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*APPLICATION NUMBER:*  
**103951Orig1s5173**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW ADDENDUM

Application Type sBLA  
Submission Number 103951.5173  
Submission Code Response to CR letter

Letter Date 03/22/2011  
Stamp Date 03/23/2011  
PDUFA Goal Date 05/23/2011

Reviewer Name Kaushik Shastri, M.D

Through Patricia Keegan, M.D  
Acting Team Leader &  
Division Director

Review Completion Date 04/22/2011

Established Name Darbepoeitin alfa  
Trade Name Aranesp  
Therapeutic Class Erythropoiesis Stimulating Protein  
Applicant Amgen

Priority Designation Class 1 resubmission

Formulation Polysorbate solution  
Albumin solution

Dosing Regimen	2.25 µg/kg SC QW 500µg SC, Q3W
Indication	Treatment of anemia due to myelosuppressive chemotherapy in patients with non-myeloid malignancies
Intended Population	Anemic patients with malignancy undergoing myelosuppressive chemotherapy

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## **1. Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

This reviewer recommends the approval of this supplement.

### **1.2 Risk Benefit Assessment**

This is the second resubmission of this supplement, in response to a CR letter issued on April 27, 2010 for the original submission dated December 20, 2007. The CR letter was primarily due to lack of agreement on the labeling. This resubmission contains a package insert that is acceptable to the FDA.

A Risk Evaluation and Mitigation Strategy (REMS) was approved by the FDA on 2/16/10 under STN 103951/5197. With the ongoing REMS, the risk/benefit assessment favors continuing marketing of this drug for use in cancer patients with anemia due to myelosuppressive chemotherapy.

### **1.3 Recommendations for Postmarketing Risk Management Activities**

A REMS program was already approved.

### **1.4 Recommendations for other Post Marketing Study Commitments**

No other post marketing study commitment is recommended to this supplement.

## **2. Background and Overview**

On 20 December 2007 (STN BL 103951/5173) Amgen submitted a prior approval supplement to revise the prescribing information and reformat according to the Physician Labeling Rule (PLR) and to respond, in part, to FDA's May 31, 2007 supplement request letter generated from questions raised and advice given at the May 10, 2007 ODAC meeting. The questions that were supposed to be addressed in this supplement included the threshold of baseline hemoglobin for the initiation of Aranesp, whether a lower (< 12 g/dL) hemoglobin level should be identified at which Aranesp should be suspended or terminated, and when to discontinue the use of Aranesp following the completion of the chemotherapy course. In the review of the Dec. 20, 2007 submission (see original review by Dr. Fan) it was determined that the submission did not contain robust evidence from studies sufficient to adequately address these issues. Subsequent label revisions that were approved following that Dec. 20, 2007 submission, have addressed the above issues with conservative guidance for threshold of hemoglobin at which to initiate, suspend and terminate the use of Aranesp when treating cancer patients with anemia due to myelosuppressive chemotherapy. On 24 October 2008, FDA issued a complete response letter for this supplement since agreement on the labeling was not reached.

FDA issued a second CR letter on 4/27/2010 since agreement on the final labeling again could not be reached when Amgen resubmitted this supplement on 3/22/2011.

During the later part of 2010 and earlier this year, FDA and Amgen conducted informal labeling negotiations and agreed upon the labeling language that is now submitted by Amgen in this second resubmission of this supplement.

This clinical review will only cover the Oncology portions of the submission, since the non-Oncology parts are being reviewed by Division of Hematology Products (DHP). This submission contains the necessary changes based on the agreed upon wording of the current label being approved with this supplement. The changes in the REMS are not a result of subsequent REMS assessment reports submitted by Amgen on 10/14/2011 and 2/16/11, since the content of these assessment reports did not by itself warrant changes to the REMS as such. Please see DRISK review of the REMS modifications.

## **3. Proposed Labeling Revisions (oncology portions) and Review Comments**

As noted above, FDA and Amgen had informal discussions on the acceptable language of the physician package insert and this submission contains these changes.

Amgen essentially accepted all the FDA proposed changes in the label sent to Amgen on 16 March 2011 during informal labeling negotiations. For the Oncology portions of the label, these

changes are consistent with and vary only slightly from the proposed FDA label sent to Amgen with the CR letter on 4/27/10. The main issues are noted below:

**Black Box Warning:**

In the black box warning, under the first bullet under cancer, [REDACTED] (b) (4) as follows:

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers [REDACTED] (b) (4)

**Review Comment:** [REDACTED] (b) (4)

**Section 1.2 Indication Statement:**

Aranesp is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy. (1.2)

**Review Comment:** *The indication statement clarifies that at the time of initiation of Aranesp for anemia due to myelosuppressive chemotherapy, there should be a plan to give the chemotherapy for at least two more months.*

**Section 5.2: Prescribing and Distribution Program for Aranesp in Patients with Cancer.**  
This section was revised for clarity.

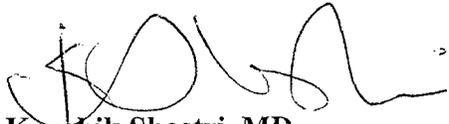
**Section 6.1:** Under adverse reactions in the oncology section, FDA accepted Amgen's proposal for the incidence of edema based on a customized search strategy as submitted by Amgen on 3/22/10 under STN 103951.5173.5016. This search strategy only altered the incidence figures for edema slightly. The changes based on this analysis are noted (see strike-out) as below:

[REDACTED] (b) (4)

Clinical Studies:

Information on Study C3 was added precisely as approved previously under [REDACTED] (b) (4) and as it appears in the currently approved non-PLR label.

**Signature Page:**



**Kaushik Shastri, MD  
Clinical Reviewer,  
DBOP**

**Through:**



**Patricia Keegan, MD  
Acting Team Leader,  
DBOP**

## Division Director Summary Review

<b>Date</b>	April 27, 2010
<b>From</b>	Patricia Keegan, M.D.
<b>Subject</b>	Division Director Summary Review
<b>BLASupplement #</b>	STN BL 103951/5173
<b>Applicant Name</b>	Amgen, Inc.
<b>Date of Submission</b>	December 26, 2007
<b>Date of CR letter</b>	October 24, 2008
<b>Date of Resubmission</b>	October 26, 2009
<b>PDUFA Goal Date</b>	April 27, 2010
<b>Proprietary Names / Established (USAN) Name</b>	Aranesp <sup>®</sup> darbepoetin alfa
<b>Dosage Forms / Strength</b>	Solution (albumin-containing or polysorbate buffer solutions) for subcutaneous or intravenous injection in single-use vials or prefilled syringes. Strengths range from 25 mcg to 300 mcg for vials and 25 mcg to 500 mcg for prefilled syringes
<b>Current Indication(s)</b>	<ol style="list-style-type: none"> <li>1. Treatment of anemia associated with chronic renal failure (CRF), including patients on dialysis and patients not on dialysis</li> <li>2. Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.</li> </ol>
<b>Action:</b>	Complete Response

<b>Material Reviewed/Consulted</b> OND Action Package, including:	<b>Names of discipline reviewers</b>
Project manager generated minutes & reviews	Monica L. Hughes Mona Patel
Medical Officer Reviews	Chaohong Fan Kaushik Shastri Minh-Ha Tranh Saleh Ayache
Statistical Reviews	Yuan-Li Shen Mark Rothmann
Pharmacology Toxicology Reviews	Andrew McDougal Anne Pilaro Yanli Ouyang
OBP Reviews	Ingrid Markovic Kimberly Rains
Clinical Pharmacology Review	Aakansha Khandelwal
Division of Risk Management Review	Melissa Huett
DDMAC, SEALD team Review	Iris Massucci
DDMAC reviews	Cynthia Collins Michelle Safarik Carole Broadnax
Pediatric and Maternal Health Staff Review	Jeanine Best Richard Araojo

OND=Office of New Drugs  
 OBP=Office of Biotechnology Products  
 DDMAC=Division of Drug Marketing, Advertising and Communication  
 SEALD=Study Endpoints and Labeling Development  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DSI=Division of Scientific Investigations  
 DRISK=Division of Risk Management

## Division Director Summary Review

### 1. Introduction

This efficacy supplement was received on December 26, 2007 as one of two supplements responding to FDA's supplement request letter of May 31, 2007. This supplement was subsequently unbundled with review of information responding to the May 31, 2007 letter conducted under BL STN 103951/5173, and review of proposed labeling changes to the Warnings and Precautions section describing the overall survival and progression-free survival results of Study 20010145. (b) (4)

The May 31, 2007 letter made specific requests for revision to product labeling to enhance safe and effective use of Aranesp for the treatment of anemia due to concomitant cancer chemotherapy. These specific requests were based on the results of six multicenter, randomized trials assessing the effect of ESAs in patients with cancer that demonstrated or suggested harmful effects (decreased survival or more rapid tumor progression/recurrence). The requested labeling changes were consistent with the recommendations from the May 10, 2007 Oncologic Drugs Advisory Committee (ODAC) meeting at which the results of these studies were presented and discussed.

Amgen provided revised labeling in response to FDA's May 31, 2007 letter under two separate supplements, a "Changes Being Effected" labeling supplement (STN BL 103951/5164) addressing items 1, 2, and 6 of the May 31, 2007, letter which was approved November 8, 2007 and the "Prior Approval Supplement" (STN BL 103951/5173), which is the subject of this review, responding to items 3, 4, and 5 of the May 31, 2007 letter. The PAS submission contains clinical study reports and an integrated dataset containing data from datasets from eleven randomized, placebo-controlled studies of darbepoetin alfa (Aranesp) in patients with anemia and non-myeloid malignancy receiving chemotherapy (20010119, 980291 schedule 1, 980291 schedule 2, 990114, 980297, 20000161, 20010103, 20010145, 20020149, 20030204, 20030232), additional analyses, and proposed labeling changes. In addition, as discussed at the July 25, 2007 meeting with Amgen, the proposed labeling provided in this submission was reformatted for consistency with the Physician's Labeling Rule (PLR). Amgen stated that the focus of the PLR conversion was made with "attention to the format, reduction of repetition and modification of the Adverse Reaction section of the PI".

The review of this application was coordinated across the Division of Biologic Oncology Products and the Division of Medical Imaging and Hematology Products. The medical oncology reviewers and supporting statistical reviewers in the Division of Biometrics V evaluated the responses to the May 31, 2007 letter and all clinical portions of product labeling for the cancer-related indication, while the review of clinical portions of product labeling for all other approved indications were conducted by reviewers in the Division of Hematology. Additional review staff, as listed above, participated in the review of product labeling changes

to conform with the requirements of 21 CFR 201.56(d) and 201.57. In addition, as appropriate, the review of the Epogen/Procrit and Aranesp labels were conducted jointly to describe class effects.

The assessment of the medical oncology reviewers and statistical reviewers, as well as secondary reviewers was that the proposed approach by Amgen to integrate data from 12 (two of these “studies” were themselves pooled data from distinctly numbered protocols of the same design) randomized, placebo-controlled studies assessing the effects of epoetin alfa and 11 randomized, placebo-controlled studies (including “continuation protocols” for two trials assessing efficacy and one protocol with two reports for Schedules 1 & 2) assessing darbepoetin alfa was not interpretable for addressing issues 3, 4, and 5 of the May 31, 2007 letter for reasons discussed below. Instead, FDA’s proposed modifications to product labeling rely on a conservative approach, further refining the indications and usage sections of the Aranesp label to attempt to limit use to the population of patients with cancer who are most likely to derive benefit as well as to attempt to mitigate the risks of increased mortality and shorter time to disease progression. Labeling changes also reflect additional information and Advisory Committee advice received during the course of the supplement review. Since submission of this supplement on December 26, 2007, product labeling has been updated to include new information on the risks of pure red cell aplasia, new study results demonstrating adverse outcomes in patients with chronic renal failure and in patients with cancer, as summarized below. Based on additional study results in patients with cancer, FDA sought advice of the ODAC on March 13, 2008 which resulted in additional labeling changes, consistent with the conservative dosing recommendations mentioned above and further limiting product use. These labeling changes were made as part of FDA-ordered safety labeling changes and approved on August 5, 2008.

A complete response letter was issued on October 24, 2008, requesting additional information to support proposed labeling; the response was received on October 26, 2009 as a Class II resubmission.

Review of this additional clinical and non-clinical information was completed and incorporated into product labeling as appropriate, however agreement on final labeling has not been reached. A complete response letter will be issued.

## **2. Background**

Erythropoietin is a glycoprotein whose main function is to stimulate the proliferation and differentiation of erythroid precursors in the bone marrow. Erythropoietin is produced mainly in the kidneys, though several other tissues produce lesser amounts of the growth factor. Aranesp (darbepoetin alfa) is an erythropoiesis-stimulating protein, closely related to endogenous human erythropoietin, which is produced in Chinese hamster ovary cells by recombinant DNA technology. Darbepoetin alfa 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. The additional carbohydrate chains increase the approximate molecular weight of the glycoprotein from 30,000 to 37,000 daltons.

Darbepoetin alfa has a three-fold longer terminal half-life than epoetin alfa and a five-fold lower affinity for erythropoietin receptors.

Aranesp was approved for marketing in the U.S. on September 17, 2001 for the treatment of anemia in patients with chronic renal failure based on the results of thirteen Amgen-sponsored studies, in which 2198 patients with chronic renal failure (CRF) were enrolled; in these trials, 1598 patients received ARANESP and 600 patients received epoetin alfa as an active comparator.

Aranesp was approved for “the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy” on July 19, 2002. This approval was based primarily on the results of Protocol 980297, “A Double-Blind, Placebo-Controlled, Randomized, Study of NESP for the Treatment of Anemia in Lung Cancer Receiving Multi-cycle Platinum Containing Chemotherapy”. This was a multicenter, multinational study in which 320 patients were enrolled and randomized 1:1 to receive either Aranesp 2.25 µg/kg QW (treatment arm) or placebo. Eligibility criteria included lung cancer (either small cell carcinoma or non-small cell carcinoma) a cancer treatment plan of at least 12 additional weeks of platinum-containing chemotherapy, and anemia (hemoglobin <11 g/dl). The primary endpoint was the estimated Kaplan-Meier proportion of subjects who received RBC transfusions between week 5 and the end of the treatment phase (EOTP). Week 5 was specified since hematologic responses to Aranesp are not observed until 3-6 weeks after the initiation of therapy. The primary efficacy analysis was conducted in patients who had completed the first 4 weeks of study. In this analysis, patients who withdrew or discontinued from the 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). 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).

The labeling for Aranesp was expanded on March 23, 2006 to include a new dosing regimen of 500 mcg once every 3 weeks (Q3W) for the treatment of anemia in adults with non-myeloid malignancies, where anemia is due to the effect of concomitantly administered chemotherapy. The safety and effectiveness of the Q3W regimen in reducing the requirement for red blood cell (RBC) transfusions in patients undergoing chemotherapy was assessed in a randomized, double-blind, multinational study. This study was conducted in anemic (Hgb < 11 g/dL) patients with non-myeloid malignancies receiving multicycle chemotherapy. Patients were randomized to receive Aranesp at 500 mcg once every 3 weeks ( $n = 353$ ) or 2.25 mcg/kg ( $n = 352$ ) administered weekly as a subcutaneous injection for up to 15 weeks. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 mcg in the once every 3 week group and 1.35 mcg/kg in the once weekly group) if hemoglobin increased by more than 1 g/dL in a 14-day period. Study drug was withheld if hemoglobin exceeded 13 g/dL. In the once every 3 week group, 254 patients (72%) required dose reductions (median time to first reduction at 6 weeks). In the once weekly group, 263 patients (75%) required dose reductions (median time to first reduction at 5 weeks).

Efficacy was determined by a comparison of the Kaplan-Meier estimates of the proportion of patients who received at least one RBC transfusion between day 29 and the end of treatment. Three hundred thirty-five patients in the once every 3 week group and 337 patients in the once weekly group remained on study through or beyond day 29 and were evaluated for efficacy. Twenty-seven percent (95% CI: 22%, 32%) of patients in the once every 3 week group and 34% (95% CI: 29%, 39%) in the weekly group required a RBC transfusion. The observed difference in the proportion of patients receiving one or more transfusions for the once every 3 week schedule as compared to the once weekly was -6.7% (95% CI: -13.8%, 0.4%).

There are two ESAs approved for the treatment of anemia due to chemotherapy in the United States, darbepoetin alfa (Aranesp, Amgen Inc) and epoetin alfa (Procrit/ Epogen, Amgen Inc). In addition, there are several ESAs approved in other countries and for which clinical experience in patients with cancer are available. FDA considers safety information derived from any ESA as relevant for characterization of risks for the entire class. Since 1993, multiple randomized controlled clinical trials conducted in patients with cancer, which were designed to isolate the effect of the erythropoiesis-stimulating agent, demonstrated or exhibited a trend towards shorter survival and/or poorer tumor outcomes in patients receiving an ESA compared to patients receiving transfusion support alone. This information has been summarized in FDA briefing documents for Oncologic Drugs Advisory Committee meetings held May 4, 2004, May 10, 2007, and March 13, 2008. In addition, this data is summarized in Warnings section of the product labeling for Aranesp and for Epogen/Procrit.

Following the May 10, 2007 ODAC meeting at which these data were discussed, FDA issued a supplement request letter to Amgen. The letter stated that, based on discussion during the May 10, 2007 meeting, FDA requested that Amgen submit a prior approval supplement (PAS) that would include revised labeling to adequately addressing the recommendations for changes or to provide data supporting current or alternate labeling changes from those recommended during that Advisory Committee meeting. Specifically, FDA requested the following:

1. Revision of the INDICATIONS AND USAGE section, to include a statement that Epogen/Procrit is not indicated for use in patients receiving chemotherapy for any of the following primary tumor types: adenocarcinoma of the breast, squamous cell cancer of the head and neck, non-small cell lung cancer, or lymphoid malignancies.
2. Revision of the INDICATIONS AND USAGE section, to clarify the severity of anemia for which Epogen/Procrit is indication, by inclusion of the maximum (and if appropriate, minimum) pretreatment hemoglobin level.
3. Revision of the DOSAGE AND ADMINISTRATION section to specify a lower maximum hemoglobin level (i.e., hemoglobin level less than 12 g/dL) at which dosing should be suspended or terminated.
4. Revision of the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections to indicate that Epogen/Procrit should be discontinued following the completion of the concomitant chemotherapy regimen.

5. Revision of the INDICATIONS AND USAGE section to indicate that Epogen/Procrit is not indicated for use in patients who are not receiving myelosuppressive chemotherapy. This statement should include patients who are receiving no active treatment, radiotherapy treatment, and treatment with non-myelosuppressive therapy such as hormonal agents and therapeutic biologic products.

Following issuance of the May 31, 2007 letter, Amgen met with FDA on July 25, 2007 to discuss the proposed contents of the requested labeling supplement. Amgen's proposed approach was to conduct re-analyses of existing data [REDACTED] (b) (4) [REDACTED] to further evaluate the impact of ESAs on tumor progression and on survival, and to identify post-marketing studies designed to assess the safety and efficacy of ESAs when administered according to more conservative dosing regimens.

On September 7, 2007, FDA issued an additional letter requesting that Amgen make specific labeling changes in a separate "Changes Being Effected" (CBE) labeling supplement. Amgen provided responses to items 1, 2, and 6 of FDA's 31 May 2007 letters in a CBE supplement (STN BL 103951/5157) submitted on September 19, 2007. A CBE supplement (STN BL 103234/5158) was submitted for Epogen/Procrit on September 19, 2007. Both supplements were approved on November 8, 2007.

In addition to the CBE supplement discussed above, the following additional safety labeling changes have been approved since submission of STN BL 103951/5173:

- STN/BL 103951/5170: Approval on March 7, 2008 to include a Boxed Warning summarizing the risks of increased mortality and/or poorer tumor outcomes obtained in randomized studies in patients with cancer and in those with chronic renal failure and to update the Warnings section to include the results of two additional randomized, controlled studies in patients with cancer (PREPARE trial and GOG-191 trial) demonstrating adverse survival or tumor outcomes in patients with cancer receiving an ESA.
- [REDACTED] (b) (4)
- STN 103951/5195: Approval on November 19, 2008 of a CBE supplement containing a medication guide, patient instructions for use, revised container and carton labeling and revised package insert. [REDACTED] (b) (4)
- STN BL 103951/5211: Approval on October 13, 2009 of a CBE supplement modifying the WARNINGS section of the Package Insert to describe the potential for pure red cell aplasia (PRCA) in the specific clinical setting of hepatitis C virus (HCV) therapy with ribavirin and interferon
- STN BL 103951/5223: Approval on January 11, 2010 of CBE labeling to include the results of the TREAT study.

- STN BL 103951/5197: Approval on February 16, 2010 of a Risk Mitigation and Evaluation Strategy, to mitigate the risk of decreased survival and/or the increased risk of tumor progression or recurrence in patients with cancer for whom Aranesp is prescribed.

The chronology of this submission is briefly summarized below

Dec. 20, 2007: STN BL 103234/5166 submitted (received by FDA on Dec. 26, 2007).

Feb. 1, 2008: Acknowledgment letter issued.

Feb 21, 2008: FDA notified Amgen that the supplement was filed and that preliminary deficiencies identified in the filing review would be communicated in a subsequent letter.

March 7, 2008: FDA letter issued with preliminary deficiencies regarding proposed labeling format and requested define document files for 4 protocols (20030232, 980297, 990114, and 980291 schedules 1 &2), SAS programs used to produce derived variables, and raw & derived datasets for protocol 20020149.

- April 18, 2008: Amgen submitted partial responses to the 3/7/08 letter
- May 30, 2008: Amgen submitted additional information (define.pdf file for 20020149) as responses to the 3/7/08 letter

August 19, 2008: FDA issued a letter requesting clarification of the relevance of Protocol 20010119 to the supplement and, if relevant, requesting that an individual study dataset be provided that datasets containing raw and derived variables and SAS programs be submitted to the supplement. The letter also requested additional information (e.g., final reports, case report forms, individual datasets, and requests for clarification of study conduct) for Protocols 20000161, 20010103, 980291 (schedules 1 & 2), 990114, 20030232, 980297, and 20020149.

- Sept 12, 2008: Amgen submitted partial responses to 8/19/08 letter
- Sept. 18, 2008: Amgen submitted partial responses to 8/19/08 letter
- Oct 15, 2008: Amgen submitted partial responses to 8/19/08 letter

October 24, 2008: FDA issued a complete response letter requesting the following items

- Resubmission of datasets for Protocol 990114 (also requested in 8/19/08 IR letter)
- Data (or source of data) for rat and rabbit reproductive toxicology studies in support of proposed labeling
- Response to comments requesting information contained in proposed labeling attached to the 10/24/08 CR letter
- Revised product labeling
- Updated information on world-wide safety experience

October 23, 2009: Amgen submitted a Complete Response to the Oct, 24, 2008 letter, which was received on October 26, 2009 and designated a Class 2 resubmission.

Additional amendments to this efficacy supplement received during this review cycle were submitted on November 2, 2009, January 11, 15, and 28, 2010, March 17, 22, 23, and 29, 2010, and on April 8 and 12, 2010.

Agreement on final labeling, including proposed changes to the Medication Guide and other modifications to the REMS, was not reached and a second CR letter is planned.

### **3. CMC/Device**

No new CMC information was submitted in or required to complete review of this application. All CMC reviewer comments regarding the package insert (Dosage and Administration, Dosage Forms and Strength, Description, and How Supplied) and carton/container labeling, based on compliance with current Guidances and FDA policies were considered and incorporated into FDA proposed labeling were conveyed to Amgen in FDA-proposed labeling revisions.

### **4. Nonclinical Pharmacology/Toxicology**

No new non-clinical pharmacology or toxicology data were submitted in the original supplement, however the CR letter issued October 24, 2008 contained information requests from the non-clinical reviewers requesting that Amgen provide the source of the data used to derive the multiples of human exposure from rat and rabbit reproductive toxicity studies cited in the product labeling. The resubmission contained 5 of 8 non-clinical study reports addressing reproductive toxicology data and the non-clinical reviewer determined that the information provided supported inclusion of the Amgen-proposed information in product labeling. The dosing in non-clinical studies was described in mcg/kg doses however extrapolation of animal PK data to human exposure was not included in product labeling due to uncertainty regarding the assay specificity used, variability of human PK, and inability to determine the impact of disease on human pharmacokinetics (animals were healthy). All non-clinical reviewer comments regarding the package insert were considered and incorporated into FDA proposed labeling to be appended to the CR letter.

### **5. Clinical Pharmacology/Biopharmaceutics**

No new clinical pharmacology data were submitted in or required for review of this supplement. The clinical pharmacology reviewer proposed modifications to the existing label for conformance with the PLR format, to be conveyed to Amgen as an appendix to the CR letter. No new data were provided in the resubmission and minor changes recommended by the Clinical Pharmacology reviewer to conform with current Guidances and enhance clarity were incorporated into section 7 and 12.3 of the FDA's proposed product labeling.

### **6. Clinical Microbiology**

No clinical microbiology data were submitted in or required for review of this supplement as determined by the CMC reviewer.

## 7. Clinical/Statistical-Efficacy

The proposed class labeling changes, submitted in response to items 3, 4, and 5 of FDA's May 31, 2007 letter, were supported by subject-level data from 23 individual studies, chosen because of study design characteristics, and on analyses conducted in pooled data within subgroups based on the source of ESA (darbepoetin alfa or epoetin alfa). The study design characteristics utilized in selecting datasets for inclusion in the pooled analysis were that data were available for individual study subjects participating in randomized, double-blind, placebo-controlled trials sponsored or supported by Amgen or J&JPRD or one of its affiliate companies. The studies included in the pooled analysis of each subgroup are listed below and identified by protocol number.

- Aranesp studies  
20010119, 980291 schedule 1, 980291 schedule 2, 990114, 980297, 20000161, 20010103, 20010145, 20020149, 20030204, 20030232
- Epoetin alfa studies  
[I88-036, I87-018/OEO-U24, I87-019/OEO-U25], [I88-037, I87-016/OEO-U22, I87-017/OEOU23], J89-040, CC2574-P-174, EPO-INT-1, EPO-INT-2, EPO-INT-3, EPO-INT-10, EPO-INT-76, N93-004, PR-27-008 (NCCTG 97-92-53), EPO-CAN-15

Key details of the study designs are presented in the following tables below.

Additional details regarding these studies were requested during the review; Amgen's responses have not addressed all of FDA's needs for additional information for 7 clinical studies, which will be needed if these studies are to be used to support labeling claims. Specifically, FDA will request individual study-specific data for all the studies used in combined analyses in the CR letter.

Amgen also provided the following information

- Revised package insert labeling in PLR format
- A rationale document discussing the approach to the re-analysis of safety information in the proposed package insert
- A rationale document discussing the specific data supporting proposed labeling (or lack of proposed labeling) in response to items 3, 4, and 5 of the May 31, 2007 letter
- Proposed modifications to for inclusion of updated information on two studies already included in the product labeling, the BEST study (Cancer Study 1) and the study conducted in anemic patients not receiving chemotherapy (Cancer Study 8)
- Proposed new language to include the results of Study 20010145
- Proposed language, contained in earlier versions of product labeling but removed during previous labeling revisions, to include the results of Study N93-004.

Study Identifier	Design	Total subjects (ESA : Placebo)	Population	Hemoglobin entry criteria	Treatment Duration	Product Schedule	Upper Hgb Limit Resulting in Dose Modification	Harmful Effects reported
980291 Schedule 1	Randomized placebo-control, dose-ranging, parallel group	249 (32:17:46:28:35:40:51)	Anemic patients with solid tumors receiving multicycle chemotherapy	≤ 11 g.dL	12 wks (blinded phase)	darbepoetin alfa 4.5, 6.75, 9, 12, 13.5, or 15 mcg Q3W	≥15 g/dl (men) ≥14 g/dL (women)	N
980201 Schedule 2	Randomized placebo-control, dose-ranging, parallel group	156 (31:31:33:30:31)	Anemic patients with solid tumors receiving multicycle chemotherapy	≤ 11 g.dL	12 wks (blinded phase)	darbepoetin alfa 9, 12, 15, or 18 mcg/kg Q4W	≥15 g/dl (men) ≥14 g/dL (women)	N
990114	Randomized (1:2:1) placebo-control, dose-ranging, parallel group	66 (11:22:22: 11)	Anemic patients with lymphoproliferative cancers receiving multicycle chemotherapy	≤ 11 g.dL	12 wks	darbepoetin alfa 1.0, 2.25, or 4.5 mcg/kg QW	≥15 g/dl (men) ≥14 g/dL (women)	N
980297	randomized (1:1) placebo-control	314 (156:158)	Anemic patients with lung cancer receiving multicycle platinum-based chemotherapy	≤ 11 g.dL	12 wks	darbepoetin alfa 2.25 mcg/kg QW	≥15 g/dl (men) ≥14 g/dL (women)	N
20000161	randomized placebo-control	344 (174:170)	Anemic patients with lymphoproliferative cancers receiving multicycle chemotherapy	≤ 11 g.dL	12 wks	darbepoetin alfa 300 mcg QW	≥15 g/dl (men) ≥14 g/dL (women)	N
20030232	randomized placebo-control	386 (193:193)	Anemic patients with non-myeloid cancers receiving multicycle chemotherapy	≤ 11 g.dL	15 weeks	darbepoetin alfa 300 mcg Q3W	Hgb ≥13 g/dL Hgb increase 1 g/dL in 14 days	No
20010145	randomized placebo-control	596 (298:298)	Patients with SCLC receiving multicycle platinum/etoposide chemotherapy	Hgb ≥ 9 g/dL and ≤ 13 g/dL	24 weeks	darbepoetin alfa 300 mcg QW x 4 →300 mcg Q3W	≥14 g/dL	No

Study Identifier	Design	Total subjects (ESA : Placebo)	Population	Hemoglobin entry criteria	Treatment Duration	Product Schedule	Upper Hgb Limit Resulting in Dose Modification	Harmful Effects reported
20010103	Randomized; stratified by baseline Hb (<10 vs. ≥ 10 g/dL) placebo-control	985 (515:470)	Anemic patients with non-myeloid cancers receiving no therapy; of hormonal or biologic therapy (i.e., non-myelosuppressive)	≤ 11 g.dL	16 weeks	darbepoetin alfa 6.75 mcg/kg Q4W	>12 g/dL	Yes
20020149	randomized placebo-control extension study of 20010103	371 (198:173)	Anemic patients with non-myeloid cancers receiving no therapy; of hormonal or biologic therapy (i.e., non-myelosuppressive)	Participation in 20010103	16 weeks	darbepoetin alfa 6.75 mcg/kg Q4W	>12 g/dL	Yes

***FDA Reviewers' Assessment of the Amgen's Analysis Approach***

Both the statistical and the clinical review staff raised concerns regarding the validity of Amgen's approach to the assessment of adverse effects of ESAs.

With regard to assessment of effects on overall survival, the review teams noted that there is potential bias based on the selection of studies included in this analysis, in that some studies specifically designed to assess effects on overall survival have not been included (e.g., DAHANCA10 study). [REDACTED] (b) (4)

[REDACTED]

[REDACTED] Reproduced below are Dr. Rothmann's summarization of these methodologic issues (abstracted from his review):

[REDACTED] (b) (4)

Dr. Fan and Dr. Shen both noted limitations in the interpretation of the pooled data based on differences across studies in underlying primary cancer type and stage, differences in chemotherapy regimen, and differential length of follow-up. For these reasons, analysis of results by study rather than by pooling results may be more valid where distinctions in study population and length of followup can be appropriately weighted. Additional limitations, both for individual studies and for the pooled analysis, are the lack of prospective stratification at randomization for baseline hemoglobin levels and the lack of prospective designs assessing appropriate duration of treatment or maximum hemoglobin targets.

***FDA Reviewers' assessment of Amgen's proposed labeling changes***

Item 3 from the May 31, 2007 letter

Revision of the INDICATIONS AND USAGE section to clarify the severity of anemia for which Aranesp/PROCRT is indicated, by inclusion of the maximum, and if appropriate minimum, pretreatment hemoglobin level.

Amgen proposed addition of the following text to Dosage and Administration section of the label:

*FDA Review of Amgen's proposal*

Since the initial submission in December 2007, the product label has been modified as described in Section 2 of this summary review. The following safety labeling change ordered under 505(o) was approved on August 5, 2008 and included the statement

*"Do not initiate Epogen/Procrit for hemoglobin >10 g/dL"*

Based on this action, Amgen's proposed labeling language was replaced with the safety-ordered language.

I concur with the assessment of the clinical and statistical reviewers that Amgen did not provide adequate justification for the proposed target of <sup>(b) (4)</sup> in their original presentation and that these data did not result in a determination that the proposed target was better

supported that the language ordered for inclusion in product labeling by FDA. The FDA reviewers assessment of the rationale provided by Amgen in support of their initial proposal <sup>(b) (4)</sup> is summarized below.



For these reasons, and considering the advice of the March 2008 ODAC, FDA ordered safety language stating that initiation of an ESA should occur only when the hemoglobin was less than 10 g/dL in order to make the drug available to patients with the highest apparent need for RBC transfusions, based on highest proportion of patients at risk for transfusion and noting that the absolute reduction in risk of transfusion appears grossly similar in the various subgroups.

Item 4 from the May 31, 2007 letter

*Revision of the DOSAGE AND ADMINISTRATION section to specify a lower maximum hemoglobin level (ie, hemoglobin level less than 12 g/dL) at which dosing should be suspended or terminated.*



(b) (4)



(b) (4)



the inclusion of  
the following in the Boxed Warning section of the label:

- ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with advanced breast, head and neck, lymphoid, and non-small cell lung malignancies when dosed to target a hemoglobin of  $\geq 12$  g/dL.
- The risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target a hemoglobin of  $< 12$  g/dL.

(b) (4)



*FDA Review of Amgen's proposal*

Since the initial submission in December 2007, the product label was modified as described in Section 2 of this summary review. The final labeling approved on August 5, 2008 contained the following information in the Dosage and Administration subsection for Cancer Patients on Chemotherapy:

FDA's assessment of Amgen's rationale for retaining language from Nov. 2007 is summarized below.

The statistical and clinical reviewers rejected Amgen's proposal not to modify the Dosage and Administration section for Cancer Patients on Chemotherapy for different reasons. The

The clinical reviewer noted that statisticians' assessment of the analyses and agreed that the data did not support the proposed "target". However, she also stated that there is no evidence which directly addresses this question and recommended that the target be left to the treating physician's discretion.

I concur with the conclusions of the statisticians and Dr. Fan that the data provided by Amgen do not support the safety of the hemoglobin target of 12 g/dL as the maximum threshold which should result in withholding of darbepoetin alfa. I do not concur with Dr. Fan's statement that product labeling should remain silent on this issue or leave it to the discretion of physicians. Studies conducted in patients with cancer and in patients with chronic renal failure have indicated that outcomes are poorer with a higher hemoglobin threshold and in the absence of data, I find it prudent to accept the advice of the ODAC and others to target a threshold where transfusions would be avoided. This threshold should be below 12 g/dL and, if consistent with transfusion guidelines, would be closer to 8-9 g/dL. In the absence of clear data from adequately designed and conducted studies, the threshold included in product labeling on Nov. 2007 (10 g/dL) is with a range that would generally not require transfusions. Therefore, I agree with the retention of the labeling accepted in Nov. 2007.

