_hbquint_rate.rtf (Date Generated: 28JUN2001:10:25)

Table 6. Cardiovascular Events By Treatment Group by Hemoglobin Value
(All Chemotherapy Studies Analysis Set)

		Hemoglobin Quintile (g/dL)						Hemoglobin Category (g/dL)					
		Unknown	< 9.4	9.4 to < 10.3	10.3 to < 11.1	11.1 to < 12.1	≥ 12.1	≤ 10	> 10 to 11	> 11 to 12	> 12 to 13	> 13 to 14	> 14
Number of Hb Values	Placebo	418	973	743	538	363	143	1562	687	368	110	23	10
	rHuEPO	155	147	186	184	225	242	270	246	225	140	74	29
	NESP	1287	1746	1951	2033	2191	2272	3255	2470	2194	1234	687	353
	Total	1860	2866	2880	2755	2779	2657	5087	3403	2787	1484	784	392
Arrhythmia	Placebo	0	7	3	6	1	0	9	7	1	0	0	0
	rHuEPO	1	2	0	0	0	0	2	0	0	0	0	0
	NESP	7	20	12	9	10	8	32	9	10	7	1	0
	Total	8	29	15	15	11	8	43	16	11	7	1	0
CAD	Placebo	1	1	0	0	1	0	1	0	1	0	0	0
	rHuEPO	0	1	1	0	0	0	2	0	0	0	0	0
	NESP	2	4	8	2	5	1	11	3	5	1	0	0
	Total	3	6	9	2	6	1	14	3	6	1	0	0
CHF	Placebo	0	2	0	1	0	0	2	1	0	0	0	0
	rHuEPO	0	0	0	1	1	0	0	1	1	0	0	0
	NESP	3	4	4	3	3	0	8	3	3	0	0	0
	Total	3	6	4	5	4	0	10	5	4	0	0	0

Page 1 of 4

Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion. The data collected for these subjects in the open-label portion have been excluded.
Note: Number of actual events are presented.

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_hbquint.sas
Output: t_ae_cv_by_hbquint_cnt.rtf (Data Generated: 28JUN2001:10:25)

Table 6. Cardiovascular Events By Treatment Group by Hemoglobin Value
(All Chemotherapy Studies Analysis Set)

		Hemoglobin Quintile (g/dL)						Hemoglobin Category (g/dL)					
		Unknown	< 9.4	9.4 to < 10.3	10.3 to < 11.1	11.1 to < 12.1	≥ 12.1	≤ 10	> 10 to 11	> 11 to 12	> 12 to 13	> 13 to 14	> 14
CVA	Placebo	0	1	1	0	0	0	2	0	0	0	0	0
	rHuEPO	0	0	0	0	0	0	0	0	0	0	0	0
	NESP	1	0	1	0	2	1	1	0	2	0	1	0
	Total	1	1	2	0	2	1	3	0	2	0	1	0
Cardiac Arrest	Placebo	0	1	0	0	0	0	1	0	0	0	0	0
	rHuEPO	0	0	0	0	0	1	0	0	0	1	0	0
	NESP	0	0	0	0	0	0	0	0	0	0	0	0
	Total	0	1	0	0	0	1	1	0	0	1	0	0
Death (Any Cause)	Placebo	13	5	1	0	1	3	6	0	1	2	1	0
	rHuEPO	7	2	0	0	0	2	2	0	0	2	0	0
	NESP	53	7	5	1	1	6	11	2	1	3	1	2
	Total	73	14	6	1	2	11	19	2	2	7	2	2
Fluid Overload	Placebo	7	51	19	14	3	2	65	19	3	1	1	0
	rHuEPO	3	7	12	3	4	8	14	8	4	8	0	0
	NESP	39	89	75	83	62	54	144	103	62	34	10	10
	Total	49	147	106	100	69	64	223	130	69	43	11	10

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion. The data collected for these subjects in the open-label portion have been excluded.
Note: Number of actual events are presented.

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_hbquint.sas
Output: t_ae_cv_by_hbquint_cnl.rtf (Data Generated: 28JUN2001:10:25)

Table 6. Cardiovascular Events By Treatment Group by Hemoglobin Value
(All Chemotherapy Studies Analysis Set)

		Hemoglobin Quintile (g/dL)						Hemoglobin Category (g/dL)					
		Unknown	< 9.4	9.4 to < 10.3	10.3 to < 11.1	11.1 to < 12.1	≥ 12.1	≤ 10 to 11	> 10 to 11	> 11 to 12	> 12 to 13	> 13 to 14	> 14
Hypertension	Placebo	0	2	6	1	1	0	6	3	1	0	0	0
	rHuEPO	0	0	0	0	2	0	0	0	2	0	0	0
	NESP	2	1	4	6	6	13	5	6	6	7	5	1
	Total	2	3	10	7	9	13	11	9	9	7	5	1
Myocardial Infarction	Placebo	0	1	0	0	0	0	1	0	0	0	0	0
	rHuEPO	0	0	0	0	0	0	0	0	0	0	0	0
	NESP	1	0	0	0	0	1	0	0	0	1	0	0
	Total	1	1	0	0	0	1	1	0	0	1	0	0
Seizure	Placebo	0	1	0	0	0	0	1	0	0	0	0	0
	rHuEPO	0	0	0	0	0	0	0	0	0	0	0	0
	NESP	2	0	0	0	2	1	0	0	2	1	0	0
	Total	2	1	0	0	2	1	1	0	2	1	0	0
Vascular Thrombosis/ Ischemia/Infarction	Placebo	0	6	6	1	0	0	10	3	0	0	0	0
	rHuEPO	1	1	0	1	3	3	1	1	3	3	0	0
	NESP	11	2	11	10	8	7	11	12	8	2	2	3
	Total	12	9	17	12	11	10	22	16	11	5	2	3

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The data collected for these subjects in the open-label portion have been excluded.

Note: Number of actual events are presented.

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_hbquint.sas
Output: t_ae_cv_by_hbquint_cnt.rtf (Date Generated: 28JUN2001:10:25)

Table 6. Cardiovascular Events By Treatment Group by Hemoglobin Value
(All Chemotherapy Studies Analysis Set)

		Hemoglobin Quintile (g/dL)						Hemoglobin Category (g/dL)					
		Unknown	< 9.4	9.4 to < 10.3	10.3 to < 11.1	11.1 to < 12.1	≥ 12.1	≤ 10	> 10 to 11	> 11 to 12	> 12 to 13	> 13 to 14	> 14
Thrombosis of Vasculature	Placebo	0	4	4	1	0	0	7	2	0	0	0	0
	rHuEPO	1	1	0	1	1	1	1	1	1	1	0	0
	NESP	10	2	11	10	8	7	11	12	8	2	2	3
	Total	11	7	15	12	9	8	19	15	9	3	2	3
Emboli (Originated from Injured Vasculature)	Placebo	0	0	0	0	0	0	0	0	0	0	0	0
	rHuEPO	0	0	0	0	0	0	0	0	0	0	0	0
	NESP	0	0	0	0	0	0	0	0	0	0	0	0
	Total	0	0	0	0	0	0	0	0	0	0	0	0
Vascular Ischemia	Placebo	0	2	1	0	0	0	3	0	0	0	0	0
	rHuEPO	0	0	0	0	2	2	0	0	2	2	0	0
	NESP	1	0	0	0	0	0	0	0	0	0	0	0
	Total	1	2	1	0	2	2	3	0	2	2	0	0
Exacerbation of Peripheral Vascular Disease	Placebo	0	0	1	0	0	0	0	1	0	0	0	0
	rHuEPO	0	0	0	0	0	0	0	0	0	0	0	0
	NESP	0	0	0	0	0	0	0	0	0	0	0	0
	Total	0	0	1	0	0	0	0	1	0	0	0	0

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The data collected for these subjects in the open-label portion have been excluded.

Note: Number of actual events are presented.

Program: /sta/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_cv_by_hbquint.sas
Output: t_ae_cv_by_hbquint_cnt.rtf (Date Generated: 28JUN2001:10:25)

Table 7. Subject Incidence of Adverse Events by Event Category and Preferred Term
(All Chemotherapy Studies Analysis Set by Weekly Dose)

EVENT CATEGORY Preferred Term	Placebo	rHuEPO	NESP Dose (µg/kg/wk)			All NESP
			< 2.0	2.0 to < 3.0	≥ 3.0	
Number of Subjects	221	85	160	313	308	781
ACCESS INFECTION	1 (0%)	1 (1%)	4 (3%)	6 (2%)	4 (1%)	14 (2%)
Access Infection	1 (0%)	1 (1%)	4 (3%)	5 (2%)	4 (1%)	13 (2%)
Access Infection Bacterial	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)
CONGESTIVE HEART FAILURE	3 (1%)	2 (2%)	1 (1%)	8 (3%)	7 (2%)	16 (2%)
Cardiac Failure	1 (0%)	0 (0%)	1 (1%)	7 (2%)	3 (1%)	11 (1%)
Edema Pulmonary	1 (0%)	1 (1%)	0 (0%)	2 (1%)	4 (1%)	6 (1%)
Cardiomyopathy	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)
Circulatory Failure	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ejection Fraction Abnormal	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
INFECTION	36 (16%)	15 (18%)	36 (23%)	54 (17%)	67 (22%)	157 (20%)
Infection Upper Respiratory	15 (7%)	7 (8%)	18 (11%)	22 (7%)	25 (8%)	65 (8%)
Infection Urinary Tract	7 (3%)	1 (1%)	8 (5%)	13 (4%)	18 (6%)	39 (5%)
Infection	2 (1%)	2 (2%)	4 (3%)	5 (2%)	11 (4%)	20 (3%)
Sepsis	5 (2%)	3 (4%)	6 (4%)	5 (2%)	3 (1%)	14 (2%)
Infection Lower Respiratory	4 (2%)	0 (0%)	1 (1%)	5 (2%)	6 (2%)	12 (2%)
Infection Respiratory Tract	4 (2%)	0 (0%)	1 (1%)	6 (2%)	1 (0%)	8 (1%)
Abscess	1 (0%)	0 (0%)	0 (0%)	1 (0%)	4 (1%)	5 (1%)
Sepsis Bacterial	1 (0%)	1 (1%)	1 (1%)	0 (0%)	3 (1%)	4 (1%)
Infection Fungal	0 (0%)	0 (0%)	0 (0%)	2 (1%)	1 (0%)	3 (0%)
Abscess Oral	0 (0%)	0 (0%)	1 (1%)	1 (0%)	0 (0%)	2 (0%)

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion. The adverse events reported for these subjects in the open-label portion have been excluded.
n(%) = the number and percentage of subjects reporting an event in the adverse event category/preferred term

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/_lae_inf_chf_alldose.sas
Output: _lae_inf_chf_alldose.rtf (Date Generated: 20JUN2001:09:36)

Table 7. Subject Incidence of Adverse Events by Event Category and Preferred Term
(All Chemotherapy Studies Analysis Set by Weekly Dose)

EVENT CATEGORY Preferred Term	Placebo	rHuEPO	NESP Dose (µg/kg/wk)			All NESP
			< 2.0	2.0 to < 3.0	≥ 3.0	
INFECTION (Cont'd)						
Bacteremia	0 (0%)	2 (2%)	0 (0%)	1 (0%)	1 (0%)	2 (0%)
Infection Urinary Tract Bacterial	0 (0%)	1 (1%)	1 (1%)	1 (0%)	0 (0%)	2 (0%)
Infection Bacterial	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Pharyngitis Bacterial	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Rhinitis Bacterial	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)
Septic Shock	2 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
PNEUMONIA	11 (5%)	3 (4%)	8 (5%)	14 (4%)	13 (4%)	35 (4%)
Pneumonia	8 (4%)	3 (4%)	7 (4%)	13 (4%)	12 (4%)	32 (4%)
Pneumonia Bacterial	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)
Pneumonia Lobar	1 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Pneumonia Lobar Bacterial	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
Bronchopneumonia	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

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Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion. The adverse events reported for these subjects in the open-label portion have been excluded.
n(%) = the number and percentage of subjects reporting an event in the adverse event category/preferred term.

Program: /stat/nesp/onc/meta/ISS/analysis/statfiles/programs/tables/t_ae_inf_chf_alldose.sas
Output: t_ae_inf_chf_alldose.rtf (Date Generated: 20JUN2001:09:36)

Table 18. Subject Incidence of Cardiovascular and Thromboembolic Adverse Events by Treatment Group
(All Chemotherapy Studies Analysis Set)

EVENT GROUP Sub Group	Placebo	rHuEPO	All NESP	Total
Number of Subjects	221	85	781	1087
Number of Subjects Reporting Cardiovascular and Thromboembolic Events	104 (47%)	40 (47%)	373 (48%)	517 (48%)
DEATH	23 (10%)	11 (13%)	73 (9%)	107 (10%)
HYPERTENSION	7 (3%)	2 (2%)	28 (4%)	37 (3%)
ARRHYTHMIA	15 (7%)	3 (4%)	62 (8%)	80 (7%)
CAD	3 (1%)	2 (2%)	15 (2%)	20 (2%)
CHF	3 (1%)	2 (2%)	16 (2%)	21 (2%)
CVA	3 (1%)	0 (0%)	5 (1%)	8 (1%)
CARDIAC ARREST	1 (0%)	1 (1%)	0 (0%)	2 (0%)
FLUID OVERLOAD	64 (29%)	29 (34%)	281 (36%)	374 (34%)
MYOCARDIAL INFARCTION	1 (0%)	0 (0%)	2 (0%)	3 (0%)
SEIZURE	1 (0%)	0 (0%)	5 (1%)	6 (1%)
VASCULAR THROMBOSIS/ ISCHEMIA/INFARCTION	13 (6%)	6 (7%)	45 (6%)	64 (6%)
Thrombosis of Vasculature	9 (4%)	4 (5%)	44 (6%)	57 (5%)
Vascular Ischemia	3 (1%)	2 (2%)	1 (0%)	6 (1%)
Exacerbation of Peripheral Vascular Disease	1 (0%)	0 (0%)	0 (0%)	1 (0%)

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n(%) = the number and percentage of subjects reporting any adverse event in the event group.

Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The adverse events reported for these subjects in the open-label portion have been excluded.

Note: Deaths on-study include deaths occurring during study or within 30 days of last study drug administration.