In addition, I agree with the comments made by Amgen regarding their analyses, i.e., that the presence of higher hemoglobin is associated with better outcomes, this does not treatment to achieving that higher hemoglobin results in these better outcomes; this is particularly notable since better outcomes are also present in the placebo-treated arms. The entire approach is to compare make comparisons based on patient responsiveness to the drug, which is likely to be confounded by many patient factors, rather than the impact of a treatment strategy designed to achieve a specific hemoglobin target. In fact, these are the very studies in which signals emerged and there are no data to establish a lower hemoglobin target. Therefore, Amgen should complete the studies required as post-marketing commitments to establish the safety of the recommended dose and schedule in accordance with current labeling.

Item 5 from the May 31, 2007 letter

Revision of the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections to indicate that Epogen/Procrit should be discontinued following the completion of the concomitant chemotherapy regimen.

Amgen proposed the following additions to product labeling



(b) (4)

*FDA Review of Amgen's proposal*

Since the initial submission in December 2007, the product label has been modified as described in Section 2 of this summary review. The approval of a safety labeling change ordered under 505(o) was approved on August 5, 2008 to include the following statements

Boxed Warning

*"Discontinue following the completion of a chemotherapy course."*

Dosage and Administration: Cancer Patients on Chemotherapy

*"Discontinue EPOGEN/PROCRT following the completion of a chemotherapy course"*

Based on this action, FDA replaced Amgen's proposed language with the safety ordered language.

[REDACTED] (b) (4)

Dr. Fan also noted that, in light of the poorer survival outcomes in study 20010103 where patients received Aranesp but no chemotherapy, the available evidence suggests that continued dosing is unsafe and futile (there was no evidence of a reduction in transfusions). For this reason, Dr. Fan recommended that labeling require discontinuation of Aranesp dosing with the last chemotherapy dose.

In the resubmission, Amgen provided datasets and analysis programs supported the proposed data to be included in section 14.2 regarding demographic and transfusions rates for studies C1 and C2 (Protocols 980297 and 20030231). Drs. Shastri and Shen proposed minor editorial changes to Section 14.2 which were conveyed to Amgen.

I concur with Drs. Shastri's and Shen's conclusions and agree with their proposed modifications to Amgen's labeling.

## **8. Safety**

This application was provided in response to FDA requests for revision to product labeling to enhance safety. The rationale for Amgen's proposed labeling rests on aggregate analysis of efficacy (transfusion requirements) and safety [risk of vascular thrombotic events (VTE) and risk of death] from 23 randomized, placebo-controlled trials conducted by or supported by Amgen or Ortho Biotech. In addition, Amgen provided a meta-analysis of published literature

assessing the risks of death and of VTE. None of these data used in this analyses were new and no new safety signals were provided.

In addition, the application contained safety data to permit a re-assessment of safety information presented in the Adverse Reactions section of product labeling, conducted in support of conversion of the product label to PLR format. The safety datasets contained data from studies previously reviewed by FDA in support of approved labeling claims.

No new safety signals were identified through this re-analysis of the data, however the Adverse Reactions section was updated to reflect only those events occurring more frequently in the darbepoetin alfa-treated patients. Details of the FDA's approach to analysis of safety data and basis for inclusion in the Adverse Reactions sections of product labeling are described in the clinical reviews for this supplement.

Amgen also proposed updates to the Warnings and Precautions section of the labeling, describing the results of an "updated" analysis for Study 20010103 (Cancer Study 8) under the "Increased Mortality and/or Tumor Progression section (5.2)" of the product labeling. Data currently in the product labeling were obtained using the analysis data cutoff date of November 7, 2006, whereas the additional data include results through the data cut-off date of March 23, 2007. (b) (4)

[Redacted]

[Redacted] Amgen proposed the following modification to product labeling (in bold)

***"Cancer Study 8 was a Phase 3, double-blind, randomized (Aranesp vs. placebo), 16-week study in 989 anemic patients with active malignant disease, neither receiving nor planning to receive chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions.*** (b) (4)

[Redacted]

Amgen also proposed to modify language in sections 5.1 and 5.2 of the Warnings and Precautions section of the product labeling to describe "updated" results of the BEST study (Cancer Study 1). The BEST study was terminated prematurely awhen interim results demonstrated that higher mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic events (1.1% vs. 0.2%) in the first 4 months of the study were observed among subjects treated with epoetin alfa. At the time of study termination, the Kaplan-Meier estimated 12-month survival was also lower in the epoetin alfa group than in the placebo group (70% versus 76%; hazard ratio 1.37, 95% CI: 1.07, 1.75; p = 0.012). Amgen now proposes to add the "updated" information from long term-follow-up of the BEST study as follows:

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] Drs. Shastri and Shen reached the same conclusion as in the original review and proposed that the results as in current product labeling be retained.

Amgen also proposed to add the following information describing the results of Study 20010145 and Study N93-004 to the WARNINGS AND PRECAUTIONS, Increased Mortality and/or Tumor Progression section (5.2), (b) (4)

[Redacted]

[Redacted] (b) (4)

**In the resubmission:**

- Amgen’s proposed labeling included the term (b) (4) in Adverse Reactions section of the physician product labeling. Dr. Shastri recommended that this term be replaced with the term “adverse reactions” as per FDA Guidances and based on the selection of inclusion of terms in this section. Adverse reactions for cancer studies are denoted for those reactions identified as occurring at higher incidence in placebo-controlled trials. Adverse reactions for studies in patients with chronic renal failure were active controlled (vs. epoetin alfa); rates are provided for adverse reactions identified in placebo-controlled studies of epoetin alfa or with high biologic plausibility based on the product class.
- Amgen’s proposed labeling included data describing the incidence of thromboembolic adverse reactions across a pooled dataset containing the results of seven randomized, controlled trials (Protocols 990114, 980291- schedules 1 and 2, 908297, 20000161, 20010145, and 20030232). Drs. Shastri and Shen confirmed Amgen’s results and included the data in a table designated for such events. Drs. Shastri and Shen also confirmed the accuracy of the text describing the pooled dataset.

- [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]  
[REDACTED] that there are sufficient data from controlled clinical trials submitted to the supplement to adequately describe these risks.
- Amgen proposed to modify the results of Study 3 (the PREPARE study) in the Warnings and Precautions section by describing the results as “interim”. Drs. Shastri and Shen stated that this qualifier was not appropriate as the results reflect data which resulted in early termination of the protocol and thus represent the final study results. This was conveyed to Amgen in the FDA-proposed labeling revisions.
- Amgen proposed to modify the results describing Study 6 (the DAHANCA study) in the Warnings and Precautions section by describing the results as derived from an (b) (4) analysis. Drs. Shastri and Shen stated that this qualifier was not accurate as [REDACTED] (b) (4). Therefore, the reviewers indicated that “formal interim analysis” would be a more accurate description.

All clinical and statistical reviewer comments (see reviews by Drs. Chaohong Fan, Minh-Ha Tranh, Kaushik Shastri, and Yuan-Li Shen) regarding the package insert were considered and incorporated into FDA proposed labeling to be appended to the CR letter.

## 9. Advisory Committee Meeting

There were three meetings of the Oncologic Drugs Advisory Committee (ODAC) in which FDA to seek advice regarding the safety of Erythropoiesis-stimulating agents (ESA) for treatment of anemia due to cancer chemotherapy. The first ODAC was held in May 2004 and the second was held in May 2007, both of which were prior to submission of this supplement. However, a third ODAC meeting was held on March 13, 2008 based on the results of additional studies, not presented at the May 2007 ODAC, which suggested or demonstrated harmful effects. The March 13, 2008 ODAC meeting was convened to review the results of two additional trials (GOG-191 and PREPARE) and progress made on addressing the risks of ESAs since the 2007 ODAC, in order to provide advice on Amgen’s and FDA’s proposed risk mitigation strategies. The key issues on which ODAC advice was sought was whether available data continue to demonstrate that there is a favorable benefit to risk relationship for ESA use for treatment of chemotherapy-induced anemia in patients with cancer and if so, whether the current product labeling is sufficient to ensure safe and effective use.

The following questions, posed to the ODAC, and the Committee’s response are summarized:

1. Considering all the available data on the benefit and risks of ESAs in the treatment of anemia due to concomitant cancer chemotherapy, do you recommend that these products continue to be marketed for the indications listed above?

- Panel members noted that ESAs are more convenient than blood transfusions with one panel member questioning whether there was hard data on the benefit of ESAs other than convenience.
- A point was noted that there may not be a quality of life benefit
- It was questioned that based on the data, ESAs could be 2<sup>nd</sup> line therapy with possible use in patients whom transfusion was not appropriate.
- Overall, the committee agreed that these products should continue to be marketed for the indication listed in Question 1.

**Vote :**            **Yes=13**                      **No = 1**                      **Abstain = 0**

2. If you recommend that the current indication should be retained, should FDA require that product labeling be modified? Below are four potential approaches to mitigating risks through revised labeling. Please address each of them separately.

a. **Vote:** To date, only clinical trials in small cell lung cancer have reasonably excluded an increased risk for death among patients receiving ESAs. Trials have demonstrated an increased risk of death and/or tumor promotion in head/neck, non-small cell lung cancer, breast (neoadjuvant and metastatic settings), lymphoid malignancies, and cervical cancers. Tumor types, other than those listed above, have not been adequately studied. ***Should the current indication be modified to restrict use only to patients with small cell lung cancer?***

- One panel member noted that ESAs should only be approved in disease where there is little/no risk while other settings require additional studies.

**Vote :**            **Yes=6**                      **No = 8**                      **Abstain = 0**

b. **Vote:** The PREPARE trial demonstrated decreased relapse-free and overall survival in breast cancer patients receiving neoadjuvant chemotherapy. The risk/benefit assessment is different for patients receiving neoadjuvant and adjuvant chemotherapies than for patients with metastatic or incurable cancers. ***Should the current indication be modified to include a statement that ESA use is not indicated for patients receiving potentially curative treatments?***

- One panel member noted that those with metastatic disease should not receive ESAs any different than those in the adjuvant setting.
- One panel member noted that using ESAs in the curative group, may convert from a curative patient to a non-curative patient.
- Overall, the panel agreed that the current indication should be modified to include a statement that ESA use is not indicated for patients receiving potentially curative treatments.

**Vote :**            **Yes=11**                      **No = 2**                      **Abstain = 1**

c. **Vote:** Although increased tumor promotion and/or decreased survival have been demonstrated in several tumor types, adverse findings have been duplicated in two malignancies—breast cancer and head and neck cancer. ***Should the current indication be modified to include a statement that ESA use is not indicated for patients with breast and/or head & neck cancers?*** (If yes, please specify breast and/or head & neck cancer).

- *Panel members questioned the definition/appropriateness of the terminology “tumor progression” and “tumor promotion” in regards to the use of ESAs.*
- *It was noted that the question could also read with “metastatic” in front of breast and/or head & neck cancers.*

**Vote :**            **Yes=9**            **No = 5**            **Abstain = 0**

d. The only objective evidence of efficacy demonstrated for ESAs has been avoidance of RBC transfusions; however, not all patients with anemia require an RBC transfusion. Product labeling does not specify the hemoglobin level at which ESA treatment should be initiated. ***Assuming a patient is asymptomatic and has no co-morbid conditions, please specify the hemoglobin level at which initiation of an ESA is appropriate.***

- *Panel members agreed that treatment should be based on physician judgment and tailored to individual patients. Panelists did not feel that setting levels was appropriate for a hypothetical patient.*

3. If the Committee recommends that the indication for treatment of anemia due to concomitant chemotherapy should be retained (as currently approved or with additional labeling changes as above), discuss additional strategies that FDA could require to minimize risk. Below are two options that could be considered. If you have other suggestions, please state them.

a. **Vote:** An informed consent/patient agreement would explicitly require the oncology patient's authorization or agreement to undergo treatment with an ESA. Both patient and physician (or designate) signatures would be required. In the process, the physician prescribing the ESA treatment would discuss the risks and benefits of ESA therapy and alternative treatments. ***Should the FDA require the implementation of an informed consent/patient agreement for the treatment of chemotherapy induced anemia?***

(Question 3a-b was clarified to ask for the principle instead of the logistics of the informed content/patient agreement)

- ***The panel agreed that adequate patient education is necessary, however disagreed on whether a written informed consent should be required***

**Vote :**            **Yes=8**            **No = 5**            **Abstain = 1**

- b. **Vote:** Examples of restricted distribution programs include STEPS (thalidomide), RevAssist (lenalidomide), and iPLEDGE (isotretinoin). Restricted distribution systems link product access to planned safe and effective use. These programs may require identification and enrollment of healthcare providers who agree to prescribe only in accordance with product labeling and who commit to patient education regarding safe use. Registration of patients may also be required. Certain patient characteristics would be recorded at individual patient registrations (e.g., hemoglobin, chemotherapy type, malignant diagnosis). *Should FDA mandate a restricted distribution system for oncology patients receiving ESAs? YES or NO*

*Vote :            Yes=1            No = 10            Abstain = 2*

- *The committee agreed that a restricted distribution system was not necessary in regard to the above question. It was noted that to address the issue of safety, physician incentives should be reduced.*

## 10. Pediatrics

Not applicable to this application as a new indication, new dosing regimen, or new presentation was not sought.

## 11. Other Relevant Regulatory Issues

Division of Scientific Investigations audits were not requested for any studies since most of the studies included for the combined analysis were more than 10 to 15 years old and primary records would not be available.

## 12. Labeling

No changes to the proprietary name or carton/container labeling were proposed by Amgen and the FDA did not identify need for modifications to these components of product labeling in the original submission. Verbal comments provided by DDMAC and DRISKØSE during labeling meetings were considered and incorporated as appropriate in FDA proposals for revisions to the submitted product labeling.

Amgen has requested changes to product labeling in response to FDA's request for a labeling supplement, as discussed in Section 7 of this review. In the original submission (Dec. 26, 2007), Amgen proposed additional labeling changes not requested by FDA

- An update to clinical information on Study 20010103 (Cancer Study 8) in the WARNINGS AND PRECAUTIONS, Increased Mortality and/or Tumor Progression section (5.2) of the label. The updated information is derived from survival data obtained in a post-treatment follow-up period. The current labeling section is reproduced below with the change in bold font:

*“Cancer Study 8 was a Phase 3, double-blind, randomized (Aranesp vs. placebo), 16-week study in 989 anemic patients with active malignant disease, neither receiving nor planning to receive chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. (b) (4)*

FDA Assessment: The clinical and statistical reviewer have rejected this proposed change (b) (4)

- The addition of information on Study 20010145 to the WARNINGS AND PRECAUTIONS, Increased Mortality and/or Tumor Progression section (5.2) of the label. The proposed new language to be included in the label is reproduced below (b) (4)

FDA Assessment: Both the clinical and statistical reviewer rejected inclusion of this study in the Warnings and Precautions section. (b) (4)

- An update of clinical information on the “BEST” Study (Cancer Study 1) in the WARNINGS AND PRECAUTIONS section of the label. The proposed new language to be included in the label is reproduced below.

[Redacted] (b) (4)

FDA assessment: The clinical and statistical reviewers have rejected this proposed modification to language in the current labeling. The reviewers find this “updated” data not acceptable for inclusion in the labeling because [Redacted] (b) (4)

[Redacted]

- To add the information on Study N93-004 to the WARNINGS AND PRECAUTIONS, Increased Mortality and/or Tumor Progression section of the label. The proposed new language to be included in the label is reproduced below

[Redacted] (b) (4)

FDA Assessment: Both the clinical and statistical reviewer rejected inclusion of this study in the Warnings and Precautions section. [Redacted] (b) (4)

[Redacted]

FDA reviewers recommended numerous additional modifications to Amgen’s proposed package insert. The changes are briefly itemized below.

**(1) Boxed Warning**

- a. “minimize” changed to “decrease” because of the lack of certainty regarding the magnitude of the reduction in the risk in patients who receive any amount of an ESA.

b.

(b) (4)

- c. "adverse reactions" substituted for (b) (4) throughout labeling.
- d. Inclusion of wording to reference the REMS program.
- e. Information in the Boxed Warning presented in bullet form to enhance legibility.

**(2) Indications and Usage section**

- a. New subsection "Limitations of Use" created to limit repetition of the same information across both indications.
- b. Currently approved indications statements re-worded for brevity and clarity
- c. Titles of subsections shortened for brevity.
- d. Inclusion of wording to reference the REMS program.

**(3) Dosage and Administration**

- a. Extensively revised for brevity and re-worded for "active voice"
- b. References to "lack or loss of response" deleted; product labeling is not intended to cover aspects of general medical management (e.g., differential diagnosis of anemia) and clinical indications clarify the types of anemia for which Epopen is indicated.

**(4) Dosage Forms and Strengths**

Information in this section moved to section 16; remaining information shortened for brevity and consistency with other labeling.

**(5) Warnings and Precautions**

a.

(b) (4)

b.

- c. Section 5.2: Editorial changes to remove the word "Cancer" from the study titles as this may lead to confusion with references to studies in section 14.3. Also, references to the study phase (e.g., phase 3) deleted throughout this section, as superfluous to other information describing study design and as per FDA Guidance. Deleted alternate names of studies (e.g., ENHANCE) throughout sections 5.1 and 5.3.
- d. Revised text describing results of study 6 for accuracy. The goals of treatment in the Aranesp arm were to achieve and maintain hemoglobin levels at levels above that which would be classified as anemia.
- e.

(b) (4)

- f. Section 5.3 (Hypertension) revised to delete unnecessary information on

(b) (4)

- g. Moved up “Seizures” to section 5.4 as next most common serious adverse event. Revised for brevity and active voice
- h. Deleted sections on “loss of response”, “general”, and “CRF patients not on dialysis”. Product labeling should not include information related to general practice of medicine (i.e., differential diagnosis and diagnostic work-up of anemia) or to general care for underlying medical conditions.
- i. Revised subsection on PRCA to remove references to deleted subsection on loss of response; edited for brevity and active voice.
- j. Deleted subsection on Hematology. Relevant information now included in section on laboratory testing.
- k. Subsection on Dialysis Management edited for brevity and critical information.
- l. Subsection on Laboratory testing re-titled to clarify the focus of this subsection. Edited for brevity and active voice and to limit redundancy with D&A section.
- m.  (b) (4)
- n. Addition of new subsection (5.2) to reference the approved REMS

**(6) Adverse Reactions**

- a. Extensively edited for brevity and for consistency with current FDA Guidance on Adverse Reactions section of product labeling.
- b. Adverse events probably unrelated to ESA’s in the judgment of the Div of Hematology reviewer were removed from adverse event tables.
- c.  (b) (4)
- d. The subsection on annualized rates of thrombotic events in patients with CRF deleted due to lack of confidence in ascertainment and completeness of follow-up, leading to a potential underestimation of the event rate.
- e. Added subsection on Post-marketing Experience, with recommended caveats regarding inadequate information to characterized incidence of such reactions.
- f. Immunogenicity subsection edited to delete phrase “other products in this class” for consistency with current Guidances on product labeling.
- g. Amgen’s proposal to use the term  (b) (4) in this section, per the Oct. 26, 2009 resubmission, was deleted and replaced with the term “adverse reactions” as per FDA Guidances. Adverse reactions for cancer studies are denoted for those reactions identified as occurring at higher incidence in placebo-controlled trials. Adverse reactions for studies in patients with chronic renal failure were active controlled (vs. epoetin alfa); rates are provided for adverse reactions identified in placebo-controlled studies of epoetin alfa or with high biologic plausibility based on the product class.

h. Data describing the incidence of thromboembolic adverse reactions across 7 randomized, controlled trials were confirmed and included in a table designated for such events.; text description of the pooled dataset was determined to be acceptable.

i. (b) (4)  
[REDACTED]  
[REDACTED]  
[REDACTED] there are sufficient data from controlled clinical trials submitted to the supplement to adequately describe these risks.

**(9) Use in Specific Populations**

- a. Pregnancy Category C: Editorial changes.
- b. Nursing mothers: Animal data in this section moved to Non-clinical toxicology section. This section modified in accordance with recommendations from Maternal-Fetal Health team.
- c. Pediatric Use: Re-worded for clarity. References to Clinical Pharmacology (12.3) and Clinical Studies (14.1) added. The term “conversion” replaced with “transition”.
- d. Geriatric Use: Minor editorial changes for clarity.

**(10) Overdosage**

- This section was revised to clarify both subacute and chronic effects of overdosage and to provide more specific directions regarding appropriate actions to be taken (e.g., drug discontinuation). Edited for brevity with deletion of non-essential information (e.g., information in Dosage and Administration on monitoring hemoglobin rate of rise).

**(11) Description**

- Edited for brevity and essential information; resulting in deletion of phrase “closely related to erythropoietin” and “additional carbohydrate chains increase the” as non-essential information.

**(12) Clinical Pharmacology**

- a. Section on Mechanism of action: The majority of this section was deleted because it refers to endogenous erythropoietin rather than Aranesp or is either covered in other sections (PD or PK subsections of clinical pharmacology or Dosage and Administration section).
- b. Section on PD: Replaced “until” with “for” in describing time to PD effect.
- c. Section on PK: Editorial changes to spell out acronyms. Deletion of information on 2.25 mcg/kg dose from paragraph describing PK of Aranesp in patients with cancer as this is not an approved dose for an every-three-week schedule.

**(13) Non-Clinical Toxicology**

- a. Section on Reproductive and Developmental Toxicology added and includes data previously described under Pregnancy subsection; the non-clinical data were moved

to this section as recommended by the OSE consultant staff as the more appropriate section for these data.

- b. Deleted information on tissue cross-reactivity in animal species and lack of proliferative effects in non-hematologic tissues, as findings are expected.

#### **(14) Clinical Studies**

- a. In general, section revised for brevity and clarity and to include appropriate clinical trial description in accordance with the Guidance for Industry document on this section of the label.
- b. Study results for N5 trial in pediatric patients with CRF added to this subsection.
- c. General section describing design of studies supporting safety and efficacy in patients with cancer added. Subsequent paragraphs on the individual studies edited to delete information in introductory paragraph and for brevity and clarity. Description of the primary efficacy measures included. In Study C2 results, efficacy re-calculated based on primary efficacy population (for consistency with Study C1 and Epogen/Procrit analyses) of patients remaining on study between day 29 and end-of-treatment.
- d. Data limited to primary efficacy endpoints and data used by FDA as primary support to expand labeling claims.
- e. Inclusion of demographic information and crude transfusion rates for Protocols 980297 and 20030231 were deemed acceptable based on FDA's confirmation of the results through datasets provided in the resubmission.

#### **(15) How Supplied and Handling Information**

- Information previously provided in dosage forms and strengths moved to this section.

#### **(16) Patient Counseling Information**

- Re-placed previous patient labeling with Medication Guide; further labeling modification to be addressed under pending REMS supplement (BL STN 103951/5195).

#### **Medication Guide**

- Revised to refer to the REMS Program
- Updated common side effects of Aranesp for consistency with changes to the Adverse Reactions section of the Physician Package Insert

#### **Patient Instructions for Use**

- Minor editorial changes as recommended in by DRISK during labeling meetings

### **13. Decision/Action/Risk Benefit Assessment**

- Regulatory Action: Complete Response

- Risk Benefit Assessment

The benefit of Aranesp is limited to a reduction in the risk of receiving allogeneic red blood cell transfusions and their attendant risks of transfusion-associated lung injury, infection, alloimmunization, as well as the cost and inconvenience of the transfusion procedure. Based on FDA's review of the information provided in the clinical study reports for the individual darbepoetin and epoetin alfa studies included in the analysis, there is no evidence based multiple studies in which patient-reported outcome instruments were used that demonstrated a quality-of-life benefit for cancer patients receiving an ESA as compared to placebo-treated patients. In addition, available data from randomized clinical trials do not indicate that use of an ESA provides an improvement in tumor-related outcomes, despite speculation on the existence of such benefits.

This benefit in reduction in allogeneic transfusions is weighed against the risks of Aranesp (supported by data with Epogen/Procrit), which include increased mortality and shorter time-to-tumor progression in patients with cancer in whom ESAs were administered to target hemoglobin levels to normal or supraphysiologic level, and an increased risk of thrombotic events in all populations at recommended doses. Neither the risks of ESAs within patient populations defined by baseline hemoglobin at initiation of Aranesp or Epogen/Procrit in patients with cancer nor the benefits (reduction in the risks of RBC transfusion) are sufficiently well-characterized to provide accurate estimates either of these risks. However, as noted by Dr. Fan, the approval of the first epoetin alfa product occurred in an era where substantial concerns regarding the risks of transfusion, particularly the risks of transmission of HIV, Hepatitis B, and potentially other infections, existed. Since that time, the science of transfusion medicine has advanced with resultant decrease in risks, while increasing evidence has been generated to support the previously theoretical possibility of adverse effects on tumor outcomes as well as poorer survival when ESAs are used to achieve high normal and supraphysiologic hemoglobin levels in patients with cancer and chronic renal failure. Thus, the risk-benefit profile has substantially changed over time.

In the absence of data clearly demonstrating harm at the currently recommended dose, with use limited to the indicated patient population, the risks have not been demonstrated to outweigh the benefits. This determination was based both on FDA review staff and advice received from members of the ODAC during the March 13, 2008 meeting. However, labeling must retain language included in product labeling following the March 2008 ODAC meeting which provide appropriate directions for use to minimize risks to subjects.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

The license application for Aranesp is subject to a REMS under 505(o). Agreement on language for the Medication Guide will proceed under a separate supplement (BL STN 103951/5195).

- Recommendation for other Postmarketing Requirements and Commitments

No additional post-marketing requirements or commitments will be requested under this supplement.

SIGNATURES PAGE

/s/Patricia Keegan/

April 27, 2010

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Patricia Keegan, M.D.

Date

Director, Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

## CLINICAL REVIEW ADDENDUM

Application Type sBLA  
Submission Number 103951.5173  
Submission Code Response to CR letter

Letter Date 10/23/2009  
Stamp Date 10/26/2009  
PDUFA Goal Date 4/27/2010

Reviewer Name Kaushik Shastri, M.D

Through Patricia Keegan, M.D  
Acting Team Leader &  
Division Director

Review Completion Date 03/22/2010

Established Name Darbepoeitin alfa  
Trade Name Aranesp  
Therapeutic Class Erythropoiesis Stimulating Protein  
Applicant Amgen

Priority Designation Class 2 resubmission

Formulation Polysorbate solution  
Albumin solution

Dosing Regimen	2.25 µg/kg SC QW 500µg SC, Q3W
Indication	Treatment of anemia due to myelosuppressive chemotherapy in patients with non-myeloid malignancies
Intended Population	Anemic patients with malignancy undergoing myelosuppressive chemotherapy

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## **1. Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

This reviewer recommends the approval of this supplement with the with the FDA suggested revisions to the labeling submitted in the Physician Labeling Rule (PLR) format, medication guide and the patient instructions for use.

### **1.2 Risk Benefit Assessment**

This supplement was originally submitted on December 20, 2007 to convert the label to physician labeling rule format and to address some of the issues raised at March 13, 2007 ODAC meeting for the use of Aranesp in anemic cancer patients, i.e. the threshold of baseline hemoglobin for the initiation of Aranesp, a lower (< 12 g/dL) hemoglobin level at which Aranesp should be suspended or terminated, and when to discontinue the use of Aranesp following the completion of the chemotherapy course. In the review of the original submission (see original review by Dr. Fan) it was determined that the submission did not contain robust evidence from studies to adequately address these issues. Subsequent label revisions that were approved following the original submission, have addressed the above issues with a conservative guidance for threshold of hemoglobin at which to initiate, suspend and terminate the use of Aranesp when treating cancer patients with anemia due to myelosuppressive chemotherapy. The physician package insert in this resubmission contains the conservative guidance for the use of this product already in the approved label.

During the course of the review of this resubmission a Risk Evaluation and Mitigation Strategy was approved by the FDA on 2/16/10 under STN 103951/5197.

The risk/benefit assessment with the already approved REMS favors continuing marketing of this drug for use in cancer patients with anemia due to myelosuppressive chemotherapy.

### **1.3 Recommendations for Postmarketing Risk Management Activities**

A REMS program was already approved.

### **1.4 Recommendations for other Post Marketing Study Commitments**

No other post marketing study commitment is recommended to this supplement.

## 2. Background and Overview

On 20 December 2007 (STN BL 1039511/5173) Amgen submitted a prior approval supplement to revise the prescribing information and reformat according to the Physician Labeling Rule (PLR) and address some of the questions raised at the March 13, 2007 ODAC meeting. The questions that were supposed to be addressed included the threshold of baseline hemoglobin for the initiation of Aranesp, a lower (< 12 g/dL) hemoglobin level at which Aranesp should be suspended or terminated, and when to discontinue the use of Aranesp following the completion of the chemotherapy course. In the review of that submission (see original review by Dr. Fan) it was determined that the submission did not contain robust evidence from studies to adequately address these issues. Subsequent label revisions that were approved following that submission, have addressed the above issues with a conservative guidance for threshold of hemoglobin at which to initiate, suspend and terminate the use of Aranesp when treating cancer patients with anemia due to myelosuppressive chemotherapy.

On 24 October 2008 FDA issued a complete response letter for this submission since agreement on the labeling for the PLR conversion of the currently approved label was not reached. As noted above, the CR letter focused mainly on the PLR conversion of the label, since Amgen did not conduct studies specifically designed to address the issues raised at the March 13, 2007 ODAC meeting and the more conservative dosing and administration guidance in the subsequently approved labels acknowledged the lack of studies to address those issues.

This re-submission contains Amgen's response to the FDA's complete response letter. This clinical review will only cover the Oncology portions of the submission, since the non-Oncology parts are being reviewed by another division (DMIHP).

Amgen has provided the responses to the CR letter:

- (1) Resubmission of datasets as requested in item 5b of the August 19, 2008 letter (pertained to study 990114).
- (2) Clarification of the source of non-clinical data regarding rat and rabbit reproductive studies: Amgen has provided this- reviewed by non-clinical reviewer.
- (3) submission of additional information requested in the comments embedded in the revised labeling sent to Amgen; these comments for the Oncology portion of the label pertained to providing the exposure information for study 10010145 and demographic and exposure information for study C1 (980297).
- 4) submit a revised label
- 5) through 11) provide a safety update including worldwide experience

Review of items 1, 3, and 4 are addressed in the following labeling review. Item 2 is addressed in the non-clinical review.

Under items 5 through 11 Amgen has provided adverse events tables, study discontinuation information and exposure information from pooled data from studies 980297, 980291,

980291SCH2, 990114, 20000161, 20010145 and 20030232 comparing it to data from study 20010145. All the individual studies were reviewed previously (see Dr. Fan's review of the original submission). The data for inclusion in the product label are discussed under proposed labeling changes.

As per Amgen a total of 6569 subjects with nonmyeloid malignancies receiving chemotherapy have received at least 1 dose of darbepoetin alfa in 23 Amgen-sponsored clinical studies. Total exposure to darbepoetin alfa was 93,898 patient-weeks. Data for subjects receiving an active control (ie, epoetin alfa) were not included. The analysis also excluded single-arm studies that collected only serious adverse events or that were primarily pharmacokinetic studies, studies in MDS, or oncology studies where chemotherapy was not administered.

A total of 1203 subjects have received darbepoetin alfa in randomized, double-blind, placebo-controlled studies in the chemotherapy setting (980291, 980297, 990114, 20000161, 20010145, and 20030232). Total exposure to darbepoetin alfa was 15,534 patient-weeks in this combined analysis set.

Regarding worldwide experience, Amgen states that darbepoetin alfa was initially darbepoetin alfa has been approved for use in 49 countries for the treatment of anemia associated with chronic renal failure, including patients receiving dialysis and patients not receiving dialysis. In addition, darbepoetin alfa is approved in 48 countries for the treatment of anemia in cancer patients receiving concomitant myelosuppressive chemotherapy. Cumulatively, since the initiation of darbepoetin alfa clinical trials in December 1996 through 30 April 2009, an estimated 4.8 million patients (2.8 million patient-years) have been exposed worldwide to darbepoetin alfa in clinical trials and the commercial setting combined.

### **3. Proposed Labeling Revisions, Supporting Data and Review Comments**

Amgen's proposed labeling revisions and the data supporting them as related to the oncology indication are discussed below:



*Reviewer Comments and recommendations: The adverse reactions data are derived from placebo-controlled studies and hence should retain the term adverse reactions.*



(b) (4)

**Update on Study Results in Section 5 Warnings and Precautions:**

Study 20010103

As per Amgen, in the original submission, Amgen proposed a revision of description of the study 20010103 (b) (4)

Amgen's red-line labeling revision of the OS results for study 20010103 is shown below:

(b) (4)

***Review Comments:*** This reviewer rejects the changes proposed by Amgen. Please also see the statistical review. (b) (4)

PREPARE Study:

Amgen states that the current label reflects the interim analysis and the study is now complete and proposed the following change to the label:

(b) (4)

***Reviewer Comments and recommendation:*** Please see statistical review for detailed analysis of the updated data. (b) (4)

(b) (4)  
t. Hence the proposed changes should  
be rejected.

Results based on DAHANCA (study 6)

Amgen proposed to add the word (b) (4)' before the interim analysis in describing this study results. Amgen also wants to clarify that the subjects in this study did not receive chemotherapy.

Amgen's revision on the labeling is shown below:

(b) (4)

*Reviewer's comments:*

The addition of (b) (4) to qualify the interim analysis should be rejected. (b) (4)

Therefore, FDA  
considers the analysis as the formal interim analysis. (b) (4)

**Adverse Events Section:**

In the original labeling proposal in December 2007, Amgen submitted adverse events data from randomized, double-blind, placebo-controlled studies in subjects with cancer receiving chemotherapy that were included in the initial darbepoetin alfa Biologics License Supplement (BLS) and 120-day safety update for the oncology indication (Studies 990114, 980291 schedule 1, and 980297) as well as subsequent, randomized, double-blind, placebo-controlled studies (Studies 980291 schedule 2, 20000161, 20010145, and 20030232). These studies were combined for analysis.

In the complete response letter, FDA commented that the broad, pooled safety dataset could obscure safety signals. The adverse reaction table in the FDA-proposed labeling included data from Study 20010145 (n=597) only, as this is the largest placebo-controlled study with a homogeneous tumor type and chemotherapy regimen.

In this submission, Amgen has proposed (b) (4)

The demographic information for Study 20010145 is shown below:

	Darbepoetin alfa (N=301)	Placebo (N=296)	Total (N=597)
<b>Sex - n(%)</b>			
Male	188 (62)	197 (67)	385 (64)
Female	113 (38)	99 (33)	212 (36)
<b>Race - n(%)</b>			
White	301 (100)	296 (100)	597 (100)
Other	0 (0)	0 (0)	0 (0)
<b>Age - years</b>			
n	301	296	597
Mean	60.6	61.3	61.0
SD	9.2	8.3	8.8
Median	61.0	61.0	61.0
Q1, Q3	55.0, 68.0	55.0, 67.0	55.0, 67.0
Min, Max	28, 81	37, 82	28, 82
<b>Age Group - n(%)</b>			
< 65 years	194 (64)	195 (66)	389 (65)
≥ 65 years	107 (36)	101 (34)	208 (35)
<b>Geriatric Age Group - n(%)</b>			
< 75 years	286 (95)	278 (94)	564 (94)
≥ 75 years	15 (5)	18 (6)	33 (6)
<b>Geographic Region<sup>a</sup> - n(%)</b>			
Western Europe	67 (22)	65 (22)	132 (22)
Australia/ North America	10 (3)	9 (3)	19 (3)
Rest of the World	224 (74)	222 (75)	446 (75)

The exposure information for Study 20010145 is shown below:

	Darbepoetin alfa (N=301)	Placebo (N=296)
<b>Total Number of Doses</b>		
n	301	296
Mean	9.44	12.78
SD	4.80	6.02
Median	9.00	13.00
Q1, Q3	6.00, 13.00	8.00, 18.00
Min, Max	1.0, 21.0	1.0, 24.0
<b>Duration of Exposure (excl. zero doses) (Weeks)<sup>a</sup></b>		
n	301	296
Mean	16.02	16.51
SD	7.00	7.20
Median	19.00	19.00
Q1, Q3	10.00, 22.00	13.00, 22.00
Min, Max	1.0, 26.0	1.0, 26.0

The demographic information for the pooled safety dataset is as follows:



The exposure information for the pooled dataset is shown in the Table below:



Amgen has proposed the following for inclusion in the label:



Table 4 lists adverse reactions occurring in  $\geq 1\%$  patients treated with Aranesp.

(b) (4)

*Review Comments: The above information was confirmed upon review of the adverse event data. Additionally based on analysis of data this reviewer recommends addition of the following to the Oncology adverse events section:*

(b) (4)

**Oncology Clinical Study Section (section 14.2):**

In the embedded comments in the FDA revised label sent to Amgen with the complete response letter, Amgne was asked to insert/confirm the demographic information for the two studies included in this section and change the incidence of transfusions in the study based on crude rates for both studies C1(980297) and C2 (20030231). Amgen proposed the following for inclusion in the label:

(b) (4)

*Reviewer Comments: Please see statistical review. The demographics and efficacy results were confirmed by the statistician. The demographics relate to the ITT population. Amgen has been asked to provide the demographic information for the efficacy population.*

**Labeling Changes related to REMS Approval:**

Since this re-submission, a REMS was approved on 2/16/10. This necessitated changes in the product label to include information about the REMS program. This included the following additions:

**Black box warning:** *Prescribers and hospitals must enroll in and comply with the ESA APPRISE Oncology Program to prescribe and/or dispense Aranesp to patients with cancer. To enroll in the ESA APPRISE Oncology Program, visit [www.esa-apprise.com](http://www.esa-apprise.com) or call 1-866-284-8089 for further assistance [see Warnings and Precautions (5.2)].*

### **Section 2.3 Cancer Patients on Chemotherapy:**

*Only prescribers enrolled in the ESA APPRISE Oncology Program may prescribe and/or dispense Aranesp [see Warnings and Precautions (5.2)].*

### **Section 5.2**

#### **Risk Mitigation Prescribing and Distribution Program**

(b) (4)

### **Other Labeling Changes:**

In addition to the above changes the label was extensively revised for clarity. Those changes that pertain to the Oncology indication are summarized below:

Information in the black box warning was bulleted.

The indication and usage section in the highlight section and section 1.2 was revised to include the information that Aranesp is indicated for treatment of anemia due to effects of concomitant myelosuppressive chemotherapy that will be administered for a minimum of two additional months in patients with non-myeloid malignancies.

The section on limitations of use was streamlined and bulleted.

The highlight section on adverse events in cancer patients was changed to reflect the changes in the adverse events section of the label.

### **Review of Medication Guide:**

The medication guide was revised to include information on the REMS program, update the adverse event information to be consistent with the PI, and streamlined for ease of reading.

Under "**What is the most important information I should know about Aranesp?**" the following information was added.

(b) (4)

Under '**what is Aranesp?**' the following was added:  
*Aranesp should not be used for treatment of anemia.*

(b) (4)

Under '**Who should not take Aranesp?**' the following information was added.

*Do not take Aranesp if you:*

(b) (4)

Under "**What should I tell my healthcare provider before taking Aranesp?**" in the bullet beginning with 'Are pregnant or planning to become pregnant...the following was added:

*If you are pregnant, discuss with your healthcare provider about enrolling in Amgen's Pregnancy Surveillance Program or call 1-800-772-6436 (1-800-77-AMGEN).*

Under '**How should I take Aranesp?**' a separate section for patients with cancer was created, which reads as follows:

*Patients with cancer:*

*Before you begin to receive Aranesp, your healthcare provider will:*

- *Ask you to review this Aranesp Medication Guide*
- *Explain the risks of Aranesp and answer all your questions about Aranesp*

(b) (4)

Under '**What are the possible side effects of Aranesp?**', in the subheading of common side effects of Aranesp, the following information was updated:

*Common side effects of Aranesp include:*

(b) (4)

### **Review of Patient Instructions for Use (PIU).**

Please see DRISK review.

### **Single-Dose Prefilled Syringe (SingleJect):**

Under the heading of '*Intravenous route*', the following change was made:

Aranesp can be injected in your vein through a special access port (b) (4) placed by your healthcare provider.

**Single Dose Vial:** Under the heading *'When you receive your Aranesp vial and syringes make sure that'*, the following change was made:

[Redacted] (b) (4)

Under the heading of *'Intravenous route'*, the following change was made:  
Aranesp can be injected in your vein through a special access port [Redacted] (b) (4) placed by your healthcare provider.

[Redacted] (b) (4)

**Addendum to the Oncology Adverse Events in the Physician's Package insert:**

On March 22, 2010, Amgen submitted a response to FDA proposed PLR changes to Aranesp labeling sent to them on February 22, 2010, March 3, 2010, and March 10, 2010. In this submission, Amgen proposed a revised Table 4 in the Oncology ADR section, stating that in Amgen's original proposal for Table 4 in the Adverse Reactions section (Thrombovascular Adverse Reactions in Patients Receiving Chemotherapy), a programming error resulted in the inclusion of adverse events that are usually excluded from such analyses (ie, adverse events that occurred before the administration of investigational product or after crossover to a post-treatment extension phase for those studies with a crossover design). This error was corrected in their proposed revised table and the description of the Oncology adverse events.

In response to FDA's request, Amgen provided separate adverse events dataset for the 145 study and the pulled AE dataset for the studies represented in the table on 3/29/10. On 4/12/10 submission Amgen further corrected the Oncology adverse event Table 4 stating the incidences for the ADR of myocardial infarction proposed on 3/22/10 were inadvertently taken from the Preferred Term level within the Embolic and Thrombotic events rather than at the Myocardial Infarction SMQ level. The proposed description of Table 4 and the text was as follows:

**Table 4. Thrombovascular Adverse Reactions in Patients Receiving Chemotherapy**

(b) (4)

**Reviewer Comments and Recommended revisions:**

This reviewer recommends the following revisions to the adverse reaction incidences described in the table and text in order to use incidences determined by narrow scope SMQ (except using the preferred term for pulmonary embolism (not identified in the SMQ). For the incidence of abdominal pain, the high level term for gastrointestinal and abdominal pain excluding oral and throat pain should be used and for edema high level term Oedema NEC should be used.

**Table 4. Thrombovascular Adverse Reactions in Patients Receiving Chemotherapy**

Adverse Reaction	SCLC Study		All Placebo-controlled Studies	
	Aranesp (n = 301)	Placebo (n = 296)	Aranesp (n = 1203)	Placebo (n = 909)
Thromboembolic Adverse Reactions, n (%)	24 (8.0%)	13 (4.4%)	73 (6.1%)	37 (4.1%)
Arterial	10 (3.3%)	3 (1.0%)	15 (1.2%)	5 (0.6%)
Myocardial infarction	5 (1.7%)	0	7 (0.6%)	2 (0.2%)
Venous	14 (4.7%)	10 (3.4%)	60 (5.0%)	32 (3.5%)
Pulmonary embolism	5 (1.7%)	3 (1.0%)	16 (1.3%)	6 (0.7%)
Cerebrovascular disorders*	14 (4.7%)	9(3.0%)	20 (1.7%)	17 (1.9%)

\* "Cerebrovascular disorders" encompasses CNS hemorrhages and cerebrovascular accidents (ischemic and hemorrhagic). Events in this category may also be included under "thromboembolic adverse reactions."

In addition to the thrombovascular adverse reactions, abdominal pain and edema occurred at a higher incidence in patients taking Aranesp compared to patients on placebo. Among all placebo-controlled studies, abdominal pain (13.2% vs. 9.4%) and edema (12.8% vs. 10%) were reported more frequently in patients receiving Aranesp compared to the placebo group. In the SCLC study the incidence of abdominal pain (10.3% vs. 3.4%) and edema (7.0% vs. 5.7%) in the Aranesp-treated patients compared those receiving placebo.

**Signature Page:**



**Kaushik Shastri, MD  
Clinical Reviewer,  
DBOP**

**Through:**



**Patricia Keegan, MD  
Acting Team Leader,  
DBOP**

## Summary Review for Regulatory Action

<b>Date</b>	October 24, 2008
<b>From</b>	Patricia Keegan, M.D. <i>P. Keegan</i> 10.24.08
<b>Subject</b>	Division Director Summary Review
<b>BLASupplement #</b>	STN BL 103951/5173
<b>Applicant Name</b>	Amgen, Inc.
<b>Date of Submission</b>	December 26, 2007
<b>PDUFA Goal Date</b>	October 24, 2008
<b>Proprietary Names / Established (USAN) Name</b>	Aranesp <sup>®</sup> darbepoetin alfa
<b>Dosage Forms / Strength</b>	Solution (albumin-containing or polysorbate buffer solutions) for subcutaneous or intravenous injection in single-use vials or prefilled syringes. Strengths range from 25 mcg to 300 mcg for vials and 25 mcg to 500 mcg for prefilled syringes
<b>Current Indication(s)</b>	<ol style="list-style-type: none"> <li>1. Treatment of anemia associated with chronic renal failure (CRF), including patients on dialysis and patients not on dialysis</li> <li>2. Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.</li> </ol>
<b>Action:</b>	Complete Response

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Project manager generated minutes & reviews	Monica L. Hughes
Medical Officer Reviews	Chaohong Fan Minh-Ha Tranh
Statistical Reviews	Yuan-Li Shen Mark Rothman
Pharmacology Toxicology Reviews	Andrew McDougal Yanli Ouyang
CMC Review/OBP Review	Ingrid Markovic
Clinical Pharmacology Review	Aakansha Khandelwal

OND=Office of New Drugs  
 OBP=Office of Biotechnology Products  
 DDMAC=Division of Drug Marketing, Advertising and Communication  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DSI=Division of Scientific Investigations  
 DRISK=Division of Risk Management

## Division Director Summary Review

### 1. Introduction

This efficacy supplement was received on December 26, 2007 as one of two supplements responding to FDA's supplement request letter of May 31, 2007. This supplement was subsequently unbundled with review of information responding to the May 31, 2007 letter conducted under BL STN 103951/5173, and review of proposed labeling changes to the Warnings and Precautions section describing the overall survival and progression-free survival results of Study 20010145, [REDACTED] (b) (4)

[REDACTED] The May 31, 2007 letter made specific requests for revision to product labeling to enhance safe and effective use of Aranesp for the treatment of anemia due to concomitant cancer chemotherapy. These specific requests were based on the results of six multicenter, randomized trials assessing the effect of ESAs in patients with cancer that demonstrated or suggested harmful effects (decreased survival or more rapid tumor progression/recurrence). The requested labeling changes were consistent with the recommendations from the May 10, 2007 Oncologic Drugs Advisory Committee (ODAC) meeting at which the results of these studies were presented and discussed.

Amgen provided revised labeling in response to FDA's May 31, 2007 letter under two separate supplements, a "Changes Being Effected" labeling supplement (STN BL 103951/5164) addressing items 1, 2, and 6 of the May 31, 2007, letter which was approved November 8, 2007 and the "Prior Approval Supplement" (STN BL 103951/5173), which is the subject of this review, responding to items 3, 4, and 5 of the May 31, 2007 letter. The PAS submission contains clinical study reports and an integrated dataset containing data from datasets from eleven randomized, placebo-controlled studies of darbepoetin alfa (Aranesp) in patients with anemia and non-myeloid malignancy receiving chemotherapy (20010119, 980291 schedule 1, 980291 schedule 2, 990114, 980297, 20000161, 20010103, 20010145, 20020149, 20030204, 20030232), additional analyses, and proposed labeling changes. In addition, as discussed at the July 25, 2007 meeting with Amgen, the proposed labeling provided in this submission was reformatted for consistency with the Physician's Labeling Rule (PLR). Amgen stated that the focus of the PLR conversion was made with "attention to the format, reduction of repetition and modification of the Adverse Reaction section of the PI".

The review of this application was coordinated across the Division of Biologic Oncology Products and the Division of Medical Imaging and Hematology Products. The medical oncology reviewers and supporting statistical reviewers in the Division of Biometrics V evaluated the responses to the May 31, 2007 letter and all clinical portions of product labeling for the cancer-related indication, while the review of clinical portions of product labeling for all other approved indications were conducted by reviewers in the Division of Hematology. Additional review staff, as listed above, participated in the review of product labeling changes

to conform with the requirements of 21 CFR 201.56(d) and 201.57. In addition, as appropriate, the review of the Epogen/Procrit and Aranesp labels were conducted jointly to describe class effects.

The assessment of the medical oncology reviewers and statistical reviewers, as well as secondary reviewers was that the proposed approach by Amgen to integrate data from 12 (two of these “studies” were themselves pooled data from distinctly numbered protocols of the same design) randomized, placebo-controlled studies assessing the effects of epoetin alfa and 11 randomized, placebo-controlled studies (including “continuation protocols” for two trials assessing efficacy and one protocol with two reports for Schedules 1 & 2) assessing darbepoetin alfa was not interpretable for addressing issues 3, 4, and 5 of the May 31, 2007 letter for reasons discussed below. Instead, FDA’s proposed modifications to product labeling rely on a conservative approach, further refining the indications and usage sections of the Aranesp label to attempt to limit use to the population of patients with cancer who are most likely to derive benefit as well as to attempt to mitigate the risks of increased mortality and shorter time to disease progression. Labeling changes also reflect additional information and Advisory Committee advice received during the course of the supplement review. Since submission of this supplement on December 26, 2007, product labeling has been updated to include new information on the risks of pure red cell aplasia, new study results demonstrating adverse outcomes in patients with chronic renal failure and in patients with cancer, as summarized below. Based on additional study results in patients with cancer, FDA sought advice of the ODAC on March 13, 2008 which resulted in additional labeling changes, consistent with the conservative dosing recommendations mentioned above and further limiting product use. These labeling changes were made as part of FDA-ordered safety labeling changes and approved on August 5, 2008.

All reviewers concurred with FDA proposed labeling changes during labeling negotiations with Amgen however agreement on final labeling was not reached. FDA will request additional information in support of proposed labeling changes or as justification for retention of current statements in the product labeling.

## **2. Background**

Erythropoietin is a glycoprotein whose main function is to stimulate the proliferation and differentiation of erythroid precursors in the bone marrow. Erythropoietin is produced mainly in the kidneys, though several other tissues produce lesser amounts of the growth factor. Aranesp (darbepoetin alfa) is an erythropoiesis-stimulating protein, closely related to endogenous human erythropoietin, which is produced in Chinese hamster ovary cells by recombinant DNA technology. Darbepoetin alfa 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. The additional carbohydrate chains increase the approximate molecular weight of the glycoprotein from 30,000 to 37,000 daltons. Darbepoetin alfa has a three-fold longer terminal half-life than epoetin alfa and a five-fold lower affinity for erythropoietin receptors.

Aranesp was approved for marketing in the U.S. on September 17, 2001 for the treatment of anemia in patients with chronic renal failure based on the results of thirteen Amgen-sponsored studies, in which 2198 patients with chronic renal failure (CRF) were enrolled; in these trials, 1598 patients received ARANESP and 600 patients received epoetin alfa as an active comparator.

Aranesp was approved for “the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy” on July 19, 2002. This approval was based primarily on the results of Protocol 980297, “A Double-Blind, Placebo-Controlled, Randomized, Study of NESP for the Treatment of Anemia in Lung Cancer Receiving Multi-cycle Platinum Containing Chemotherapy”. This was a multicenter, multinational study in which 320 patients were enrolled and randomized 1:1 to receive either Aranesp 2.25 µg/kg QW (treatment arm) or placebo. Eligibility criteria included lung cancer (either small cell carcinoma or non-small cell carcinoma) a cancer treatment plan of at least 12 additional weeks of platinum-containing chemotherapy, and anemia (hemoglobin <11g/dl). The primary endpoint was the estimated Kaplan-Meier proportion of subjects who received RBC transfusions between week 5 and the end of the treatment phase (EOTP). Week 5 was specified since hematologic responses to Aranesp are not observed until 3-6 weeks after the initiation of therapy. The primary efficacy analysis was conducted in patients who had completed the first 4 weeks of study. In this analysis, patients who withdrew or discontinued from the 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). 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).

The labeling for Aranesp was expanded on March 23, 2006 to include a new dosing regimen of 500 mcg once every 3 weeks (Q3W) for the treatment of anemia in adults with non-myeloid malignancies, where anemia is due to the effect of concomitantly administered chemotherapy. The safety and effectiveness of the Q3W regimen in reducing the requirement for red blood cell (RBC) transfusions in patients undergoing chemotherapy was assessed in a randomized, double-blind, multinational study. This study was conducted in anemic (Hgb < 11 g/dL) patients with non-myeloid malignancies receiving multicycle chemotherapy. Patients were randomized to receive Aranesp at 500 mcg once every 3 weeks ( $n = 353$ ) or 2.25 mcg/kg ( $n = 352$ ) administered weekly as a subcutaneous injection for up to 15 weeks. In both groups, the dose was reduced by 40% of the previous dose (e.g., for first dose reduction, to 300 mcg in the once every 3 week group and 1.35 mcg/kg in the once weekly group) if hemoglobin increased by more than 1 g/dL in a 14-day period. Study drug was withheld if hemoglobin exceeded 13 g/dL. In the once every 3 week group, 254 patients (72%) required dose reductions (median time to first reduction at 6 weeks). In the once weekly group, 263 patients (75%) required dose reductions (median time to first reduction at 5 weeks).

Efficacy was determined by a comparison of the Kaplan-Meier estimates of the proportion of patients who received at least one RBC transfusion between day 29 and the end of treatment. Three hundred thirty-five patients in the once every 3 week group and 337 patients in the once weekly group remained on study through or beyond day 29 and were evaluated for efficacy.

Twenty-seven percent (95% CI: 22%, 32%) of patients in the once every 3 week group and 34% (95% CI: 29%, 39%) in the weekly group required a RBC transfusion. The observed difference in the proportion of patients receiving one or more transfusions for the once every 3 week schedule as compared to the once weekly was -6.7% (95% CI: -13.8%, 0.4%).

There are two ESAs approved for the treatment of anemia due to chemotherapy in the United States, darbepoetin alfa (Aranesp, Amgen Inc) and epoetin alfa (Procrit/ Epogen, Amgen Inc). In addition, there are several ESAs approved in other countries and for which clinical experience in patients with cancer are available. FDA considers safety information derived from any ESA as relevant for characterization of risks for the entire class. Since 1993, multiple randomized controlled clinical trials conducted in patients with cancer, which were designed to isolate the effect of the erythropoiesis-stimulating agent, demonstrated or exhibited a trend towards shorter survival and/or poorer tumor outcomes in patients receiving an ESA compared to patients receiving transfusion support alone. This information has been summarized in FDA briefing documents for Oncologic Drugs Advisory Committee meetings held May 4, 2004, May 10, 2007, and March 13, 2008. In addition, this data is summarized in Warnings section of the product labeling for Aranesp and for Epogen/Procrit.

Following the May 10, 2007 ODAC meeting at which these data were discussed, FDA issued a supplement request letter to Amgen. The letter stated that, based on discussion during the May 10, 2007 meeting, FDA requested that Amgen submit a prior approval supplement (PAS) that would include revised labeling to adequately addressing the recommendations for changes or to provide data supporting current or alternate labeling changes from those recommended during that Advisory Committee meeting. Specifically, FDA requested the following:

1. Revision of the INDICATIONS AND USAGE section, to include a statement that Epogen/Procrit is not indicated for use in patients receiving chemotherapy for any of the following primary tumor types: adenocarcinoma of the breast, squamous cell cancer of the head and neck, non-small cell lung cancer, or lymphoid malignancies.
2. Revision of the INDICATIONS AND USAGE section, to clarify the severity of anemia for which Epogen/Procrit is indication, by inclusion of the maximum (and if appropriate, minimum) pretreatment hemoglobin level.
3. Revision of the DOSAGE AND ADMINISTRATION section to specify a lower maximum hemoglobin level (i.e., hemoglobin level less than 12 g/dL) at which dosing should be suspended or terminated.
4. Revision of the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections to indicate that Epogen/Procrit should be discontinued following the completion of the concomitant chemotherapy regimen.
5. Revision of the INDICATIONS AND USAGE section to indicate that Epogen/Procrit is not indicated for use in patients who are not receiving myelosuppressive chemotherapy. This statement should include patients who are receiving no active treatment, radiotherapy

treatment, and treatment with non-myelosuppressive therapy such as hormonal agents and therapeutic biologic products.

Following issuance of the May 31, 2007 letter, Amgen met with FDA on July 25, 2007 to discuss the proposed contents of the requested labeling supplement. Amgen's proposed approach was to conduct re-analyses of existing data (b) (4) to further evaluate the impact of ESAs on tumor progression and on survival, and to identify post-marketing studies designed to assess the safety and efficacy of ESAs when administered according to more conservative dosing regimens.

On September 7, 2007, FDA issued an additional letter requesting that Amgen make specific labeling changes in a separate "Changes Being Effected" (CBE) labeling supplement. Amgen provided responses to items 1, 2, and 6 of FDA's 31 May 2007 letters in a CBE supplement (STN BL 103951/5157) submitted on September 19, 2007. A CBE supplement (STN BL 103234/5158) was submitted for Epogen/Procrit on September 19, 2007. Both supplements were approved on November 8, 2007.

In addition to the CBE supplement discussed above, the following additional safety labeling changes have been approved since submission of STN BL 103951/5173:

- STN/BL 103951/5170: Approval on March 7, 2008 to include a Boxed Warning summarizing the risks of increased mortality and/or poorer tumor outcomes obtained in randomized studies in patients with cancer and in those with chronic renal failure and to update the Warnings section to include the results of two additional randomized, controlled studies in patients with cancer (PREPARE trial and GOG-191 trial) demonstrating adverse survival or tumor outcomes in patients with cancer receiving an ESA.

- (b) (4)

The chronology of this submission is briefly summarized below

Dec. 20, 2007: STN BL 103234/5166 submitted (received by FDA on Dec. 26, 2007).

Feb. 1, 2008: Acknowledgment letter issued.

Feb 21, 2008: FDA notified Amgen that the supplement was filed and that preliminary deficiencies identified in the filing review would be communicated in a subsequent letter.

March 7, 2008: FDA letter issued with preliminary deficiencies regarding proposed labeling format and requested define document files for 4 protocols (20030232, 980297, 990114, and 980291 schedules 1 &2), SAS programs used to produce derived variables, and raw & derived datasets for protocol 20020149.

- April 18, 2008: Amgen submitted partial responses to the 3/7/08 letter
- May 30, 2008: Amgen submitted additional information (define.pdf file for 20020149) as responses to the 3/7/08 letter

August 19, 2008: FDA issued a letter requesting clarification of the relevance of Protocol 20010119 to the supplement and, if relevant, requesting that an individual study dataset be provided that datasets containing raw and derived variables and SAS programs be submitted to the supplement. The letter also requested additional information (e.g., final reports, case report forms, individual datasets, and requests for clarification of study conduct) for Protocols 20000161, 20010103, 980291 (schedules 1 & 2), 990114, 20030232, 980297, and 20020149.

- Sept 12, 2008: Amgen submitted partial responses to 8/19/08 letter
- Sept. 18, 2008: Amgen submitted partial responses to 8/19/08 letter
- Oct 15, 2008: Amgen submitted partial responses to 8/19/08 letter

October 24, 2008: FDA issued a complete response letter

### **3. CMC/Device**

No new CMC information was submitted in or required to complete review of this application. All CMC reviewer comments regarding the package insert and carton/container labeling were considered and incorporated into FDA proposed labeling are to be conveyed to Amgen in the CR letter.

### **4. Nonclinical Pharmacology/Toxicology**

No new non-clinical pharmacology or toxicology data were submitted in the original supplement, however the CR letter will contain information requests from the non-clinical reviewer requesting that Amgen provide the source of the data used to derive the multiples of human exposure from rat and rabbit reproductive toxicity studies cited in the product labeling. All non-clinical reviewer comments regarding the package insert were considered and incorporated into FDA proposed labeling to be appended to the CR letter.

### **5. Clinical Pharmacology/Biopharmaceutics**

No new clinical pharmacology data were submitted in or required for review of this supplement. The clinical pharmacology reviewer proposed modifications to the existing label for conformance with the PLR format, to be conveyed to Amgen as an appendix to the CR letter.

### **6. Clinical Microbiology**

No clinical microbiology data were submitted in or required for review of this supplement as determined by the CMC reviewer.

## 7. Clinical/Statistical-Efficacy

The proposed class labeling changes, submitted in response to items 3, 4, and 5 of FDA's May 31, 2007 letter, were supported by subject-level data from 23 individual studies, chosen because of study design characteristics, and on analyses conducted in pooled data within subgroups based on the source of ESA (darbepoetin alfa or epoetin alfa). The study design characteristics utilized in selecting datasets for inclusion in the pooled analysis were that data were available for individual study subjects participating in randomized, double-blind, placebo-controlled trials sponsored or supported by Amgen or J&JPRD or one of its affiliate companies. The studies included in the pooled analysis of each subgroup are listed below and identified by protocol number.

- Aranesp studies  
20010119, 980291 schedule 1, 980291 schedule 2, 990114, 980297, 20000161, 20010103, 20010145, 20020149, 20030204, 20030232
- Epoetin alfa studies  
[I88-036, I87-018/OEO-U24, I87-019/OEO-U25], [I88-037, I87-016/OEO-U22, I87-017/OEOU23], J89-040, CC2574-P-174, EPO-INT-1, EPO-INT-2, EPO-INT-3, EPO-INT-10, EPO-INT-76, N93-004, PR-27-008 (NCCTG 97-92-53), EPO-CAN-15

Key details of the study designs are presented in the following tables below.

Additional details regarding these studies were requested during the review; Amgen's responses have not addressed all of FDA's needs for additional information for 7 clinical studies, which will be needed if these studies are to be used to support labeling claims. Specifically, FDA will request individual study-specific data for all the studies used in combined analyses in the CR letter.

Amgen also provided the following information

- Revised package insert labeling in PLR format
- A rationale document discussing the approach to the re-analysis of safety information in the proposed package insert
- A rationale document discussing the specific data supporting proposed labeling (or lack of proposed labeling) in response to items 3, 4, and 5 of the May 31, 2007 letter
- Proposed modifications to for inclusion of updated information on two studies already included in the product labeling, the BEST study (Cancer Study 1) and the study conducted in anemic patients not receiving chemotherapy (Cancer Study 8)
- Proposed new language to include the results of Study 20010145
- Proposed language, contained in earlier versions of product labeling but removed during previous labeling revisions, to include the results of Study N93-004.

Study Identifier	Design	Total subjects (ESA : Placebo)	Population	Hemoglobin entry criteria	Treatment Duration	Product Schedule	Upper Hgb Limit Resulting in Dose Modification	Harmful Effects reported
980291 Schedule 1	Randomized placebo-control, dose-ranging, parallel group	249 (32:17:46:28:35:40:51)	Anemic patients with solid tumors receiving multicycle chemotherapy	≤ 11 g.dL	12 wks (blinded phase)	darbepoetin alfa 4.5, 6.75, 9, 12, 13.5, or 15 mcg Q3W	≥15 g/dL (men) ≥14 g/dL (women)	N
980201 Schedule 2	Randomized placebo-control, dose-ranging, parallel group	156 (31:31:33:30:31)	Anemic patients with solid tumors receiving multicycle chemotherapy	≤ 11 g.dL	12 wks (blinded phase)	darbepoetin alfa 9, 12, 15, or 18 mcg/kg Q4W	≥15 g/dL (men) ≥14 g/dL (women)	N
990114	Randomized (1:2:2:1) placebo-control, dose-ranging, parallel group	66 (11:22:22:11)	Anemic patients with lymphoproliferative cancers receiving multicycle chemotherapy	≤ 11 g.dL	12 wks	darbepoetin alfa 1.0, 2.25, or 4.5 mcg/kg QW	≥15 g/dL (men) ≥14 g/dL (women)	N
980297	randomized (1:1) placebo-control	314 (156:158)	Anemic patients with lung cancer receiving multicycle platinum-based chemotherapy	≤ 11 g.dL	12 wks	darbepoetin alfa 2.25 mcg/kg QW	≥15 g/dL (men) ≥14 g/dL (women)	N
20000161	randomized placebo-control	344 (174:170)	Anemic patients with lymphoproliferative cancers receiving multicycle chemotherapy	≤ 11 g.dL	12 wks	darbepoetin alfa 300 mcg QW	≥15 g/dL (men) ≥14 g/dL (women)	N
20030232	randomized placebo-control	386 (193:193)	Anemic patients with non-myeloid cancers receiving multicycle chemotherapy	≤ 11 g.dL	15 weeks	darbepoetin alfa 300 mcg Q3W	Hgb ≥13 g/dL Hgb increase 1 g/dL in 14 days	No
20010145	randomized placebo-control	596 (298:298)	Patients with SCLC receiving multicycle platinum/etoposide chemotherapy	Hgb ≥ 9 g/dL and ≤ 13 g/dL	24 weeks	darbepoetin alfa 300 mcg QW x 4 →300 mcg Q3W	≥14 g/dL	No

Study Identifier	Design	Total subjects (ESA : Placebo)	Population	Hemoglobin entry criteria	Treatment Duration	Product Schedule	Upper Hgb Limit Resulting in Dose Modification	Harmful Effects reported
20010103	Randomized; stratified by baseline Hb (<10 vs. ≥ 10 g/dL) placebo-control	985 (515:470)	Anemic patients with non-myeloid cancers receiving no therapy; of hormonal or biologic therapy (i.e., non- myelosuppressive) Anemic patients with non-myeloid cancers receiving no therapy; of hormonal or biologic therapy (i.e., non- myelosuppressive)	≤ 11 g/dL	16 weeks	darbepoetin alfa 6.75 mcg/kg Q4W	>12 g/dL	Yes
20020149	randomized placebo-control extension study of 20010103	371 (198:173)		Participation in 20010103	16 weeks	darbepoetin alfa 6.75 mcg/kg Q4W	>12 g/dL	Yes

***FDA Reviewers' Assessment of the Amgen's Analysis Approach***

Both the statistical and the clinical review staff raised concerns regarding the validity of Amgen's approach to the assessment of adverse effects of ESAs.

With regard to assessment of effects on overall survival, the review teams noted that there is potential bias based on the selection of studies included in this analysis, in that some studies specifically designed to assess effects on overall survival have not been included (e.g., DAHANCA10 study). [REDACTED] (b) (4)

[REDACTED]

[REDACTED] Reproduced below are Dr. Rothmann's summarization of these methodologic issues (abstracted from his review):

[REDACTED] (b) (4)

Dr. Fan and Dr. Shen both noted limitations in the interpretation of the pooled data based on differences across studies in underlying primary cancer type and stage, differences in chemotherapy regimen, and differential length of follow-up. For these reasons, analysis of results by study rather than by pooling results may be more valid where distinctions in study population and length of followup can be appropriately weighted. Additional limitations, both for individual studies and for the pooled analysis, are the lack of prospective stratification at randomization for baseline hemoglobin levels and the lack of prospective designs assessing appropriate duration of treatment or maximum hemoglobin targets.

***FDA Reviewers' assessment of Amgen's proposed labeling changes***

Item 3 from the May 31, 2007 letter

Revision of the INDICATIONS AND USAGE section to clarify the severity of anemia for which Aranesp/PROCRIT is indicated, by inclusion of the maximum, and if appropriate minimum, pretreatment hemoglobin level.

Amgen proposed addition of the following text to Dosage and Administration section of the label:

*FDA Review of Amgen's proposal*

Since the initial submission in December 2007, the product label has been modified as described in Section 2 of this summary review. The following safety labeling change ordered under 505(o) was approved on August 5, 2008 and included the statement

*"Do not initiate Epogen/Procrit for hemoglobin >10 g/dL"*

Based on this action, Amgen's proposed labeling language was replaced with the safety-ordered language.

I concur with the assessment of the clinical and statistical reviewers that Amgen did not provide adequate justification for the proposed target of (b) (4) in their original presentation and that these data did not result in a determination that the proposed target was better

supported that the language ordered for inclusion in product labeling by FDA. The FDA reviewers assessment of the rationale provided by Amgen in support of their initial proposal (b) (4) is summarized below.



For these reasons, and considering the advice of the March 2008 ODAC, FDA ordered safety language stating that initiation of an ESA should occur only when the hemoglobin was less than 10 g/dL in order to make the drug available to patients with the highest apparent need for RBC transfusions, based on highest proportion of patients at risk for transfusion and noting that the absolute reduction in risk of transfusion appears grossly similar in the various subgroups.

Item 4 from the May 31, 2007 letter

*Revision of the DOSAGE AND ADMINISTRATION section to specify a lower maximum hemoglobin level (ie, hemoglobin level less than 12 g/dL) at which dosing should be suspended or terminated.*





[Redacted text block]

the inclusion of the following in the Boxed Warning section of the label:

- ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with advanced breast, head and neck, lymphoid, and non-small cell lung malignancies when dosed to target a hemoglobin of  $\geq 12$  g/dL.
- The risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target a hemoglobin of  $< 12$  g/dL.



*FDA Review of Amgen's proposal*

Since the initial submission in December 2007, the product label was modified as described in Section 2 of this summary review. The final labeling approved on August 5, 2008 contained the following information in the Dosage and Administration subsection for Cancer Patients on Chemotherapy:

FDA's assessment of Amgen's rationale for retaining language from Nov. 2007 is summarized below.

The statistical and clinical reviewers rejected Amgen's proposal not to modify the Dosage and Administration section for Cancer Patients on Chemotherapy for different reasons. The

The clinical reviewer noted that statisticians' assessment of the analyses and agreed that the data did not support the proposed "target". However, she also stated that there is no evidence which directly addresses this question and recommended that the target be left to the treating physician's discretion.