Program: /stat/nsp/nci/metal/ISS/adhoc/statfiles/programs/tables/t_ae_cv_alldose.sas

Output: t_ae_cv_alldose.rtf (Date Generated: 27MAR2002:14:43)

Table 19. Subject Incidence of Cardiovascular and Thromboembolic Adverse Events by Weekly Dose of NESP
(All Chemotherapy Studies Analysis Set)

EVENT GROUP Sub Group	NESP Dose (µg/kg/wk)						All NESP
	< 2.0	2.0 to < 3.0	3.0 to < 4.0	4.0 to < 5.0	5.0 to < 6.0	≥ 6.0	
Number of Subjects	160	313	78	146	40	44	781
Number of Subjects Reporting Cardiovascular and Thromboembolic Events	85 (53%)	135 (43%)	38 (49%)	67 (46%)	18 (45%)	30 (68%)	373 (48%)
DEATH	13 (8%)	31 (10%)	10 (13%)	12 (8%)	1 (3%)	6 (14%)	73 (9%)
HYPERTENSION	7 (4%)	13 (4%)	2 (3%)	5 (3%)	0 (0%)	1 (2%)	28 (4%)
ARRHYTHMIA	15 (9%)	24 (8%)	7 (9%)	11 (8%)	1 (3%)	4 (9%)	62 (8%)
CAD	3 (2%)	7 (2%)	3 (4%)	1 (1%)	1 (3%)	0 (0%)	15 (2%)
CHF	1 (1%)	8 (3%)	3 (4%)	4 (3%)	0 (0%)	0 (0%)	16 (2%)
CVA	0 (0%)	2 (1%)	1 (1%)	2 (1%)	0 (0%)	0 (0%)	5 (1%)
FLUID OVERLOAD	70 (44%)	93 (30%)	28 (36%)	49 (34%)	16 (40%)	25 (57%)	281 (36%)
MYOCARDIAL INFARCTION	1 (1%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0%)
SEIZURE	1 (1%)	1 (0%)	2 (3%)	1 (1%)	0 (0%)	0 (0%)	5 (1%)
VASCULAR THROMBOSIS/ ISCHEMIA/INFARCTION	7 (4%)	10 (3%)	10 (13%)	13 (9%)	1 (3%)	4 (9%)	45 (6%)
Thrombosis of Vasculature	6 (4%)	10 (3%)	10 (13%)	13 (9%)	1 (3%)	4 (9%)	44 (6%)
Vascular Ischemia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)

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n(%) = the number and percentage of subjects reporting any adverse event in the event group.

Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The adverse events reported for these subjects in the open-label portion have been excluded.

Note: Deaths on-study include deaths occurring during study or within 30 days of last study drug administration.

Program: /stat/nesp/onc/metal/ISS/adhoc/statfiles/programs/tables/t_ae_cv_alldose_nesp.sas
Output: t_ae_cv_alldose_nesp.rtf (Date Generated: 27MAR2002:14:45)

Table 20. Subject Incidence of Cardiovascular and Thromboembolic Adverse Events by Actual Dose of NESP
(All Chemotherapy Studies Analysis Set)

EVENT GROUP Sub Group	NESP Dose (µg/kg)						All NESP
	< 2.0	2.0 to < 4.0	4.0 to < 6.0	6.0 to < 8.0	8.0 to < 10.0	≥ 10.0	
Number of Subjects	95	298	114	79	92	103	781
Number of Subjects Reporting Cardiovascular and Thromboembolic Events	42 (44%)	138 (46%)	56 (49%)	45 (57%)	43 (47%)	49 (48%)	373 (48%)
DEATH	6 (6%)	30 (10%)	10 (9%)	9 (11%)	11 (12%)	7 (7%)	73 (9%)
HYPERTENSION	4 (4%)	13 (4%)	6 (5%)	1 (1%)	3 (3%)	1 (1%)	28 (4%)
ARRHYTHMIA	12 (13%)	24 (8%)	5 (4%)	8 (10%)	10 (11%)	3 (3%)	62 (8%)
CAD	2 (2%)	8 (3%)	1 (1%)	1 (1%)	2 (2%)	1 (1%)	15 (2%)
CHF	1 (1%)	8 (3%)	1 (1%)	1 (1%)	3 (3%)	2 (2%)	16 (2%)
CVA	0 (0%)	1 (0%)	1 (1%)	0 (0%)	2 (2%)	1 (1%)	5 (1%)
FLUID OVERLOAD	32 (34%)	94 (32%)	47 (41%)	38 (48%)	30 (33%)	40 (39%)	281 (36%)
MYOCARDIAL INFARCTION	0 (0%)	1 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (0%)
SEIZURE	0 (0%)	1 (0%)	1 (1%)	2 (3%)	1 (1%)	0 (0%)	5 (1%)
VASCULAR THROMBOSIS/ ISCHEMIA/INFARCTION	3 (3%)	11 (4%)	8 (7%)	8 (10%)	8 (9%)	7 (7%)	45 (6%)
Thrombosis of Vasculature	3 (3%)	11 (4%)	7 (6%)	8 (10%)	8 (9%)	7 (7%)	44 (6%)
Vascular Ischemia	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)

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n(%) = the number and percentage of subjects reporting any adverse event in the event group.

Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The adverse events reported for these subjects in the open-label portion have been excluded.

Note: Deaths on-study include deaths occurring during study or within 30 days of last study drug administration.

Program: /stat/nesp/nci/metal/ISS/adhoc/statfiles/programs/tables/t_ae_cv_alldose_nesp_actual.sas

Output: t_ae_cv_alldose_nesp_actual.rtf (Date Generated: 27MAR2002:14:46)

Table 21. Subject Incidence of Cardiovascular and Thromboembolic Adverse Events by Dosing Schedule
(All Chemotherapy Studies Analysis Set)

EVENT GROUP Sub Group	QWK			Q2WK		Q3WK	
	Placebo	rHuEPO	NESP	rHuEPO	NESP	Placebo	NESP
Number of Subjects	170	53	455	32	128	51	198
Number of Subjects Reporting Cardiovascular and Thromboembolic Events	85 (50%)	27 (51%)	214 (47%)	13 (41%)	56 (44%)	19 (37%)	103 (52%)
DEATH	19 (11%)	6 (11%)	43 (9%)	5 (16%)	11 (9%)	4 (8%)	19 (10%)
HYPERTENSION	7 (4%)	0 (0%)	20 (4%)	2 (6%)	4 (3%)	0 (0%)	4 (2%)
ARRHYTHMIA	13 (8%)	3 (6%)	41 (9%)	0 (0%)	12 (9%)	2 (4%)	9 (5%)
CAD	3 (2%)	1 (2%)	10 (2%)	1 (3%)	2 (2%)	0 (0%)	3 (2%)
CHF	3 (2%)	1 (2%)	10 (2%)	1 (3%)	2 (2%)	0 (0%)	4 (2%)
CVA	3 (2%)	0 (0%)	1 (0%)	0 (0%)	2 (2%)	0 (0%)	2 (1%)
CARDIAC ARREST	1 (1%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)
FLUID OVERLOAD	51 (30%)	21 (40%)	152 (33%)	8 (25%)	43 (34%)	13 (25%)	86 (43%)
MYOCARDIAL INFARCTION	1 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
SEIZURE	1 (1%)	0 (0%)	1 (0%)	0 (0%)	3 (2%)	0 (0%)	1 (1%)
VASCULAR THROMBOSIS/ ISCHEMIA/INFARCTION	9 (5%)	3 (6%)	22 (5%)	3 (9%)	7 (5%)	4 (8%)	16 (8%)
Thrombosis of Vasculature	5 (3%)	3 (6%)	22 (5%)	1 (3%)	7 (5%)	4 (8%)	15 (8%)
Vascular Ischemia	3 (2%)	0 (0%)	0 (0%)	2 (6%)	0 (0%)	0 (0%)	1 (1%)
Exacerbation of Peripheral Vascular Disease	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

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n(%) = the number and percentage of subjects reporting any adverse event in the event group.

Note: Fourteen subjects received placebo in the double-blind portion of study 980291 and then received NESP in the open-label portion.

The adverse events reported for these subjects in the open-label portion have been excluded.

Note: Deaths on-study include deaths occurring during study or within 30 days of last study drug administration.

Program: /stat/nesplonclmetal/ISS/adhoc/statfiles/programs/tables/t_ae_cv_allsched.sas

Output: t_ae_cv_allsched.rtf (Date Generated: 27MAR2002:14:47)

Table Hemoglobin at Time of RBC Transfusion
(ITT Analysis Set)

	Placebo	NESP 2.25 ($\mu\text{g/kg/wk}$)	Total
Number of Subjects	158	156	314
Overall			
n	192	84	276
Mean	8.0	8.2	8.1
SD	1.2	1.0	1.1
Median	7.9	8.1	8.0
Q1, Q3	7.30, 8.80	7.55, 8.85	7.40, 8.80
Min, Max	4.9, 12.0	6.2, 10.2	4.9, 12.0
By Indication			
Study Specific Trigger Reached			
n	121	50	171
Mean	7.5	7.6	7.6
SD	1.0	0.7	0.9
Median	7.6	7.7	7.6
Q1, Q3	7.00, 8.00	7.00, 8.10	7.00, 8.00
Min, Max	4.9, 11.3	6.2, 9.8	4.9, 11.3
Medically Indicated			
n	65	29	94
Mean	9.0	9.0	9.0
SD	1.0	0.7	0.9
Median	8.9	9.0	9.0
Q1, Q3	8.30, 9.50	8.30, 9.50	8.30, 9.50
Min, Max	7.0, 12.0	7.7, 10.2	7.0, 12.0
Prophylactic for Hemoglobin			
n	2	0	2
Mean	8.4	.	8.4
SD	1.6	.	1.6
Median	8.4	.	8.4
Q1, Q3	7.30, 9.50	.	7.30, 9.50
Min, Max	7.3, 9.5	.	7.3, 9.5
Other			
n	4	5	9
Mean	8.6	8.8	8.7
SD	0.5	0.6	0.5
Median	8.5	8.7	8.6
Q1, Q3	8.30, 8.95	8.30, 9.00	8.30, 9.00
Min, Max	8.2, 9.3	8.2, 9.8	8.2, 9.8

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Note: n = number of transfusions with a hgb value within past 7 days.

Note: Hgb values on the day of transfusion were used, if present. Otherwise the closest hgb value prior to the transfusion within the past 7 days was used.

Program: /stat/nesp/nc/nesp980297/analysis/lda_apr2002/statfiles/programs/tables/t_hgb_tm_by_indic.sas
Output: t_hgb_tm_by_indic.rtf (Date Generated: 10APR2002:16:54)

ATTACHMENT FOUR

Financial Disclosure Analysis:

The purpose of the analysis of financial disclosure is to determine whether or not investigators with financial interests between themselves and the sponsor could affect the outcomes of studies they participated in. Certification/disclosure forms were sent to all clinical investigators and sub-investigators on the following "covered clinical studies":

(b) (6). Each investigator was asked to indicate whether financial arrangements of concern to the FDA did or did not exist during the study period. Table 3 of the Financial Disclosure section of the submission listed approximately 135 investigators and a larger number of sub-investigators, each of whom indicated they had no financial interest in the outcome of the study. Seven investigators, who failed to respond, are listed under Table 2 of the Financial Disclosure section of the sponsor submission. Nine sub-investigators responded that they had an interest in Amgen in that they owned shares (> \$50,000). The nine sub-investigators are listed in Table 4 of the Financial Disclosure section.

A sensitivity analysis was performed by excluding the patients treated by these 9 sub-investigators from each of the studies these sub-investigators participated in (studies (b) (6)). The results were then compared to those results obtained in the original analyses. The endpoints analyzed were the proportion of patients who responded (had a ≥ 2 g/dL increase over baseline hemoglobin in the absence of RBC transfusions in the prior 28 days) and the proportion of patients who had an RBC transfusion from week 5 to EOTP inclusive. Table 1 shows the original results for study (b) (6).

Table 1. Hemoglobin response (ITT analysis set - (b) (6))

Stats	Doses (mcg/kg/wk)							Total
	0.5	1.0	1.5	2.25	4.5	6.0	8.0	
N	13	36	35	59	29	30	14	216
# resp	3	13	12	29	19	17	8	101
# cens	10	23	23	30	10	13	6	115
Prop resp	23	43	44	52	76	73	62	
95% CI for prop resp	0, 46	25, 61	25, 63	39, 66	59, 94	52, 95	35, 90	

Table 2. Hemoglobin response (ITT analysis set - (b) (6)) excluding sub-investigators with financial interests

Stats	Doses (mcg/kg/wk)							Total
	0.5	1.0	1.5	2.25	4.5	6.0	8.0	
N	13	27	27	42	23	19	9	160
# resp	3	8	9	22	15	13	7	77
# cens	10	19	18	20	8	6	2	83
Prop resp	23	36	43	55	71	84	78	
95% CI for prop resp	0, 46	16, 56	22, 65	40, 71	51, 91	59, 100	51, 100	

Table 2 shows the results excluding patients who were treated by sub-investigators with financial interests. The estimates and 95% confidence intervals of the proportion of patients who responded differ slightly for doses 1.0, 6.0, and 8.0 when comparing the two analysis sets. However, they do not differ much for doses 0.5, 1.5, 2.25, and 4.5. Therefore, the outcomes of patients treated by sub-investigators with a financial interest in Amgen do not appear to alter the original analysis results much for doses 0.5, 1.5, 2.25, and 4.5.

The analysis results on proportion of patients transfused in weeks 5 to EOTP in study (b) (6) are shown in Tables 3 and 4.

Table 3. RBC transfusions from week 5 to EOTP (primary analysis set – (b) (6))

Stats	Doses (mcg/kg/wk)							Total
	0.5	1.0	1.5	2.25	4.5	6.0	8.0	
N	13	32	29	58	26	28	13	199
# resp	2	3	7	7	1	4	0	24
# cens	11	29	22	51	25	24	13	175
Prop resp	15	10	26	13	6	16	0	
95% CI for prop resp	0, 35	0, 20	9, 43	4, 23	0, 18	2, 30	NE, NE	

Table 4. RBC transfusions from week 5 to EOTP (primary analysis set – (b) (6)) excluding sub-investigators with financial interests

Stats	Doses (mcg/kg/wk)							Total
	0.5	1.0	1.5	2.25	4.5	6.0	8.0	
N	13	23	22	41	22	18	9	148
# resp	2	3	4	4	1	3	0	17
# cens	11	20	18	37	21	15	9	131
Prop resp	15	13	20	11	8	18	0	
95% CI for prop resp	0, 35	0, 27	2, 37	1, 21	0, 22	0, 36	NE, NE	

The estimates and 95% confidence intervals of the proportion of patients that require an RBC transfusion between weeks 5 and EOTP do not differ much for all doses of NESP. Therefore, the outcomes of patients treated by sub-investigators who owned > \$50,000 worth of shares in Amgen did not significantly alter the original results.

For study (b) (6), the results of the analyses on proportion of patients who responded are shown in Tables 5 and 6.