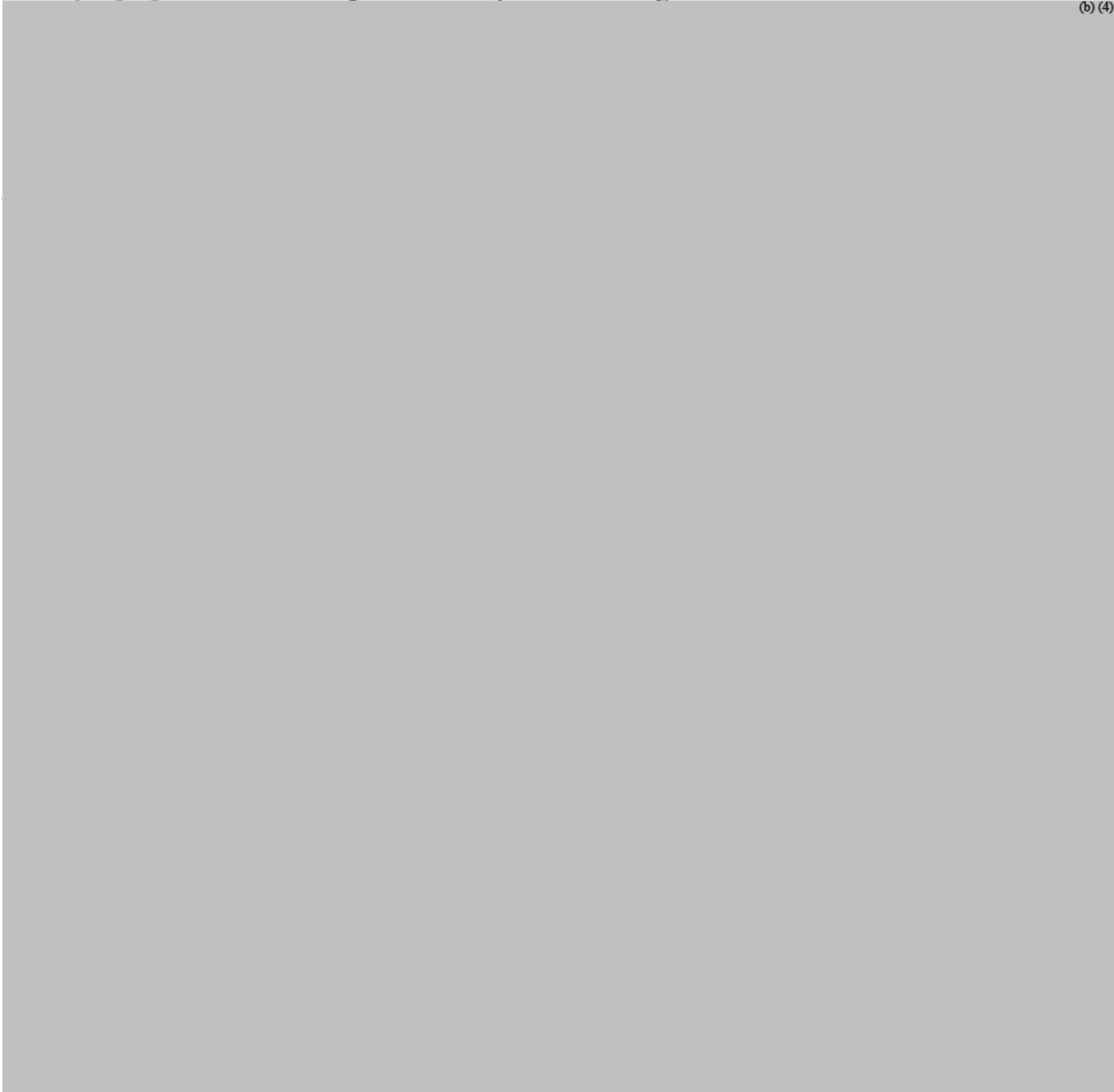
I concur with the conclusions of the statisticians and Dr. Fan that the data provided by Amgen do not support the safety of the hemoglobin target of 12 g/dL as the maximum threshold which should result in withholding of darbepoetin alfa. I do not concur with Dr. Fan's statement that product labeling should remain silent on this issue or leave it to the discretion of physicians. Studies conducted in patients with cancer and in patients with chronic renal failure have indicated that outcomes are poorer with a higher hemoglobin threshold and in the absence of data, I find it prudent to accept the advice of the ODAC and others to target a threshold where transfusions would be avoided. This threshold should be below 12 g/dL and, if consistent with transfusion guidelines, would be closer to 8-9 g/dL. In the absence of clear data from adequately designed and conducted studies, the threshold included in product labeling on Nov. 2007 (10 g/dL) is with a range that would generally not require transfusions. Therefore, I agree with the retention of the labeling accepted in Nov. 2007.

In addition, I agree with the comments made by Amgen regarding their analyses, i.e., that the presence of higher hemoglobin is associated with better outcomes, this does not treatment to achieving that higher hemoglobin results in these better outcomes; this is particularly notable since better outcomes are also present in the placebo-treated arms. The entire approach is to compare make comparisons based on patient responsiveness to the drug, which is likely to be confounded by many patient factors, rather than the impact of a treatment strategy designed to achieve a specific hemoglobin target. In fact, these are the very studies in which signals emerged and there are no data to establish a lower hemoglobin target. Therefore, Amgen should complete the studies required as post-marketing commitments to establish the safety of the recommended dose and schedule in accordance with current labeling.

Item 5 from the May 31, 2007 letter

Revision of the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections to indicate that Epogen/Procrit should be discontinued following the completion of the concomitant chemotherapy regimen.

Amgen proposed the following additions to product labeling



(b) (4)

*FDA Review of Amgen's proposal*

Since the initial submission in December 2007, the product label has been modified as described in Section 2 of this summary review. The approval of a safety labeling change ordered under 505(o) was approved on August 5, 2008 to include the following statements

Boxed Warning

*"Discontinue following the completion of a chemotherapy course."*

Dosage and Administration: Cancer Patients on Chemotherapy

*"Discontinue EPOGEN/PROCRT following the completion of a chemotherapy course"*

Based on this action, FDA replaced Amgen's proposed language with the safety ordered language.

[REDACTED] (b) (4)

Dr. Fan also noted that, in light of the poorer survival outcomes in study 20010103 where patients received Aranesp but no chemotherapy, the available evidence suggests that continued dosing is unsafe and futile (there was no evidence of a reduction in transfusions). For this reason, Dr. Fan recommended that labeling require discontinuation of Aranesp dosing with the last chemotherapy dose.

I concur with Dr. Fan's conclusion and agree that the wording included in product labeling in Nov. 2007 be retained.

## **8. Safety**

This application was provided in response to FDA requests for revision to product labeling to enhance safety. The rationale for Amgen's proposed labeling rests on aggregate analysis of efficacy (transfusion requirements) and safety [risk of vascular thrombotic events (VTE) and risk of death] from 23 randomized, placebo-controlled trials conducted by or supported by Amgen or Ortho Biotech. In addition, Amgen provided a meta-analysis of published literature assessing the risks of death and of VTE. None of these data used in this analyses were new and no new safety signals were provided.

In addition, the application contained safety data to permit a re-assessment of safety information presented in the Adverse Reactions section of product labeling, conducted in support of conversion of the product label to PLR format. The safety datasets contained data from studies previously reviewed by FDA in support of approved labeling claims.



All clinical reviewer comments (see reviews by Drs. Chaohong Fan and Minh-Ha Trinh) regarding the package insert were considered and incorporated into FDA proposed labeling to be appended to the CR letter.

## 9. Advisory Committee Meeting

There were three meetings of the Oncologic Drugs Advisory Committee (ODAC) in which FDA to seek advice regarding the safety of Erythropoiesis-stimulating agents (ESA) for treatment of anemia due to cancer chemotherapy. The first ODAC was held in May 2004 and the second was held in May 2007, both of which were prior to submission of this supplement. However, a third ODAC meeting was held on March 13, 2008 based on the results of additional studies, not presented at the May 2007 ODAC, which suggested or demonstrated harmful effects. The March 13, 2008 ODAC meeting was convened to review the results of two additional trials (GOG-191 and PREPARE) and progress made on addressing the risks of ESAs since the 2007 ODAC, in order to provide advice on Amgen's and FDA's proposed risk mitigation strategies. The key issues on which ODAC advice was sought was whether available data continue to demonstrate that there is a favorable benefit to risk relationship for

ESA use for treatment of chemotherapy-induced anemia in patients with cancer and if so, whether the current product labeling is sufficient to ensure safe and effective use.

The following questions, posed to the ODAC, and the Committee's response are summarized:

1. Considering all the available data on the benefit and risks of ESAs in the treatment of anemia due to concomitant cancer chemotherapy, do you recommend that these products continue to be marketed for the indications listed above?

- *Panel members noted that ESAs are more convenient than blood transfusions with one panel member questioning whether there was hard data on the benefit of ESAs other than convenience.*
- *A point was noted that there may not be a quality of life benefit*
- *It was questioned that based on the data, ESAs could be 2<sup>nd</sup> line therapy with possible use in patients whom transfusion was not appropriate.*
- *Overall, the committee agreed that these products should continue to be marketed for the indication listed in Question 1.*

*Vote :            Yes=13                    No = 1                    Abstain = 0*

2. If you recommend that the current indication should be retained, should FDA require that product labeling be modified? Below are four potential approaches to mitigating risks through revised labeling. Please address each of them separately.

a. **Vote:** To date, only clinical trials in small cell lung cancer have reasonably excluded an increased risk for death among patients receiving ESAs. Trials have demonstrated an increased risk of death and/or tumor promotion in head/neck, non-small cell lung cancer, breast (neoadjuvant and metastatic settings), lymphoid malignancies, and cervical cancers. Tumor types, other than those listed above, have not been adequately studied. *Should the current indication be modified to restrict use only to patients with small cell lung cancer?*

- *One panel member noted that ESAs should only be approved in disease where there is little/no risk while other settings require additional studies.*

*Vote :            Yes=6                    No = 8                    Abstain = 0*

b. **Vote:** The PREPARE trial demonstrated decreased relapse-free and overall survival in breast cancer patients receiving neoadjuvant chemotherapy. The risk/benefit assessment is different for patients receiving neoadjuvant and adjuvant chemotherapies than for patients with metastatic or incurable cancers. *Should the current indication be modified to include a statement that ESA use is not indicated for patients receiving potentially curative treatments?*

- One panel member noted that those with metastatic disease should not receive ESAs any different than those in the adjuvant setting.
- One panel member noted that using ESAs in the curative group, may convert from a curative patient to a non-curative patient.
- Overall, the panel agreed that the current indication should be modified to include a statement that ESA use is not indicated for patients receiving potentially curative treatments.

**Vote :**            **Yes=11**            **No = 2**            **Abstain = 1**

- c. **Vote:** Although increased tumor promotion and/or decreased survival have been demonstrated in several tumor types, adverse findings have been duplicated in two malignancies—breast cancer and head and neck cancer. ***Should the current indication be modified to include a statement that ESA use is not indicated for patients with breast and/or head & neck cancers?*** (If yes, please specify breast and/or head & neck cancer).

- Panel members questioned the definition/appropriateness of the terminology “tumor progression” and “tumor promotion” in regards to the use of ESAs.
- It was noted that the question could also read with “metastatic” in front of breast and/or head & neck cancers.

**Vote :**            **Yes=9**            **No = 5**            **Abstain = 0**

- d. The only objective evidence of efficacy demonstrated for ESAs has been avoidance of RBC transfusions; however, not all patients with anemia require an RBC transfusion. Product labeling does not specify the hemoglobin level at which ESA treatment should be initiated. ***Assuming a patient is asymptomatic and has no co-morbid conditions, please specify the hemoglobin level at which initiation of an ESA is appropriate.***

- Panel members agreed that treatment should be based on physician judgment and tailored to individual patients. Panelists did not feel that setting levels was appropriate for a hypothetical patient.

3. If the Committee recommends that the indication for treatment of anemia due to concomitant chemotherapy should be retained (as currently approved or with additional labeling changes as above), discuss additional strategies that FDA could require to minimize risk. Below are two options that could be considered. If you have other suggestions, please state them.

- a. **Vote:** An informed consent/patient agreement would explicitly require the oncology patient's authorization or agreement to undergo treatment with an ESA. Both patient and physician (or designate) signatures would be required. In the process, the physician prescribing the ESA treatment would discuss the risks and benefits of ESA therapy and alternative treatments. ***Should the FDA require the implementation of an***

***informed consent/patient agreement for the treatment of chemotherapy induced anemia?***

(Question 3a-b was clarified to ask for the principle instead of the logistics of the informed content/patient agreement)

- ***The panel agreed that adequate patient education is necessary, however disagreed on whether a written informed consent should be required***

***Vote :            Yes=8            No = 5            Abstain = 1***

- b. ***Vote:*** Examples of restricted distribution programs include STEPS (thalidomide), RevAssist (lenalidomide), and iPLEDGE (isotretinoin). Restricted distribution systems link product access to planned safe and effective use. These programs may require identification and enrollment of healthcare providers who agree to prescribe only in accordance with product labeling and who commit to patient education regarding safe use. Registration of patients may also be required. Certain patient characteristics would be recorded at individual patient registrations (e.g., hemoglobin, chemotherapy type, malignant diagnosis). ***Should FDA mandate a restricted distribution system for oncology patients receiving ESAs? YES or NO***

***Vote :            Yes=1            No = 10            Abstain = 2***

- ***The committee agreed that a restricted distribution system was not necessary in regard to the above question. It was noted that to address the issue of safety, physician incentives should be reduced.***

## **10. Pediatrics**

Not applicable to this application as a new indication, new dosing regimen, or new presentation was not sought.

## **11. Other Relevant Regulatory Issues**

Division of Scientific Investigations audits were not requested for any studies since most of the studies included for the combined analysis were more than 10 to 15 years old and primary records would not be available.

## **12. Labeling**

No changes to the proprietary name or carton/container labeling were proposed by Amgen and the FDA did not identify need for modifications to these components of product labeling in the

original submission. Verbal comments provided by DDMAC and OSE during labeling meetings were considered and incorporated as appropriate in FDA proposals for revisions to the submitted product labeling.

Amgen has requested changes to product labeling in response to FDA's request for a labeling supplement, as discussed in Section 7 of this review. In the original submission (Dec. 26, 2007), Amgen proposed additional labeling changes not requested by FDA

- An update to clinical information on Study 20010103 (Cancer Study 8) in the WARNINGS AND PRECAUTIONS, Increased Mortality and/or Tumor Progression section (5.2) of the label. The updated information is derived from survival data obtained in a post-treatment follow-up period. The current labeling section is reproduced below with the change in bold font:

*"Cancer Study 8 was a Phase 3, double-blind, randomized (Aranesp vs. placebo), 16-week study in 989 anemic patients with active malignant disease, neither receiving nor planning to receive chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. (b) (4)*

[Redacted]

FDA Assessment: The clinical and statistical reviewer have rejected this proposed change (b) (4)

[Redacted]

- The addition of information on Study 20010145 to the WARNINGS AND PRECAUTIONS, Increased Mortality and/or Tumor Progression section (5.2) of the label. The proposed new language to be included in the label is reproduced below

[Redacted] (b) (4)

FDA Assessment: Both the clinical and statistical reviewer rejected inclusion of this study in the Warnings and Precautions section. (b) (4)

[Redacted]

- An update of clinical information on the “BEST” Study (Cancer Study 1) in the WARNINGS AND PRECAUTIONS section of the label. The proposed new language to be included in the label is reproduced below

[Redacted] (b) (4)

FDA assessment: The clinical and statistical reviewers have rejected this proposed modification to language in the current labeling. The reviewers find this “updated” data not acceptable for inclusion in the labeling because (b) (4)

[Redacted]

- To add the information on Study N93-004 to the WARNINGS AND PRECAUTIONS, Increased Mortality and/or Tumor Progression section of the label. The proposed new language to be included in the label is reproduced below

[Redacted] (b) (4)

FDA Assessment: Both the clinical and statistical reviewer rejected inclusion of this study in the Warnings and Precautions section. (b) (4)

[Redacted]

FDA reviewers recommended numerous additional modifications to Amgen’s proposed package insert. The changes are briefly itemized below.

**(1) Boxed Warning**

a. “minimize” changed to “decrease” because of the lack of certainty regarding the magnitude of the reduction in the risk in patients who receive any amount of an ESA.

b. [Redacted] (b) (4)

c. “adverse reactions” substituted for [Redacted] (b) (4) throughout labeling.

**(2) Indications and Usage section**

- a. New subsection “Limitations of Use” created to limit repetition of the same information across both indications.
- b. Currently approved indications statements re-worded for brevity and clarity
- c. Titles of subsections shortened for brevity.

**(3) Dosage and Administration**

- a. Extensively revised for brevity and re-worded for “active voice”
- b. References to “lack or loss of response” deleted; product labeling is not intended to cover aspects of general medical management (e.g., differential diagnosis of anemia) and clinical indications clarify the types of anemia for which Epogen is indicated.

**(4) Dosage Forms and Strengths**

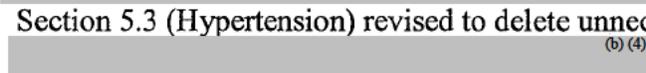
Information in this section moved to section 16; remaining information shortened for brevity and consistency with other labeling.

**(5) Warnings and Precautions**

a. [Redacted] (b) (4)

b. [Redacted]

- c. Section 5.2: Editorial changes to remove the word “Cancer” from the study titles as this may lead to confusion with references to studies in section 14.3. Also, references to the study phase (e.g., phase 3) deleted throughout this section, as superfluous to other information describing study design and as per FDA Guidance. Deleted alternate names of studies (e.g., ENHANCE) throughout sections 5.1 and
- d. Revised text describing results of study 6 for accuracy. The goals of treatment in the Aranesp arm were to achieve and maintain hemoglobin levels at levels above that which would be classified as anemia.

- e.  (b) (4)
- f. Section 5.3 (Hypertension) revised to delete unnecessary information on  (b) (4)
- g. Moved up “Seizures” to section 5.4 as next most common serious adverse event. Revised for brevity and active voice
- h. Deleted sections on “loss of response”, “general”, and “CRF patients not on dialysis”. Product labeling should not include information related to general practice of medicine (i.e., differential diagnosis and diagnostic work-up of anemia) or to general care for underlying medical conditions.
- i. Revised subsection on PRCA to remove references to deleted subsection on loss of response; edited for brevity and active voice.
- j. Deleted subsection on Hematology. Relevant information now included in section on laboratory testing.
- k. Subsection on Dialysis Management edited for brevity and critical information;
- l. Subsection on Laboratory testing re-titled to clarify the focus of this subsection. Edited for brevity and active voice and to limit redundancy with D&A section.

**(6) Adverse Reactions**

- a. Extensively edited for brevity and for consistency with current FDA Guidance on Adverse Reactions section of product labeling.
- b. Adverse events probably unrelated to ESA’s in the judgment of the Div of Hematology reviewer were removed from adverse event tables.
- c.  (b) (4)
- d. The subsection on annualized rates of thrombotic events in patients with CRF deleted due to lack of confidence in ascertainment and completeness of follow-up, leading to a potential underestimation of the event rate.
- e. Added subsection on Post-marketing Experience, with recommended caveats regarding inadequate information to characterized incidence of such reactions.
- f.
- g. Immunogenicity subsection edited to delete phrase “other products in this class” for consistency with current Guidances on product labeling.

**(9) Use in Specific Populations**

- a. Pregnancy Category C: Editorial changes.
- b. Nursing mothers: Animal data in this section moved to Non-clinical toxicology section. This section modified in accordance with recommendations from Maternal-Fetal Health team.

- c. Pediatric Use: Re-worded for clarity. References to Clinical Pharmacology (12.3) and Clinical Studies (14.1) added. The term “conversion” replaced with “transition”.
- d. Geriatric Use: Minor editorial changes for clarity.

**(10) Overdosage**

- This section was revised to clarify both subacute and chronic effects of overdosage and to provide more specific directions regarding appropriate actions to be taken (e.g., drug discontinuation). Edited for brevity with deletion of non-essential information (e.g., information in Dosage and Administration on monitoring hemoglobin rate of rise).

**(11) Description**

- Edited for brevity and essential information; resulting in deletion of phrase “closely related to erythropoietin” and “additional carbohydrate chains increase the” as non-essential information.

**(12) Clinical Pharmacology**

- a. Section on Mechanism of action: The majority of this section was deleted because it refers to endogenous erythropoietin rather than Aranesp or is either covered in other sections (PD or PK subsections of clinical pharmacology or Dosage and Administration section).
- b. Section on PD: Replaced “until” with “for” in describing time to PD effect.
- c. Section on PK: Editorial changes to spell out acronyms. Deletion of information on 2.25 mcg/kg dose from paragraph describing PK of Aranesp in patients with cancer as this is not an approved dose for an every-three-week schedule.

**(13) Non-Clinical Toxicology**

- a. Section on Reproductive and Developmental Toxicology added and includes data previously described under Pregnancy subsection; the non-clinical data were moved to this section as recommended by the OSE consultant staff as the more appropriate section for these data.
- b. Deleted information on tissue cross-reactivity in animal species and lack of proliferative effects in non-hematologic tissues, as findings are expected.

**(14) Clinical Studies**

- a. In general, section revised for brevity and clarity and to include appropriate clinical trial description in accordance with the Guidance for Industry document on this section of the label.
- b. Study results for N5 trial in pediatric patients with CRF added to this subsection.
- c. General section describing design of studies supporting safety and efficacy in patients with cancer added. Subsequent paragraphs on the individual studies edited to delete information in introductory paragraph and for brevity and clarity. Description of the primary efficacy measures included. In Study C2 results, efficacy re-calculated based on primary efficacy population (for consistency with

Study C1 and Epogen/Procrit analyses) of patients remaining on study between day 29 and end-of-treatment.

- d. Data limited to primary efficacy endpoints and data used by FDA as primary support to expand labeling claims.

**(15) How Supplied and Handling Information**

- Information previously provided in dosage forms and strengths moved to this section.

**(16) Patient Counseling Information**

- Re-placed previous patient labeling with Medication Guide; further labeling modification to be addressed under pending REMS supplement (BL STN 103951/5195).

### **13. Decision/Action/Risk Benefit Assessment**

- Regulatory Action: Complete Response
  
- Risk Benefit Assessment

The benefit of Aranesp is limited to a reduction in the risk of receiving allogeneic red blood cell transfusions and their attendant risks of transfusion-associated lung injury, infection, alloimmunization, as well as the cost and inconvenience of the transfusion procedure. Based on FDA's review of the information provided in the clinical study reports for the individual darbepoetin and epoetin alfa studies included in the analysis, there is no evidence based multiple studies in which patient-reported outcome instruments were used that demonstrated a quality-of-life benefit for cancer patients receiving an ESA as compared to placebo-treated patients. In addition, available data from randomized clinical trials do not indicate that use of an ESA provides an improvement in tumor-related outcomes, despite speculation on the existence of such benefits.

This benefit in reduction in allogeneic transfusions is weighed against the risks of Aranesp (supported by data with Epogen/Procrit), which include increased mortality and shorter time-to-tumor progression in patients with cancer in whom ESAs were administered to target hemoglobin levels to normal or supraphysiologic level, and an increased risk of thrombotic events in all populations at recommended doses. Neither the risks of ESAs within patient populations defined by baseline hemoglobin at initiation of Aranesp or Epogen/Procrit in patients with cancer nor the benefits (reduction in the risks of RBC transfusion) are sufficiently well-characterized to provide accurate estimates either of these risks. However, as noted by Dr. Fan, the approval of the first epoetin alfa product occurred in an era where substantial concerns regarding the risks of transfusion, particularly the risks of transmission of HIV, Hepatitis B, and potentially other infections, existed. Since that time, the science of transfusion medicine has advanced with resultant decrease in risks, while increasing

evidence has been generated to support the previously theoretical possibility of adverse effects on tumor outcomes as well as poorer survival when ESAs are used to achieve high normal and supraphysiologic hemoglobin levels in patients with cancer and chronic renal failure. Thus, the risk-benefit profile has substantially changed over time.

In the absence of data clearly demonstrating harm at the currently recommended dose, with use limited to the indicated patient population, the risks have not been demonstrated to outweigh the benefits. This determination was based both on FDA review staff and advice received from members of the ODAC during the March 13, 2008 meeting. However, labeling must retain language included in product labeling following the March 2008 ODAC meeting which provide appropriate directions for use to minimize risks to subjects.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

The license application for Aranesp is subject to a REMS under 505(o). Agreement on language for the Medication Guide will proceed under a separate supplement (BL STN 103951/5195).

- Recommendation for other Postmarketing Requirements and Commitments

No additional post-marketing requirements or commitments will be requested under this supplement.

## CLINICAL REVIEW

Application Type sBLA  
Submission Number 103951.5173  
Submission Code PAS

Letter Date 12/20/2007  
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PDUFA Goal Date 10/25/2008

Reviewer Name Chaohong Fan, M.D. *Chaohong Fan 10/23/2008*

Through Patricia Keegan, M.D. *Patricia Keegan*  
Acting Team Leader &  
Division Director

Review Completion Date 10/23/2008

Established Name Darbepoetin alfa  
(Proposed) Trade Name Aranesp  
Therapeutic Class Erythropoiesis Stimulating Protein  
Applicant Amgen

Priority Designation Standard

Formulation Polysorbate solution  
Albumin solution

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## 1. Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

This reviewer recommends a complete response (CR) action be taken for this supplement because this application is not ready to be approved. A CR letter will be issued to request that Amgen submit revised labeling that incorporates FDA's proposed revisions and additional information as requested in the comments embedded in the attached labeling.

### 1.2 Risk Benefit Assessment

Since Darbepoetin alfa (Aranesp) was approved on July 19, 2002 for reducing red blood cell (RBC) transfusions in patients with anemia and non-myeloid malignancies receiving chemotherapy, FDA has become aware of new safety information including increased mortality and/or increased tumor progression/recurrence in patients receiving erythropoiesis-stimulating agents (ESAs, e.g. Aranesp and Procrit) as compared with patients receiving transfusion support alone from multiple randomized controlled clinical studies. The package insert (PI) for Aranesp has been updated several times to incorporate emerging safety information since November 2006, with the last update revision to the PI in March 2008. These safety concerns also led to three Oncologic Drugs Advisory Committee meetings held on May 4, 2004, May 10, 2007 and March 13, 2008. Following the most recent ODAC meeting on March 13, 2008, on April 22, 2008, FDA issued a letter to Amgen indicating that Aranesp is a product that poses a serious and significant public health concern and requesting Amgen submit a prior approval supplement containing Risk Evaluation and Mitigation Strategy (REMS) for Aranesp,

This supplement was submitted to address some of the issues raised at March 13, 2007 ODAC meeting, i.e. the threshold of baseline hemoglobin for the initiation of Aranesp, a lower (< 12 g/dL) hemoglobin level at which Aranesp should be suspended or terminated, and to discontinue the use of Aranesp following the completion of the chemotherapy course. During the review of this supplement, no new information on the risk and benefit considerations of Aranesp use in the oncology setting was identified in this supplement.

It is this reviewer's opinion that the initial regulatory approval of ESAs for reducing the proportion of subjects receiving RBC transfusions in anemic patients receiving concomitant chemotherapy was granted in the era when the concerns for the risks for RBC transfusions, were significant, for example, the serious concerns on the risks of HIV contaminated RBC transfusions, and when the safety information and concerns were limited. However, in the light of the significant advancement in the safety of RBC transfusion, particularly the significantly decreased risks of receiving HIV contaminated RBC transfusion in the present era, and the accumulating evidence indicating serious risks of ESAs to increase mortality and increase risk for tumor progression and recurrence in patients receiving chemotherapy, this reviewer believes that the benefits of patients receiving ESAs to reduce RBC transfusion during chemotherapy are

marginal and may be outweighed by the serious risks of increased mortality and worse tumor outcome..

### 1.3 Recommendations for Postmarketing Risk Management Activities

As discussed in section 1.2 Risk Benefit Assessment, following the most recent ODAC meeting, on April 22, 2008, FDA issued a letter requesting Amgen submit REMS for Aranesp including safety labeling changes, a Medication Guide, a communication plan for ensuring that healthcare professionals understand risks and benefits for Aranesp, elements to assure safe use, an implementation system, and a timetable for assessment of the REMS. In the FDA April 22, 2008 letter, Amgen was also requested to conduct post-marketing clinical trials to assess the serious risk of Araneso to increase mortality and increase tumor progression in patients receiving chemotherapy.

### 1.4 Recommendations for other Post Marketing Study Commitments

No other post marketing study commitment is recommended to this supplement.

## 2. Introduction and Regulatory Background

### 2.1 Product Information

Darbepoetin alfa (Aranesp) is an erythropoiesis-stimulating protein, closely related to endogenous human erythropoietin, which is produced in Chinese hamster ovary cells by recombinant DNA technology. Darbepoetin alfa 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. The 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. Darbepoetin alfa is formulated as a sterile, colorless, preservative-free protein solution for intravenous or subcutaneous administration.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2.2.1 Currently available ESAs for treatment of anemia in patients with non-myeloid malignancies receiving concomitant chemotherapy.

Brand-name	Generic name	Sequence homology to human erythropoetin	Year approved for chemotherapy induced anemia
Procrit®	Epoetin alfa	100%	1993
Aranesp®	Darbepoetin alfa	97%	2002
Eprex®	Epoetin alfa	100%	1994
NeoRecormon®	Epoetin beta	100%	1995

## 2.3 Availability of Proposed Active Ingredient in the United States

Single-dose vials and single-dose prefilled syringes of Darbepoetin alfa containing 25, 40, 60, 100, 150, 200, 300 and 500 mcg are available in the United States.

## 2.4 Important Safety Issues With Consideration to Related Drugs

Important safety issues in ESAs in the oncology setting include the increased risks for mortality, tumor progression and recurrence, and thromboembolic events as warned and described in the Aranesp and Procrit package inserts.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

On May 10, 2007, an Oncologic Drugs Advisory Committee (ODAC) meeting was convened to re-assess the risk to benefit ratio of the ESAs in light of emerging data from Dec. 2006 through Feb 2007. The results of the six studies (BEST, ENHANCE, EPO-CAN-20, 2001-0103, 2000-0161, DAHANCA 10) were reviewed and discussed at the meeting.

On May 30, 2007, FDA issued a letter requesting Amgen submit a PAS labeling supplement to address safety issues and recommendations raised at the May 10, 2007 ODAC.

(b) (4)

Specifically, Amgen submitted this supplement primarily in response to the following items listed in FDA May 30, 2007 letter:

- 1. FDA Item 3:** *Revision of the INDICATIONS AND USAGE section to clarify the severity of anemia for which Aranesp/PROCRIT is indicated, by inclusion of the maximum, and if appropriate minimum, pretreatment hemoglobin level,*
- 2. FDA Item 4:** *Revision of the DOSAGE AND ADMINISTRATION section to specify a lower maximum hemoglobin level (i.e., hemoglobin level less than 12 g/dL) at which dosing should be suspended or terminated, and*
- 3. FDA Item 5:** *Revision of the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections to indicate that Aranesp/PROCRIT should be discontinued following the completion of the concomitant chemotherapy regimen.*

## 2.6 Other Relevant Background Information

From November 30, 2007 to December 4, 2007, FDA was informed by Amgen of the findings in two additional clinical studies showing harmful trends; these were decreased survival and decrease recurrence-free survival in patients receiving adjuvant chemotherapy for breast cancer patients (PREPARE) and updated results suggesting a higher death rate in patients receiving chemotherapy and radiotherapy for cervical cancer (GOG-191) who received ESAs as compared to those who received placebo. The results of the PREPARE and GOG-191 studies were included in safety labeling changes that were approved on March 7, 2008.

On March 13, 2008, an ODAC meeting was convened to reassess the risks and management of ESAs in patients with cancer. On April 22, 2008, FDA issued a letter under FDAAA, requesting that Amgen submit a PAS labeling changes to address safety issues and recommendations raised at March 13 2008 ODAC within 30 days of April 22, 2008. Amgen was also requested to submit a Risk Evaluation and Mitigation Strategy proposal within 120 days of April 22, 2008.

(b) (4)

On August 5, 2008, Amgen submitted a new labeling supplement (103951.5195) containing

(b) (4)

Parallel labeling revisions in the Procrit/Epogen PI has been submitted to STN BL 103234/5166 and review is conducted by Dr. Kaushik Shastri.

### **3. Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

Division of Scientific Investigations (DSI) audit processes were not used to audit or check the accuracy of the submitted data.

This reviewer considers the overall submission quality of this supplement to be inadequate for the purpose of conducting a comprehensive in-depth review of each study's conduct and the results. However, for the purpose of reviewing this supplement in order to evaluate Amgen's proposed labeling revisions in response to FDA requested items, this reviewer considers Amgen's submissions of the available clinical study reports from nine randomized, placebo controlled studies of Aranesp acceptable. Major issues related to the submission quality include the following:

- Missing clinical study reports (CSRs) and datasets (including primary, derived, and analyses datasets) for multiple studies from the original submission (20000161, 20010103, 20020149)
- Missing case report forms (CRFs) for patients who died on study or did not complete the study due to adverse events for multiple studies (980291, 990114, 20000161, 20030232 and 20020149)
- No hyperlink or malfunctioned hyperlinks in the content of the submission (980297, 20000161, 20010103), and 20020149).
- Missing information on SAS programs used to conduct analyses as described in the Summary of Clinical Safety and for studies 980291, 980297, 20000161, 20030232, 20010145, and 20010103.

#### **3.2 Compliance with Good Clinical Practices**

In the clinical study reports of nine randomized controlled studies included in this submission, Amgen stated that each study was conducted in accordance with the principles of the International Conference on Harmonization (ICH) Tripartite Guidelines for Good Clinical Practice (GCP).

### 3.3 Financial Disclosures

For studies 20000161, 20010145, and 20030232, Amgen submitted forms FDA 3454: CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS, to certify that Amgen has not entered into any financial arrangements with the clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a), and that these investigators were not the recipients of significant payments of other sorts as defined in 21 CFR 54.2(f).

Amgen did not submit Forms FDA 3454 on certification of financial disclosure for investigator for studies 980291, 990114, 980297, and 20010103 to this supplement, but indicates that the certifications were submitted in the past. From FDA's clinical review documents on STN BL 103951.x5001, it appears that Amgen certified that there was a lack of direct financial arrangements or payments between Amgen and investigators which could affect the outcome of study for studies 980291, 990114, and 980297. It is unclear whether Amgen previously submitted certificate for financial disclosure for study 20010103.

## **4. Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### 4.1 Chemistry Manufacturing and Controls

No new information on the chemistry, manufacturing and controls of Aranesp is contained this supplement.

### 4.2 Clinical Microbiology

There is no new information on the clinical microbiology submitted to this supplement.

### 4.3 Preclinical Pharmacology/Toxicology

No new information on the preclinical pharmacology/toxicology of Aranesp is contained this supplement.