Table 5. Hemoglobin response (ITT analysis set – (b) (6))

Stats	Doses (mcg/kg/wk)				
	3.0	5.0	7.0	9.0	Total
N	33	31	32	32	128
# resp	15	18	14	18	65
# cens	18	13	18	14	63
Prop resp	60	79	54	67	
95% CI for prop resp	39, 80	56, 100	31, 76	48, 85	

Table 6. Hemoglobin response (ITT analysis set – (b) (6)) excluding sub-investigators with financial interests

Stats	Doses (mcg/kg/wk)				
	3.0	5.0	7.0	9.0	Total
N	19	24	21	22	86
# resp	10	14	10	13	47
# cens	9	10	11	9	39
Prop resp	67	79	65	66	
95% CI for prop resp	43, 92	56, 100	34, 97	44, 87	

In a comparison of the two analysis sets, the estimates and 95% confidence intervals of the proportion of patients who respond differ slightly in the 7.0 dose arm but do not differ much for the other doses of NESP.

Table 7. RBC transfusions from weeks 5 to EOTP (primary analyses set – (b) (6)h)

Stats	Doses (mcg/kg/wk)				
	3.0	5.0	7.0	9.0	Total
N	30	30	30	29	119
# resp	1	6	6	3	16
# cens	29	24	24	26	103
Prop resp	4	22	23	11	
95% CI for prop resp	0, 11	6, 37	7, 39	0, 23	

With respect to the proportion of patients requiring an RBC transfusion between weeks 5 and EOTP, a comparison of the two analysis sets (Tables 7 and 8) shows that the estimates and 95% confidence intervals do not differ much. Therefore, the outcomes from the patients treated by sub-investigators with financial interests in Amgen did not bias results in favor of Aranesp.

Table 8. RBC transfusions from week 5 to the EOTP (primary analysis set - (b) (6) excluding sub-investigators with financial interests

Stats	Doses (mcg/kg/wk)				Total
	3.0	5.0	7.0	9.0	
N	16	23	19	21	79
# resp	0	5	4	1	10
# cens	16	18	15	20	69
Prop resp	0	24	24	5	
95% CI for prop resp	NE, NE	6, 43	4, 45	0, 14	

The results of the analyses on proportion of patients who responded in study (b) (6) are shown in Tables 9 and 10. Upon examination of the estimates of the proportion of patients who responded and the 95% confidence intervals for these estimates, the results are similar between the original analysis and the sensitivity analysis. As a result, it would appear that outcomes of patients treated by the sub-investigators did not alter the original results.

Table 9. Hemoglobin response (ITT analysis set - (b) (6))

Stats	Doses (mcg/kg/wk)				Total
	0.5	1.0	2.25	4.5	
N	6	33	33	30	102
# resp	4	20	19	25	68
# cens	2	13	14	5	34
Prop resp	80	68	66	92	
95% CI for prop resp	45, 100	50, 86	49, 84	80, 100	

Table 10. Hemoglobin response (ITT analysis set - (b) (6) excluding sub-investigators with financial interests

Stats	Doses (mcg/kg/wk)				Total
	0.5	1.0	2.25	4.5	
N	6	31	24	22	83
# resp	4	19	14	17	54
# cens	2	12	10	5	29
Prop resp	80	70	67	87	
95% CI for prop resp	45, 100	52, 88	46, 87	71, 100	

The results of the analyses on proportion of patients who required an RBC transfusion between weeks 5 and EOTP in study (b) (6) are shown in Tables 11 and 12. Upon examination of the estimates of the proportion of patients who required an RBC

transfusion between weeks 5 and EOTP, the results are similar between the original analysis and the sensitivity analysis. As a result, it would appear that patients treated by the sub-investigators did not alter the original results with respect to this endpoint.

Table 11. RBC transfusions from weeks 5 to EOTP (primary analyses set)

Stats	Doses (mcg/kg/wk)				
	0.5	1.0	2.25	4.5	Total
N	5	32	30	29	96
# resp	1	8	4	2	15
# cens	4	24	26	27	81
Prop resp	20	36	14	7	
95% CI for prop resp	0, 55	10, 62	1, 26	0, 17	

Table 12. RBC transfusions from week 5 to the EOTP (primary analysis set) excluding sub-investigators with financial interests

Stats	Doses (mcg/kg/wk)				
	0.5	1.0	2.25	4.5	Total
N	5	30	21	21	
# resp	1	7	3	2	
# cens	4	23	18	19	
Prop resp	20	34	14	10	
95% CI for prop resp	0, 55	8, 61	0, 29	0, 23	

Overall, the sensitivity analyses performed by excluding patients, who were treated by sub-investigators with financial interests in Amgen, did not drastically alter the point estimates or the 95% confidence intervals for the proportion of patients who responded or for the proportion of patients requiring RBC transfusion in weeks 5 to EOTP. Slight differences appeared in higher doses. The licensed dose of 2.25 was essentially unaffected. Therefore, the original results were shown to be robust to the fact that some sub-investigators held shares of > \$50,000 in Amgen. There does not appear to be any bias in favor of Aranesp with respect to either endpoint.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

103951/5001

CHEMISTRY REVIEW(S)

Memo**Date:** July 18, 2002*Blum 7-18-02***To:** Barry Cherney, Deputy Director, DTP, OTRR, CBER; Amy Rosenberg, Director, DTP, OTRR, CBER**Cc:** Dov Pluznik and Gary Kikuchi, DTP, OTRR, CBER; Jeanne Delasko and Mike Harlow, DARP, OTRR, CBER**From:** Frederick C. Mills, Staff Scientist, DTP, OTRR, CBER**Subject:** CM & C Review of BLS 103951/5001

Darbepoetin alfa for the treatment of anemia in cancer patients with non-myeloid malignancies.

Executive Summary

BLS 103951/ 5001 for treatment of anemia in cancer contains Amgen's request for licensing of three new dosage forms in the darbepoetin alfa albumin formulation, which are 150 µg, 300 µg, and 500 µg. Adequate CM & C information for these forms is provided; i.e. manufacturing information for the 150 µg dose is contained in the BLS, and information for the 300 and 500 µg doses was reviewed in the original Aranesp BLA. Amgen has supplied data sufficient to support an expiry dating of 36 months for the new dosage forms, and has proposed a satisfactory stability protocol for annually placing one lot each of low, medium and high dosage forms on stability. Amgen has also agreed to set an acceptance criterion for the darbepoetin alfa (b) (4) species, which is measured as a stability indicating parameter. In addition, Amgen has provided a Phase IV commitment to revise this specification after manufacture of 30 commercial lots by July 30, 2003. All CM & C issues with this licensing supplement have been resolved.

original

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Comments to the Sponsor

1. Licensing of the 150, 300 and 500 µg darbepoetin dosage forms:

Approval is granted for the 150, 300, and 500 µg dosage forms for the albumin formulation of the darbepoetin alfa final product.

The dating period for the new dosage strengths of Darbepoetin alfa shall be 36 months from the date of manufacture.

Results of ongoing stability studies should be submitted throughout the dating period, as they become available. The stability protocol in your supplement is considered approved for the purpose of extending the expiration dating period of your drug product as specified in 21 CFR 601.12.

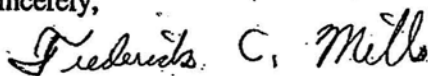
Post Marketing commitments

As described in your letter of July 18, 2002:

To establish a specification for the amount of oxidized darbepoetin alfa in the albumin formulation of the final product. The (b) (4) darbepoetin alfa species will be detected by SPE/LC-MS in accordance with analytical method (b) (4). Amgen will set this specification for lot release and stability at $\leq 5\%$ and a copy of the revised specification will be submitted to the BLS by 30 August 2002.

To submit revised release specifications for the amount of oxidized darbepoetin alfa in the final albumin formulated product based upon the analysis of data obtained from 30 commercial lots of final material. This information will be submitted to the biologics license application (BLA) by July 30, 2003.

Sincerely,



Frederick C. Mills
Staff Scientist
DTP, OTRR, CBER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
103951/5001

PHARMACOLOGY REVIEW(S)

TOXICOLOGIST'S REVIEW

BLS: STN #103951/5001

SPONSOR: Amgen, Inc.

PRODUCT: Novel Erythropoiesis Stimulating Protein; darbepoetin alfa; NM321; NESP; ARANESP™

FORMULATION/CHEMISTRY: Produced in a mammalian (CHO cells) expression system in a hyper-glycosylated form, with a MW of 37.1 kD. The glycoprotein is composed of 165 amino acids. The protein is the hyperglycosylated recombinant human EPO analog. NESP differs from native or recombinant EPO in the form of two additional N-linked oligosaccharide chains. The additional carbohydrate chains increase the MW of the glycoprotein from 30 to 37 kD. The protein is formulated as a sterile, colorless, preservative-free solution.

PROPOSED INDICATION: Treatment of anemia in patients with non-myeloid associated malignancies where anemia is associated with the effect of concomitantly administered chemotherapy. (b) (4)

ABBREVIATIONS: recombinant human erythropoietin = EPO; Novel Erythropoiesis Stimulating Protein = NESP; peripheral blood progenitor cell = PBPC; subcutaneous = SC; intravenous = IV; platelet = PLT; red blood cell = RBC; bone marrow = BM; hemoglobin = HGB; chronic renal failure = CRF

received 10/01; completed 10/02

CROSS-REFERENCES: IND #7413, 8223; BLA # (b) (4)

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INTRODUCTION:

NESP is a well-characterized recombinant protein, which is an analog of recombinant human erythropoietin (EPO). NESP stimulates erythropoiesis in a manner identical to endogenous human EPO, as well as recombinant human EPO - which is approved for use in the Rx of anemia in patients with chronic renal failure (CRF). NESP binds to cell surface receptors that are specific for EPO, resulting in the promotion of survival, proliferation, & differentiation of cells of the

erythroid lineage. The in vitro potency of NESP is lower than that of EPO due to an increase in negative charge resulting from the addition of sialic acid containing carbohydrate & consequently weaker receptor binding. However, due to the addition of this carbohydrate, the in vivo activity of NESP is increased relative to EPO because of its longer serum half-life [~3-fold longer].

Amgen's NESP, consisting of 165 amino acids, is produced by CHO cells in which a gene has been inserted for (b) (4). The protein is hyperglycosylated & has a theoretical MW of 37,100 daltons, based on the amino acid sequence & nominal carbohydrate structure. The protein contains (b) (4), which form (b) (4). NESP is different from natural & recombinant EPO by five amino acids. This difference allows for new sequences for N-linked glycosylation.

The proposed clinical indication [per the package insert] for NESP is for the treatment of anemia in patients with nonmyeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. The proposed package insert submitted by the sponsor states that once weekly SC injections of 2.25 µg/kg/dose of NESP have resulted in efficacious results in cancer patients. Single SC injections as low as 1.5 µg/kg/wk have been shown to be effective with higher response rates and decreased time to response observed with increasing doses of NESP, up to 4.5 µg/kg/wk.

The PI-recommended starting dose of NESP for the specified patient population is 2.25 µg/kg/dose, once weekly, via SC injection. The dose of NESP for each patient is variable, thus should be adjusted as clinically indicated to achieve & maintain a target HGB not to exceed 12 g/dL. The proposed wording in the PI states that if there is <1 g/dL increase in HGB after six wks of therapy, the dose of NESP should be doubled to 4.5 µg/kg/dose. If the HGB approaches 12 g/dL, the dose of NESP should be reduced by 25%. If the HGB continues to increase, NESP doses should be withheld until the HGB begins to decrease, then NESP administration can reinitiate at (b) (4) % of the previous dose level. If the HGB increases by >1 g/dL in a 2-wk period, the NESP dose level should be decreased by 25%.

Formulation - ARANESP™ will be distributed in single-dose vials [containing 25, 40, 60, 100, 150, 200, (b) (4), or 500 µg ARANESP] & is manufactured in two formulations: either a polysorbate [free of serum-derived albumin] or albumin [human] formulation. ARANESP is formulated in a sterile, preservative-free solution, containing: [Polysorbate soln] 2.12 mg sodium phosphate monobasic mono-hydrate, 0.66 mg sodium phosphate dibasic anhydrous, 0.05 mg polysorbate 80, 8.18 mg sodium chloride in Water for Injection USP, pH 6.2 ±0.2; and [Albumin soln] 2.5 mg human albumin, 2.23 mg sodium phosphate monobasic monohydrate, 0.53 mg sodium phosphate dibasic anhydrous, 8.18 mg sodium chloride in Water for Injection USP, pH 6.0 ±0.3.

Unless specified, all preclinical studies were performed using the NESP formulation containing HSA.

NESP is already approved for use in the treatment of anemia in chronic renal failure. Please refer to the toxicologist's review of BLA # (b) (4) for many of the preclinical studies submitted in support of the oncology indication. This document is a review of the preclinical studies that were not included in BLA # (b) (4).

Preclinical Pharmacology Studies

In vitro

1. Limited Tissue *In Vitro* Binding Study of De-Sialylated NESP & EPO to Human Tissue; study #101119/IM648; performed at PAI (non-GLP); lot (b) (4) (D-NESP), # (b) (4) (D-r-HuEPO); 6/00
2. Limited Tissue *In Vitro* Binding Study of De-Sialylated NESP & De-Sialylated EPO to Human Tissue; study #101280/IM689; performed at PAI (non-GLP); lot #unknown; 12/00
3. The *In Vitro* Activity of Desialylated (DS) NESP and rHuEPO on Human Erythroid Progenitor Cells; study #01-0128; performed at Amgen (non-GLP); lot #unknown; 4/01

In vivo

1. NESP Relative to Single Dose Chemotherapy; report #PP01101; performed at Amgen (non-GLP); lot (b) (4) [HSA-free]; 5/01
2. The Effect of NESP Dose and Scheduling in a Murine Model of Multicycle Chemo/Radiotherapy; report #01-026; performed at Amgen (non-GLP); lot (b) (4) [HSA-free]; 4/01
3. NESP Alleviates Anemia in a Rat Anemia of Chronic Disorders (ACD) Model; report #PP01100; performed at Amgen (non-GLP); lot # (b) (4) [HSA-free]; 4/01
4. Dose and Dosing Frequency of NESP in Normal Mice; report #01-025; performed at Amgen (non-GLP); lot # (b) (4) [HSA-free]; 4/01

Pharmacology Studies

In vitro

1. Limited Tissue *In Vitro* Binding Study of De-Sialylated NESP & EPO to Human Tissue

Concentrations of 1 µg/mL of desialylated NESP (D-NESP) or desialylated recombinant human EPO (D-r-HuEPO, positive control) were exposed to a panel of 23 tissues from two human donors [refer to study report for tissue list]. Desialylation was achieved by incubating NESP & EPO with (b) (4) NESP placebo served as the negative control & human liver & pancreas served as the negative control tissues [no expression of EpoR] & BM served as the positive control tissue. Note that NESP & r-HuEPO were about (b) (4) desialylated, respectively.