### 4.4 Clinical Pharmacology

No new information on the clinical pharmacology of Aranesp is contained this supplement.

## **5. Sources of Clinical Data**

### 5.1 Tables of Clinical Studies

Amgen submitted clinical study reports and datasets from nine randomized, placebo controlled studies to support the proposed labeling revisions for this supplement (Studies 980291-schedule 1, 980291-schedule 2, 990114, 980297, 20000161, 20030232, 20010145, 20010103 and 20020149). The study design characteristics are listed in the following table 5.1.1.

Table 5.1.1 List of nine randomized, double-blind, and placebo controlled studies of Aranesp submitted by Amgen to support the proposed labeling revisions in the supplement 103951.5173.

Study Number / Study period	Study Design	Aranesp Dose (N per ITT : NESP vs. placebo)	Hgb/Hct Entry Criteria / Upper Hgb/Hct Limit on Study	Treatment Duration
980291 (n = 249 <sup>a</sup> )  (6/30/1999- 7/30/2001)	Schedule 1: A randomized, double-blind, placebo-controlled, dose-finding study of novel erythropoiesis stimulating protein (NESP) administered once every 3 weeks by subcutaneous (SC) injection for the treatment of anemia in subjects with <b>solid tumors receiving multicycle chemotherapy</b>	4.5, 6.75, 9.0, 12.0, 13.5, 15.0 µg/kg Q3W  (N: 198 vs. 51)	Hgb ≤ 11 g/dL  /Hgb 15g/dL (men) or 14g/dL (women)	12weeks (blinded treatment)
980291 (n = 156 <sup>a</sup> )  (6/30/1999- 7/30/2001)	Schedule 2: A randomized, double-blind, placebo-controlled, dose-finding study of novel erythropoiesis stimulating protein (NESP) administered by subcutaneous (SC) injection for the treatment of anemia in subjects with <b>solid tumors receiving multicycle chemotherapy</b>	9.0, 12.0, 15.0, or 18.0 µg/kg Q4W  (N: 125 vs. 31)	Hgb ≤ 11 g/dL  /Hgb 15g/dL (men) or 14g/dL (women)	12weeks (blinded treatment)
990114 (n = 66 <sup>a</sup> )  (11/2//1999- 7/18/2000)	A multi-centre, blinded, placebo-controlled, randomized, dose-finding study of novel erythropoiesis stimulating protein (NESP) administered by subcutaneous injection in subjects with <b>lymphoproliferative malignancies receiving chemotherapy</b>	1.0, 2.25, 4.5 µg/kg QW  (N: 55 vs. 11))	Hgb ≤ 11 g/dL  /Hgb 15g/dL (men) or 14g/dL (women)	12 weeks
980297 (n = 314 <sup>a</sup> )  (9/14/1999- (11/8/2000)	A double-blind, placebo-controlled, randomized study of novel erythropoiesis stimulating protein (NESP) for the treatment of <b>in lung cancer subjects receiving multicycle platinum-containing chemotherapy</b>	2.25µg/kg QW  (N: 159 vs. 161)	Hgb ≤ 11 g/dL  /Hgb 15g/dL (men) or 14g/dL (women)	12 weeks
20000161 (n = 344 <sup>a</sup> )  (10/30/2000- 3/12/2002)	A multicenter, blinded, placebo-controlled, randomized study of novel erythropoiesis stimulating protein (NESP) for the treatment of anemia in subjects with <b>lymphoproliferative malignancies receiving chemotherapy</b>	2.25 µg/kg QW  (N : 176 vs. 173)	Hgb ≤ 11 g/dL  /Hgb 15g/dL (men) or 14g/dL (women)	12 weeks
20030232 (n = 386 <sup>a</sup> )  (2/20/2004- 3/3/2005)	A randomized, double-blind, placebo-controlled study of darbepoetin alfa for the treatment of anemia in subjects with <b>non-myeloid malignancy receiving multicycle chemotherapy</b>	300 µg Q3W  (N: 193 vs. 193)	Hgb < 11 g/dL  / Hgb 13 g/dL Hgb increase 1 g/dL in 14 days	15 weeks

20010145 (n = 596 <sup>a</sup> ) (12/10/2002- 2/22/2007)	A randomized, double-blind, placebo-controlled study of subjects with previously untreated extensive-stage <b>small-cell lung cancer (SCLC) treated with platinum plus etoposide chemotherapy</b> with or without darbepoetin alfa	300 µg QW followed by 300 µg Q3W (N: 299 vs. 301)	Hgb ≥ 9 g/dL and ≤ 13 g/dL / Hgb 14 g/dL	24 weeks
20010103 (n = 985) (4/15/2004- 11/7/2006)	A Multicenter, Randomized, Double-blind, Placebo-controlled Study of Darbepoetin Alfa for the Treatment of Anemia of Cancer	6.75 µg/kg Q4W (N : 517 vs. 472)	Hgb ≤ 11 g/dL /12 g/dl	16 weeks
20020149 (n = 985) (8/10/2004- 1/17/2007)	A Multicenter, Double-blind, Placebo-controlled Rollover Study to Protocol 20010103 of Darbepoetin Alfa for the Treatment of Anemia of Cancer	6.75 µg/kg Q4W (N : 198 vs. 173)	Hgb ≤ 11 g/dL /12 g/dl	16 weeks

a Randomized subjects who received at least 1 dose of investigational product QW = once weekly, Q3W = once every 3 weeks, Q4W = once every 4 weeks,  
 Hgb = hemoglobin, Hct = hematocrit, TIW = 3 times

## 5.2 Review Strategy

### 5.2.1 Materials reviewed:

#### 5.2.1.1 sBLA 103951.5173

#### Chronology of sBLA 103951.5173 and amendments submissions

- December 20, 2007 ( Labeling supplement, eCTD sequence No. 0164)
- January 18, 2008 (Amendment 1, eCTD sequence No. 208)
- April 18, 2008 (Amendment 2, eCTD sequence No. 224)
- May 30, 2008 (Amendment 3, eCTD sequence No. 251)
- September 12, 2008 (Amendment 4, eCTD sequence No. 251)
- September 18, 2008 (Amendment 5, eCTD sequence No. 256) and
- October 15, 2008 (Amendment 6, eCTD sequence No. 263)

#### Overview of sBLA 103951.7173

To address FDA items 3, 4, and 5 of the May 30, 2008 letter, Amgen submitted proposed labeling revisions and the supportive clinical study reports and datasets from seven randomized, placebo-controlled studies of darbepoetin alfa (Aranesp) in patients with anemia and non-myeloid malignancy receiving chemotherapy (studies 980291-schedule 1, 980291-schedule 2, 990114, 980297, 20000161, 20010145, and 20030232).

Amgen proposed labeling revisions are summarized as follows:

- In response to FDA item 3, *Revision of the INDICATIONS AND USAGE section to clarify the severity of anemia for which Aranesp/PROCRIT is indicated, by inclusion of the maximum, and if appropriate minimum, pretreatment hemoglobin level*, Amgen proposes labeling revisions as (b) (4)
- In response to FDA item 4, *Revision of the DOSAGE AND ADMINISTRATION section to specify a lower maximum hemoglobin level (i.e., hemoglobin level less than 12 g/dL) at which dosing should be suspended or terminated*, Amgen proposes that (b) (4)
- In response to FDA item 5, *Revision of the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections to indicate that Aranesp/PROCRIT should be discontinued following the completion of the concomitant chemotherapy regimen*, Amgen proposes the following statements for inclusion in the **BOXED WARNING** section:

(b) (4)

Amgen also proposes the following statements for inclusion in the **DOSAGE AND ADMINISTRATION** section:

(b) (4)

In addition, Amgen proposes to include the information on study 20010145 to the **WARNINGS AND PRECAUTIONS, Increased Mortality and/or Tumor Progression** section (5.2) of the label,

(b) (4)

(b) (4)

(b) (4)

(b) (4)

from the current supplement 103951.5173.

Moreover, Amgen proposes labeling revisions to include an update to clinical information on Study 20010103 (Cancer Study 8) in the WARNINGS AND PRECAUTIONS, Increased Mortality and/or Tumor Progression section (5.2) of the label in Physician Labeling Rule (PLR) format. To support the proposed updated information on study 20010103, Amgen submitted clinical study reports and datasets on study 20010103, a randomized, placebo-controlled study of darbepoetin alfa in patients with anemia and non-myeloid malignancies but not receiving chemotherapy or radiotherapy, and on study 20020149, a follow-up and roll-over study in patients who completed the study 2010103 and opted to remain on the study for another 16 weeks.

Amgen proposes to include the following update (bolded sentences) on study 20010103 in the labeling:

*Cancer Study 8 was a Phase 3, double-blind, randomized (Aranesp vs. placebo), 16-week study in 989 anemic patients with active malignant disease, neither receiving nor planning to receive chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions.* (b) (4)

#### 5.2.1.2 (b) (4) sBLA 103951.5195

Subsequent to FDA's request for Amgen to submit this labeling supplement to provide labeling revisions based on May 10 2007 ODAC recommendations, further safety concerns of increased mortality and/or increased tumor progression in the use of ESAs were identified in two additional studies, triggering March 13, 2008 ODAC meeting to re-assess the safety and risk management issues of ESA use in oncology setting. As a result, Amgen was requested to submit a CBE labeling supplement to address issues discussed and recommendations made at the ODAC meeting. Amgen submitted CBE labeling supplement (b) (4) containing revised labeling revisions pertinent to the FDA requested items triggering the current supplement 103951.5173. Due to failure to reach agreement between FDA and Amgen on some of the Amgen proposed labeling changes, FDA issued a complete response (CR) letter to Amgen on July 30, 2008 and ordered Amgen to make labeling changes as recommended by FDA on the statements regarding the threshold of hemoglobin level to initiate ESAs and on the criteria of hemoglobin level at which to withhold ESAs (b) (4). On August 5, 2008, Amgen submitted a CBE labeling supplement 103951.5193 containing revised labeling revisions pertinent to the issues triggering the submission of current supplement (103951.5173) and the revised labeling revisions are agreeable to FDA.

#### 5.2.1.3 May 10, 2007 ODAC meeting documents including the following:

- FDA May 10, 2007 ODAC briefing documents and slide presentation

- Amgen May 10, 2007 ODAC briefing documents and slide presentation
- Summary minutes of May 10, 2007 ODAC meeting
- Transcript of May 10, 2007 ODAC meeting

### 5.2.2 Review Strategy

The review of this supplement will primarily focus on Amgen proposed labeling revisions and supportive clinical study reports and datasets submitted to address issues on hemoglobin initiation level (FDA Item 3), maximum hemoglobin level (FDA Item 4), and discontinuation of ESA therapy post-chemotherapy (FDA Item 5).

Clinical study reports from nine randomized, placebo controlled studies of Aranesp (980291-1, 980291-2, 990114, 980297, 20000161, 20030232, 20010145, 200103 and 20020149) are the primary source of information reviewed for this supplement. Descriptions of individual study designs and reviews of individual study results will be presented in section 5.3.

Integrated efficacy and safety review are conducted by discussing individual and combined data from studies in which a uniform starting dose of Aranesp was used (980297, 20000161, 20030232, 20010145 and 20010103). Exploratory analyses are conducted in an attempt to address FDA requested items triggering the submission of this supplement.

Reviews and discussions on Amgen's proposed labeling revisions and the supporting analyses, rationales and justifications in response to FDA requested items are also provided in the review sections 6 and 7.

Furthermore, some issues and considerations on the review strategy and the inherent difficulties to address FDA requested items are discussed in the following subsections.

5.2.2. 1. Review strategy for response to FDA Item 3: *Revision of the INDICATIONS AND USAGE section to clarify the severity of anemia for which Aranesp/PROCRIT is indicated, by inclusion of the maximum, and if appropriate minimum, pretreatment hemoglobin level.*

This reviewer considers that issues related to FDA requested item 3, i.e., the appropriate baseline hemoglobin levels for the initiation of Aranesp/Procrit, present a very important question to be addressed in the use of Aranesp/procrit in the oncology setting. However, as discussed below, due to the inherent complexities and difficulties in addressing the issues related to FDA requested items, there are severe limitations in inferring scientifically sound and valid responses to the FDA requested items from the available study information contained in this supplement.

Aranesp and Procrit are indicated to reduce RBC transfusions in patients with anemia and receiving chemotherapy. There is lack of information to predict which patient will need RBC transfusions during the course of receiving chemotherapy. There is vast heterogeneity involved in risk factors for requiring RBC transfusions: individual disease status, type of chemotherapy,

co-morbidity among patients and even within patients during different course of chemotherapy. Therefore, who will likely receive RBC transfusion during the course of chemotherapy and therefore, likely benefit from receiving Aranesp/Procrit to avoid RBC transfusion becomes a clinical judgment call and a decision made by individual physician and patient. Though in general, patients with lower pretreatment hemoglobin level will be more likely to receive RBC transfusions during the chemotherapy, it is a challenge to specify a clear-cut level of hemoglobin value to initiate Aranesp/Procrit for all the patients with different disease statuses receiving different types of chemotherapies.

There is no prospective study conducted to address the question as to when, i.e., at what baseline hemoglobin levels, ESAs should be initiated. In fact, this reviewer recognizes the very difficulties and challenges that would be involved in designing such a study to address the question as to when, i.e., at what baseline hemoglobin levels, ESAs should be initiated because of the following reasons:

- vast heterogeneity of the indicated patient populations with different tumor types and different chemotherapies;
- lack of predictors for patients who would need RBC transfusions during chemotherapy;
- lack of well-defined terms and the unavoidable imprecision involved in defining efficacy outcome measurements such as a decrease in RBC transfusion rates and the related response variables, for example, decrease in proportions of subjects requiring RBC transfusions would inevitably include the compound and imprecise criteria for RBC transfusions as to hemoglobin levels and the subjective anemia-associated symptoms;
- the important component of subjectivity and individuality involved in the decision making for RBC transfusions, and therefore, the use of ESAs to avoid RBC transfusion, in patients receiving chemotherapy.

Most of the studies of Aranesp in patients receiving chemotherapy, including all of seven studies contained in this supplement, enrolled patients with hemoglobin levels < 11 g/dL without stratification by baseline hemoglobin levels. Therefore, the exploratory analyses on the efficacy and safety of Aranesp based on subgroups of different hemoglobin levels would only provide limited valid and meaningful information to compare the efficacy and safety profile of Aranesp in patients with different baseline hemoglobin levels and to address issues related to at what hemoglobin level Aranesp should be initiated.

In summary, it is this reviewer's opinion that by the nature of the study designs and the challenges involved in addressing the issues of concern, none of the studies contained in this supplement would provide valid and meaningful information to address the FDA requested items 3, 4 or 5 either by individual or combined analyses of study results. Judging from the available information of Aranesp use in oncology setting, this reviewer considers the appropriate answer for recommending a hemoglobin level to initiate Aranesp in patients receiving chemotherapy would be largely an individual clinical judgment call; any recommendation for a specific hemoglobin level to initiate ESAs in patients receiving chemotherapy would be arbitrary and need to weigh in the risks of requiring RBC transfusions and the risks and benefits of receiving ESAs during the course of chemotherapy.

Nevertheless, Amgen's proposed labeling revisions and the supporting analyses and arguments in response to FDA requested item 3 will be reviewed and discussed in section 6. Exploratory analyses on the effect of Aranesp in reducing RBC transfusions based on different baseline Hb levels will be conducted on individual study level for studies 980291, 20000161, 20030232, 20010145 and 20010103 in an attempt to compare the efficacy of Aranesp based on subgroups of baseline Hb levels.

**5.2.2.2. Review strategy for FDA Item 4:** *Revision of the DOSAGE AND ADMINISTRATION section to specify a lower maximum hemoglobin level (i.e., hemoglobin level less than 12 g/dL) at which dosing should be suspended or terminated*

In reviewing the FDA requested item 4: *Revision of the DOSAGE AND ADMINISTRATION section to specify a lower maximum hemoglobin level (i.e., hemoglobin level less than 12 g/dL) at which dosing should be suspended or terminated*, this reviewer recognizes the inherent complexities and difficulties involved in response to FDA requested item 4 from the available study information contained in this supplement. The challenges to address the issues raised in FDA item 4 are similar to the challenges described in the previous review subsection 5.2.2.1 in response to FDA item 3 and are summarized as follows:

There is no prospective study conducted to address the important question raised in the FDA item 4, i.e., the hemoglobin level at which dosing of Aranesp should be suspended or terminated. There is lack of scientific data or evidence indicating that there is a hemoglobin level at which dosing of Aranesp should be suspended or terminated based on the safety and safety analyses of Aranesp use in patients receiving chemotherapy. It is generally accepted that the higher hemoglobin levels patients have, the lower likelihood would be for the patients to receive RBC transfusions, and therefore it may be safely assumed that patients with higher hemoglobin levels would have lower likelihood of benefiting from receiving Aranesp. However, there is no clear cut baseline hemoglobin levels at which patients would not receive RBC transfusions during the chemotherapy course nor is there clear cut standard in measuring the benefits of Aranesp in reducing RBC transfusions during the chemotherapy.

Even though there are theoretical concerns of increased adverse events including thromboembolic and cardiovascular events in patients receiving Aranesp and achieving higher hemoglobin levels or having rapid rate of hemoglobin increase, this reviewer has not come upon substantial evidence to warrant the concern from the available information contained in this supplement nor from the literature search. It is of this reviewer's opinion that it is somewhat implausible that achieving a hemoglobin level of > 12 g/dL by Aranesp in patients receiving chemotherapy would potentially subject patients to a harmful adverse events because our normal physiological levels of hemoglobin ranges from 12 to 15 g/dL.

Therefore, it is of this reviewer's opinion that the decision on when (at what hemoglobin level) dosing of Aranesp should be suspended or terminated can only be a clinical judgment call based on individual consideration of risk factors for RBC transfusions and the risks and benefits ratio in receiving Aranesp in order to avoid the RBC transfusions during the chemotherapy course.

Considering the vast heterogeneity involved in the risk factors for RBC transfusions, including patients' disease status, the chemotherapy types and cycles, and co-morbidities, this reviewer suspects that there is no uniform standard to be recommended on the hemoglobin level at which dosing of Aranesp should be suspended or terminated.

Nevertheless, review and discussion of Amgen's responses and the supporting analyses and arguments in response to FDA item 4 are presented in section 7.5 Other Safety Explorations.

**5.2.2.3. Review strategy for Amgen's response to FDA Item 5:** *Revision of the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections to indicate that Aranesp/PROCRIT should be discontinued following the completion of the concomitant chemotherapy regimen.*

Similar to the discussions presented under previous sections 5.2.2.2 and 5.2.2.3 in response to FDA items 3 and 4, this reviewer considers inadequate information exist to address issues raised by FDA requested item 5; i.e., *Revision of the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections to indicate that Aranesp/PROCRIT should be discontinued following the completion of the concomitant chemotherapy regimen.*

There are no prospect studies conducted to address the question as to when to discontinue the use of Aranesp/Procrit following the completion of the concomitant chemotherapy regimen as raised in FDA requested item 5. This reviewer recognizes the significant challenges that would be involved in designing such studies to address the requested item 5 because there are no clearly defined conditions, for example, at what hemoglobin level, under which Aranesp/Procrit should be discontinued following the completion of the concomitant chemotherapy.

However, extrapolating the results from study 20010103 in which patients did not receive chemotherapy where a harmful effect of Aranesp increased on study mortality and decreased overall survival during the follow-up period was observed in addition to the futility of Aranesp in reducing RBC transfusions, this reviewer strongly recommends that Aranesp/Procrit should be discontinued immediately following the completion of the chemotherapy regimen.

Review and discussion of Amgen's proposed labeling revisions and the supporting analyses and arguments in response to FDA item 5 are presented in Section 6.1.9 Additional Efficacy Analyses/Issues.

### 5.3 Discussion of Individual Studies

#### 5.3.1 Study 980291-schedule 1

#### 5.3.1.1 Study Title, Phase, and Purpose:

**Title:** A Randomized, Double-blind, Placebo-controlled, Dose-finding Study of Novel Erythropoiesis Stimulating Protein (NESP) Administered Once Every Three Weeks by Subcutaneous (SC) Injection for the Treatment of Anemia in Subjects with Solid Tumors Receiving Multicycle Chemotherapy

Phase 1, dose-finding, sequential escalation study

**Purpose:** The primary objective of this study was to assess the safety of darebepoetin alfa (NESP) administered by subcutaneous (SC) injection once every 3 weeks in anemic subjects with solid tumor(s) who were receiving multicycle chemotherapy.

Secondary objectives were to determine the clinically effective dose (CED) of NESP; to investigate the effect of NESP during a 12-week dose-maintenance phase; and to assess the feasibility, reliability, validity, sensitivity, and timing of quality-of-life surveys (QOLS) in this setting.

#### 5.3.1.2 Study design and dates conducted:

**Design:** Randomized, double-blind, placebo-controlled, dose-finding study conducted to evaluate the safety (dose limiting toxicity) and hemoglobin effect of various dosing regimens of darbepoetin alfa administered subcutaneously every 3 weeks in anemic patients with solid tumors receiving multi-cycle chemotherapy.

The study course includes 2-part phases of study (Part A and Part B). A minimum of 20 and a maximum of 225 subjects were planned (5 to 45 subjects in each of the 4 planned dose groups and an intermediate or alternative dose group). In Part A (treatment phase), eligible subjects were randomized in a 1:1:1:1:1 ratio to receive NESP at one of four doses (4.5, 6.75, 9.0, and 13.5 µg/kg) or placebo administered once every 3 weeks for 12 weeks. The study was amended to include two additional dose groups of 12.0 and 15.0 µg/kg. In Part B (maintenance phase), subjects who completed Part A and continued to receive multicycle chemotherapy were given the option to receive open-label NESP for up to 12 additional weeks. Subjects who received placebo in Part A were assigned a NESP dose in Part B according to their Part A dose cohort.

**Dates conducted:** The first subject signed the informed consent document on 30 June 1999, and the last subject completed the end-of-study assessments on 30 July 2001.

#### 5.3.1.3 Inclusion, exclusion criteria, study procedures, timelines

**Inclusion:**

- ≥ 18 years of age
- with solid tumor(s) who were receiving cyclic chemotherapy

- hemoglobin concentration  $\leq$  11.0 g/dL predominantly due to cancer and/or chemotherapy
- $\geq$  6-month life expectancy
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
- adequate renal and liver function

**Exclusion:**

- iron deficient
- received rHuEPO within 8 weeks before randomization
- 2 red blood cell (RBC) transfusions within 4 weeks of randomization
- RBC transfusion within 2 weeks of randomization
- known primary hematologic disorders that could cause anemia and central nervous system, cardiac, or inflammatory diseases

**Study procedures:**

Vital signs, adverse events, and complete blood counts are monitored weekly from week one to the end of study period (EOP) (weeks 18 for Part A, and weeks 30 for part B). ECOG performance status, chemistry panels, and quality of life survey are checked every 3 weeks until the end of study (EOS).

No long term follow-up was planned in the protocol.

A schema for study procedure and assessment (Part A) is copied below from the study protocol.

15.6. Appendix F: Schedule of Assessments - Part A

STUDY WEEK	Screen/ Enroll (c,d)	TREATMENT PHASE - PART A												FOLLOW-UP (a)					EOS (b)
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
<b>GENERAL AND SAFETY ASSESSMENTS</b>																			
Informed Consent (e)	X																		
Medical History	X																		
Physical Examination (f)	X																		
Vital Signs (g,h)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X			X			X			X			X			X		
Overall disease response assessment																			X
Adverse Event and Hospitalisation Reporting		X																	▶▶▶
Blood Product Transfused		X																	▶▶▶
Chemotherapy (i)		X																	▶▶▶
Quality of Life Survey		X			X			X			X			X			X		X
Study Drug Administration		X			X			X			X			X			X		X
<b>LAB ASSESSMENTS</b>																			
Serum Pregnancy Test	X																		
Anti-NESP Antibody Testing		X			X						X								
Pharmacokinetics (j)		X			X						X								X
EPO levels (h)		X																	
CBC (h,k)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry (h,l)	X	X			X			X			X			X			X		X
Coagulation (h,m)	X	X						X											X
Serum iron and iron binding capacity	X	X			X			X			X			X			X		X
Ferritin and transferrin saturation	X	X			X			X			X			X			X		X
Folate, vitamin B12	X																		

- (a) The end of Part A is scheduled for week 12. Subjects participating in Part A, but not participating in Part B will be followed-up for 8 weeks after their last dose of study drug
- (b) End-of-study for subjects completing Part A and not participating in Part B
- (c) Screening will occur within 7 days before study day 1
- (d) Randomisation will occur within 3 days before study day 1
- (e) Signed informed consent must be obtained before any study specific procedures
- (f) And actual body weight
- (g) Will include resting systolic/diastolic blood pressure and pulse
- (h) Before administration of study drug (on day that study drug is administered)
- (i) Chemotherapy will be administered for up to 12 weeks
- (j) Serum samples will be collected pre-dose and 48 hours post-dose to determine NESP serum concentrations
- (k) CBC will consist of RBC, Hct, Hb, platelet count, reticulocytes, MCV, MCH, MCHC, RDW and WBC with differential
- (l) Chemistries will consist of sodium, potassium, calcium, phosphorus, chloride, bicarbonate, total protein, albumin, glucose, BUN, creatinine, uric acid, total bilirubin, alkaline phosphatase, LDH, ALT, AST
- (m) Coagulation will include PT and aPTT

**Safety Analysis:**

The safety of NESP was assessed by the occurrence of dose-limiting toxicity (DLT); defined as a grade 3, 4, or fatal adverse event reported by the investigator as having a reasonable possibility of being related to study drug), the incidence of adverse events, and evaluation of potential antibody formation to NESP.

All adverse events were grouped according to the body system affected and by preferred term within body system according to an Amgen-modified World Health Organization adverse reaction term (WHOART) dictionary. The number of subjects experiencing adverse events was tabulated by treatment group. The number and proportion of subjects with anti-NESP antibodies were summarized by dose group. The number and proportion of subjects with hemoglobin concentrations > 14.0 g/dL (for women) or > 15.0 g/dL (for men) were also summarized by treatment group

**Secondary Endpoint Analyses:**

The potential efficacy of NESP in Part A was assessed by the number and proportion of subjects who achieved a hemoglobin response ( $\geq 2.0$ -g/dL increase in hemoglobin concentration from baseline during the 12-week treatment phase in the absence of any RBC transfusions during the preceding 28 days). The number and proportion of subjects with a correction in hemoglobin to  $\geq 12.0$  g/dL during the treatment phase, the time to hemoglobin response and to hemoglobin

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correction after the initiation of treatment, and the change in hemoglobin from baseline during the treatment phase were also assessed. Data on the number and proportion of subjects who received RBC transfusions, the number of units of RBC transfused, and the number of days with at least 1 RBC transfusion during week 5 to the end of the treatment phase (EOTP) was also evaluated.

Efficacy was not assessed in Part B.

Point estimates and 95% confidence intervals (CIs) were provided for the proportion of subjects who achieved a hemoglobin response at the end of the treatment phase. Time to hemoglobin response was analyzed using both the crude rate and Kaplan-Meier methods. The number and proportion of subjects receiving a RBC transfusion during week 5 to the EOTP were summarized by treatment group.

The CED of NESP, when administered once every 3 weeks in this treatment setting, was determined from the safety and efficacy data using pre-specified criteria. The CED was defined as the dose at which  $\geq 50\%$  of subjects achieved a hemoglobin response;  $\leq 20\%$  of subjects in the safety analysis set had clinical sequelae associated with a hemoglobin concentration that exceeded the highest acceptable level ( $> 14.0$  g/dL for women,  $> 15.0$  g/dL for men); and  $\leq 20\%$  of subjects in the safety analysis set experienced a DLT. If  $> 1$  dose met the criteria and if the hemoglobin response rates were similar, the lowest dose was selected as the CED.

The pharmacokinetics of NESP was assessed by evaluating NESP serum concentrations at weeks 1, 4, and 10 (trough and 48-hours post dose) within each dose cohort. In addition, endogenous erythropoietin serum concentrations at weeks 1, 4, and 10 were summarized.

Summary statistics including means and 95% CIs were calculated. Descriptive statistics were calculated for the outcomes of the Health Related Quality of Life (HRQoL) assessments at the protocol-specified time points. Multivariate statistical methods were used to assess the reliability, validity, and sensitivity of the QOL.

#### 5.3.1.4 Treatments and ancillary management

Aranesp, at doses of 4.5, 6.75, 9.0, 12.0, 13.5, or 15.0  $\mu\text{g}/\text{kg}$ , or placebo were administered every 3 weeks for 12 weeks. Subjects who received placebo in Part A were assigned a NESP dose in Part B corresponding to their Part A dose cohort. The maximum duration of treatment: NESP was administered for a maximum of 24 weeks

#### 5.3.1.5 Study sites, including enrollment

This was an international multicenter study conducted at 26 sites. A minimum of 20 and a maximum of 225 subjects were planned (5 to 45 subjects in each of the 4 planned dose groups

and an intermediate or alternative dose group). Two hundred fifty nine patients were randomized into the study: 51 were allocated to receive placebo, and 208 were allocated receive to NESP.

#### 5.3.1.6 Study population

The intent-to-treat analysis set consists of all subjects randomized in the study that received least one dose of study drug and was used for the safety analysis for both part A and part B.

The efficacy evaluable analysis set applicable only to part A consists of all properly consented subjects randomized in the study who meet the following criteria:

- Received at least 75% of the planned number of doses during Part A
- Did not receive  $\geq 30$  Gy of radiation to the whole pelvis during Part A
- Did not receive myeloablative chemotherapy or radiotherapy during Part A as conditioning therapy for stem cell transplant

Subjects who meet all of the above criteria were included in the efficacy analysis of Part A data according to the treatment actually received.

#### 5.3.1.7 Patient Disposition

In Part A, thirty-seven subjects (73%) receiving placebo and 148 subjects (71%) receiving NESP completed the study (Table 5.3.7.1, copied from Amgen's Table 8-1). Similar percentage of subjects in the placebo arm and NESP arm (27% versus 29%) did not complete the study. The most common reasons for early discontinuation included chemotherapy either delayed or discontinued (32 subjects), consent withdrawn (10 subjects), and death (10 subjects).

Table 5.3.1.7.1 Subject disposition (Part A) (Screened Subjects) in study 980291-1, copied from Amgen's submission.

**Table 8-1. Subject Disposition (Part A) (Screened Subjects)**

	Placebo		All NESP		Total	
Subjects Screened						362
Subjects Randomized	51		208			259
Subjects Receiving Study Drug	51	(100%)	198	(95%)	249	(96%)
Subjects Completing Part A	37	(73%)	148	(71%)	185	(71%)
Subjects Not Completing Part A	14	(27%)	60	(29%)	74	(29%)
Ineligibility Determined	0	(0%)	8	(4%)	8	(3%)
Protocol Violation	0	(0%)	1	(0%)	1	(0%)
Subject Noncompliance	0	(0%)	1	(0%)	1	(0%)
Adverse Event <sup>a</sup>	0	(0%)	1	(0%)	1	(0%)
Consent Withdrawn	1	(2%)	9	(4%)	10	(4%)
Disease Progression	0	(0%)	6	(3%)	6	(2%)
Administrative decision	0	(0%)	1	(0%)	1	(0%)
Lost to Follow-up	0	(0%)	2	(1%)	2	(1%)
Death	3	(6%)	7	(3%)	10	(4%)
Other <sup>b</sup>	10	(20%)	24	(12%)	34	(13%)

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Note: Percentages based on subjects randomized.

<sup>a</sup>Excluding Disease Progression and Death

<sup>b</sup>Other includes: 32 subjects with chemotherapy either delayed or discontinued; 1 subject with disease progression who wanted to consider entry to vaccine program and 1 subject on healthcare - vacation.

Program: /stat/nesp/onc/nesp980291/analysis/final/statfiles/programs/tables/t\_dispa.sas  
 Output: t14-4\_t\_dispa.rtf (Date Generated: 05MAR2002:12:58)

Of the subjects who completed Part A, 119 enrolled in Part B (24 subjects who received placebo in Part A and 95 subjects who received NESP in Part A, (Table 5.3.1.7.2). Subjects who received placebo in Part A were assigned NESP doses in Part B according to their Part A dose cohort and are identified as Placebo-NESP subjects. The proportion of subjects who completed the optional Part B phase of the study was slightly higher in the Placebo-NESP group (54%) than in the NESP-NESP group (35%). The primary reason for not completing Part B of the study for both treatment groups was that chemotherapy was discontinued. Seven subjects who were enrolled in Part B did not receive study drug.

Table 5.3.1.7.2 Subject disposition (Par B) (Screened Subjects) in study 980291-1, copied from Amgen's submission.

**Table 8-2. Subject Disposition (Part B) (Screened Subjects)**

	All Placebo-NESP		All NESP-NESP	
Subjects Enrolled in Part B	24		95	
Subjects Receiving Study Drug in Part B	23	( 96%)	89	( 94%)
Subjects Completing Part B	13	( 54%)	33	( 35%)
Subjects Not Completing Part B	10	( 42%)	56	( 59%)
Ineligibility Determined	0	( 0%)	0	( 0%)
Protocol Violation	0	( 0%)	0	( 0%)
Subject Noncompliance	0	( 0%)	2	( 1%)
Adverse Event <sup>a</sup>	0	( 0%)	2	( 1%)
Consent Withdrawn	3	( 6%)	5	( 2%)
Disease Progression	1	( 2%)	1	( 0%)
Administrative decision	0	( 0%)	0	( 0%)
Lost to Follow-up	0	( 0%)	2	( 1%)
Death	1	( 2%)	11	( 5%)
Other <sup>b</sup>	5	( 10%)	33	( 16%)

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Note: Percentages based on subjects enrolled.

<sup>a</sup>Excluding Disease Progression and Death

<sup>b</sup>Other includes: 35 subjects with chemotherapy discontinued; 1 subject with chemotherapy delayed; 1 subject with early follow-up; and 1 subject who withdrew consent to follow-up.

Program: /stat/nesp/onc/nesp980291/analysis/final/statfiles/programs/tables/t\_disp.sas  
 Output: t\_disp\_overall.rtf (Date Generated: 28NOV2001:10:31)

### 5.3.1.8 Demographics, underlying disease and drug treatments

Demographic characteristics for the 249 subjects (198 NESP; 51 placebo) who received study drug were the following: 72 men/ 177 women, mean Age: 57.9 years (standard deviation [SD] 12.0 years), and ethnic groups: 240 white/2 black/3 Asian/3 Hispanic/1 Native American.

Overall, no clinically meaningful differences in demographic characteristics were observed between the NESP dose groups or the NESP and placebo groups.

In general, baseline disease characteristics were similar between the NESP and the placebo arm (Table 5.3.1.8.1). The most common tumor type was breast cancer, followed by gynecologic, gastrointestinal, lung, genitourinary and other cancers. No clinically meaningful differences in baseline disease characteristics were observed among the NESP dose groups or the NESP and placebo groups.