Findings: Both desialylated proteins bound to select hematopoietic cells in adult BM tissue with equal frequency & intensity. The binding observed was consistent with binding through the EpoR - primary receptor by which EPO attaches to cells. There is a subset of erythroid precursor cells that express the EpoR. No binding was noted to any of the other tissues evaluated. The binding responses of D-NESP & D-r-HuEPO were identical to those shown by non-desialylated (i.e., intact) NESP & EPO [refer to study #100160 in BLA # (b) (4)].

2. Limited Tissue *In Vitro* Binding Study of De-Sialylated NESP & De-Sialylated EPO to Human Tissue

Concentrations of 1 µg/mL of desialylated NESP (D-NESP) or desialylated recombinant human EPO (D-r-HuEPO, positive control) were exposed to a panel of 23 tissues from two human donors [refer to study report for tissue list]. Desialylation was achieved by incubating NESP & EPO with (b) (4) NESP placebo (HSA-free) served as the negative control & human liver & pancreas served as the negative control tissues [no expression of EpoR] & BM served as the positive control tissue. Note that NESP & r-HuEPO were about (b) (4) desialylated, respectively.

Findings: Both desialylated proteins bound to select hematopoietic cells in adult BM tissue with equal frequency & intensity. The binding observed was consistent with binding through the EpoR - primary receptor by which EPO attaches to cells. There is a subset of erythroid precursor cells that express the EpoR. No binding was noted to any of the other tissues evaluated. The binding responses of D-NESP & D-r-HuEPO were identical to those shown by non-desialylated NESP & EPO [refer to study #100160 in BLA # (b) (4)].

3. The *In Vitro* Activity of Desialylated (DS) NESP and rHuEPO on Human Erythroid Progenitor Cells

Concentrations from 1 pg/mL to 10 ng/mL of desialylated NESP (DS-NESP), desialylated recombinant human EPO (DS-rHuEPO), NESP, or rHuEPO were cultured with (b) (4)

Findings: Concentrations of 100, 1000 or 10,000 pg/mL of either desialylated protein resulted in significantly higher BFU-E colonies as compared to equal concentrations of NESP or EPO. Cultures containing 100 or 1000 pg/mL of EPO had significantly higher numbers of BFU-E colonies as compared to cultures containing NESP, while no statistical difference between the two desialylated proteins was noted.

The highly glycosylated [thus, increased sialic acid content] NESP, which displays a longer residence time in the circulation as compared to EPO, show a lower *in vitro* activity relative to EPO – possibly due to steric hindrance [sponsor postulation].

In vivo

1. NESP Relative to Single Dose Chemotherapy

Normal BDF₁ mice [15/grp] were singly SC injected at 100 µg/kg on different days relative to single agent cytotoxic administration (one cycle). The chemotherapeutic agents used were 5FU (antimetabolite), cyclophosphamide (cross-link & alkylate DNA), busulfex (alkylating agent), and carboplatin + whole body irradiation (DNA cross-linking). The single injection of NESP occurred on different days relative to the chemotherapy administration for each agent [refer to the study for specific doses of each chemotherapy agent, as well as for the days that NESP was injected]. Sets of mice were bled on protocol-specified days in predetermined order in order to avoid anemia due to phlebotomy.

Findings: The injection of NESP resulted in higher HGB levels for all grps. When NESP was injected prior to chemotherapy, the mice exhibited extremely high HGB levels, which reflected in a disproportionately high HGB level in the post-chemo interval. Note that the dose of busulfex was not high enough to cause anemia, thus the NESP-dosed mice exhibited very high HGB levels post-chemo also. [Per the sponsor] There was no evidence of a sensitization of the erythroid compartment due to exposure to NESP prior to chemo and the resultant RBCs appeared to be more resistant to the effect of the chemotherapy relative to the RBCs produced by mice not treated with NESP.

2. The Effect of NESP Dose and Scheduling in a Murine Model of Multicycle Chemo/Radiotherapy

Normal BDF₁ mice [15/grp] were SC injected at 100 µg/kg on different days relative to single agent cytotoxic administration (q28 days x 4 cycles) for each cycle. The chemotherapeutic agents used were carboplatin or carboplatin + whole body irradiation. The single injection of NESP occurred on different days relative to the chemotherapy administration for each agent [refer to the study for specific doses of each chemotherapy agent, as well as for the days that NESP was injected]. Sets of mice were bled on protocol-specified days in predetermined order in order to avoid anemia due to phlebotomy. In addition, in one experiment EPO was also administered to separate grps of mice at a dose & dosing regimen identical to NESP, as well as at doses 10-fold higher than NESP.

Findings: The model was used as repeated administration of the cytotoxic therapy would result in an accumulation of damage to the BM progenitor cells, stem cells, & BM stromal populations. Weekly injections of NESP resulted in more effective alleviation of anemia seen in the cycles compared to dosing with NESP every two weeks, or compared to equi-molar doses of EPO. As the cycles progress, the effect of NESP & EPO decrease – possibly due to BM damage, resulting in severe progenitor damage and/or erythroid precursor cell damage upon progressive exposure to the chemo. The sponsor postulates that more frequent dosing of NESP may increase its effectiveness as the chemo cycles progress, however, if the erythroid populations in the BM have a limited response capability to either endogenous or exogenous EPO, then this regimen may not be any more effective.

When NESP was injected prior to chemotherapy, the mice exhibited extremely high HGB levels, which reflected in a disproportionally high HGB level in the post-chemo interval.

3. NESP Alleviates Anemia in a Rat Anemia of Chronic Disorders (ACD) Model

Normal female Lewis rats [5-6/grp] were IP injected on day 0 with saline or PG-APS [polymers derived from group A streptococci] to induce chronic systemic inflammation, characterized by granuloma formation & spontaneously relapsing arthritis, as well as severe acute anemia that is followed by a chronic anemia [decreased numbers of microcytic RBCs, reduced RBC lifespan, increased retention of iron in macrophages, increased WBCs, increased M/E ratios in BM]. NESP was SC injected at various dose levels & dosing regimens beginning on day 30/36, dosing up to day 93/105/112. Measurements included histology, BM progenitor assays, cytokine analysis, and sera EPO levels.

Findings: Although NESP-Rx rats displayed normal or higher HGB levels, with a reduction in the iron sequestration, the RBCs produced stayed microcytic & hypochromic, compared to controls. When dosing with NESP ceased, the HGB levels fell to an anemic state. ACD rats injected with a single 30 µg/kg loading dose, followed by weekly maintenance doses of 1-3 µg/kg/dose, resulted in normalization of HGB levels. Total serum iron levels increased in the NESP-Rx rats from days 96 –112 (study term), but the levels were still notably lower than controls. The reduction in iron retention/stimulation of iron release was seen in the splenic macrophages.

4. Dose and Dosing Frequency of NESP in Normal Mice

Normal BDF₁ mice [15/grp] were SC injected with 0, 0.3, 1, 3, 10, 30, or 100 µg/kg/day of NESP via various dosing schedules – tiw, qiw, q2wks, q3wks, q4wks, or by 14-day continuous SC infusion (via Alzet pumps), followed by blood collection out to day 88/110. Samples were analyzed for CBC, differential, retics, and Abs.

Findings: Increased HGB levels were seen in a general, dose-level and dose-frequency related pattern. The longer the time interval between NESP doses, the greater the fluctuation in the HGB levels and the greater the magnitude of the drop in HGB levels between injections. With q2wks dosing, ≥30 µg/kg/dose of NESP was needed to maintain HGB levels at 1 g/dL higher than baseline, while with dosing q3wks; NESP levels as high as 100 µg/kg/dose were not able to maintain this HGB level. The cycle of q4wks resulted in a progressive drop in HGB with each cycle, as well as a worsening anemia between injections. NESP injections of <1 µg/kg/dose given tiw resulted in maintenance of the 1 g/dL HGB increment over baseline.

Mice dosed via SC infusion were anemic by the end of dosing (day 14). Anemia was observed in many of the mice injected intermittently with the higher doses of NESP – attributed by the sponsor to the development of anti-NESP Abs. Two mice that developed severe anemia [one each at 100 µg/kg/dose, q2wks & q3wks] also displayed neutralizing Abs.

Neutrophil & PLT levels fluctuated greatly, while eosinophilia correlated with NESP dosing. [Mice RBC lifespan is 40 days vs. human RBCs of 120 days]

PK/ADME Studies

List of Studies:

Note that the dates presented with each study are the dates the report was issued, not the date of study completion.

1. PK and PD Multidose Study of NESP Administered SC to Female BDF₁ Mice Following Carboplatin and Irradiation Exposure; study #101269; performed at Amgen (non-GLP); lot # (b) (4) [polysorbate formulation]; 4/01

2. Pilot PK Study to Determine the Effect of a Partial Hepatectomy on the Clearance of NESP, rHuEPO, & ³H-Mannitol in Male SD Rats Following IV Administration; study #101157; performed at Amgen (non-GLP); lot (b) (4) [HSA formulation]; 4/01

3. TK From “A 4-Week Toxicity & TK Study of NESP & G-CSF in the Rat via SC Administration with a 4-Week Recovery Period”; study #101185; performed at (b) (4) (per GLP); lot (b) (4) (NESP – HSA-free), # (b) (4) (G-CSF); 5/01

PK/ADME Studies**1. PK and PD Multidose Study of NESP Administered SC to Female BDF₁ Mice Following Carboplatin and Irradiation Exposure**

Normal BDF₁ female mice [30-65/grp] were exposed to carboplatin + irradiation for three 4-wk cycles (days 0, 28, 56) or to no chemotherapy. Mice were SC injected with 30 µg/kg/dose of NESP, qiw, for 4 or 9 wks [see below]. Blood was collected at protocol-specified intervals for PD (CBC, differentials, retics) and PK (via ELISA) analysis.

Treatment		Group			
		A (PK)	B (PK)	C (PD)	D (PD)
n		65	65	30	35
NESP	SC Dose (µg/kg)	30	30	30	30
NESP	Dosing Days (during cycles, C*)	0, 7, 14, 21	C1: 0, 7, 14, 21, C2: 28, 35, 42, 49 C3: 56	C1: 0, 7, 14, 21, C2: 28, 35, 42, 49 C3: 56	C1: 0, 7, 14, 21, C2: 28, 35, 42, 49 C3: 56
Carboplatin/Irradiation	Treatment	None [control]	Carboplatin and Irradiation	None [control]	Carboplatin and Irradiation
Carboplatin/Irradiation	Days (Cycles 1, 2, 3)	None [control]	C1: 0 C2: 28 C3: 56	None [control]	C1: 0 C2: 28 C3: 56

* C indicates Cycle.

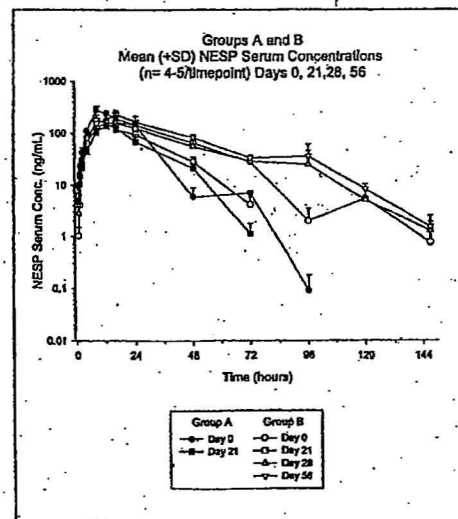
Findings: The PK profile was similar for wk 1 of each of the three chemo cycles, with a 1.5 to 2-fold higher exposure to NESP compared to controls. However, the wk 4 exposure for cycle 1 (day 21) was diminished compared to wk 1, with a shorter half-life & lower C_{max} – similar to the PK profile for the controls. The mice exposed to chemotherapy exhibited a lower increase in HGB levels compared to controls [maximum change from baseline of 4 g/dL vs. 7 g/dL for controls]. PK data are presented below:

NESP 30 µg/kg, SC Dosing							
Parameter	Units	Controls (Group A)		Carboplatin Irradiation Treated (Group B)			
		Day		Day			
		0	21	0	21	28	56
		-	-	C1 W1 ^a	C1 W4	C2 W1	C3 W1
T _{max}	hr	8	12	16	8	16	16
C _{max}	ng/mL	280	144	165	177	157	234
t _{1/2,z}	hr	6.89	8.08	16.0	10.6	18.2	18.0
AUC (0-∞)	ng•hr/mL	5470	3350	6830	4420	6760	9370
CL/F	mL/hr/kg	5.48	8.97	4.39	6.79	4.43	3.20

^a Numbers are rounded to 3 significant figures where possible.

^b C1 W1 - cycle 1, week 1.

* Analysis performed using naïve-averaged data (n=5).



2. Pilot PK Study to Determine the Effect of a Partial Hepatectomy on the Clearance of NESP, rHuEPO, & ³H-Mannitol in Male SD Rats Following IV Administration

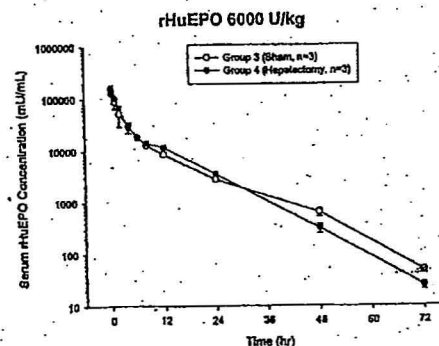
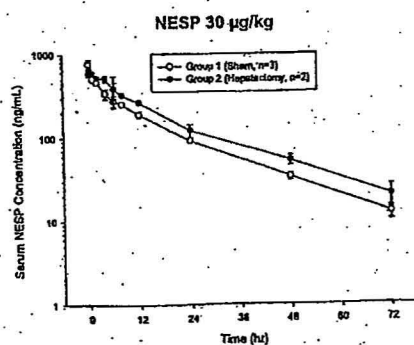
Normal male SD rats [3/grp] had either sham surgery or the medial & left lateral lobes of the liver (about 70% of total mass) removed, followed by single IV injection with 30 µg/kg of NESP, 6000 U/kg of rHuEPO, or 100 mg/kg of ³H-mannitol [NESP & EPO doses are equivalent on a peptide mass basis]. Blood was collected at protocol-specified intervals for PK (via ELISA) analysis [lower limit of detection = 0.078 ng/mL].

[Mannitol included as a negative control, as it distributes in total body water & its clearance should not be influenced by the partial hepatectomy]

Findings: The sera levels of NESP, EPO, & ³H-mannitol were similar for sham-operated & hepatectomy models. The NESP, EPO, & ³H-mannitol were detectable for 72, 72, & 3 hrs postRx, respectively. The surgery resulted in about a 20% loss in volume of distribution at steady state [V_{ss}] & in the clearance of all three agents. The sponsor postulates that the changes in the PK profile in the hepatectomized rats were likely a result of the physical removal of a significant amount of the liver, thus also causing about a 15% reduction in total blood volume of the rat [note that the PK profile was altered to a similar extent in the negative control grp].