Table 5.3.1.8.1, Baseline disease characteristics in study 980291-1 (Amgen source Table 8.6)

Table 8-6. Baseline Disease Characteristics by Dose of Study Drug in Part A (ITT Analysis Set)

	Placebo	NESP Dose (µg/kg/3wk)				All NESP	Total
		4.5	6.75	9.0			
Number of Subjects	51	32	17	46	198	249	
Primary Tumor Type							
Breast	13 (25%)	8 (25%)	4 (24%)	7 (15%)	61 (31%)	74 (30%)	
Gynecologic	9 (18%)	7 (22%)	4 (24%)	11 (24%)	46 (23%)	55 (22%)	
Gastrointestinal	13 (25%)	7 (22%)	1 (6%)	7 (15%)	34 (17%)	47 (19%)	
Lung	10 (20%)	4 (13%)	4 (24%)	13 (28%)	33 (17%)	43 (17%)	
Genitourinary	2 (4%)	4 (13%)	2 (12%)	5 (11%)	15 (8%)	17 (7%)	
Other	4 (8%)	2 (6%)	2 (12%)	3 (7%)	9 (5%)	13 (5%)	
Disease Stage <sup>a</sup>							
I	3 (6%)	1 (3%)	0 (0%)	1 (2%)	4 (2%)	7 (3%)	
II	1 (2%)	5 (16%)	0 (0%)	7 (15%)	18 (9%)	19 (8%)	
III	11 (22%)	6 (19%)	4 (24%)	8 (17%)	37 (19%)	48 (19%)	
IV	36 (71%)	20 (63%)	13 (76%)	30 (65%)	139 (70%)	175 (70%)	
Subjects with Known Hepatic Metastases	16 (31%)	5 (16%)	2 (12%)	13 (28%)	53 (27%)	69 (28%)	
Subjects with Known Bone Marrow Involvement	2 (4%)	0 (0%)	0 (0%)	2 (4%)	14 (7%)	16 (6%)	
ECOG							
0	16 (31%)	17 (53%)	4 (24%)	19 (41%)	71 (36%)	87 (35%)	
1	29 (57%)	12 (38%)	11 (65%)	24 (52%)	109 (55%)	138 (55%)	
2	6 (12%)	3 (9%)	2 (12%)	3 (7%)	18 (9%)	24 (10%)	

<sup>a</sup>Disease stage as defined by the investigator

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Table 8-6. Baseline Disease Characteristics by Dose of Study Drug in Part A (ITT Analysis Set) (Continued)

	Placebo	NESP Dose (µg/kg/3wk)			All NESP	Total
		12.0	13.5	15.0		
Number of Subjects	51	28	35	40	198	249
Primary Tumor Type						
Breast	13 (25%)	17 (61%)	10 (29%)	15 (38%)	61 (31%)	74 (30%)
Gynecologic	9 (18%)	3 (11%)	11 (31%)	10 (25%)	46 (23%)	55 (22%)
Gastrointestinal	13 (25%)	2 (7%)	9 (26%)	8 (20%)	34 (17%)	47 (19%)
Lung	10 (20%)	4 (14%)	4 (11%)	4 (10%)	33 (17%)	43 (17%)
Genitourinary	2 (4%)	1 (4%)	1 (3%)	2 (5%)	15 (8%)	17 (7%)
Other	4 (8%)	1 (4%)	0 (0%)	1 (3%)	9 (5%)	13 (5%)
Disease Stage <sup>a</sup>						
I	3 (6%)	0 (0%)	1 (3%)	1 (3%)	4 (2%)	7 (3%)
II	1 (2%)	2 (7%)	2 (6%)	2 (5%)	18 (9%)	19 (8%)
III	11 (22%)	4 (14%)	9 (26%)	6 (15%)	37 (19%)	48 (19%)
IV	36 (71%)	22 (79%)	23 (66%)	31 (78%)	139 (70%)	175 (70%)
Subjects with Known Hepatic Metastases	16 (31%)	9 (32%)	14 (40%)	10 (25%)	53 (27%)	69 (28%)
Subjects with Known Bone Marrow Involvement	2 (4%)	3 (11%)	5 (14%)	4 (10%)	14 (7%)	16 (6%)
ECOG						
0	16 (31%)	6 (21%)	16 (46%)	9 (23%)	71 (36%)	87 (35%)
1	29 (57%)	19 (68%)	17 (49%)	26 (65%)	109 (55%)	138 (55%)
2	6 (12%)	3 (11%)	2 (6%)	5 (13%)	18 (9%)	24 (10%)

<sup>a</sup>Disease stage as defined by the investigator

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HT\_Med Writ (Source: Table 14-14 and Table 14-15) (Date Generated: 26MAY2001:14:42)

#### 5.3.1.9 Outcome efficacy

NESP doses  $\geq 9.0$   $\mu\text{g}/\text{kg}$  fulfilled the efficacy criterion for the CED. The subjects in the next lowest NESP dose tested,  $6.75$   $\mu\text{g}/\text{kg}$ , had a 48% (95% CI 22, 74) hemoglobin response rate, which was just under the prespecified efficacy criterion.

Formal testing of dose response revealed a treatment effect for NESP versus placebo for the hemoglobin response and correction endpoints, as well as a NESP dose effect for hemoglobin response. A lower incidence of RBC transfusions was observed for NESP than for placebo.

#### 5.3.1.10 Outcome of safety assessments

In Part A (the randomized, placebo-controlled portion of the study), the safety profile of NESP was considered to be consistent with that expected for a patient population with cancer receiving chemotherapy, without any evidence of a dose relationship.

No placebo subjects and 8 NESP subjects [4%]) withdrew prematurely from the study because of adverse events, including progressive diseases in 7 subjects and a right lower leg venous thrombosis in 1 subject. Deaths on study (4 placebo subjects [8%] and 10 NESP subjects [5%]) were attributed to be related with complications of progressive disease. Serious adverse events and severe adverse events were reported with comparable frequency in subjects receiving either NESP or placebo. The most frequently reported adverse events in both treatment groups were gastrointestinal and constitutional symptoms including nausea, fatigue, vomiting, constipation, diarrhea, dysnea, abdominal pain, peripheral edema. One DLT (pulmonary embolism on study day 5) occurred in a NESP subject with non-small cell lung cancer (NSCLC).

In Part A, NESP administration was associated with both a greater proportion of subjects exceeding the maximum hemoglobin concentration threshold ( $> 15.0$  g/dL for men and  $> 14.0$  g/dL for women) and a greater proportion of subjects who had a rapid rise in hemoglobin defined as a  $\geq 2.0$ -g/dL increase over 28 days). No evidence was seen to suggest a difference in the incidence of adverse events in subjects who either did or did not reach the maximum hemoglobin concentrations or had a rapid rise in hemoglobin. In general, the reported adverse events were not associated with a drug-induced rapid rise in hemoglobin or exceeding the maximum hemoglobin concentration threshold.

In Part B, during which all subjects received NESP (23 subjects in the Placebo-NESP group and 89 subjects in the NESP-NESP group), the safety profile was similar to that observed for NESP in Part A of this study

#### 5.3.1.11 Discussion of findings/conclusions

Amgen's conclusions:

The safety profile of subjects in this study was consistent with the underlying disease of this population and the toxicities associated with chemotherapy administration. In general, all doses showed demonstrable activity, and the dose of 9.0 µg/kg was selected as the CED because it was the lowest NESP dose to meet all of the prospectively defined criteria. Subcutaneous administration of NESP at doses ranging from 4.5 to 15.0 µg/kg every 3 weeks appears to be well tolerated and generally comparable with placebo, even after long-term use, as demonstrated in Part B of the study. A dose-response relationship was apparent between doses of 4.5 and 12.0 µg/kg for the hemoglobin response and mean change in hemoglobin endpoints.

*Reviewer's comments:*

*Study 980291 schedule-1 is a dose finding study conducted to evaluate the safety of Aranesp given subcutaneously every 3 weeks and to identify the protocol defined clinical effective dose (CED). The CED was defined as the dose at which ≥ 50% of subjects achieved a hemoglobin response; ≤ 20% of subjects in the safety analysis set had clinical sequelae associated with a hemoglobin concentration that exceeded the highest acceptable level (> 14.0 g/dL for women, > 15.0 g/dL for men); and ≤ 20% of subjects in the safety analysis set experienced a DLT.*

*No approved dosage regimen of Aranesp, 2.25 ug/kg, SC, QW or 500 ug, SC, Q3W was used in the study. However, a dosage of Aranesp 6.75 ug/kg, SC, Q3W was used as the basis for using Aranesp 500 ug, Q3W in major efficacy study design intended for labeling efficacy approval.*

*Efficacy and Safety information is limited to data collected during the first 12 weeks of part A blinded phase study because subjects receiving placebo in Part A were allowed to cross over to receive Aranesp in open-labeled optional Part B study phase.*

*The efficacy and safety outcome from study 980291-schedule has no impact on the current labeling of Aranesp.*

*The results of study 980291-schedule 1 are of limited value to address the pertinent PAS supplement issues on hemoglobin initiation level (FDA Item 3), maximum hemoglobin level (FDA Item 4), and discontinuation of ESA therapy post-chemotherapy (FDA Item 5).*

### 5.3.2 Study 980291-schedule 2

#### 5.3.2.1 Study Title, Phase, and Purpose

Title: A Randomized, Double-blind, Placebo-controlled, Dose-finding Study of Novel Erythropoiesis Stimulating Protein (NESP) Administered by Subcutaneous (SC) Injection for the Treatment of in Subjects with Solid Receiving Multicycle Chemotherapy

Phase: 1

**Purpose:** The primary objective of this study was to assess the safety of NESP administered by SC injection once every 4 weeks in anemic subjects with solid tumor(s) who were receiving multicycle chemotherapy.

Secondary objectives of this study were to determine the clinically effective dose (CED) of NESP; to investigate the effect of NESP during a 12-week dose-maintenance phase; and to assess the feasibility, timing, reliability, validity, sensitivity, and relationship to hemoglobin of the quality-of-life surveys (QOLS) in this setting.

#### 5.3.2.2 Study Design including dates conducted

A randomized, double-blind, placebo-controlled, dose-finding study to evaluate the safety (dose limiting toxicity) and hemoglobin effect of various darbepoetin alfa dosing regimen (9.0, 12.0, 15.0, or 18.0 µg/kg or placebo) administered subcutaneously every 4 weeks in anemic patients with solid tumors receiving multi-cycle chemotherapy.

The study course includes 2-part phases of study (Part A and Part B).

Approximately 180 subjects were planned (30 subjects in each of the 5 planned dose groups and an intermediate or alternative dose group).

#### Study Period:

The first subject signed the informed consent on 30 June 1999, and the last subject completed the end-of-study assessments on 30 July 2001.

#### 5.3.2.3 Inclusion, exclusion criteria, study procedures,

##### **Inclusion:**

- ≥ 18 years of age
- with solid tumor(s) who were receiving cyclic chemotherapy
- hemoglobin concentration ≤ 11.0 g/dL predominantly due to cancer and/or chemotherapy
- ≥ 6-month life expectancy
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
- adequate renal and liver function

##### **Exclusion:**

- iron deficient
- received rHuEPO within 8 weeks before randomization
- 2 red blood cell (RBC) transfusions within 4 weeks of randomization
- RBC transfusion within 2 weeks of randomization
- known primary hematologic disorders that could cause anemia and central nervous system, cardiac, or inflammatory diseases

### Study procedures

This multicenter study was conducted in 2 parts: a randomized, double-blind, placebo-controlled, parallel, dose-finding part A and an optional, open-label Part B in which all subjects received NESP.

The primary endpoint of this study was the safety of NESP, as measured by the following:

- incidence of dose-limiting toxicities (DLTs)
- incidence of adverse events
- antibody formation to NESP concomitant medication use
- laboratory values
- vital signs
- number of days hospitalized
- maximum increase in hemoglobin
- maximum increase in hemoglobin in the absence of RBC transfusions
- maximum hemoglobin concentration
- rapid rise in hemoglobin
- exposure to investigational product
- hemoglobin after dose withheld
- disease response at the end of the study

### Secondary Endpoints:

- proportion of subjects achieving a hemoglobin response (increase of  $\geq 2.0$  g/dL from baseline during the treatment phase in the absence of any RBC transfusions on the day of response and during the preceding 28 days) during the treatment phase
- proportion of subjects achieving hemoglobin correction (concentration of  $\geq 12.0$  g/dL during the treatment phase in the absence of any RBC transfusions on the day of correction and during the preceding 28 days) during the treatment phase time to hemoglobin response during the treatment phase
- time to hemoglobin correction during the treatment phase
- change in hemoglobin from baseline to the end of the treatment phase (EOTP)
- proportion of subjects receiving RBC transfusions from week 5 to the EOTP
- time to the first RBC transfusion from week 5 to the EOTP
- number of standard units of packed RBCs transfused from week 5 to the EOTP
- number of days with at least 1 RBC transfusion from week 5 to the EOTP
- feasibility and timing of QOLS (including the Functional Assessment of Cancer Therapy - General [FACT-G], FACT - Anemia [FACT-An], Brief Symptom Inventory [BSI], and de novo questions) and the relationship between health-related quality of life (HRQOL) and hemoglobin

### Analysis plan:

Descriptive statistics were calculated for all endpoints. Point estimates and approximate 95% confidence intervals (CIs) were provided for the proportion of subjects who achieved a hemoglobin response at the end of the treatment phase.

Time to hemoglobin response was analyzed using both the crude rate and Kaplan- Meier methods. The number and proportion of subjects achieving hemoglobin correction or receiving a RBC transfusion during week 5 to the EOTP also were analyzed using these methods. The change in hemoglobin was calculated using the last value carried forward and for the subset of subjects who completed 12 weeks of treatment.

The CED of NESP, when administered once every 4 weeks in this treatment setting, was determined from the safety and efficacy data using pre-specified criteria.

The CED was defined as the dose at which  $\geq 50\%$  of subjects achieved a hemoglobin response;  $\leq 20\%$  of subjects in the safety analysis set had clinical sequelae associated with a hemoglobin concentration that exceeded the highest acceptable level ( $> 14.0$  g/dL for women,  $> 15.0$  g/dL for men); and  $\leq 20\%$  of subjects in the safety analysis set experienced a DLT. If  $> 1$  dose met the criteria and if the hemoglobin response rates were similar, the lowest dose was selected as the CED.

The pharmacokinetics of NESP were assessed by evaluating NESP serum concentrations at weeks 1, 5, and 9 (trough and 48-hours post-dose) within each dose cohort. In addition, endogenous erythropoietin serum concentrations in subjects receiving placebo at weeks 1, 5, and 9 were summarized. Summary statistics including means and 95% CIs were calculated. Descriptive statistics were calculated for the outcomes of the HRQOL assessments at the protocol-specified time points. Multivariate statistical methods were used to assess the reliability, validity, and sensitivity of the QOLS.

A flow chart for study procedures and assessment for part A (blinded phase) is copied below from the protocol.

15.6. Appendix F: Schedule of Assessments – Schedule 1 - Part A

STUDY WEEK	Screen/Enrol (c,d)	PRELIMINARY PHASE - PART A												TO FOLLOW (e)		ECS (f)			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14		15	16	17
<b>GENERAL AND SAFETY ASSESSMENTS</b>																			
Informed Consent (a)	X																		
Medical History	X																		
Physical Examination (g)	X																		
Vital Signs (g,h)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X			X			X			X			X			X		X
Overall disease response assessment																			X
Adverse Event and Hospitalisation Reporting		X																	X
Blood Product Transfused		X																	X
Chemotherapy (i)		X																	X
Quality of Life Survey		X			X			X			X			X			X		X
Study Drug Administration		X			X			X			X			X			X		X
<b>LABORATORY TESTS</b>																			
Serum Pregnancy Test	X																		
Anti-NESP Antibody Testing		X			X						X								
Pharmacokinetics (j)		X			X						X								X
EPO levels (h)		X			X						X								X
CBC (h,k)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry (h,l)	X	X			X			X			X			X			X		X
Coagulation (h,m)	X	X			X			X			X			X			X		X
Serum iron and iron binding capacity	X	X			X			X			X			X			X		X
Ferritin and transferrin saturation	X	X			X			X			X			X			X		X
Folate, vitamin B <sub>12</sub>	X																		X

- (a) The end of Part A is scheduled for week 12. Subjects participating in Part A, but not participating in Part B will be followed-up for 8 weeks after their last dose of study drug.
- (b) End-of-study for subjects completing Part A and not participating in Part B.
- (c) Screening will occur within 7 days before study day 1.
- (d) Randomisation will occur within 3 days before study day 1.
- (e) Signed informed consent must be obtained before any study specific procedures.
- (f) And actual body weight.
- (g) Will measure resting systolic/diastolic blood pressure and pulse.
- (h) Before administration of study drug (on day that study drug is administered).
- (i) Chemotherapy will be administered for up to 12 weeks.
- (j) Serum samples will be collected pre-dose and 48 hours post-dose to determine NESP serum concentrations.
- (k) CBC will consist of RBC, Hct, Hb, platelet count, reticulocyte, MCV, MCH, MCHC, RDW and WBC with differential.
- (l) Chemistry will consist of sodium, potassium, calcium, phosphorus, chloride, bicarbonate, total protein, albumin, glucose, BUN, creatinine, ure acid, total bilirubin, alkaline phosphatase, LDH, ALT, AST.
- (m) Coagulation will include PT and aPTT.

5.3.2.4 Treatment, ancillary management

In the blinded part A phase, eligible subjects were randomized in a 1:1:1:1 ratio to receive subcutaneous (SC) NESP at doses of 9.0, 12.0, 15.0, or 18.0 µg/kg or placebo. Subjects allocated to placebo were randomly assigned to receive 1 of 4 matched placebo volumes to maintain the blind.

NESP or placebo was administered once every 4 weeks for 12 weeks, starting on the first day of chemotherapy. Subjects completing the blinded phase (Part A) and continuing to receive cyclic chemotherapy had the option of receiving NESP at the same dose once every 4 weeks for an additional 12 weeks in the open-label phase (Part B). Subjects who received placebo in the blinded phase were assigned a NESP dose in the open-label phase according to their blinded-phase placebo volume. All subjects were followed for 8 weeks after the last dose of investigational product.

Duration of Treatment

Darbepoetin alfa was administered for a maximum of 24 weeks

5.3.2.5 Study Sites including enrollment:

This study was conducted internationally at 26 centers. One hundred sixty-one subjects were enrolled, and 156 received at least 1 dose of investigational product.

Best Available Copy

#### 5.3.2.6 Study populations:

The intent-to-treat analysis set consists of all subjects randomized in the study that received least one dose of study drug and was used for the safety analysis for both part A and part B.

The efficacy evaluable analysis set applicable only to part A consists of all properly consented subjects randomized in the study who meet the following criteria:

- Received at least 75% of the planned number of doses during Part A
- Did not receive  $\geq 30$  Gy of radiation to the whole pelvis during Part A
- Did not receive myeloablative chemotherapy or radiotherapy during Part A as conditioning therapy for stem cell transplant

Subjects who meet all of the above criteria were included in the efficacy analysis of Part A data according to the treatment actually received.

#### 5.3.2.7 Patient Disposition:

A total of 161 subjects were enrolled and randomized to NESP 9.0  $\mu\text{g}/\text{kg}$  ( $n = 31$ ), 12.0  $\mu\text{g}/\text{kg}$  ( $n = 32$ ), 15.0  $\mu\text{g}/\text{kg}$  ( $n = 33$ ), 18.0  $\mu\text{g}/\text{kg}$  ( $n = 33$ ), or placebo ( $n = 32$ ). Four subjects (3%) randomized to NESP and 1 subject (3%) randomized to placebo did not receive investigational product. Overall, 71% of subjects randomized to NESP and 75% of subjects randomized to placebo completed investigational product. The percentage of subjects randomized to NESP who completed treatment was similar between dose groups.

#### 5.3.2.8 Demographics, underlying disease and drug treatment:

One hundred fifty six subjects received at least 1 dose of investigational product and were included in the analysis: including 105 women and 51 men; Mean (SD) Age of 60.7 (12.2) years, and Ethnicity (Race): 139 white, 4 black, 3 Asian, 6 Hispanic, 4 others.

Overall, the treatment groups were comparable with respect to baseline demographic characteristics, and the baseline disease characteristics.

Table 5.3.2.8.1 copied from Amgen's submission summarizes the baseline disease characteristics in NESP and placebo groups. The most common primary tumor types were breast cancer (26% NESP, 32% placebo), gastrointestinal cancers (29% NESP, 16% placebo), and lung cancer (16% NESP, 26% placebo). Overall, 87% percent of subjects had stage III or IV disease, and 35% had hepatic metastases.

Table 5.3.2.8.1 Baseline Disease Characteristics for Study 980291-schedule 2 (copied from Amgen CSR Table 8.6).

Table 8-6. Baseline Disease Characteristics (ITT Analysis Set)

	Placebo (N=31)	NESP (µg/kg Q4W)				All NESP (N=125)	Total (N=156)
		9.0 (N=31)	12.0 (N=31)	15.0 (N=33)	18.0 (N=30)		
<b>Primary Tumor Type</b>							
Lung	6 (25)	3 (10)	6 (19)	7 (21)	4 (13)	20 (16)	28 (18)
Gastrointestinal	5 (16)	11 (35)	11 (35)	6 (18)	8 (27)	36 (29)	41 (26)
Gynecologic	5 (16)	2 (6)	2 (6)	5 (15)	4 (13)	13 (10)	18 (12)
Genitourinary	0 (0)	3 (10)	3 (10)	3 (9)	2 (7)	11 (9)	11 (7)
Breast	10 (32)	8 (26)	6 (19)	9 (27)	10 (33)	33 (26)	43 (28)
Other	3 (10)	4 (13)	3 (10)	3 (9)	2 (7)	12 (10)	15 (10)
<b>Disease Stage<sup>a</sup></b>							
I	2 (6)	2 (6)	1 (3)	2 (6)	2 (7)	7 (6)	9 (6)
II	2 (6)	1 (3)	1 (3)	1 (3)	3 (10)	6 (5)	8 (5)
III	3 (10)	5 (16)	3 (10)	6 (18)	7 (23)	21 (17)	24 (15)
IV	23 (74)	23 (74)	26 (84)	23 (70)	18 (60)	90 (72)	113 (72)
Unknown	1 (3)	0 (0)	0 (0)	1 (3)	0 (0)	1 (1)	2 (1)
<b>Subjects with Known Hepatic Metastases</b>							
No	22 (71)	16 (52)	16 (52)	20 (61)	18 (60)	70 (56)	92 (59)
Yes	9 (29)	13 (42)	11 (35)	11 (33)	11 (37)	46 (37)	55 (35)
Unknown	0 (0)	2 (6)	4 (13)	2 (6)	1 (3)	9 (7)	9 (6)

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<sup>a</sup> Disease stage as defined by investigator.

Program: /stat/nesp/0nc/nesp00291b/analysis/trao/statfiles/programs/tables/\_dix\_char.sas  
 Output: \_dix\_char\_01.rtf (Date Generated: 02APR04:09:39:10) Source Data: c\_dsp.sas7bdat

Table 8-6. Baseline Disease Characteristics (ITT Analysis Set)

	Placebo (N=31)	NESP (µg/kg Q4W)				All NESP (N=125)	Total (N=156)
		9.0 (N=31)	12.0 (N=31)	15.0 (N=33)	18.0 (N=30)		
<b>Subjects with Known Bone Marrow Involvement</b>							
No	16 (52)	18 (58)	17 (55)	16 (48)	15 (50)	66 (53)	82 (53)
Yes	3 (10)	3 (10)	4 (13)	2 (6)	3 (10)	12 (10)	15 (10)
Unknown	12 (39)	10 (32)	10 (32)	15 (45)	12 (40)	47 (38)	59 (38)
<b>ECOG</b>							
0	9 (29)	11 (35)	10 (32)	6 (24)	10 (33)	39 (31)	46 (31)
1	19 (61)	19 (61)	16 (52)	21 (64)	17 (57)	73 (59)	92 (59)
2	3 (10)	1 (3)	5 (16)	4 (12)	3 (10)	13 (10)	16 (10)
<b>Tumor Status (Response)</b>							
Unknown	5 (16)	9 (29)	8 (26)	13 (39)	9 (30)	39 (31)	44 (28)
Complete	1 (3)	3 (10)	1 (3)	1 (3)	1 (3)	6 (5)	7 (4)
Partial	4 (13)	2 (6)	0 (0)	2 (6)	2 (7)	6 (5)	10 (6)
Progression	9 (29)	10 (32)	11 (35)	7 (21)	4 (13)	32 (26)	41 (26)
Not Evaluated	8 (25)	0 (0)	4 (13)	5 (15)	9 (30)	18 (14)	26 (17)
Stable	4 (13)	7 (23)	7 (23)	5 (15)	5 (17)	24 (19)	28 (18)

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<sup>a</sup> Disease stage as defined by investigator.

Program: /stat/nesp/0nc/nesp00291b/analysis/trao/statfiles/programs/tables/\_dix\_char.sas  
 Output: \_dix\_char\_01.rtf (Date Generated: 02APR04:09:39:10) Source Data: c\_dsp.sas7bdat

### 5.3.2.9 Outcome efficacy (exposure/response)

The NESP dose of 15.0 µg/kg every 4 weeks fulfilled the protocol –specified efficacy criterion for the CED.

#### 5.3.2.10 Outcome of Safety Assessments:

In the randomized, double-blind, placebo-controlled phase of the study, the safety profile of NESP appears to be consistent with that expected for a patient population with cancer receiving chemotherapy, with no apparent evidence of a dose-response effect.

Deaths on study (13 of 125 subjects receiving NESP [10%] and 0 of 31 subjects receiving placebo) generally were attributed by the investigators to the underlying disease.

Serious adverse events, reported in 30% of subjects receiving NESP and 23% of subjects receiving placebo, were primarily attributed by the investigators to be associated with toxicities of chemotherapy and disease complications. Few subjects (5% NESP, 6% placebo) withdrew from the study because of adverse events, mostly attributed as a result of disease progression.

The most frequently reported adverse events in both treatment groups were gastrointestinal and constitutional symptoms.

No subject experienced a DLT. The incidence of adverse events of historical interest (i.e., thrombotic events, hypertension, and convulsions) was higher in the NESP arm compared with the placebo arm (6% NESP versus 0% placebo).

No antibody formation due to NESP administration was observed.

In general, the safety results from the open-label phase of the study were consistent with the results of the double-blind, placebo-controlled phase.

#### 5.3.2.11 Discussion of Findings/Conclusions

##### Amgen's Conclusions:

The safety profile of NESP in this study was consistent with the underlying disease of this population and the toxicities associated with chemotherapy administration. The dose of 15.0 µg/kg was selected as the CED because it met all of the prospectively defined criteria. Subcutaneous administration of NESP at doses ranging from 9.0 to 18.0 µg/kg every 4 weeks appears to be well tolerated, with a safety profile generally comparable to that of placebo. The difference in the incidence of deaths and thrombotic events between treatment groups may have been the result of an unusually low rate of these events in subjects receiving placebo relative to previous clinical studies of NESP. In addition, NESP appears to be well tolerated even after long-term use, as demonstrated in the open-label phase of the study.

##### *Reviewer's comments:*

*Study 980291 schedule-2 is a dose finding study conducted to evaluate the safety of Aranesp given subcutaneously every 3 weeks and to identify the protocol defined clinical effective dose*

*(CED), i.e., The CED was defined as the dose at which  $\geq 50\%$  of subjects achieved a hemoglobin response;  $\leq 20\%$  of subjects in the safety analysis set had clinical sequelae associated with a hemoglobin concentration that exceeded the highest acceptable level ( $> 14.0$  g/dL for women,  $> 15.0$  g/dL for men); and  $\leq 20\%$  of subjects in the safety analysis set experienced a DLT.*

*The patient population is heterogeneous in disease characteristics and in concomitant chemotherapy regimen.*

*No approved dosage regimen of Aranesp, 2.25 ug/kg, SC, QW or 500 ug, SC, Q3W was used in the study.*

*The protocol-defined primary efficacy endpoint, i.e., clinical effective dose (CED), is not valid clinically meaningful endpoints for regulatory purpose.*

*Efficacy and Safety information is limited to data collected during the first 12 weeks of part A blinded phase study because subjects receiving placebo in Part A were allowed to cross over to receive Aranesp in open-labeled optional Part B study phase.*

*The efficacy and safety outcomes from study 980291-schedule 2 have no impact on the current labeling of Aranesp.*

*The results of study 980291-schedule 1 are of limited value to address the pertinent PAS supplement issues on hemoglobin initiation level (FDA Item 3), maximum hemoglobin level (FDA Item 4), and discontinuation of ESA therapy post-chemotherapy (FDA Item 5).*

### 5.3.3 Study 990114

#### 5.3.3.1 Study Title, Phase, and Purpose

Title “A Multi-centre, Blinded, Placebo-controlled, Randomized, Dose-finding Study of Novel Erythropoiesis Stimulating Protein Administered by Subcutaneous Injection for the Treatment of in Subjects With Lymphoproliferative Malignancies Receiving Chemotherapy”

Study Phase: 2

Study Objectives:

The primary objective of this study was to assess the relationship between the dose of NESP and hemoglobin response.

Secondary objectives were to investigate the effect of NESP on red blood cell (RBC) transfusions and hemoglobin concentrations; to assess the feasibility, timing, and validity of the health-related quality-of-life (HRQOL) surveys; and to investigate the safety of NESP in this setting.

#### 5.3.3.2 Study Design, including dates conducted

This was a randomized, double-blind, placebo-controlled, dose-finding study to assess the safety and hemoglobin effects of various dosing regimen of darbepoetin alfa (1.0, 2.25, or 4.5 µg/kg) administered subcutaneously every week in patients with anemia and lymphoproliferative malignancies receiving multi-cycle chemotherapy. The randomization was stratified to balance the treatment groups with respect to malignancy type (myeloma versus lymphoma).

#### Study Period:

The first written informed consent was obtained on 22 November 1999 and the last subject completed the end-of-study assessments on 18 July 2000.

#### 5.3.3.3 Inclusion, exclusion criteria, study procedures, timelines

##### Inclusion:

- legal age for consent
- lymphoproliferative malignancy (multiple myeloma or lymphoma)
- hemoglobin  $\leq$  11.0 g/dL) predominantly because of cancer or chemotherapy
- adequate liver and renal function
- receiving or scheduled to receive chemotherapy for at least 12 weeks
- life expectancy of  $\geq$  6 months
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

##### Exclusion:

- high grade non-Hodgkin's lymphoma
- receiving myeloablative chemotherapy or radiotherapy for transplantation or chemotherapy regimens containing investigational agents
- iron deficient
- prior whole pelvis radiation therapy
- received rHuEPO therapy within 8 weeks of randomization

##### Study procedures:

Eligible subjects were randomized in a 1:2:2:1 ratio to receive NESP at doses of 1.0, 2.25, or 4.5 µg/kg or a matched volume of placebo administered by subcutaneous (SC) injection once weekly for 12 weeks. The 4 dose groups (3 NESP and pooled placebo) were run in parallel.

##### Primary Efficacy analysis plan

The primary efficacy endpoint was the time to sustained hemoglobin response, which provided estimates of the proportion of subjects achieving a sustained hemoglobin response by the end of the treatment phase in each group. A sustained hemoglobin response was defined as an increase in hemoglobin of  $\geq$  2.0 g/dL from baseline that was sustained for at least 28 days or until the end of the treatment phase (in the absence of RBC transfusion during the period of sustained

response and the preceding 28 days). The period of sustained hemoglobin response must have included  $\geq 3$  hemoglobin measurements.

#### Secondary efficacy analysis plan

- hemoglobin response (defined as an increase in hemoglobin of  $\geq 2.0$  g/dL from baseline in the absence of RBC transfusion within the preceding 28 days)
- sustained hemoglobin correction (defined as a hemoglobin concentration of  $\geq 12.0$  g/dL that was sustained for at least 28 days or until the end of the treatment phase in the absence of RBC transfusion during the period of sustained correction and the preceding 28 days).
- hemoglobin correction (defined as a hemoglobin concentration of  $\geq 12.0$  g/dL in the absence of RBC transfusion during the preceding 28 days) change in hemoglobin from baseline to the end of the treatment phase
- RBC transfusions during the treatment phase
- number of standard units of RBCs transfused and number of days with RBC transfusions

#### Safety endpoints

- incidence and severity of adverse events
- excess rise in hemoglobin
- maximum hemoglobin concentration
- maximum increase in hemoglobin
- concomitant medication use
- laboratory variables and vital signs
- number of days hospitalized
- antibody formation to NESP

#### Statistical Methods:

Descriptive statistics were calculated for all endpoints by treatment group. For continuous variables, the mean, standard deviation, median, quartiles, minimum, and maximum were calculated. For categorical variables, the number and proportion of subjects in each category were calculated. Two-sided 95% confidence intervals (CIs) were calculated for point estimates. The time to sustained hemoglobin response was summarized by plotting the Kaplan-Meier curve for subjects in each treatment group, and the proportions of subjects achieving a sustained hemoglobin response at the end of the treatment phase were calculated with approximate 95% CIs. Logistic regression analyses were used to assess the dose-response relationship and the effect of treatment after adjusting for covariates. Hemoglobin response, sustained hemoglobin correction, hemoglobin correction, and RBC transfusions during the treatment phase and from week 5 and week 9 to the end of the treatment phase were analyzed in the same manner. Descriptive statistics were summarized for the change in hemoglobin over the 12-week treatment phase. Analysis of covariance was used to assess the dose-response relationship and the effect of treatment after adjusting for covariates. Descriptive statistics were calculated for the number of units of RBCs transfused, the number of days with RBC transfusions, and the outcomes of the HRQOL assessments at the protocol-specified time points.

#### 5.3.3.4 Treatments and ancillary management

Duration of Treatment: NESP was administered for a maximum of 12 weeks.

#### 5.3.3.5 Study Sites including enrollment:

Sixty-six patients were enrolled at 15 study centers in Europe and Australia.

#### 5.3.3.6 Study populations:

The primary statistical analysis of efficacy data was conducted using the intent-to-treat (ITT) population. All randomized subjects who received at least one dose study drug were included in the safety analyses set. Sensitivity analyses were performed using the efficacy evaluable population (per protocol set) to evaluate the robustness of the study results.