PK data are presented below:

30 µg/kg NESP				
Parameter	Units	Group 1: Sham (n=3)	Group 2: Hepatectomy (n=2)	Ratio of Hepatectomy to Sham Values
CL	mL/hr/kg	3.89 (0.040)	2.89 (0.302)	0.74
C ₀	ng/mL	741 (137)	714 (13.9)	0.96
t _{1/2α}	hr	18.8 (1.46)	18.4 (1.51)	1.11
V _{ss}	mL/kg	77.2 (8.51)	62.7 (0.736)	0.81
V _d	mL/kg	41.4 (7.39)	42.0 (0.815)	1.01
6000 U/kg rHuEPO				
Parameter	Units	Group 3: Sham (n=3)	Group 4: Hepatectomy (n=3)	Ratio of Hepatectomy to Sham Values
CL	mL/hr/kg	12.5 (1.30)	10.9 (0.440)	0.87
C ₀	mU/mL	180000 (52100)	162000 (22700)	0.90
t _{1/2α}	hr	8.21 (0.125)	6.68 (0.125)	0.81
V _{ss}	mL/kg	97.5 (18.6)	78.1 (3.37)	0.80
V _d	mL/kg	35.9 (8.81)	37.6 (4.89)	1.07
100 mg/kg ³ H-Mannitol				
Parameter	Units	Group 5: Sham (n=3)	Group 6: Hepatectomy (n=3)	Ratio of Hepatectomy to Sham Values
CL	mL/hr/kg	1300 (57.6)	1040 (83.6)	0.80
C ₀	dpm/mL	237000 (26400)	249000 (28200)	1.05
t _{1/2α}	hr	1.05 (0.125)	0.730 (0.189)	0.70
V _{ss}	mL/kg	956 (99.4)	739 (87.6)	0.77
V _d	mL/kg	569 (59.9)	542 (58.3)	0.95



3. TK From "A 4-Week Toxicity & TK Study of NESP & G-CSF in the Rat via SC Administration with a 4-Week Recovery Period"; study #101185

Refer to study #101185 under "Preclinical Toxicology Studies" for the TK data.

Preclinical Toxicology Studies

List of Studies:

Note that the dates presented with each study are the dates the report was issued, not the date of study completion.

1. A 4-Week Toxicity & TK Study of NESP & G-CSF in the Rat via SC Administration with a 4-Week Recovery Period; study #101185; performed at (b) (4) (per GLP); lot # (b) (4) (NESP - HSA-free), # (b) (4) (G-CSF); 5/01

Toxicity Studies

1. A 4-Week Toxicity & TK Study of NESP & G-CSF in the Rat via SC Administration with a 4-Week Recovery Period

Species: SD rats (10-15/sex/grp - tox; 12/sex/grp - TK).

Dose Levels: 0 µg/kg - GR1

30 µg/kg/dose (NESP) + 100 µg/kg/day (G-CSF) - GR2

30 µg/kg/dose (NESP) + 1000 µg/kg/day (G-CSF) - GR3

100 µg/kg/dose (NESP) + 100 µg/kg/day (G-CSF) - GR4

100 µg/kg/dose (NESP) + 1000 µg/kg/day (G-CSF) - GR5

100 µg/kg/dose (NESP) - GR6

1000 µg/kg/day (G-CSF) - GR7

Route/Duration: SC/qiw (NESP), daily (G-CSF) for 4 wks + kills at wk 4 & recovery (wk 8)

Methods: Clinical signs, BWs, food consumption, ophthalmology, hematology* [baseline & days 7, 14, 29/30, 44, 56/58], coag*[days 29/30, 56/58], chemistry* [days 29/30, 56/58], urinalysis [days 29/30, 55/57], TK profile [2/sex/timepoint], antibodies [baseline & days 29/30, 56/58], and gross & histopathologic* evaluation

[Histo - Term kill - std set of tissues for GR1, 3, 5, 6, 7; bone, liver, spleen, kidneys, adrenals, mediastinal LNs - GR2, 4

Recovery kill - bone, liver, spleen, kidneys, adrenals, mediastinal LNs - GR1, 4, 5

* - toxicology animals only

Findings:

Deaths – 1/30 rats – GR1 (on day 7, due to an injury); 1/30 rats – GR4 (on day 35, cause of death not established); 1/24 rats – GR4 (TK, on day 31)

Swelling/cyanosis – paws; abnormal gait – 0% (control), 95% (GR2), 90% (GR3), 77% (GR4), 87% (GR5), 20% (GR6), 50% (GR7)

Onset – during wk 2

Abnormal gait incidence highest in GR5

Trend toward recovery

↓ BWs – GR2-5 [15-21% (males), 9-11% (females)] & GR7 [18% (males), 7% (females)] – trend toward recovery [8-11% loss for GR 4, 5 (males); 7% loss for GR4, 5 (females)]

↓ Food consumption – paralleled BWs

Abs - (via BIACORE 3000) –

Anti-G-CSF – 59/120 rats [GR2-5; 7] seropositive at wk 4

20-30% higher incidence of Abs in GR2-5 than in GR7

24% incidence at 100 µg/kg G-CSF vs. 67% at 1000 µg/kg

By wk 8 – most of the high-dose rats were negative

Placebo – total of 4 rats that were weakly positive at wk 4/8

Neutralizing activity – not measured due to the lack of a G-CSF bioassay for neutralizing activity; but 4 rats in GR2-5 that had Abs also had low neutrophil levels

Anti-NESP – 12/120 of GR2-6 – seropositive at wk 4; one also seroconverted at wk 8

No difference was noted between GR2-5 & GR6

Neutralization activity – 0/14 rats preRx; 9/14 postRx [from GR2-5] – 8/9 positive rats had ↓ retics

TK - (via ELISA) – Day 0 – similar PK profile for the combination, as compared to single agent administration

Combination grps - ↑ CL/F (16-51%) & in Vz/F (7-46%) for NESP – day 0-28

C_{max} & half-life remained constant

PK profile of NESP when given with G-CSF was similar to NESP alone. Gender did not affect the PK profile.

Vol 24, p. 1926

Clinical Pathology

↑ HCT, HGB – GR2-5 (not dose-related), GR6 – wk 4 – recovery (GR4, 5)

↑ RBCs (5-15%, wk 1; 15-25%, wk 2; 30-60%, wk 4) – GR2-5 (not dose-related, females slightly higher) – trend toward recovery (GR 4, 5)

↑ RBCs (15%, wk 1; 35-45%, wk 2; 60-70%, wk 4) - GR6 [no recovery interval]

↑ Retics – GR2-6 - 4-8-fold above control (wk 1), 2-5-fold above control (wks 2, 4) – dose-related, females slightly higher [NESP] – recovery – 60-65% (males), 85% (females) below control (wk 6); 70-75% (males), 90% (females) below control (wk 8)

↑ MCV – GR2-6 – wks 1, 2, 4 [no recovery interval]

↓ MCHC – GR2-6 – wks 1, 2, 4 [reflective of Fe depletion, resulting in undersized, ↓ HGB-containing RBCs]

↓ MCV, MCH, MCHC – GR4, 5 – wks 6, 8

↑ PLTs – GR6 – 36-84% - wks 1, 2, 4

↓ PLTs – GR2-6 females – wks 1, 2, 4 – recovery (GR4, 5)

↓ PLTs (slight) – GR7

↑ PT, APTT – GR2-6 - wk 4 – recovery

[Serum Fe & Fe-binding capacity not evaluated]

- ↑ WBCs – 2-4-fold control (GR2, 4) – wks 1, 2, 4 – recovery (GR4)
- ↑ WBCs – GR3, 5 – 4-5-fold (wk 1), 5-8-fold (wk 2), 7-9-fold (wk 4) – recovery (GR5)
- ↑ WBCs – GR7 – 5-6-fold (wk 1), 6-11-fold (wk 2), 12-fold (wk 4)
- ↑ monocytes – GR2-5, 7 (3-25-fold the controls) – wks 1, 2, 4 – recovery (GR4, 5)
- ↑ eosinophils – GR7 (2-fold) – wk 4
- ↑ lymphocytes – GR2-5, 7 (variable) – wks 1, 2, 4 – recovery (GR4, 5)
- ↑ neutrophils – GR2-5, 7 – wks 1, 2, 4 – recovery (GR4, 5)
- ↑ basophils – GR2-5, 7 – wks 1, 2, 4 – recovery (GR4, 5)
- ↑ M/E ratios – GR2-5, 7 [GR7 had the most prominent response]
- ↓ M/E ratio; ↑ polychromatophilic rubricytes, metarubricytes – GR6
- ↓ metarubricytes – GR2-5
- ↓ glucose – 25-45% for males & 50-65% for females, compared to control – GR2-6 – recovery (GR4, 5)
- ↑ bilirubin – 20-70% compared to control – GR2-6 – recovery (GR4, 5)
- ↑ AlkP – 3-19-fold compared to control (G-CSF-dose-related) – GR2-5, 7 – recovery (GR4, 5)
- ↓ triglycerides – 40-60% of control – GR3, 7
- ↑ AST – 30-100% compared to controls – Rx grps – recovery (GR4, 5)
- ↓ cholesterol – 20-25% of controls – Rx males – recovery (GR4, 5)
- ↓ albumin – 12-25% of controls; ↑ globulin – 8-40% of controls – GR2-5 – recovery (GR4, 5)
- ↑ calcium, phosphorus – 3-40% of controls – Rx grps – recovery (GR4, 5)
- ↓ urine electrolytes – GR2-6

Gross

- ↑ spleen; ↓ thymus wts – Rx grps – recovery (GR4, 5)

Spleen – enlarged – Rx grps – greater severity seen in GR 3, 5 – trend toward recovery (GR4, 5)

Limb extremities – swelling [paws, hindlimbs] – GR2-5, 7 – trend toward recovery (GR4, 5)

Histo – Term Kill

BM – prominent granulopoiesis & production of mature neutrophils – extended beyond periosteum, into adjacent tissue – GR2-5, 7

- ↑ erythropoietic activity – GR6

Spleen - extramedullary hematopoiesis (erythroid); granulopoiesis & production of mature neutrophils; ↑ red pulp histiocytes – GR2-5, 7 – with G-CSF effects predominating

Increased erythropoietic activity – GR6

Liver, Kidney, Adrenals, Mediastinal LNs - extramedullary hematopoiesis (erythroid) - Rx grps – more widespread tissue involvement with GR7

Renal vascular congestion – GR2-6

Vascular congestion – adrenals – GR2-6

Mesenteric LNs – medullary sinus histiocytosis/granulopoiesis – GR3, 5, 7

Femoral/Sternal Bone – bone remodeling [expanded femoral intertrabecular spaces, cortical bone loss]; proliferation [endosteal new bone, myelofibrosis] – GR2-5, 7

Extremities – hypertrophic osteopathy [periosteal/endosteal new bone, cortical bone loss, myelofibrosis, marrow necrosis, inflammatory changes in soft tissue] – GR2-5, 7

Other – gastric mucosal necrosis – limited animals in GR5, 6

Histo – Recovery Kill – GR4, 5

Femoral/Sternal Bone – mild femoral osseous changes – endosteal new bone, myelofibrosis; resolving hypertrophic osteopathy – GR4, 5

The NOAEL was 100 µg/kg/dose for NESP. A NOAEL was not achieved for G-CSF, due to bone changes seen with G-CSF alone or in combination with NESP.

CONCLUSION:

The proposed clinical indication for ARANESP™ is for the treatment of anemia in patients with nonmyeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy, as NESP has been shown to stimulate erythropoiesis in this patient population. This treatment has been correlated with a reduction in RBC transfusions.

NESP is a well-characterized recombinant protein, which is an analog of recombinant human erythropoietin (EPO). NESP stimulates erythropoiesis in a manner identical to endogenous human EPO, as well as recombinant human EPO - which is approved for use in the Rx of anemia in patients with chronic renal failure (CRF). NESP binds to cell surface receptors that are specific for EPO, resulting in the promotion of survival, proliferation, & differentiation of cells of the erythroid lineage. The in vitro potency of NESP is lower than that of EPO due to an increase in negative charge resulting from the addition of sialic acid containing carbohydrate & consequently weaker receptor binding. However, due to the addition of this carbohydrate, the in vivo activity

of NESP is increased relative to EPO because of its longer serum half-life [~3-fold longer]. NESP is already approved for use in the treatment of anemia in chronic renal failure. Please refer to the toxicologist's review of BLA # (b) (4) for many of the preclinical studies submitted in support of the CRF indication, as that review is also applicable for the oncology indication. This document is a review of the preclinical studies that were not included in BLA # (b) (4).

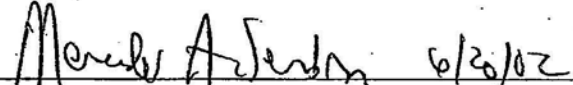
Activity studies performed in rodents and dogs in support of the CRF indication showed that NESP injection resulted in a dose-dependent increase in red cell mass production.

Additional *in vivo* studies in BDF₁ mice exposed to various chemotherapeutic agents showed that single SC injection of 100 µg/kg NESP both prior to, and after one cycle of chemotherapy, resulted in maintenance of HGB levels, with elevation above baseline in some animals. Administration of NESP at 100 µg/kg to BDF₁ mice on different days relative to single agent cytotoxic administration (q28 days x 4 cycles) for each cycle [carboplatin or carboplatin + whole body irradiation] resulted in more effective alleviation of anemia compared to parallel dosing with equi-molar doses of rHuEPO. A rat model of the anemia of chronic disease (ACD), thought to represent the anemia intrinsic to the inflammatory processes associated with cancer, was developed. Injection of a 30 µg/kg/dose loading dose of NESP, followed by weekly maintenance doses of 1-3 µg/kg/dose, resulted in normalization of HGB levels, with a trend toward increasing total serum iron levels.

Rats were SC injected qiw, for 4 weeks at NESP doses of 30 or 100 µg/kg/dose, as a single agent or in combination with 100 or 1000 µg/kg/day of G-CSF [given daily]. The toxicologic & TK profile of NESP in combination with G-CSF was similar to that of NESP alone. Findings included decreased body weights; increased red cell mass, neutrophils, and reticulocytes; decreased PLTs, MCH, MCHC; increased liver transaminases; decreased glucose, cholesterol, protein; extramedullary hematopoiesis in the spleen and liver; congestion in various major organs [due to the polycythemia]; and bone marrow hyper-cellularity. The only finding with the combination of NESP & G-CSF and with G-CSF alone was the bone changes observed. Bone remodeling was evident in femoral & sternal bone, as well as hypertrophic osteopathy in various extremities - manifested as swelling in the paws & hindlimbs in the rats. Mild femoral osseous changes were still present in the NESP + G-CSF rats after four wks of nontreatment. The development of anti-NESP antibodies occurred in some rats administered NESP alone or in combination with G-CSF; neutralizing in 9/14 rats. The development of anti-G-CSF antibodies occurred in 50% of the rats administered G-CSF alone or in combination with NESP [G-CSF neutralization activity was not measured]. A NOAEL for G-CSF could not be achieved in due to the bone changes seen with G-CSF alone or in combination with NESP. The NOAEL for NESP was considered to be 100 µg/kg/dose.