#### 5.3.3.7 Patient Disposition

Of 66 enrolled subjects, 63( 95%) subjects completed the study; two subjects in the darbepoetin alfa arm did not complete the study due to delays in chemotherapy administration, and one subject in the placebo arm withdrew consent (Table 5.3.3.7.1)

Table 5.3.3.7.1 Subject Disposition in study 990114 (copied from Amgen’s submission)

**Table 8-1. Subject Disposition  
(Screened Subjects)**

	Placebo	All NESP	Total
Subjects Screened			78
Subjects Randomized	11	55	66
Subjects Receiving Study Drug	11 (100%)	55 (100%)	66 (100%)
Subjects Completing Study	10 (91%)	53 (96%)	63 (95%)
Subjects Not Completing Study	1 (9%)	2 (4%)	3 (5%)
Ineligibility Determined	0 (0%)	0 (0%)	0 (0%)
Protocol Violation	0 (0%)	0 (0%)	0 (0%)
Subject Noncompliance	0 (0%)	0 (0%)	0 (0%)
Adverse Event*	0 (0%)	0 (0%)	0 (0%)
Consent Withdrawn	1 (9%)	0 (0%)	1 (2%)
Disease Progression	0 (0%)	0 (0%)	0 (0%)
Administrative Decision	0 (0%)	0 (0%)	0 (0%)
Lost to Follow-up	0 (0%)	0 (0%)	0 (0%)
Death	0 (0%)	0 (0%)	0 (0%)
Study Specific Reason	0 (0%)	2 (4%)	2 (3%)
Other	0 (0%)	0 (0%)	0 (0%)

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Note: Percentages based on subjects randomized.

\* Excluding Disease Progression and Death

Program: /stat/nesp/onc/nesp990114/analysis/final/statfiles/programs/tables/t\_disp.sas  
 Output: t14-2\_t\_disp.rtf (Date Generated: 09FEB2001:21:58)

#### 5.3.3.8 Demographics, underlying disease and drug treatment

Sixty-six patients were enrolled into the study, including 37 men and 29 women with a median age of 67 (20-84) years, and ethnicity of 63 White, 3 Asian (Table 5.3.3.8.1). Baseline disease characteristics are summarized in Table 5.3.3.8.2. Apparent imbalances between subjects enrolled in the Aranesp and placebo arms were observed as follows: higher percentage of subjects were women in the placebo arm than in the Aranesp arm (82% versus 36%); median age of subjects in the placebo arm was 63 years compared to 68 years in the Aranesp arm; higher percentage of subjects in the placebo arm had Hodgkin's disease than in the Aranesp arm (27% versus 15%); higher percentage of subjects in the placebo arm had ECOG status of 0 than in the Aranesp arm (45% versus 29%); and higher percentage of subjects with Waldenstrom's macroglobulinaemia in the Aranesp arm than in the placebo arm (20% versus 0).

Table 5.3.3.8.1 Demographic in study 990114

Table 8-4. Subject Demography by Dose of Study Drug (ITT Population)

	Placebo	NESP Dose (µg/kg/wk)			All NESP	Total
		1.0	2.25	4.5		
Number of Subjects	11	11	22	22	55	66
Sex						
Men	2 (18%)	7 (64%)	14 (64%)	14 (64%)	35 (64%)	37 (56%)
Women	9 (82%)	4 (36%)	8 (36%)	8 (36%)	20 (36%)	29 (44%)
Race						
Asian	1 (9%)	1 (9%)	1 (5%)	0 (0%)	2 (4%)	3 (5%)
White	10 (91%)	10 (91%)	21 (95%)	22 (100%)	53 (96%)	63 (95%)
Age (years)*						
Subjects < 65 years	8 (55%)	6 (55%)	5 (23%)	7 (32%)	18 (33%)	24 (36%)
Subjects ≥ 65 years	5 (45%)	5 (45%)	17 (77%)	15 (68%)	37 (67%)	42 (64%)
Subjects ≥ 75 years	3 (27%)	3 (27%)	5 (23%)	3 (14%)	11 (20%)	14 (21%)
n	11	11	22	22	55	66
Mean	60.1	61.2	66.7	68.3	68.2	65.2
SD	17.5	16.2	15.0	8.2	13.0	13.9
Median	63.0	64.0	69.0	69.5	68.0	67.0
Q1, Q3	53.0, 77.0	53.0, 77.0	66.0, 74.0	63.0, 72.0	63.0, 74.0	63.0, 74.0
Min, Max	25, 80	26, 80	20, 84	52, 84	20, 84	20, 84

\* These categories are not mutually exclusive.

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Program: /statistics/nesp/nc/nesp00114/analysis/na/tables/programs/tables/demog\_by\_dose.sas  
 Output: t14-8\_L\_demog\_by\_dose\_it.rtf (Date Generated: 09FEB2007:22:01)

Table 5.3.3.8.2 Baseline disease characterizes in study 990114

Table 8-6. Baseline Disease Characteristics by Dose of Study Drug (ITT Population)

	Placebo	NESP Dose (µg/kg/wk)			All NESP	Total
		1.0	2.25	4.5		
Number of Subjects	11	11	22	22	55	66
Primary Tumor Type						
Chronic Lymphocytic Leukemia	2 (18%)	2 (18%)	1 (5%)	7 (32%)	10 (18%)	12 (18%)
Hodgkin's disease	3 (27%)	3 (27%)	4 (18%)	1 (5%)	8 (15%)	11 (17%)
Multiple Myeloma	3 (27%)	3 (27%)	6 (27%)	6 (27%)	15 (27%)	18 (27%)
Non-Hodgkin's lymphoma	3 (27%)	2 (18%)	5 (23%)	4 (18%)	11 (20%)	14 (21%)
Waldenstrom's Macroglobulinaemia	0 (0%)	1 (9%)	6 (27%)	4 (18%)	11 (20%)	11 (17%)
Disease Stage						
I	1 (9%)	0 (0%)	1 (5%)	0 (0%)	1 (2%)	2 (3%)
II	3 (27%)	0 (0%)	4 (18%)	5 (23%)	9 (16%)	12 (18%)
III	4 (36%)	5 (45%)	8 (27%)	7 (32%)	18 (33%)	22 (33%)
IV	3 (27%)	5 (45%)	5 (23%)	6 (27%)	18 (29%)	19 (29%)
Unknown	0 (0%)	1 (9%)	8 (27%)	4 (18%)	11 (20%)	11 (17%)
Subjects with Known Hepatic Metastases	0 (0%)	0 (0%)	1 (5%)	0 (0%)	1 (2%)	1 (2%)
Subjects with Known Bone Marrow Involvement	5 (45%)	5 (45%)	12 (55%)	18 (82%)	35 (64%)	40 (61%)
ECOG						
0	5 (45%)	1 (9%)	7 (32%)	8 (36%)	16 (29%)	21 (32%)
1	6 (55%)	7 (64%)	13 (59%)	12 (55%)	32 (58%)	38 (58%)
2	0 (0%)	3 (27%)	2 (9%)	2 (9%)	7 (13%)	7 (11%)

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Program: /statistics/nesp/nc/nesp00114/analysis/na/tables/programs/tables/ds\_char2\_by\_dose.sas  
 Output: L\_ds\_char2\_by\_dose\_it.rtf (Date Generated: 09FEB2007:22:04)

Sixty-six subjects were randomized to receive NESP 1.0 µg/kg (n = 11), 2.25 µg/kg (n = 22), 4.5 µg/kg (n = 22), or placebo (n = 11).

5.3.3.9 Outcome efficacy (exposure/response)

In the ITT population, a significantly higher proportion of all subjects receiving NESP combined (41%; 95% CI: 27%, 54%) achieved a sustained hemoglobin response relative to subjects receiving placebo (0%; 95% CI: not estimable) ( $p = 0.002$ ).

No subject in the placebo group achieved a sustained response, whereas 45% (95% CI: 16%, 75%) of subjects in the NESP 1.0- $\mu\text{g}/\text{kg}$  group, 23% (95% CI: 5%, 40%) in the 2.25- $\mu\text{g}/\text{kg}$  group, and 57% (95% CI: 36%, 79%) in the 4.5- $\mu\text{g}/\text{kg}$  group met the sustained response criteria.

The subject incidence of transfusions from week 5 to the end of the treatment phase was lower in the NESP dose groups than in the placebo group.

No statistically significant linear dose effects were observed.

#### 5.3.3.10 Outcome of safety assessments

Fifty-two of 55 subjects (95%) receiving NESP and 10 of 11 subjects (91%) receiving placebo experienced at least 1 adverse event. Serious adverse events were reported for 15 subjects (27%) receiving NESP and 6 subjects (55%) receiving placebo. No relationship was evident between NESP dose and adverse event incidence, severity, or seriousness. No deaths or adverse events leading to withdrawal occurred during the study. Changes in laboratory variables and vital signs were similar between the NESP and placebo groups, and no serum samples were reactive in the anti-NESP antibody screening assay, indicating that no anti-NESP antibodies were detected.

#### 5.3.3.11 Discussion of Findings/Conclusions

##### Amgen's Conclusions:

Aranesp, administered at doses of 1.0, 2.25, and 4.5  $\mu\text{g}/\text{kg}/\text{week}$  in subjects with lymphoproliferative malignancies, is associated with significantly greater effects on hemoglobin than placebo, as measured by the proportion of subjects achieving sustained hemoglobin response, hemoglobin response, and hemoglobin correction. NESP appears to be well tolerated at the doses administered and, despite the limited subject numbers in this study, does not appear to be associated with any safety concerns in this treatment setting.

##### *Reviewer's comments:*

*Study 990114 was a phase 2, dose finding study conducted to evaluate the relationship of Aranesp given subcutaneously at varying doses ( 1.0 ug/kg/wk, 2.25 ug/kg/wk, and 4.5 ug/kg/wk) and hemoglobin response, defined as an increase in hemoglobin of  $\geq 2.0$  g/dL from baseline that was sustained for at least 28 days or until the end of the treatment phase (in the absence of RBC transfusion during the period of sustained response and the preceding 28 days) in patients with lymphoproliferative malignancies.*

*The patient population is heterogeneous in disease characteristics and in concomitant chemotherapy regimen. Imbalances between two study arms were observed in demographics and baseline disease characteristics.*

*Study 990114 enrolled a total of 66 patients with 55 patients randomized to receive various Aranesp regimens (1.0 ug/kg/wk, 2.25 ug/kg/wk, and 4.5 ug/kg/wk) and 11 patients randomized to placebo. The study results based on such a small sample size have very limited value to draw any generalized conclusion, even though the observed hemoglobin response among various Aranesp dose regimens compared to placebo arm indicated that the dosage regimen was perhaps not critical.*

*Only one of the approved dosage regimen of Aranesp, 2.25 ug/kg, SC, QW was tested in 22 enrolled subjects in the study. .*

*The efficacy and safety outcomes from study 990114 have no impact on the current labeling of Aranesp.*

*The results of study 990114 are of limited value to address the pertinent PAS supplement issues on hemoglobin initiation level (FDA Item 3), maximum hemoglobin level (FDA Item 4), and discontinuation of ESA therapy post-chemotherapy (FDA Item 5).*

#### 5.3.4 Study 980297

##### 5.3.4.1 Study Title, Phase and Purpose

Title: A Double-blind, Placebo-controlled, Study of Novel Erythropoiesis Stimulating Protein (NESP) for the Treatment of Anemia in Lung Cancer Subjects Receiving Multicycle Platinum-containing Chemotherapy

Study Phase: 3

##### Study Objectives:

The primary objective of this study was to compare the efficacy of NESP with placebo in the treatment of anemia in subjects with lung cancer who were receiving multicycle, platinum containing chemotherapy by assessing the proportion of subjects who received a red blood cell (RBC) transfusion from week 5 to the end of the treatment phase (EOTP).

Secondary objectives were to compare the effectiveness of NESP with placebo, based on the proportion of subjects achieving a hemoglobin response ( $\geq 2.0$ -g/dL increase from baseline hemoglobin in the absence of RBC transfusion in the preceding 28 days), hemoglobin correction (hemoglobin  $\geq 12.0$  g/dL in the absence of RBC transfusion in the preceding 28 days), the timing and quantity of RBC transfusions, and quality-of-life survey (QOLS) scores. In addition, the safety of NESP in this treatment setting was assessed.

#### 5.3.4.2 Study Design:

This was a multicenter, randomized, double-blind, placebo-controlled pivotal study to evaluate the safety and efficacy of darbepoetin alfa versus placebo in reducing the proportion of patients who received RBC transfusion in patients with anemia and lung cancer receiving motorcycles of platinum-containing chemotherapy. Approximately 310 subjects were planned (approximately 155 subjects in each treatment arm).

Study Period: 14 September 1999 to 08 November 2000

#### 5.3.4.3 Inclusion/exclusion criteria, study procedures, timelines

##### Inclusion:

- Subjects with lung cancer (either small-cell lung cancer [SCLC] or non-smallcell lung cancer[NSCLC])
- 12 additional planned weeks of platinum-containing cyclic chemotherapy
- anemia (hemoglobin  $\leq$ 11.0 g/dL) predominantly due to the cancer and/or chemotherapy
- $\geq$ 6-month life expectancy
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
- Adequate liver and renal function

##### Exclusions:

- iron deficient (transferrin saturation < 15% and serum ferritin < 10  $\mu$ g/L)
- received erythropoietin therapy within 8 weeks
- > 2 RBC transfusions within 4 weeks or any RBC transfusion within 2 weeks before randomization
- known primary hematologic disorders that could cause anemia and central nervous system, cardiac, or inflammatory diseases

##### Efficacy endpoints

The primary efficacy endpoint was the Kaplan-Meier estimated proportion of subjects who received a RBC transfusion from week 5 to the end-of-treatment period (EOTP).

##### Secondary Endpoints:

- time to the first RBC transfusion from week 5 to the EOTP
- proportion of subjects receiving a RBC transfusion from week 1 to the EOTP and weeks 1 to 4
- number of standard units of RBCs transfused from week 5 to the EOTP
- number of days with RBC transfusions from week 5 to the EOTP
- proportion of subjects achieving a hemoglobin response ( $\geq$ 2.0 g/dL increase in hemoglobin from baseline in the absence of a RBC transfusion in the preceding 28 days)
- time to hemoglobin response after the initiation of treatment

- proportion of subjects achieving hemoglobin correction (hemoglobin  $\geq 12.0$  g/dL in the absence of RBC transfusion in the preceding 28 days)
- time to hemoglobin correction after the initiation of treatment
- change in hemoglobin from baseline to the EOTP

#### Health-related Quality of Life (HRQOL)

change from baseline to the EOTP on the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) scale score

#### Safety Endpoints

- exposure to study drug
- incidence of death
- incidence and severity of adverse events
- proportion of subjects with hemoglobin concentrations  $> 15.0$  g/dL (for men) or  $> 14.0$  g/dL (for women) at any time during the study in the presence and absence of RBC transfusions
- maximum increase in hemoglobin (with or without RBC transfusions) during the preceding 28 days

#### Study procedures:

After a screening period of up to 14 days, subjects with lung cancer and anemia (hemoglobin  $\leq 11.0$  g/dL) were randomized to receive subcutaneous (SC) injections of Aranesp at a starting dose of 2.25  $\mu\text{g}/\text{kg}/\text{week}$  or placebo for 12 weeks.

After 6 weeks of treatment, the dose of study drug could be increased to 4.5  $\mu\text{g}/\text{kg}/\text{week}$  for subjects who had increases in hemoglobin of  $\leq 1.0$  g/dL from baseline.

Subjects were to complete a 4-week follow-up evaluation after the last dose of study drug.

Tumor status and survival information are being collected during an open-label, long-term follow-up period for a minimum of 1 year after the EOTP for the last ongoing subject.

#### Statistical Analysis Plan:

All randomized subjects who received at least 1 dose of study drug and completed weeks 1 to 4 were included in the efficacy analysis set for the analysis of the primary endpoint, and are referred to as the primary analysis set.

Randomized subjects who received at least 1 dose of study drug were included in the intent-to-treat (ITT) efficacy analysis set for all other efficacy endpoints.

Summary statistics were provided for primary and secondary efficacy and safety endpoints. For continuous variables, the mean, standard deviation (SD) (standard error [SE] for comparative variables), median, quartiles (25th and 75th percentiles), minimum, and maximum were calculated. For discrete data, the frequency and percent distributions were calculated.

The primary analysis of efficacy was based on the proportion of subjects receiving a RBC transfusion from week 5 to the EOTP and was estimated using the Kaplan-Meier method. Subjects who withdrew from the study for reasons other than death or disease progression were considered transfused at the end of their treatment phase.

Unless otherwise specified, analyses for the primary and secondary efficacy endpoints were adjusted for tumor type (SCLC vs. NSCLC) and geographic region (Central and Eastern Europe [CEE] vs. the rest of the world [ROW]).

Time to first RBC transfusion during week 5 to the EOTP, time to hemoglobin response, and time to hemoglobin correction were analyzed using the Kaplan-Meier method. Cox-proportional hazards regression was used for the comparison of treatment groups, and the hazards ratio for treatment was presented with 95% confidence intervals.

The changes from baseline for the FACT-F score and other subscale scores were analyzed using analysis of covariance.

#### 5.3.4.3 Study Sites including enrollment

This was a multicenter study conducted at 70 sites in Australia, Canada, and Europe. Three hundred twenty patients were enrolled and randomized in this study (161 to receive placebo and 159 to receive Aranesp).

#### 5.3.4.4 Treatments and ancillary management

Subjects with lung cancer and anemia (hemoglobin  $\leq$  11.0 g/dL) who were scheduled to receive multicycle platinum-containing chemotherapy were enrolled and randomized to receive subcutaneous (SC) injections of NESP at a starting dose of 2.25  $\mu$ g/kg/week or placebo for 12 weeks. After 6 weeks of treatment, the dose of study drug could be increased to 4.5  $\mu$ g/kg/week for subjects who had increases in hemoglobin of  $<$  1.0 g/dL from baseline. Subjects were to complete a 4-week follow-up evaluation after the last dose of study drug.

#### 5.3.4.5 Study populations:

All randomized subjects who received at least 1 dose of study drug and completed weeks 1 to 4 were included in the efficacy analysis set for the analysis of the primary endpoint, and are referred to as the primary analysis set.

Randomized subjects who received at least 1 dose of study drug were included in the intent-to-treat (ITT) analysis set for safety analyses and for secondary efficacy endpoint analyses.

Two hundred ninety-seven subjects (93%) were included in the primary analysis set and 314 (98%) were included in the ITT analysis set.

#### 5.3.4.6 Patient Disposition

Three hundred twenty subjects were randomized to receive NESP 2.25 µg/kg /week (n = 159) or placebo (n = 161). Six subjects (2%) withdrew from the study before receiving study drug and 219 subjects (110 NESP, 109 placebos) completed the study (Table 5.3.4.6.1, copied from Amgen’s submission) Similar percentage of subjects did not complete the study between the Aranesp group and the placebo group (32%). The most common reasons for early study discontinuation in both groups are death, disease progression and discontinued chemotherapy.

Table 5.3.4.6.1 Subject Disposition for study 980297

**Table 8-2. Subject Disposition  
(Screened Subjects)**

	Placebo	NESP 2.25 (µg/kg/wk)	Total
Subjects Screened			413
Subjects Randomized	161	159	320
Subjects Receiving Study Drug	158 (98%)	156 (98%)	314 (98%)
Subjects Completing Study	109 (68%)	110 (69%)	219 (68%)
Subjects Not Completing Study	52 (32%)	49 (31%)	101 (32%)
Adverse Event <sup>a</sup>	5 (3%)	2 (1%)	7 (2%)
Consent Withdrawn	5 (3%)	5 (3%)	10 (3%)
Disease Progression	9 (6%)	9 (6%)	18 (6%)
Administrative Decision	2 (1%)	2 (1%)	4 (1%)
Lost to Follow-up	3 (2%)	6 (4%)	9 (3%)
Death	19 (12%)	14 (9%)	33 (10%)
Study Specific Reason	0 (0%)	0 (0%)	0 (0%)
Chemotherapy Delayed	1 (1%)	3 (2%)	4 (1%)
Chemotherapy Discontinued	7 (4%)	7 (4%)	14 (4%)
Other	1 (1%)	1 (1%)	2 (1%)

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Note: Percentages based on subjects randomized.

<sup>a</sup> Excluding Disease Progression and Death

Program: /stat/nesp/onc/nesp980297/analysis/final/statfiles/programs/tables/t\_disp.sas  
 Output: t\_disp.rtf (Date Generated: 19MAY2001:01:18)

#### 5.3.4.7 Demographics, underlying disease and drug treatments

A total of 320 patients with non-small cell lung cancer and small cell lung cancer receiving multi-cycle chemotherapy were randomized to receive placebo (n=161) and darbepoetin alfa (n=159), including 232 men and 88 women with a mean (SD) age of 61.5 (9.0) years, and a ethnicity of 100% of white patients (Table 5.3.4.7.1, copied from Amgen’s submission).

All subjects had lung cancer: 222 subjects (71%) had NSCLC and 92 subjects (29%) had SCLC. Most subjects had extensive SCLC (18%) or stage III/IV NSCLC (69%). In general, baseline disease characteristics are similar between the Aranesp group and the placebo groups (Table 5.3.4.7.2, copied from Amgen’s submission).

Table 5.3.4.7.1 Demographics for study 980297 (copied from Amgen's submission).

**Table 8-5. Subject Demography  
 (ITT Analysis Set)**

	Placebo	NESP 2.25 (µg/kg/wk)	Total
Number of Subjects	158	156	314
Sex			
Men	116 (73%)	111 (71%)	227 (72%)
Women	42 (27%)	45 (29%)	87 (28%)
Race			
White	158 (100%)	156 (100%)	314 (100%)
Age (years) <sup>a</sup>			
Subjects < 65 years	92 (58%)	97 (62%)	189 (60%)
Subjects ≥ 65 years	66 (42%)	59 (38%)	125 (40%)
Subjects ≥ 75 years	8 (5%)	12 (8%)	20 (6%)
n	158	156	314
Mean	61.3	61.6	61.4
SD	8.8	9.2	8.9
Median	61.0	62.5	62.0
Q1, Q3	56.0, 68.0	55.0, 69.0	55.0, 68.0
Min, Max	36, 79	39, 80	36, 80

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<sup>a</sup> These categories are not mutually exclusive.

Program: /statistics/nesp/onc/nesp980297/analysis/final/statfiles/programs/tables/t\_demog.sas  
 Output: t\_demog\_itf.rtf (Date Generated: 19MAY2001:01:19)

Table 5.3.4.7.2 Baseline Disease Characteristics for study 980297 (copied from Amgen's submission)

**Table 8-6. Baseline Disease Characteristics  
 (ITT Analysis Set)**

	Placebo	NESP 2.25 (µg/kg/week)	Total
Number of Subjects	158	156	314
<b>Type of Tumor</b>			
Small Cell Lung Cancer			
Limited Disease	44 (28%)	48 (31%)	92 (29%)
Extensive Disease	19 (12%)	16 (10%)	35 (11%)
Non-Small Cell Lung Cancer			
Stage I	25 (16%)	32 (21%)	57 (18%)
Stage II	114 (72%)	108 (69%)	222 (71%)
Stage III	2 (1%)	2 (1%)	4 (1%)
Stage IV	2 (1%)	2 (1%)	4 (1%)
Stage III	48 (30%)	29 (19%)	77 (25%)
Stage IV	62 (39%)	75 (48%)	137 (44%)
Subjects with Hepatic Metastases	31 (20%)	31 (20%)	62 (20%)
Subjects with Bone Marrow Involvement	6 (4%)	10 (6%)	16 (5%)
<b>ECOG Performance Status</b>			
0	23 (15%)	22 (14%)	45 (14%)
1	98 (62%)	109 (70%)	207 (66%)
2	37 (23%)	24 (15%)	61 (19%)
>2	0 (0%)	1 (1%)	1 (0%)

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Program: /statistics/nesp/onc/nesp980297/analysis/final/statfiles/programs/tables/t\_dis\_char.sas  
 Output: t\_dis\_char\_itt.rtf (Date Generated: 19MAY2001:01:18)

### 5.3.4.9 Outcome Efficacy

#### Amgen's analysis of efficacy

NESP reduced the Kaplan-Meier proportion of subjects receiving RBC transfusions from week 5 to the EOTP from 51% in the placebo group to 21% in the NESP group. This weighted (by tumor type and region strata) difference of 24% (95% CI: 13, 35) is highly significant (p < 0.001).

This finding was consistently demonstrated regardless of methods used to account for subject withdrawals (different censoring definitions or analysis sets analyzed) or statistical analysis methods (Kaplan-Meier, crude proportions, Cox-proportional hazards, and logistic regression).

Independent effects of tumor type, region, and baseline hemoglobin were observed. However, despite these effects, NESP significantly reduced the proportion of subjects requiring a RBC transfusion.

NESP also reduced the mean (SE) number of standard units of RBCs transfused: NESP 0.67 (0.14) units, placebo 1.92 (0.27) units. The mean (SE) number of days a transfusion was required was also reduced: NESP 0.3 (0.1) days, placebo 0.9 (0.1) days a transfusion was required.

NESP demonstrated a statistically significant and clinically meaningful increase in the proportion of subjects achieving hemoglobin response, hemoglobin correction, and the change in hemoglobin from baseline.

HRQOL Results: For the primary HRQOL endpoint, change in FACT-F score from baseline, the mean change score at the EOTP in the NESP group increased by 0.8 points (95% CI: -1.0, 2.5) while the mean change score at the EOTP in the placebo group decreased by 0.6 points (95% CI: -2.5, 1.3) (p = 0.286). The mean difference between treatment groups was not considered statistically significant (p = 0.286)

FDA’s analysis of efficacy abstracted from FDA clinical review of study 980297 submitted for the initial approval of Aranesp in oncology setting (STN BL 103951.5001) is presented as follows:

Primary endpoint: The Kaplan-Meier proportion of subjects transfused study weeks 5 to 12 in the placebo arm was 51% in contrast to 21 % in the Aranesp arm. 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 on page 29 this Section)) which only utilized data from patients who had completed the first 4 weeks of study. The same analysis was also performed as a secondary endpoint 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 who were transfused 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 (see table below) likewise did not affect results substantially (see table below) .

EFFICACY ENDPOINT OF PROPORTION OF SUBJECTS  
 TRANSFUSED USING PRIMARY ANALYSIS DATASET

		Placebo arm	NESP arm
		N= 149*	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 evaluated subjects had to have completed the first 4 weeks of study and so the numbers used are less than the number of subjects randomized. See patient disposition.

EFFICACY ENDPOINT OF PROPORTION OF SUBJECTS TRANSFUSED  
 USING ITT ANALYSIS DATASET

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

5.3.4.10 Outcome of Safety Assessments

Twenty-two subjects (15%) in the NESP group and 19 subjects (12%) in the placebo group died during the study. No deaths were considered treatment related by the investigators and the most common cause of death was attributed to disease progression.

Serious adverse events were reported for 60 subjects (39%) receiving NESP and 58 subjects (36%) receiving placebo.

Of note, during the review of study 980297 submitted for the initial approval of Aranesp in the oncology setting (STN BL 103951.5001), the FDA clinical reviewer obtained similar information on the death, serious adverse events and common adverse events to that described by Amgen.

5.3.4.11 Discussion of Findings/Conclusions

Amgen's Conclusion:

Aranesp 2.25 µg/kg administered SC once weekly to subjects with lung cancer receiving platinum containing chemotherapy significantly decreased the proportion of subjects requiring a RBC transfusion and significantly increased the proportion of subjects achieving a hemoglobin response and a hemoglobin correction compared with placebo.

*Reviewer comments:*

*Study 980297 was previously reviewed as the pivotal study submitted by Amgen to support the initial approval of Aranesp oncology indication in 2002. The initial approved dosage regimen of Aranesp, 2.25 ug/kg, SC, QW was used in the study.*

*The patient population was relatively homogenous in disease characteristics (SCLC and NSCLC) and in concomitant chemotherapy regimen (platinum-containing regimen). The efficacy and safety results observed in study 980297 may not be generalized to patient population with different tumor types and receiving different chemo-agents.*

*Baseline hemoglobin level was not a randomization stratification factor, therefore, the efficacy and safety results of study 980297 are of limited value to address the pertinent PAS issues on hemoglobin initiation level (FDA Item 3). No comparative hemoglobin targets were pre-specified on efficacy and safety endpoints during the study. Therefore, the study is limited in being able to address the pertinent PAS issue on maximum hemoglobin level (FDA Item 4). Finally, the hemoglobin information was only followed up to 4 weeks after the last dose of chemotherapy. Therefore, the study is limited in being able to address the pertinent PAS issue on discontinuation of ESA therapy post-chemotherapy (FDA Item 5).*

*No difference was observed on HRQoL outcomes between the Aranesp and the placebo groups.*

*The negligible discrepancies observed between FDA and Amgen's analyses results for efficacy and safety outcomes in study 980297 render Amgen's analyses results as described in the clinical study reports a reliable source for the review of this supplement.*

### 5.3.5 Study 20000161

#### 5.3.5.1 Study Title, Phase, and Purpose

Title: "A Multicenter, Blinded, Placebo-controlled, Randomized Study of Novel Erythropoiesis Stimulating Protein (NESP) for the Treatment of Anemia in Subjects with Lymphoproliferative Malignancies Receiving Chemotherapy"

Study Phase: 3

#### Study Objectives:

The primary objective of this study was to compare the efficacy of NESP and placebo in the treatment of anemia in subjects with lymphoproliferative malignancies receiving chemotherapy by assessing the proportion of subjects who, by the end of the treatment phase (EOTP), achieved a hemoglobin response, defined as an increase in hemoglobin of  $\geq 2.0$  g/dL over the baseline hemoglobin that occurred in the absence of red blood cell (RBC) transfusions in the 28 days before lab sampling.

Secondary objectives were to compare the efficacy of NESP with that of placebo based on the need for RBC transfusions, the correction of anemia, mean hemoglobin change from baseline to the EOTP, and health-related quality of life (HRQOL) scores.

The safety of NESP in this treatment setting was also assessed.

#### 5.3.5.2 Study Design:

This was a multicenter, randomized, blinded, placebo-controlled study to assess the safety and activity of darbepoetin alfa administered at 2.25 ug/kg subcutaneously every week versus

placebo to increase hemoglobin levels in patients with lymphoproliferative malignancies receiving multi-cycle chemotherapy.

Study Period:

The first written informed consent was obtained on 30 October 2000 and the last subject completed the end-of-study assessments on 12 March 2002.

5.3.5.3 Inclusion/exclusion Criteria, study procedures, timelines

Inclusion:

- Subjects with lymphoproliferative malignancies (multiple myeloma, non-Hodgkin's lymphoma, Waldenström's macroglobulinaemia, chronic lymphocytic leukemia (CLL), and Hodgkin's disease (HD))
- hemoglobin  $\leq 11.0$  g/dL that was predominantly caused by cancer or chemotherapy
- life expectancy of  $\geq 4$  months
- Eastern Cooperative Oncology Group performance status of 0 to 3
- adequate liver and renal function

Exclusion:

- Subjects with Burkitt's or lymphoblastic lymphoma
- Receiving myeloablative chemotherapy, radiotherapy for transplantation, or chemotherapy regimens containing investigational agents
- scheduled to receive a stem-cell transplant within 16 weeks of randomization
- iron deficient
- received  $> 2$  RBC transfusions within 4 weeks
- any RBC transfusion within 2 weeks before randomization
- received rHuEPO therapy within 8 weeks before randomization
- known primary hematologic disorders that could cause anemia and central nervous system, cardiac, or inflammatory diseases

Study procedures:

After a screening period of 14 days, subjects with lymphoproliferative malignancies were randomized in a 1:1 ratio to receive NESP 2.25  $\mu\text{g}/\text{kg}$  or placebo administered subcutaneously (SC) once weekly for 12 weeks. Randomization was stratified by malignancy type (myeloma versus lymphoma), chemotherapy before randomization (heavily pretreated versus not heavily pretreated; heavily pretreated subjects were those who had received 2 or more lines of chemotherapy or 1 line of chemotherapy and a stem cell transplant), and region (Australia versus Canada versus Western Europe).

After 5 weeks of treatment, the dose (i.e., volume) of study drug could be doubled for subjects who had increases in hemoglobin of  $\leq 1.0$  g/dL from baseline (week 1). Subjects were to complete a 4-week follow-up evaluation period after the last dose of study drug.

A flowchart of study procedures and assessments is copied below from the study protocol.

15. Appendices Appendix A. Schedule of Assessments

STUDY DAY	TREATMENT <sup>b</sup>																F-U <sup>c</sup>	EOS <sup>d,1</sup>
	Screen. <sup>a</sup>	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13	W16			
<b>GENERAL AND SAFETY ASSESSMENTS</b>																		
Informed Consent	X																	
Medical History	X																	
Physical Examination	X																	
Disease Response Assessment																	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X				X				X						X	X	
Adverse Event Reporting		X															X	
Concomitant Medication Reporting		X															X	
Blood Product Usage Reporting	X	X															X	
Chemotherapy		X															X	
Health-Related Quality of Life Survey		X				X				X					X		X	
Study Drug Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
<b>LAB ASSESSMENTS</b>																		
Serum Pregnancy Test	X																	
Anti-NEGP Antibody Testing		X						X									X	
EPO Levels		X																
Blood Count	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood Chemistry	X	X					X										X	
Soluble Transferrin Receptor (sTfR)		X		X														
Serum Iron, Ferritin, Transferrin Saturation, Serum Iron-binding Capacity	X	X				X				X					X		X	
Folate, Vitamin B <sub>12</sub>	X																	

Best Available Copy

<sup>a</sup> Screening will occur within 14 days before planned study day 1, except hemoglobin value for eligibility, which must be within 7 days of planned study day 1. Samples may be analyzed at local or central lab.  
<sup>b</sup> Laboratory assessments will be performed by the central laboratory.  
<sup>c</sup> Weekly from study week 1 to study week 16 inclusive.  
<sup>d</sup> Subjects will be followed-up after the EOS visit at regular intervals for disease and survival status.

Primary Endpoints:

The primary efficacy endpoint was the proportion of subjects who, by the EOTP, achieved a hemoglobin response (defined as an increase in hemoglobin of  $\geq 2.0$  g/dL over baseline in the absence of RBC transfusions in the 28 days before laboratory sampling), estimated using the Kaplan-Meier method.

Secondary Endpoints:

- proportion of subjects who received a RBC transfusion from week 5 to the EOTP, estimated using the Kaplan-Meier method.
- proportion of subjects who received a RBC transfusion from week 1 to the EOTP and week 1 to 4, estimated using the Kaplan-Meier method
- time to hemoglobin response after initiation of treatment
- proportion of subjects who, by the EOTP, achieved a hemoglobin correction (defined as a hemoglobin concentration  $\geq 12.0$  g/dL in the absence of RBC transfusions in the 28 days before laboratory sampling), estimated using the Kaplan-Meier method
- time to hemoglobin correction after initiation of treatment

- change in hemoglobin from baseline to the EOTP in the presence and absence of RBC transfusions
- time to first RBC transfusion from week 5 to the EOTP and week 1 to the EOTP
- number of standard units of RBCs transfused from week 5 to the EOTP, week 1 to the EOTP, and week 1 to 4
- number of days with RBC transfusions from week 5 to the EOTP, week 1 to the EOTP, and week 1 to 4
- reasons for transfusions

### ***Health-related Quality of Life***

The main HRQOL endpoint was the mean change from baseline to the EOTP for the Functional Assessment of Cancer Therapy (FACT) Fatigue Scale score.