Evaluation of the distribution of NESP in rats with partial hepatectomies revealed about a 20% decrease in the volume of distribution of steady state & clearance for NESP, EPO, & ³H-mannitol – considered a result of the physical removal of the sections of liver & the approximate parallel loss of 15% of the total blood volume of the rat. Following *in vitro* exposure to 23 different human tissues, desialylated NESP, desialylated EPO, and EPO bound only to bone marrow, which expresses EpoR.

The preclinical data adequately support use of the product, ARANESPTM, for the indication specified by the sponsor.


Mercedes A. Serabian, M.S., D.A.B.T., Toxicologist

Key Words: EPO; NESP; ARANESPTM; recombinant human erythropoietin; glycosylation; chronic renal failure; cancer; chemotherapy; RBC; HCT; HGB; transfusion; anemia

concurrences: 
OTRR/C,P-T/MGreen

DATE: June 27, 2002

FROM: Sharon K. Gershon, Pharm.D., CBER/OBE/DE

THRU: Timothy R. Coté MD, MPH
Chief, Therapeutics and Blood Safety Branch

TO: STN 103951/5001:Amgen:Darbepoetin alfa

SUBJECT: Epidemiology Review - Post-licensure reports of "pure red cell aplasia" (PRCA) associated with darbepoetin alfa (Aranesp, Amgen)

Through June 27, 2002 there are 3 post-licensure reports of PRCA and 1 case of "therapeutic response decrease" associated with Aranesp. These cases are described below, and the corresponding Medwatch reports attached.

Case 1

- PURE RED CELL APLASIA
- 21yo male, Spain
- Indication: anemia of CRF
- Began tx w/ epoetin beta 8/14/2001 at dose of 2000 IU/week. Hgb level increased and treatment was stopped. Hgb level decreased, so epoetin beta was restarted at dose of 6000 IU/week. HCT decreased and dose of epoetin beta was increased to 12,000 IU/week. Pure red cell aplasia was confirmed (dx unknown) and tx w/ epoetin beta was stopped. Treatment restarted after 1 month plus corticosteroids. Patient had good response (Hgb 12 g/dL), and the drugs were stopped. Hgb dropped.
- Recruited to Aranesp clinical trial (Jan, 2002). A sample was sent to a Spanish hospital for anti-Epo antibody testing and the result was positive

Case 2

- PURE RED CELL APLASIA
- 59yo female, San Diego CA
- Indication: anemia of CRF
- Dialysis patient w/ failed renal transplant x 2, multi-infectious episodes, 10 mo hx Epogen became transfusion dependent & was diagnosed w/ PRCA after 3 months darbepoetin alfa. BM showed PRCA. Antibody to darbepoetin alfa was negative.

Case 3

- PURE RED CELL APLASIA
- 48yo male, Germany
- Indication: anemia of CRF
- Patient begun Erypo, with initial good response x 10 mos. Began to develop wheals at inj site, and patient switched to Recormon (epoetin beta) x 2 doses. Devel'd injection site wheals after 2 doses, so was switched to Aranesp x 2 doses. Pt developed urticaria, pruritis more intense than w/ Erypo. Pt was hosp for

transfusion due to decreasing Hgb, and BM biopsy confirmed PRCA. Antibodies to erythropoietin were confirmed.

Case 4

- THERAPEUTIC RESPONSE DECREASED, ANEMIA
- 73yo female, New York
- Indication: anemia of CRF
- Received decreasing doses Epogen ex despite declining Hgb, & was switched to Aranesp. Hgb level con't to decline & pt was hosp for addl transfusions; Pt. Discharged 5 days later. Antibody test pending

APPEARS THIS WAY ON ORIGINAL

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
103951/5001

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

FDA Number: 103951/5001

Task/Type: BLA (submission received 9/20/01)

Sponsor: Amgen Inc.

Product: Darbepoetin-alfa (Aranesp)

Indication: Treatment of anemia in lung cancer patients receiving platinum-containing chemotherapy

Date: 7/1/02

From: Clara Chu, Ph.D. CC

Through: G. Gupta, Ph.D./HFM-219

To: Dr. Stephen Litwin/HFM-573

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Shashyan Euro
7-2-02

Background

Amgen Inc. has submitted a supplement for the approval of Darbepoetin-alfa (Aranesp) for the treatment of anemia in patients with lung cancer receiving platinum-containing chemotherapy. This BLS consists of 3 Phase II dose-finding studies (980290a, 980290b, 980291) and one Phase III (980297) trial. This review will discuss only the Phase III study.

Study 980297 (Phase III)

Trial Design

This is a multi-center, double-blinded, randomized, placebo-controlled Phase III trial. Patients were randomized in a 1:1 ratio to receive weekly injections of NESP at an initial dose of 2.25 µg/kg or placebo. Patients received study drug once a week for 12 weeks. If the hemoglobin measured at the beginning of week 6 increased by ≤ 1.0 g/dL from baseline, then the dose of study drug was doubled for the remaining 6 weeks of the treatment phase. Following the treatment phase of the study, patients were observed weekly until the end-of-study (EOS) phase, 4 weeks later. Subsequent to the EOS phase, patients were followed for a minimum of 1 year after the end of the treatment phase (EOTP) for the last patient who completed the treatment phase. Tumor status and survival status data were collected during this long term follow-up period.

The sample size was calculated to be 310 patients randomized from up to 75 centers in Europe, Australia, and Canada. This calculation is based on the following assumptions: a 40% incidence of RBC transfusions from week 5 to (EOTP) period on the placebo arm vs. a 20% incidence of RBC transfusions from week 5 to (EOTP) period on the NESP arm, 90% power, 2-sided significance level of 5%, and dropout rate of 30%. Using an uncorrected chi-square test, a sample size of 155 patients per arm is recommended. The transfusion incidence is estimated by the Kaplan-Meier method and then pooling the proportions across tumor type/region strata using inverse squared standard error weights (Cochran, 1954; Whitehead, et al 1991). The test of significance is a chi-squared test. This analysis approach, although different from the uncorrected chi-square test, should not be less powerful. Therefore, 310 patients are still recommended for the study.

The randomization was stratified to balance the treatment groups within geographic region: Australia (AUS), Canada (CAN), or Europe - including Western (WEU) and Central/Eastern Europe (CEE) - and by tumor type: small cell lung cancer (SCLC) vs. non-small cell lung cancer (NSCLC) within region. The randomization was not stratified by study center.

Primary and Secondary Endpoints

The primary endpoint is the proportion of subjects who received an RBC transfusion from week 5 to EOTP inclusive, which was estimated using the K-M method. The time to first RBC transfusion is defined in weeks from study day 1 to the first administration of an RBC transfusion from week 5 to EOTP, inclusive of the treatment phase (i.e. on or after day 29). Any RBC transfusion given between randomization and week 4 inclusive was ignored. For the primary endpoint, a patient must have had their EOTP on or after day 1 of week 5 for inclusion in the analysis.

Selected secondary endpoints included the following:

1. proportion of patients receiving RBC transfusions from week 1 to week 4, estimated using the K-M method
2. proportion of patients receiving RBC transfusions from week 1 to EOTP, estimated using the K-M method
3. proportion of patients achieving a high response (an increase in hemoglobin of ≥ 2 g/dL over baseline) in the absence of RBC transfusions in the prior 28 days, estimated using the K-M method
4. change in hemoglobin from baseline to EOTP.

HRQOL data was also collected. The FACT-Fatigue scale score measured from baseline to EOTP is the primary secondary endpoint. The FACT-Fatigue scale consists of questions 8 a through j on the FACT questionnaire. These questions consist of response values of 1 to 5. Since the original FACT questionnaire has response values of 0 to 4, the FACT-Fatigue responses must be transformed back to the 0 to 4 scale by subtracting 1 from each score. Then the negatively stated items must be reversed before being summed to obtain scale totals. This is done by subtracting the response from 4. If there is no missing data for a subscale, the raw subscale is obtained by summing the question

scores for scale items. Higher scores indicate better HRQOL. If there is missing data for a scale, but at least 50% of the items have been answered, then raw subscales can still be estimated using the following formula:

$$\text{Prorated subscale score} = \frac{[\text{Sum of item scores in subscale}] \times [\text{N of items in subscale}]}{\text{N of items answered in the subscale}}$$

If there are missing data for a subscale and < 50% of the items have been answered, the raw subscale score cannot be validly calculated and are considered missing.

The following factors on treatment differences for efficacy endpoints were assessed: tumor type (NSCLC, SCLC), geographic region (AUS, CAN, WEU, CEE), sex, baseline hemoglobin concentration (< 9 g/dL, 9 to < 10 g/dL, 10 to < 11 g/dL, ≥ 11 g/dL), and baseline serum endogenous EPO concentration (≤ 100 mU/mL, > 100 mU/mL). Additionally, the following covariates may be assessed for efficacy endpoints: age (< 65, ≥ 65), race (Caucasian, Black, Asian, other), study drug dose increased after week 6 (yes, no), and baseline hemoglobin as a continuous variable.

Interim analysis

No interim analysis was planned for any efficacy endpoints evaluated during the treatment phase or the 4-week follow-up period. If an analysis of efficacy data should become necessary, then it will be carried out using a significance level of 0.001 (Peto 1976; Haybittle, 1971). No interim analysis was conducted for this study.

Statistical Analysis Plan (SAP)

Analysis Populations

The primary statistical analysis was performed on the ITT population. Sensitivity analyses were performed on the evaluable population to evaluate robustness of study results. The ITT population for the primary endpoint is defined as all randomized patients who received at least 1 dose of study medication and whose EOTP date occurred after day 1 of week 5 (day 29). This population is referred to as the primary analysis population. For efficacy endpoints being measured from week 1 to EOTP, such as hemoglobin response and proportion of RBC transfusions starting from week 1, the ITT population is all patients randomized who received at least 1 dose of study medication.

The evaluable population for HRQOL consists of all patients who received at least 1 dose of study medication, whose EOTP date occurred after day 1 of week 5 (day 29), and who completed the FACT-Fatigue scale at baseline and at least one time from week 5 to EOTP.

Censored Data

For the primary endpoint, proportion of patients with an RBC transfusion from week 5 to EOTP, the following approach was used: patients were considered transfused at their EOTP if they had not previously received a transfusion after day 1 of week 5 until their EOTP if they withdrew for the following reasons:

1. adverse events related or unrelated to study drug
2. consent withdrawn
3. administrative decision
4. discontinuation or delay of chemotherapy
5. loss to follow-up
6. other.

If patient withdrawals were due to disease progression or death after week 5, then patients were analyzed as observed in the following way:

1. considered transfused if they were transfused after day 1 of week 5 but prior to EOTP
2. considered not transfused if they were not transfused after day 1 of week 5 until EOTP.

This approach was considered the primary approach to censoring. An alternative censoring approach, which consists of counting all patients who withdrew after week 5 for any reason as transfused, was also implemented. This approach was considered the secondary approach to censoring.

For transfusions from week 1 to EOTP, censored data were handled in the following way: all patients who terminated early for any of the following reasons were considered transfused at their EOTP if they had not previously received a transfusion prior to the EOTP:

1. adverse event related or unrelated to study drug
2. consent withdrawn
3. administrative decision
4. discontinuation or delay of chemotherapy
5. loss to follow-up
6. other.

Patients who withdrew due to disease progression or death were analyzed as observed at the time of censoring in the following way:

1. considered transfused if they were transfused prior to EOTP
2. considered not transfused if they were not until EOTP.

For secondary endpoints such as hemoglobin response, patients were analyzed as observed at the time of censoring and considered a responder if they responded prior to EOTP or considered a non-responder if they had not responded prior to EOTP.

Handling of Missing Data

Missing HRQOL data were handled using the following approach: for patients who withdrew from study after week 5 due to disease progression or death, the change in FACT-Fatigue score from baseline was calculated using the last observed FACT-Fatigue

score during the treatment phase. For all other patients who withdrew after week 5 or did not have a FACT-Fatigue score at the planned EOTP, the patient's minimum score observed between week 5 and the EOTP were used. This approach was considered the primary approach.

Two secondary approaches to handle missing data were used to show robustness of the results. In the first approach, for subjects who withdrew after week 5 for reasons other than death or disease progression or did not have a FACT-Fatigue score at the planned EOTP, either the subject's minimum score observed between week 5 and the EOTP or the baseline score were used; whichever is lower. In the second approach, multiple imputation was used to assign an EOTP score. Covariates that were planned as possible predictors of HRQOL included hemoglobin values, ECOG status, chemotherapy data, disease progression, and the proximity of the patient to death.

Efficacy Analysis

For the primary endpoint, proportion of subjects with a red blood cell (RBC) transfusion from week 5 to the EOTP, Kaplan-Meier (K-M) proportions were estimated for each tumor type/region combination (stratum $i = 1$ to k , where k is the total number of strata evaluated) as:

$\hat{p}_{N_i}$ = K-M proportion for an RBC transfusion from week 5 to the EOTP for NESP in stratum i

$\hat{p}_{P_i}$ = K-M proportion for an RBC transfusion from week 5 to the EOTP for placebo in stratum i

where stratum 1 = SCLC, WEU
 2 = SCLC, AUS
 3 = SCLC, CAN
 4 = SCLC, CEE
 5 = NSCLC, WEU
 6 = NSCLC, AUS
 7 = NSCLC, CAN
 8 = NSCLC, CEE

If a tumor type/region stratum for either treatment group contained < 10 patients or its K-M proportion was 0, then strata were pooled before analysis. Pooling occurred across regions (not tumor type) until all strata had > 10 patients and all K-M proportions were > 0 . The variances of the proportions were estimated using Greenwood's formula (Kalbfleisch and Prentice, 1980).

The difference between the proportions responding for NESP and placebo,

$\hat{\theta}_i = \hat{p}_{N_i} - \hat{p}_{P_i}$ and its variance, $Var(\hat{\theta}_i)$, were calculated for each stratum. Before

combining the estimates of difference from the strata, a chi-square test for homogeneity across the strata was done. Homogeneity of the stratum-specific differences between NESP and placebo was assumed if the resulting p-value from this test was > 0.10 . If

there was evidence of a lack of homogeneity across strata ($p \leq 0.10$), the nature of this would be explored and results presented separately by tumor type and region, or alternative methods would be used.

Assuming no evidence of heterogeneity across strata, the overall estimate of the difference in proportion responding on NESP compared with placebo, $\hat{\theta}$, was calculated. The 95% confidence interval for the difference in proportion responding to NESP compared to placebo was obtained from $\hat{\theta} \pm 1.96\sqrt{\text{Var}(\hat{\theta})}$

A chi-square test (Cochran 1954; Whitehead and Whitehead, 1991) was used to test the hypothesis of no difference in the proportion responding for the 2 treatment groups. If the resulting p-value was < 0.05 , the difference between the proportion responding on NESP and the proportion responding on placebo was considered statistically significant. This statistical hypothesis supports the primary clinical hypothesis that treatment with NESP 2.25 $\mu\text{g/kg/week}$ results in a reduction in RBC transfusion requirements during week 5 to EOTP compared with placebo. The primary endpoint, the proportion of patients with an RBC transfusion from week 5 to EOTP, was presented for each treatment group along with approximate 95% confidence intervals. The same approach was used for sensitivity analyses of the primary endpoint, and time to event measured secondary endpoints: proportion of patients receiving RBC transfusions from week 1 to EOTP and proportion of patients achieving a high response.

The results from inferential statistical analyses were assessed at the 0.05 level of significance unless otherwise stated. No adjustments for multiplicity were planned for analyses of secondary efficacy endpoints, quality of life scale scores, safety data or secondary analyses of the primary efficacy endpoint and therefore, p-values from such analyses were considered descriptive.

Summary statistics were provided for the hemoglobin change from baseline to the EOTP by treatment group for the ITT and evaluable populations. Change from baseline was also summarized by presenting the frequency distribution for each treatment group as follows: < 0 , ≥ 0 and < 1 , ≥ 1 and < 2 , ≥ 2 .

The primary comparison between the NESP and placebo arms for changes in the FACT-Fatigue scale from baseline was to be made using the stratified Wilcoxon rank sum test. This test was chosen because of potential non-normality in the FACT-Fatigue scale. The primary analysis would stratify by tumor type. Secondary analyses would also include region as an additional stratification factor.

Efficacy Results

The study consists of 320 patients with 159 randomized to the NESP arm and 161 randomized to the placebo arm. The ITT population is comprised of 314 patients with 156 in the NESP arm and 158 in the placebo arm. The primary analysis population consists of 148 patients in the NESP arm and 149 in the placebo arm. Table 1 shows the number of patients by treatment group, by country and by tumor type for each of the

three populations. Table 1 shows that the treatment groups are balanced by the stratification variables for each population.

Table 1. Treatment group by stratification factors

Country	Tumor Type	Treatment					
		NESP			Placebo		
		Rand	ITT	PA	Rand	ITT	PA
AUS	NSCLC	5	5	5	5	5	4
	SCLC	2	2	1	1	1	1
CAN	NSCLC	5	4	3	6	6	6
	SCLC	2	2	2	3	3	3
CEE	NSCLC	41	40	36	42	42	40
	SCLC	18	18	18	17	17	16
WEU	NSCLC	60	59	58	63	61	58
	SCLC	26	26	25	24	23	21
Total		159	156	148	161	158	149

Table 2 shows the number of patients by ending study reason for each of the three populations. Table 2 shows that the two treatment groups are balanced with respect to ending study reason for each population.

Table 2. Treatment group by ending study reason

Ending Study reason	Treatment					
	NESP			Placebo		
	Rand	ITT	PA	Rand	ITT	PA
Study Completed	110	110	110	109	109	109
Adverse Event	2	2	1	5	4	3
Consent Withdrawn	5	3	1	5	5	5
Disease progression while on study	9	9	9	9	8	8
Administrative decision	2	2	1	2	1	1
Lost to followup	6	6	6	3	3	3
Death on study	14	14	11	19	19	12
Chemotherapy delayed	3	3	3	1	1	1
Chemotherapy discontinued	7	7	6	7	7	6
Other	1	0	0	1	1	1
Total	159	156	148	161	158	149

Analysis of selected prospectively defined baseline variables revealed that the two treatment groups are balanced in the primary analysis population as shown in Table 3 with the exception of the group with baseline hemoglobin > 11 g/dL.

Table 3. Treatment group by baseline variables for the primary analysis population

Baseline variable		Treatment	
		NESP (N=148)	Placebo (N=149)
Age	≥ 65 years	55	63
	< 65 years	93	86
Sex	Male	105	110
	Female	43	39
Baseline hgb (g/dL)	< 9	18	26
	[9, 10)	28	39
	[10,11]	72	70
	> 11	30	14

Time to first RBC transfusion was calculated from the first date that treatment was administered. This reviewer checked the randomization dates and the first dates that treatment was administered by treatment group. The analysis revealed that similar numbers of patients from both groups had a different first date of treatment than randomization date. An analysis on the mean differences between these 2 dates by treatment group revealed that there was no statistically significant difference between the two groups. Hence, there was no bias between the NESP and placebo groups with respect to delay in therapy.

Time to RBC transfusion was defined from the first date of treatment to the date of transfusion or the EOTP period in days. The time to transfusion variable was defined by adding 7 days and then dividing by 7 to get the number of weeks. For example, if treatment started on study day 1, and an event occurred on study day 14, then time to RBC transfusion is calculated as 2.9 weeks. The sponsor started measuring time to transfusion at week 1 instead of week 0. **This method of calculating time to transfusion was not prospectively defined in the analysis plan.** Analyses on time to transfusion variables were performed using number of study days instead of number of study weeks.

Primary endpoint

Because there were not sufficient numbers of subjects in Australia and Canada, the sponsor combined those subjects with those in Western Europe. This new grouping resulted in 2 region strata, Central & Eastern Europe and Rest of the World (CEE, ROW). Subsequently, the analyses were performed using 4 strata defined by 2 regions (CEE, ROW) and 2 tumor types (NSCLC, SCLC).

Patients were censored using the primary approach as described in the SAP. The analysis of the primary endpoint was performed using the Kaplan-Meier (K-M) method. The analysis revealed that there is a statistically significant difference between the NESP and the placebo groups with respect to the proportion of patients receiving RBC transfusions from week 5 to EOTP after stratifying by tumor type and region (Table 4). The test for stratum-specific differences between the NESP and placebo arms resulted in a p-value of 0.63. Therefore, it was assumed that the strata were homogeneous. According to Table

4, the proportion of RBC transfusions was reduced from 51% (43, 60) to 21% (15, 28). The weighted (by tumor type and region) difference of 24% (13, 35) is highly significant.

Table 4. RBC transfusions from week 5 to EOTP stratified by tumor type and region

	Placebo	NESP	Difference in Proportions (NESP-Placebo)	p-value
Number of Subjects	149	148		
Number of Subjects w/ RBC transfusions from Week 5 to EOTP	74	39		
KM Proportion (95% CI)	51 (43, 60)	21 (15, 28)	-24 (-35, -13)	< 0.001

Sensitivity analyses were performed by the sponsor to show that this statistically significant difference is robust. A subset of these analyses consisted of using alternative censoring definitions, an alternative primary endpoint definition, and covariate analyses. Two alternative censoring definitions used. One of these definitions, referred to as the secondary approach in the SAP, counted all patients who withdrew after week 5 for any reason as being transfused. The other definition, counted only those patients who had an RBC transfusion after week 5 as being transfused (non-imputed approach). Table 5 shows the results of these analyses.

Table 5. RBC transfusions from week 5 to EOTP stratified by tumor type and region using alternative censoring approaches

		Placebo	NESP	Difference in Proportions (NESP-Placebo)	p-value
Censoring Approach	Number of Subjects	149	148		
Secondary Approach	Number of Subjects w/ RBC transfusions from Week 5 to EOTP	83	49		
	KM Proportion (95% CI)	56 (48, 64)	25 (18, 31)	-23 (-34, -12)	< 0.001
Non-imputed Approach	Number of Subjects w/ RBC transfusions from Week 5 to EOTP	68	28		
	KM Proportion (95% CI)	48 (40, 56)	16 (10, 22)	-28 (-38, -18)	< 0.001

The test for stratum specific differences did not show statistical significance for either approach. Therefore, homogeneity was assumed in computing the difference in

proportions between the two groups. Table 5 shows that the statistically significant difference between the NESP and placebo groups is consistent across the different censoring approaches.

Another sensitivity analysis used an alternative primary endpoint definition, which defined an event to be either a hemoglobin measurement ≤ 8 g/dL or an RBC transfusion between week 5 and EOTP. This definition was used to assess whether the different transfusion policies across centers affected the difference in the proportion of patients transfused in the NESP and placebo groups. Analyses were performed using the three censoring approaches.

Table 6. RBC transfusions from week 5 to EOTP stratified by tumor type and region using alternative primary endpoint definition

		Placebo	NESP	Difference in Proportions (NESP-Placebo)	p-value
Censoring Approach	Number of Subjects	149	148		
Primary Approach	Number of Subjects w/ RBC transfusions from Week 5 to EOTP	89	45		
	KM Proportion (95% CI)	62 (54, 70)	29 (21, 36)	-30 (-41, -19)	< 0.001
Secondary approach	Number of Subjects w/ RBC transfusions from Week 5 to EOTP	95	54		
	KM Proportion (95% CI)	64 (56, 72)	33 (25, 40)	-28 (-38, -17)	< 0.001
Non-imputed Approach	Number of Subjects w/ RBC transfusions from Week 5 to EOTP	83	35		
	KM Proportion (95% CI)	58 (50, 66)	23 (16, 30)	-34 (-44, -23)	< 0.001

There were no significant differences among strata in any of the three different approaches. Therefore homogeneity was assumed in all three analyses. The three approaches yield similar results for the difference in proportions between the NESP and placebo groups (Table 6). In comparison to the primary endpoint, the analysis yielded slightly higher estimates of the difference in proportions between the two groups.

Because of an imbalance in baseline hemoglobin, further analyses were conducted to determine if the statistically significant difference in proportions between the placebo and

the NESP groups remained. There were 44 patients, including 30 in the NESP group and 14 in the placebo group, with a baseline hemoglobin > 11 g/dL. It was believed that having a baseline hemoglobin > 11 g/dL is considered a violation of the inclusion criteria in the study protocol. As a result, analyses were performed excluding these 44 patients. The results of these analyses are presented in Table 7.

Table 7. RBC transfusions from week 5 to EOTP stratified by tumor type and region excluding patients w/ a baseline hemoglobin > 11 g/dL

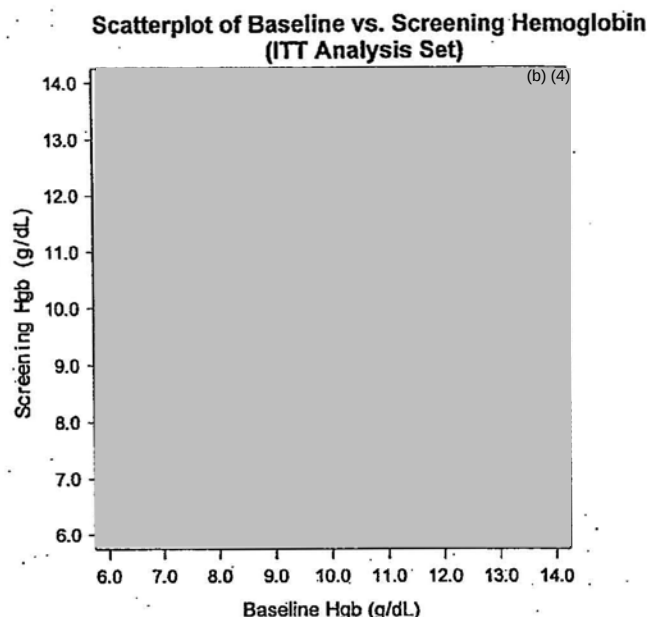
		Placebo	NESP	Difference in Proportions (NESP-Placebo)	p-value
Censoring Approach	Number of Subjects	135	118		
Primary Approach	Number of Subjects w/ RBC transfusions from Week 5 to EOTP	71	34		
	KM Proportion (95% CI)	55 (47, 63)	23 (16, 30)	-25 (-36, -13)	< 0.001
Secondary approach	Number of Subjects w/ RBC transfusions from Week 5 to EOTP	78	43		
	KM Proportion (95% CI)	58 (50, 66)	27 (20, 35)	-22 (-34, -10)	< 0.001

Table 7 shows that the statistically significant difference in proportions between the NESP and the placebo groups is consistent with that of the primary analysis population under the primary and the secondary censoring approaches.

Additionally, when treatment group, tumor type, region, and baseline hemoglobin (categorized into 4 levels) were included in a Cox proportional hazards model, a significantly lower proportion of patients in the NESP group had an RBC transfusion during week 5 to EOTP than those patients in the placebo group (hazard ratio: 0.48 [0.33, 0.71]).

Reviewer comment: In a telecon on 4/5/02, the sponsor explained that both a screening measurement and a baseline measurement of hemoglobin were obtained for each patient. Screening occurred up to 2 weeks before randomization. A baseline measurement was recorded just before the start of treatment. Among those randomized, 6 patients (4%) in the NESP group and 2 (1%) in the placebo group had a screening above the entry criterion. By the time of the start of treatment, only 1 subject in the NESP group had a baseline hemoglobin > 11.0 g/dL. Figure 1, submitted by the sponsor shows the relationship between screening and baseline hemoglobin values for the ITT population.

Figure 1



Subject with last screening value > 11.0 g/dL (subject 13517201) had hgb value of 10.3 g/dL at day -12

Program: /stat/hesponchesp900297/analysis/fde_apr2002/statfiles/programs/graphs/compare_hgb_scatter.sas
Output: compare_hgb_scatter.cgm (Date Generated: 15APR2002:11:05)

The sponsor stated that reasons were unclear as to why an increased proportion of patients in the NESP group had a baseline hemoglobin > 11 g/dL.

Secondary Endpoints

Proportion of patients who received an RBC transfusion in weeks 1 to 4

An analysis of the proportion of patients who received an RBC transfusion in weeks 1 to 4, was performed using the same K-M approach used to analyze the primary endpoint. Under the primary approach, the proportion of RBC transfusions was reduced from 18% (13, 24) in the placebo group to 15% (10, 21) in the NESP group. The weighted difference of 4% (3.6, 12) was not statistically significant. Hence, the result showed that there was no significant difference between the NESP and placebo groups. This result is consistent for all three censoring approaches (not shown).

Proportion of patients who received an RBC transfusion in weeks 1 to EOTP

Using the same K-M method, an analysis was performed on the proportion of patients who received an RBC transfusion in weeks 1 to EOTP. This analysis was performed on the ITT population, which consists of 314 patients – 158 in the placebo arm and 156 in the NESP arm. The results are presented in Table 8.

Table 8. RBC transfusions from week 1 to EOTP stratified by tumor type and region

		Placebo	NESP	Difference in Proportions (NESP-Placebo)	p-value
Censoring Approach	Number of Subjects	158	156		
Primary Approach	Number of Subjects w/ RBC transfusions from Week 1 to EOTP	89	53		
	KM Proportion (95% CI)	60 (52, 68)	26 (20, 33)	-25 (-35, -14)	< 0.001
Secondary approach	Number of Subjects w/ RBC transfusions from Week 1 to EOTP	100	63		
	KM Proportion (95% CI)	64 (57, 71)	30 (23, 37)	-24 (-34, -13)	< 0.001
Non-imputed Approach	Number of Subjects w/ RBC transfusions from Week 1 to EOTP	84	42		
	KM Proportion (95% CI)	57 (49, 65)	21 (15, 28)	-29 (-39, -18)	< 0.001

The proportion of patients receiving an RBC transfusion in weeks 1 to EOTP was 60% (52, 68) in the placebo arm and 26% (20, 33) in the NESP arm. The weighted difference of 25% (14, 35) shows that there is a statistically significant difference between the NESP and placebo groups. This difference remains consistent under all three censoring approaches.

Reviewer's comment: The estimates of the individual group proportions and the estimate of the difference in proportions along with the corresponding 95% confidence intervals (as indicated in bold) for this secondary endpoint are included in the current label submitted by the sponsor. **This reviewer recommends including the primary endpoint instead.**

Proportion of patients achieving a high response

The analysis of the proportion of patients achieving a high response was performed using the Kaplan-Meier (K-M) method. A high response is defined as a 2g/dL or more increase over baseline hemoglobin in the absence of RBC transfusions in the prior 28 days. The analysis population utilized the ITT population. The analysis revealed that there is a statistically significant difference between the NESP and the placebo groups with respect

to the proportion of patients achieving a high response after stratifying by tumor type and region (Table 9). The test for stratum-specific differences between the NESP and placebo arms resulted in a p-value of 0.29. Therefore, it was assumed that the strata were homogeneous. According to Table 9, the proportion of responders was higher in the NESP arm 48% (39, 56) than in the placebo arm 18% (11, 24). The weighted (by tumor type and region) difference of 29% (18, 40) is highly significant.

Table 9. Responders stratified by tumor type and region

	Placebo	NESP	Difference in Proportions (NESP-Placebo)	p-value
Number of Subjects	158	156		
Number of Subjects Responding	22	66		
KM Proportion (95% CI)	18 (11, 24)	48 (39, 56)	29 (18, 40)	< 0.001

Change in hemoglobin

Change in hemoglobin was calculated as the change from baseline to EOTP. A positive change indicated an increase over baseline. Hemoglobin values were imputed using the last value carried forward. In addition, if a subject had an RBC transfusion within 28 days of the last recorded hemoglobin during the treatment phase, then the hemoglobin value before the transfusion was used.

Table 10. Change in hemoglobin (continuous) by treatment group

Change from Baseline	Placebo	NESP	Difference in Mean Change (NESP-Placebo) w/ 95% CI	p-value
N	158	156		
Mean	-0.53	0.78	1.32 (0.91, 1.73)	< 0.001
SE	0.13	0.17		
Median	-0.60	0.90		
Q1, Q3	-1.70, 0.50	-0.70, 2.0		
Max, Min	-4.50, 3.6	-4.7, 6.4		

Table 11. Change in hemoglobin (by category) by treatment group

Change from Baseline	Placebo	NESP
< 0	97	57
[0, 1)	36	24
[1, 2)	13	35
≥ 2	12	40

As shown in Table 10, the mean hemoglobin decreased 0.53 g/dL in the placebo group whereas in the NESP group, the mean hemoglobin increased 0.78 g/dL. This difference

is statistically significant. Table 11 shows that more patients experienced either a decrease (< 0) or an increase of up to 1 g/dL in the placebo group than in the NESP group. However, more patients experienced a more than 1 g/dL increase in the NESP group than in the placebo group.

An exploratory subgroup analysis was performed by the FDA to examine the relationship between a high hemoglobin response and change in hemoglobin from baseline over time for patients in the NESP arm. Of the 156 patients in the NESP arm from the ITT population, 66 were responders. Table 12 shows the summary statistics of change in hemoglobin from baseline over time for these 66 subjects.

Table 12. Hemoglobin change from baseline over time for responders

Change from Baseline	Week 4	Week 6	Week 8	Week 13	EOTP
N	45	48	57	43	66
Mean	0.42	1.12	1.63	2.54	2.43
SE	0.17	0.15	0.17	0.23	0.20
Median	0.40	1.15	1.70	2.40	2.45
Q1, Q3	-0.20, 1.00	0.50, 1.95	0.80, 2.30	1.60, 3.50	1.50, 3.60
Max, Min	-2.60, 4.77	-2.40, 3.10	-1.30, 5.40	-1.10, 6.40	-1.10, 6.40

Change in hemoglobin from baseline to each of weeks 4, 6, 8, and 13 had missing values because of RBC transfusions that occurred within 28 days of a particular week and because of withdrawals as the study progressed. Change in hemoglobin from baseline to EOTP contains imputed values (last observation carried forward). Based on the data that are available, Table 12 suggests there is an increase in mean change over time in the NESP group.

A similar analysis was performed in a subgroup of the NESP responders who had their dose doubled from 2.25 $\mu\text{g/kg}$ to 4.5 $\mu\text{g/kg}$ at some point during the study. Of the 66 patients who responded in the NESP group, 22 had their dose doubled. Table 13 shows the summary statistics of change in hemoglobin over time for these 22 patients.

Table 13. Hemoglobin change from baseline over time for responders who had dose doubled

Change from Baseline	Week 4	Week 6	Week 8	Week 13	EOTP
N	17	17	19	19	22
Mean	0.14	0.59	1.14	3.02	3.02
SE	0.28	0.17	0.26	0.31	0.26
Median	0.40	0.50	1.00	2.80	2.80
Q1, Q3	-0.50, 0.90	0.30, 0.90	0.20, 1.80	2.00, 3.70	2.20, 3.70
Max, Min	-2.60, 1.90	-0.70, 2.10	-0.20, 3.60	1.20, 6.40	1.20, 6.40

Based on available data, it appears from Table 13 that there is an increase in mean change over-time in the subgroup of subjects in the NESP group who responded and had their dose doubled.

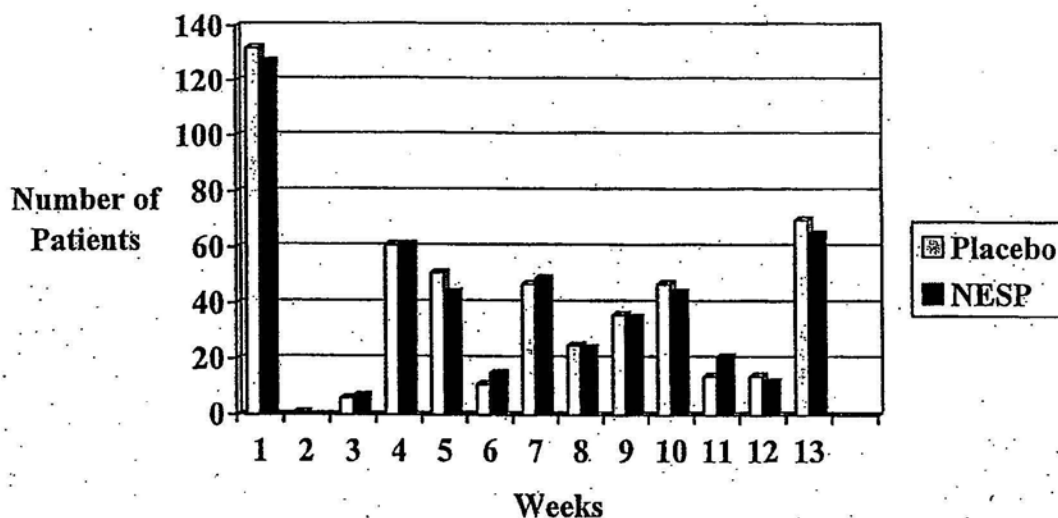
HRQOL – Fact Fatigue Scale

The evaluable population for the HRQOL analyses consists of 255 patients. The evaluable population is defined in the SAP as all patients who received at least 1 dose of study medication, whose EOTP date occurred after day 1 of week 5 (day 29), and who completed the FACT-Fatigue scale at baseline and at least one time from week 5 to EOTP.

The sponsor's assessment of compliance was performed by examining the rates of completion at baseline and EOTP for each treatment group. There was a slightly higher rate of compliance at baseline in the placebo group (placebo = 96.2%, NESP = 94.2%), which subsequently reversed at EOTP (placebo = 89.9%, NESP = 92.5%). Overall, compliance was high in both treatment groups and at both time points.

This reviewer examined compliance at all visits during the treatment period. Figure 2 shows the number of patients that completed the FACT-Fatigue scale at each visit by treatment group. The figure shows that the number of patients varied by week but that there is little difference in the numbers between the two treatment groups.

Figure 2. Number of patients completing FACT-Fatigue scale over time by treatment group



The sponsor's primary HRQOL analysis was performed on the change in FACT-Fatigue scale scores from baseline to EOTP comparing mean differences between the two groups. Consistent with the analysis of the primary endpoint, this comparison was stratified by tumor type and region. A weighted approach was used to obtain an estimate of the mean

difference between the NESP and placebo groups. Missing values were handled using both the primary and the secondary approach as defined in the SAP.

Table 14. Change in HRQOL FACT-Fatigue scores from baseline to EOTP controlling for tumor type and region

	Change from Baseline	Placebo	NESP	Difference in Mean Change (NESP-Placebo) w/ 95% CI	p-value
Primary Approach	N	128	127		
	Mean	-0.6	0.8		
	SD	10.7	10.0		
	Median	0.0	1.0		
	Q1, Q3	-5.5, 4.0	-5.0, 8.0		
	Max, Min	-45.0, 23.0	-29.0, 25.0	1.4 (-1.1, 3.9)	0.2857
Secondary Approach	Mean	-0.6	0.4		
	SD	10.7	9.9		
	Median	0.0	0.0		
	Q1, Q3	-5.5, 4.0	-5.0, 6.0		
	Max, Min	-45.0, 23.0	-29.0, 25.0	1.0 (-1.5, 3.5)	0.4353

The Mantel-Haenzel method was used to test for differences between the two groups. Table 14 shows that there is no statistically significant difference between the NESP and placebo groups.

Reviewer's comment: The sponsor was asked to explain why the Cochran-Mantel-Haenszel method was used in the analysis of the change from baseline scores of the FACT-Fatigue scale when the prespecified method for comparing the two groups was a stratified Wilcoxon Rank Sum test. In a correspondence dated 4/15/02, the sponsor stated: "Since corresponding inferential analyses presented in the study report were supplemented with confidence intervals for the mean difference between groups, a generalized Cochran-Mantel-Haenszel (CMH) approach (section 7.10.1) was used. This allowed confidence intervals and results from hypothesis testing to be consistent by using the CMH stratum weights. It should also be noted that to be consistent with the primary endpoint of the study, analyses were done controlling for both tumor type and region."

The sponsor also performed an exploratory analysis on the FACT-Fatigue change scores. An alternative endpoint, Fatigue Improvement was defined and examined. Percent improvement was calculated using the subject's baseline and EOTP scores using the primary approach of handling withdrawals. Percent improvement was defined as the (EOTP score – baseline score)/baseline score. Several magnitudes of improvement were evaluated. Comparisons were made using Pearson's Chi-Square test with p-values unadjusted for multiple testing. Estimates of the difference in proportions between the NESP and the placebo groups are provided along with corresponding 95% confidence intervals. Results are shown in Table 15.

Table 15. Comparison between NESP and Placebo groups w.r.t. FACT-Fatigue improvement

FACT-Fatigue Improvement	Placebo	NESP	Difference in Mean Change (NESP-Placebo) w/ 95% CI	p-value
Number of Subjects	128	127		
Any Improvement Proportion (95% CI)	44 (35, 52)	56 (47, 65)	12 (0, 24)	0.0522
≥ 10% Improvement Proportion (95% CI)	28 (20, 36)	42 (33, 50)	14 (2, 25)	0.0226
≥ 15% Improvement Proportion (95% CI)	24 (17, 32)	37 (29, 45)	13 (2, 24)	0.0267
≥ 20% Improvement Proportion (95% CI)	21 (14, 28)	35 (27, 44)	14 (3, 25)	0.0110
≥ 25% Improvement Proportion (95% CI)	19 (12, 26)	31 (23, 40)	13 (2, 23)	0.0189

Table 15 shows that there are statistically significant differences between the NESP and placebo groups with respect to percent improvement.

Reviewer's comment: The statistically significant difference between the two treatment groups obtained from this analysis are from an unspecified exploratory analysis. Additionally, there is no adjustment in multiple endpoints used. The sponsor had originally included the p-value (in bold) from the ≥ 25% Fatigue Improvement endpoint analysis in their proposed label. However, in a 4/15/02 correspondence, the sponsor removed the quality of life statements from their revised label.

Conclusions

1. A statistically significant difference between the NESP and the placebo groups was obtained with respect to the proportion of patients receiving an RBC transfusion in weeks 5 to EOTP. This proportion is smaller in the NESP group. This difference remains consistent in sensitivity analyses using alternative censoring approaches, an alternative endpoint definition, and in excluding patients whose baseline hemoglobin values were > 11 g/dL.
2. No statistically significant difference was detected between the proportion of patients receiving an RBC transfusion in weeks 1 to 4 in the NESP group and the proportion of patients receiving an RBC transfusion in weeks 1 to 4 in the placebo group.
3. There is a statistically significant difference between the NESP and the placebo groups with respect to the proportion of patients who received an RBC transfusion in weeks 1 to EOTP. This proportion is smaller in the NESP group.

4. The NESP and placebo groups are different with respect to the proportion of patients achieving a high response. This difference is statistically significant, where the proportion responding is larger in the NESP group.
5. A statistically significant difference between the placebo and NESP groups was obtained in the hemoglobin change from baseline to EOTP. Mean hemoglobin change increased in the NESP group, while it decreased in the placebo group.
6. From the FDA exploratory analysis, there appears to be an increasing trend in mean hemoglobin change over time among the responders in the NESP group and among the NESP responders who had their dose doubled. However, given this a subgroup analysis and the large amount of missing data present, no statistical inferences can be made.
7. No statistically significant difference was obtained between the NESP and the placebo groups with respect to change from baseline in FACT-Fatigue scale scores.

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APPLICATION NUMBER:

103951/5001

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

TELECONFERENCE SUMMARY



000635385

DATE: May 9, 2002

APPLICANT: Amgen, Incorporated

PRODUCT: Darbepoetin alfa [Aranesp]

TO: STN 103951/5001 *gms*

FROM: Jeanne M. Delasko, RN, MS
Regulatory Project Manager

PARTICIPANTS: CBER: Jeanne M. Delasko
Amgen: Doug Hunt (805) 447-1693

PURPOSE: To (b) (4)

Ms. Delasko had the following request:



OTRR:DARP: JMDelasko:5/20/02
(S:/Delasko/Amgen[Aranesp]/103951.5001Telecon005)