Other HRQOL endpoints included:

- percent change from baseline to the EOTP for the FACT-Fatigue Scale score
- proportion of subjects who achieved at least a 25% increase in FACT-Fatigue Scale score at the EOTP

### ***Safety***

- incidence and severity of adverse events
  - incidence of death
  - exposure to study drug
  - proportion of subjects exceeding the maximum hemoglobin concentration (15.0 g/dL for men, 14.0 g/dL for women) at any time on study in the presence and absence of RBC transfusion
  - maximum hemoglobin concentration in the presence and absence of RBC transfusion
  - maximum increase in hemoglobin in the presence and absence of RBC transfusion
  - proportion of subjects with confirmed antibody formation to NESP
  - incidence of concomitant medication use
  - changes from baseline and shifts in laboratory values and vital signs
  - number of days hospitalized
  - disease response
- Additional information on time to disease progression, progression-free survival, and time to death are being collected for **a minimum of 1 year** after completion of the study by the last subject and will be included in an addendum to this report.

### **Statistical Methods:**

All randomized subjects who received at least 1 dose of study drug were included in the intent-to-treat (ITT) analysis set for the analysis of primary and secondary efficacy endpoints.

The secondary analysis of RBC transfusions from week 5 to the EOTP was analyzed using a subset of the ITT analysis set referred to as the transfusion modified ITT (TFN mITT) analysis set.

Summary statistics were calculated for the primary and secondary efficacy and safety endpoints. For continuous variables, the mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum were calculated. For discrete data, the frequency and percent distributions were calculated.

The primary analysis of efficacy was based on the proportion of subjects achieving a hemoglobin response by the EOTP, estimated using the Kaplan-Meier method. The variance of the Kaplan-Meier estimate at the EOTP was calculated using Greenwood's formula. The proportions were pooled across the different combinations of malignancy type, chemotherapy before randomization, and geographic region using inverse squared standard error weights and were compared for NESP and placebo using a chi-square test.

Formal statistical significance testing was to be performed for the proportion of subjects receiving a RBC transfusion from week 5 to the EOTP if the result of the primary analysis of the proportion of subjects with a hemoglobin response was statistically significant. The proportion of subjects receiving a RBC transfusion from week 5 to the EOTP and the proportion achieving a hemoglobin correction were calculated using the same general methods as those used to evaluate hemoglobin response.

Time to hemoglobin response, time to first RBC transfusion during week 5 to the EOTP and during the entire treatment phase, and time to hemoglobin correction were analyzed using the Kaplan-Meier method. Cox proportional hazards regression was used for the comparison of treatment groups adjusting for malignancy type, chemotherapy before randomization, and region, and the hazards ratio for treatment was presented with 95% CI. The changes from baseline for the FACT-Fatigue Scale score were analyzed using a generalized Cochran-Mantel-Haenszel approach.

Statistical analyses of safety were done using the safety analysis set. Tables summarizing the subject incidence of adverse events by severity and relationship to treatment were provided.

#### 5.3.5.4 Treatment and ancillary management

Three hundred forty-nine anemic patients receiving heterogeneous chemotherapy regimens for lymphoproliferative disorders were randomized to receive Aranesp 2.25 µg/kg/week (n = 176) or placebo (n = 173).

##### Duration of Treatment:

Aranesp was to be administered for a maximum of 12 weeks.

##### 5.3.5.5 Study Sites including enrollment:

This was a multicenter study conducted at 49 centers in Australia, Canada, and Western Europe.

Approximately 340 subjects were planned (approximately 85 subjects per malignancy type in each treatment arm), and 349 subjects were enrolled into the study.

#### 5.3.5.6 Study populations

All randomized subjects who received at least 1 dose of study drug were included in the intent-to-treat (ITT) analysis set for the analysis of primary and secondary efficacy endpoints.

The secondary analysis of RBC transfusions from week 5 to the EOTP was analyzed using a subset of the ITT analysis set referred to as the transfusion modified ITT (TFN mITT) analysis set.

Three hundred forty-four subjects (99%) were included in the ITT analysis set, and 332 (95%) were included in the TFN mITT analysis set.

#### 5.3.5.7 Patient Disposition

Table 5.3.5.7.1 summarizes the patient disposition for study 20000161 (copied from Amgen's submission). Among 349 subjects randomized to receive NESP 2.25 µg/kg/week (n = 176) or placebo (n = 173), similar percentage (16%) of subjects did not complete the study in both groups. Death, consent withdrawal, and adverse events are the most common reasons for early discontinuation. There were 8 (5%) deaths for early study discontinuation in the Aranesp arm as compared to 3 (2%) deaths for early study discontinuation in the placebo arm.

Table 5.3.5.7.1 Patients disposition for study 20000161 (copied from Amgen's submission).

**Table 8-2. Subject Disposition  
 (Screened Subjects)**

	Placebo	NESP 2.25 (µg/kg/wk)	Total
Subjects Screened			403
Subjects Randomized	173	176	349
Subjects Receiving Study Drug	170 (98%)	174 (99%)	344 (99%)
Subjects Completing Study	146 (84%)	147 (84%)	293 (84%)
Subjects Not Completing Study	27 (16%)	29 (16%)	56 (16%)
Ineligibility Determined	1 (1%)	1 (1%)	2 (1%)
Protocol Violation	2 (1%)	0 (0%)	2 (1%)
Subject Noncompliance	0 (0%)	0 (0%)	0 (0%)
Adverse Event <sup>a</sup>	5 (3%)	5 (3%)	10 (3%)
Consent Withdrawn	8 (5%)	6 (3%)	14 (4%)
Disease Progression	2 (1%)	1 (1%)	3 (1%)
Administrative Decision	0 (0%)	1 (1%)	1 (0%)
Lost to Follow-up	0 (0%)	0 (0%)	0 (0%)
Death <sup>b</sup>	3 (2%)	8 (5%)	11 (3%)
Study Specific Reason			
Chemotherapy Delayed	2 (1%)	2 (1%)	4 (1%)
Chemotherapy Discontinued	3 (2%)	5 (3%)	8 (2%)
Other	1 (1%)	0 (0%)	1 (0%)

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Note: Percentages based on subjects randomized.

<sup>a</sup> Excluding Disease Progression and Death

<sup>b</sup> Excluding Deaths after the end of study visit. Three additional subjects (2 NESP, 1 Placebo) died after the end of study visit but within 30 days of the last dose (see Section 11.5).

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### 5.3.5.8 Demographics, underlying disease and drug treatment

Among 349 patients enrolled into the study, 165 were men and 179 were women; median age was 68 (18-87) years, and 98% of patients were white (Table 5.3.5.8.1). Table 5.3.5.8.2 summarizes the baseline disease characteristics of the subjects in ITT set. Overall, most patients (50%) had diagnoses of multiple myeloma, followed by patients with non-Hodgkin's lymphoma (24%), chronic lymphocytic leukemia (16%).

In general, demographics and baseline disease characteristics were similar between the Aranesp and the placebo groups.

Table 5.3.5.8.1 Demographics in study 20000161 (copied from Amgen's submission)

**Table 8-4. Subject Demography  
 (ITT Analysis Set)**

	Placebo	NESP 2.25 (µg/kg/wk)	Total
Number of Subjects	170	174	344
<b>Sex</b>			
Male	78 (46%)	87 (50%)	165 (48%)
Female	92 (54%)	87 (50%)	179 (52%)
<b>Race</b>			
Asian	0 (0%)	2 (1%)	2 (1%)
Non-white including Black	1 (1%)	1 (1%)	2 (1%)
Other	1 (1%)	2 (1%)	3 (1%)
White	168 (99%)	169 (97%)	337 (98%)
<b>Age (years)<sup>a</sup></b>			
Subjects < 65 years	76 (45%)	63 (36%)	139 (40%)
Subjects ≥ 65 years	94 (55%)	111 (64%)	205 (60%)
Subjects ≥ 75 years	34 (20%)	45 (26%)	79 (23%)
<b>n</b>	170	174	344
<b>Mean</b>	64.6	64.8	64.7
<b>SD</b>	12.2	13.8	13.0
<b>Median</b>	67.0	68.5	68.0
<b>Q1, Q3</b>	58.0, 74.0	56.0, 75.0	57.5, 74.0
<b>Min, Max</b>	18, 87	20, 86	18, 87

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<sup>a</sup> These categories are not mutually exclusive.

Table 5.3.5.8.2 Baseline Disease Characteristics in study 20000161 (copied from Amgen's submission)

**Table 8-5. Summary of Baseline Disease Characteristics (ITT Analysis Set)**

	Placebo	NESP 2.25 (µg/kg/wk)	Total
Number of subjects	170	174	344
<b>Type of Malignancy</b>			
Waldenstrom's Macroglobulinaemia	6 (4%)	5 (3%)	11 (3%)
Chronic Lymphocytic Leukemia	26 (15%)	29 (17%)	55 (16%)
Non-Hodgkin's Lymphoma	45 (26%)	39 (22%)	84 (24%)
Hodgkin's Disease	9 (5%)	12 (7%)	21 (6%)
Multiple Myeloma	84 (49%)	89 (51%)	173 (50%)
<b>Disease Stage</b>			
<b>Chronic Lymphocytic Leukemia<sup>b</sup></b>			
B(I)	1 (1%)	0 (0%)	1 (0%)
B(II)	1 (1%)	2 (1%)	3 (1%)
C(III)	13 (8%)	15 (9%)	28 (8%)
C(IV)	11 (6%)	12 (7%)	23 (7%)
<b>Non-Hodgkin's Lymphoma<sup>a</sup></b>			
I	0 (0%)	2 (1%)	2 (1%)
II	7 (4%)	4 (2%)	11 (3%)
III	6 (4%)	9 (5%)	15 (4%)
IV	32 (19%)	24 (14%)	56 (16%)
<b>Hodgkin's Disease<sup>a</sup></b>			
II	1 (1%)	3 (2%)	4 (1%)
III	4 (2%)	5 (3%)	9 (3%)
IV	4 (2%)	4 (2%)	8 (2%)
<b>Multiple Myeloma<sup>c</sup></b>			
I	4 (2%)	4 (2%)	8 (2%)
II	32 (19%)	29 (17%)	61 (18%)
IIIA	44 (26%)	54 (31%)	98 (28%)
IIIB	4 (2%)	2 (1%)	6 (2%)

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<sup>a</sup>Ann Arbor staging of Lymphoma

<sup>b</sup>International workshop on chronic lymphocytic leukemia

<sup>c</sup>Durie and Salmon staging system of multiple myelomas

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### 5.3.5.9 Outcome Efficacy

After adjusting for malignancy type, chemotherapy before randomization, and region, NESP increased the estimated Kaplan-Meier proportion of subjects achieving a hemoglobin response from 16% in the placebo group to 58% in the NESP group, a significant difference of 41% (95%

CI: 31, 50) ( $p < 0.001$ ). This treatment difference was also seen separately in subjects with lymphoma ( $p < 0.001$ ) and in subjects with myeloma ( $p < 0.001$ ).

The time to hemoglobin response was shorter in the NESP group than in the placebo group. Fifty percent of subjects achieved a hemoglobin response by week 12 in the NESP group, whereas the median time to hemoglobin response was not estimable for the placebo group because only 18% of subjects responded by week 13.

Significantly fewer subjects randomized to NESP had a RBC transfusion from week 5 to the EOTP (29%) compared with the placebo group (50%), an adjusted difference of -17% (95% CI: -27, -7;  $p < 0.001$ ). This finding was consistently demonstrated regardless of the approach used to account for subject withdrawals or the use of an alternative definition of the endpoint (RBC transfusion or hemoglobin  $\leq 8.0$  g/dL).

NESP also resulted in a statistically significant increase in the proportion of subjects achieving hemoglobin correction and the change in hemoglobin from baseline compared with placebo.

#### HRQOL Results:

For the primary HRQOL endpoint, mean change in the FACT-Fatigue from baseline, the mean scale score at the EOTP improved by 2.7 points in the NESP group and by 0.6 points in the placebo group in an analysis adjusting for malignancy type, chemotherapy before randomization, and region ( $p = 0.078$ ).

#### 5.3.5.10 Outcome of Safety Assessments

The overall safety profile of NESP in this study was similar to placebo and was considered to be consistent with that expected for subjects with lymphoproliferative malignancies who were receiving chemotherapy.

Ten subjects (6%) in the NESP group and 4 subjects (2%) in the placebo group died during the study or within 30 days after the last dose of study drug. No deaths were considered treatment related, and the most common cause of death was disease progression.

Six subjects (3%) receiving NESP and 7 subjects (4%) receiving placebo withdrew from the study because of a nonfatal adverse event.

Serious adverse events were reported for 51 subjects (29%) receiving NESP and 63 subjects (37%) receiving placebo. The incidence of serious adverse events considered related to blinded study drug by the investigator was 2% in both the NESP and placebo groups. No relationship was observed between the rise in hemoglobin or the maximum hemoglobin concentration achieved and any particular adverse event or pattern of adverse events.

#### 5.3.5.11 Discussion of Findings/Conclusions

Amgen's Conclusions:

NESP 2.25 µg/kg/week administered SC weekly to subjects with lymphoproliferative malignancies who were receiving chemotherapy significantly increased the proportion of subjects achieving a hemoglobin response and decreased the proportion of subjects requiring a RBC transfusion compared with placebo.

*Reviewer's comments:*

*Study 20000161 was conducted to compare the efficacy of Aranesp and placebo in subjects with lymphoproliferative malignancies receiving chemotherapy by assessing the proportion of subjects who, by the end of the treatment phase (EOTP), achieved a hemoglobin response, defined as an increase in hemoglobin of  $\geq 2.0$  g/dL over the baseline hemoglobin.*

*The approved dosage regimen of Aranesp, 2.25 ug/kg, SC, QW was used in the study, but the patients population (lymphoproliferative malignancies) in study 20000161 was different from the population (Lung cancer) enrolled in study 980297.*

*Of note is that the primary endpoints for study 20000161 was the proportion of subjects who, by the EOTP, achieved a hemoglobin response (defined as an increase in hemoglobin of  $\geq 2.0$  g/dL over baseline), which was not the primary endpoint used in study 980297. The efficacy results in study 20000161 demonstrate the effect of Aranesp to significantly increase the proportion of subjects achieving a hemoglobin response and decrease the proportion of subjects receiving a RBC transfusion in Aranesp group as compared with placebo, suggesting a relationship between increased hemoglobin level and decreased RBC transfusion requirement.*

*No statistically significant difference was observed on HRQoL outcomes between the Aranesp and the placebo groups*

*Baseline hemoglobin level was not a randomization stratification factor, therefore, the efficacy and safety results of study 20000161 are of limited value to address the pertinent PAS issues on hemoglobin initiation level (FDA Item 3). No comparative hemoglobin targets were pre-specified on efficacy and safety endpoint during the study. Therefore, the study is limited in being able to address the pertinent PAS issue on maximum hemoglobin level (FDA Item 4). Finally, the hemoglobin information was only followed up to 4 weeks after the last dose of chemotherapy. Therefore, the study result is of limited value to address the pertinent PAS issue on discontinuation of ESA therapy post-chemotherapy (FDA Item 5).*

*Of further note is that follow-up information on overall survival in study 20000161 indicated an increased mortality rate and decreased time to death in subjects receiving Aranesp as compared to subjects receiving placebo. In contrast, the survival follow-up information for study 980297 did not reveal an increased mortality or increased tumor progression in patients receiving Aranesp, raising a question whether disease nature and characteristics and/or chemotherapy regimen impacted the safety effects of Aranesp on overall survival and/or tumor progression.*

*The efficacy and safety out come from the study 20000161 has no impact on the current labeling of Aranesp.*

### 5.3.6 Study 20030232

#### 5.3.6.1 Study Title, Phase, and Purpose

Title: "A Randomized, Double-blind, Placebo-controlled Study of darbepoetin alfa for the Treatment of Anemia in Subjects with Non-myeloid Malignancy Receiving Multicycle Chemotherapy"

Study Phase: 3

#### Study Objectives:

To evaluate the efficacy and safety of darbepoetin alfa given once every 3 weeks (Q3W) in treating anemia in subjects with non-myeloid malignancies receiving cyclic chemotherapy.

#### 5.3.6.2 Study Design

This was a phase 3, multicenter, randomized, double-blind, and placebo- controlled study. Eligible subjects were randomized 1:1 to receive darbepoetin alfa 300 µg Q3W or placebo Q3W over a 15-week treatment period. Randomization was stratified by tumor type (lung/gynecological vs. others), screening hemoglobin concentration (< 10.0 g/dL vs. ≥ 10.0 g/dL), and region (North America vs. Australia).

#### Study Period:

20 February 2004 - 03 March 2005

#### 5.3.6.3 Inclusion/Exclusion Criteria, Study Procedures, Timelines

#### Inclusion:

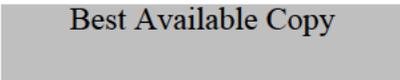
- Subjects with non-myeloid malignancies
- At least 12 additional weeks of cyclic cytotoxic chemotherapy anticipated regardless of schedule
- Of legal age
- Eastern Cooperative Oncology Groups (ECOG) performance status of 0 to 2
- Hemoglobin concentration < 11.0 g/dL within 24 hours before randomization

#### Exclusion:

- Known history of seizure disorder or currently on anti-seizure medication
- Known primary hematologic disorder that could cause anemia
- Other diagnoses not related to the cancer which can cause anemia
- Unstable or uncontrolled disease/condition related to or affecting cardiac function
- Clinically significant inflammatory disease
- Inadequate renal and liver function
- Iron deficiency
- Known positive HIV test

- Known positive neutralizing antibody response to any erythropoietic agent
- Received > 2 RBC transfusions within 4 weeks before randomization; or any RBC transfusion within 14 days before randomization; or any planned RBC transfusion between randomization and study day 1
- Received any erythropoietic therapy within 4 weeks before randomization; or any planned between randomization and study day 1

Study procedures:



A flowchart of study procedures and assessments is copied below from the study protocol:

Appendix A. Schedule of Assessments

Assessment	Screen <sup>a</sup>	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	EOTP <sup>b</sup> W16	W 17	W 18	EOS <sup>b</sup> W19	
<b>General &amp; Safety Assessments</b>																					
Informed Consent	X																				
Medical History <sup>c</sup>	X																				
Physical Exam <sup>d</sup>	X																				
Vital Signs <sup>e</sup>		X			X			X			X			X			X			X	
ECOG Performance Status	X										X						X			X	
Disease Status		X															X			X	
AEs/ Hospitalizations Reporting		X																		X	
Con Medication/ Treatments Reporting		X																		X	
Chemotherapy Reporting	X	X																		X	
PRO Assessment <sup>f</sup>		X									X						X				
Investigational product administration <sup>g</sup>		X			X			X			X			X							
<b>Laboratory Assessments</b>																					
Blood Count (Central Laboratory) <sup>h</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hgb Concentration (Local Laboratory)	X <sup>i</sup>	X <sup>i</sup>			X			X			X			X							
Blood Chemistry <sup>j</sup>	X <sup>i</sup>	X									X						X			X	
Iron Status <sup>k</sup>		X	X					X									X			X	
Folate, Vitamin B <sub>12</sub>	X	X																			
Antibody Testing		X									X							X			
EPO concentration		X																			
Serum or Urine HCG Pregnancy Test <sup>l</sup>	X																				

<sup>a</sup> Screening will occur ≤ 7 days before randomization  
<sup>b</sup> End of treatment period (EOTP) will be week 16 and end of study (EOS) visit is planned for week 19  
<sup>c</sup> Medical history including details of tumor diagnosis, RBC transfusions received within the past 12 weeks, complete chemotherapy and radiotherapy history  
<sup>d</sup> Physical examination, including height and actual body weight  
<sup>e</sup> Vital signs will include resting systolic/diastolic blood pressure and pulse  
<sup>f</sup> Patient reported outcome (PRO) assessments to be administered prior to any procedures  
<sup>g</sup> Investigational product should be administered before chemotherapy on days when both are administered  
<sup>h</sup> Blood count will include RBC, hematocrit, hemoglobin concentration, red cell distribution width, reticulocytes, platelet count, mean corpuscular volume and ANC  
<sup>i</sup> Confirmatory hemoglobin < 11.0 g/dL required within 24 hours before randomization; baseline hemoglobin required within 24 hours before study day 1.  
<sup>j</sup> Blood chemistries at screening will include creatinine and ALT; all other chemistries will include sodium, potassium, total calcium, phosphorus, total protein, albumin, random glucose, BUN/urea, creatinine, total bilirubin, alkaline phosphatase, LDH, ALT, AST  
<sup>k</sup> Iron status determined by: serum iron, ferritin, transferrin saturation, and total iron-binding capacity  
<sup>l</sup> Blood samples must be taken prior to the administration of investigational product  
<sup>m</sup> Serum or urine pregnancy test for women of childbearing potential

**Efficacy Endpoints:**

Primary efficacy outcome: The incidence of RBC transfusion from week 5 (study day 29) to the end of the treatment period (EOTP)

Secondary efficacy outcome: The incidence of achieving a hemoglobin concentration ≥ 11.0 g/dL, in the absence of RBC transfusions in the preceding 28 days, from week 5 to EOTP.

Supportive: Patient reported outcomes and the number of RBC transfusions from week 5 to the EOTP.

#### Safety Endpoints:

- Incidence and severity of adverse events
- Incidence of hemoglobin concentration > 13.0 g/dL at any time on study
- Incidence of an increase in hemoglobin concentration  $\geq 2$  g/dL in a 28-day window and any negative clinical consequences
- Incidence of an increase in hemoglobin concentration  $\geq 1$  g/dL in a 14-day window and any negative clinical consequences
- Incidence of a confirmed antibody formation to darbepoetin alfa

#### Statistical Analysis Plan:

Analyses for the primary and secondary efficacy endpoints were to be stratified by baseline hemoglobin concentration (< 10.0 g/dL or  $\geq 10.0$  g/dL), geographic region (North America and Australia), and tumor type (lung/gynecological and other cancers). The primary analyses of efficacy were based on the proportion of subjects experiencing at least one RBC transfusion from week 5 (study day 29) to the EOTP, estimated using the Kaplan- Meier approach. The proportion of subjects achieving a hemoglobin concentration of  $\geq 11.0$  g/dL was analyzed in a similar manner as the primary endpoint.

#### 5.3.6.4 Treatment and ancillary management, timeline

Eligible subjects were randomized 1:1 to receive darbepoetin alfa 300  $\mu$ g Q3W or placebo Q3W over a 15-week treatment period.

Pre-specified dose adjustments were made if the initial hemoglobin response was insufficient, or if hemoglobin concentration exceeded the threshold level, or if hemoglobin concentration increased by > 1.0 g/dL in any 2-week period in the absence of RBC transfusions during the previous 14 days.

Duration of Treatment: 15 weeks

#### 5.3.6.5 Study Sites including enrollment

The planned sample size was 380 subjects. Three hundred ninety one subjects were enrolled and randomized into the study from 81 study sites from Australia, New Zealand, and North America; 386 (193 placebo, 193 darbepoetin alfa) received at least 1 dose of study drug.

#### 5.3.6.6 Study populations

The primary efficacy analysis on the incidence of an RBC transfusion from week 5 (day 29) to the EOTP was conducted in the primary analysis set consisting of all subjects in the full analysis set who were enrolled in the study until at least day 29.

The full analyses set consist of all subjects who were randomized and received at least one dose of investigational product.

Safety analysis was conducted in the full analyses set according to the treatment subjects actually received.

#### 5.3.6.7 Patient Disposition

Table 5.3.6.7 summarizes patient disposition for study 20030232. Of 456 subjects screened, 391 subjects were randomized. Of 391 randomized subjects, 5 subjects (2 in the placebo group and 3 in the darbepoetin alfa group) did not receive investigational product. Similar proportions of subjects in either treatment group completed treatment: 70% in the placebo group and 73% in the darbepoetin alfa group. The most frequent causes were withdrawn consent (11% in the placebo group and 7% in the darbepoetin alfa group) and death (8% in both groups).

Table 5.3.6.7.1 Patient Disposition for Study 20030232 (copied from Amgen’s submission)

**Table 8-1. Subject Disposition (All Screened Subjects)**

	Placebo	Darbepoetin alfa 300 µg Q3W	Total
	n (%)	n (%)	n (%)
Subjects screened			456
Subjects randomized	195	196	391
<b>Investigational Drug Accounting</b>			
Subjects who never received investigational drug	2 (1)	3 (2)	5 (1)
Subjects who received investigational drug	193 (99)	193 (98)	386 (99)
Subjects who completed investigational drug	136 (70)	144 (73)	280 (72)
Subjects who discontinued investigational	57 (29)	49 (25)	106 (27)
<b>Study Completion Accounting</b>			
Subjects who completed study	132 (68)	138 (70)	270 (69)
Subjects who discontinued study	63 (32)	58 (30)	121 (31)

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Note: Percentages based on subjects randomized

Program: /stat/nesp/onc/nesp20030232/analysis/final/statfiles/programs/tables/t\_disp.sas  
 Output: t14\_001\_003\_001\_001\_disp\_subject\_scr.rtf (Date Generated: 24JUN05:16:21:46) Source Data:  
 c\_disp.sas7dbat

### 5.3.6.8 Demographics, underlying disease and drug treatment

Among 386 patients randomized into the study, 152 were men and 232 were women; median age was 66 (20-91) years, 79% of patients were white and 11% of patients were black (Table 5.3.6.8.1). Tables 5.3.6.8.2 and 5.3.6.8.3 summarizes baseline disease characteristics including tumor types and disease stages of the subjects in the full analysis set.

Overall, patients had diagnoses of breast cancer (23%), followed by large intestinal/colon (11%), non-small cell lung (10%), non-Hodgkin’s lymphoma (8%), ovarian (8%), other solid tumors (7%), multiple myeloma (6%), pancreatic (6%), and other cancers.

In general, demographics and baseline disease characteristics were similar between the Aranep and the placebo groups.

Table 5.3.6.8.1 Demographics in Study 20030232 (copied from Amgen's submission)

**Table 8-5. Subject Demographics (Full Analysis Set)**

	Placebo (N=193)	Darbepoetin alfa 300 µg Q3W (N=193)	Total (N=386)
<b>Sex - n(%)</b>			
Male	76 (39)	76 (39)	152 (39)
Female	117 (61)	117 (61)	234 (61)
<b>Race - n(%)</b>			
White	152 (79)	153 (79)	305 (79)
Black	20 (10)	24 (12)	44 (11)
Hispanic	15 (8)	11 (6)	26 (7)
Asian	4 (2)	2 (1)	6 (2)
Japanese	0 (0)	2 (1)	2 (1)
Pacific Islander	2 (1)	1 (1)	3 (1)
<b>Age - years</b>			
n	193	193	386
Mean	63.6	64.5	64.1
SD	12.3	12.1	12.2
Median	65.0	66.0	66.0
Q1, Q3	55.0, 74.0	56.0, 73.0	55.0, 74.0
Min, Max	21, 89	20, 91	20, 91
<b>Age Group - n(%)</b>			
< 65 years	94 (49)	84 (44)	178 (46)
≥ 65 to < 75 years	57 (30)	72 (37)	129 (33)
≥ 75 years	42 (22)	37 (19)	79 (20)

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Program: /stat/nesp/onc/nesp20030232/analysis/final/statfiles/programs/tables/t\_demog.sas  
 Output: t14\_002\_001\_001\_001\_demog\_itt.rtf (Date Generated: 24JUN05:16:14:05) Source Data:  
 c\_keyvar.sas7bdat

Table 5.3.6.8.2 Baseline disease characteristics (tumor types) in Study 20030232 (copied from Amgen's submission)

**Table 8-7. Primary Tumor Type (Full Analysis Set)**

	Placebo	Darbepoetin alfa	Total
	n (%)	300 µg Q3W n (%)	n (%)
Number of Subjects	193	193	386
Lung/Gynecological	48 (25)	46 (24)	94 (24)
Ovarian	13 (7)	19 (10)	32 (8)
Non-small Cell Lung	24 (12)	16 (8)	40 (10)
Small Cell Lung	7 (4)	8 (4)	15 (4)
Cervix	2 (1)	1 (1)	3 (1)
Uterus/Endometrial	2 (1)	2 (1)	4 (1)
Other	145 (75)	147 (76)	292 (76)
Breast	39 (20)	50 (26)	89 (23)
Large Intestine/Colon	24 (12)	19 (10)	43 (11)
Prostate	8 (4)	16 (8)	24 (6)
Non-Hodgkin's Lymphoma	17 (9)	13 (7)	30 (8)
Other Solid Tumor	14 (7)	14 (7)	28 (7)
Multiple Myeloma	14 (7)	9 (5)	23 (6)
Pancreatic	7 (4)	7 (4)	14 (4)
Chronic Lymphocytic Leukemia	3 (2)	3 (2)	6 (2)
Squamous Cell - head/neck	2 (1)	3 (2)	5 (1)
Stomach	2 (1)	4 (2)	6 (2)
Bladder	1 (1)	1 (1)	2 (1)
Bone Sarcoma	0 (0)	1 (1)	1 (0)
Esophageal	2 (1)	1 (1)	3 (1)
Hodgkin's Disease	1 (1)	1 (1)	2 (1)
Kidney	2 (1)	1 (1)	3 (1)
Soft Tissue Sarcoma	1 (1)	1 (1)	2 (1)
Testicular	0 (0)	1 (1)	1 (0)
Unknown Primary	2 (1)	1 (1)	3 (1)
Ureter	0 (0)	1 (1)	1 (0)
Melanoma	1 (1)	0 (0)	1 (0)
Oral	4 (2)	0 (0)	4 (1)
Other Hematologic Malignancy	1 (1)	0 (0)	1 (0)

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Note: Tumor type as indicated on the Case Report Form.

Program: /stat/nesp/onc/nesp20030232/analysis/final/statfiles/programs/tables/t\_primtumor.sas  
 Output: t14\_002\_002\_001\_001\_primtumor\_itt.rtf (Date Generated: 24JUN2005:17:11) Source  
 Data: c\_diag.sas7bdat

Table 5.3.6.8.3 Baseline disease characteristics (stages) in Study 20030232 (copied from Amgen's submission)

**Table 8-6. Baseline Disease Characteristics (Full Analysis Set)**

	Placebo (N=193)	Darbepoetin alfa 300 µg Q3W (N=193)	Total (N=386)
<b>Disease Stage At Diagnosis</b>			
I	15 (8)	19 (10)	34 (9)
II	34 (18)	42 (22)	76 (20)
III	45 (23)	56 (29)	101 (26)
IV	83 (43)	58 (30)	141 (37)
Missing	1 (1)	0 (0)	1 (0)
Other	5 (3)	9 (5)	14 (4)
Unknown	10 (5)	9 (5)	19 (5)
<b>Current Disease Stage</b>			
I	5 (3)	5 (3)	10 (3)
II	13 (7)	14 (7)	27 (7)
III	33 (17)	37 (19)	70 (18)
IV	118 (61)	119 (62)	237 (61)
Other	11 (6)	7 (4)	18 (5)
Unknown	13 (7)	11 (6)	24 (6)

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Program: /stat/nesp/onc/nesp20030232/analysis/final/statfiles/programs/tables/t\_dischar.sas  
 Output: t14\_002\_003\_001\_001\_dischar\_jtt.rtf (Date Generated: 24JUN05:16:16:44) Source  
 Data: c\_diag.sas7bdat

### 5.3.6.9 Efficacy Outcomes

For the primary efficacy endpoint, the K-M percentage (95% CI) of subjects receiving RBC transfusions from week 5 to the EOTP (the primary endpoint) was significantly smaller for the darbepoetin alfa group (24% [18, 30]), than for the placebo group (41% [34, 49]), a difference of – 16.3 percentage points (– 25.9, – 6.6) ( $p < 0.001$ ). Crude percentages were similar to the K-M proportions.

For the secondary efficacy endpoint, the incidence of achieving a target hemoglobin concentration  $\geq 11.0$  g/dL from week 5 to the EOTP, K-M percentages (95% CI) of 48% (41, 56) and 82% (76, 88) of subjects in the placebo and Aranesp groups, respectively, achieved this endpoint, with a difference of 27.1% (17.7, 36.5) in favor of Aranesp ( $p < 0.001$ ).

Subgroup analyses (including analyses by demographic variables, type of chemotherapy, and hemoglobin concentration) demonstrated the robustness of the results for the primary and secondary endpoints. Analysis of efficacy by weight demonstrated that fixed dosing with 300 µg was equally effective across different weight groups.

### Patient Reported Outcomes

Compliance with the FACT-F subscale was considered to be good [93% (placebo) and 96% (Aranesp) of subjects at baseline, 76% and 83% at the EOTP]. For all PRO questions, 83% (placebo) and 84% (Aranesp) of subjects completed the questions at baseline, and 63% (placebo) and 73% (darbepoetin alfa) of subjects completed the questions at the EOTP.

The FACT-F subscale score showed little overall change for either treatment group from baseline to the EOTP, changing by a mean (SD) of 0.37 (10.92) for the placebo group and – 0.08 (11.80) for the darbepoetin alfa group. Similar results were seen for the FACT-G physical, emotional, functional, and social/family subscale scores, as well as for the FACT-G total score. The change in BSI anxiety and depression scale scores similarly showed little change in either treatment group from baseline to the EOTP.

Overall, no difference was observed in PRO outcomes between the Aranesp and the placebo arms.

#### 5.3.6.10 Outcome of Safety Assessments

Four percent (placebo) and 6% (darbepoetin alfa) of subjects discontinued the study prematurely because of an adverse event.

The overall proportion of subjects who died was similar in the 2 treatment groups: 23 (12%) (placebo) and 20 (10%) (Aranesp). Causes of death were most commonly attributed to disease progression or consequences of the disease and its treatment. Cardiovascular and thromboembolic adverse events were reported in small numbers of subjects in both treatment groups, and did not generally appear to be associated with increases in hemoglobin concentration.

A total of 182 (95%) subjects in the placebo group and 182 (94%) subjects in the darbepoetin alfa group experienced at least 1 adverse event. Important differences between treatment groups were not apparent in the incidence of common adverse events. Fatigue was the most common adverse event, and occurred in similar proportions of subjects in the placebo (60 [31%]) and darbepoetin alfa (62 [32%]) groups. The greatest difference between treatment groups was observed for the incidence of pyrexia (14 [7%] in the placebo group and 30 [15%] in the darbepoetin alfa group).

Serious adverse events occurred at comparable rates in both groups: 40% and 43% in the placebo group and the darbepoetin alfa group, respectively; the types of serious adverse events observed reflected the disease state and comorbid conditions of this patient population. No important differences between groups were observed for any single type of serious adverse event. The proportion of subjects experiencing a maximum hemoglobin concentration of  $\geq 13$  g/dL was higher for subjects receiving darbepoetin alfa (25.8%) than for those receiving placebo (7.8%). While occasional adverse events showed an increased incidence of events for those subjects who

experienced a hemoglobin concentration of  $\geq 13$  g/dL compared with those who did not, the trend was the same in the placebo and darbepoetin alfa groups.

#### 5.3.6.11 Discussion of Findings/Conclusions

##### Amgen's Conclusions:

The fixed dose 300  $\mu$ g Q3W schedule of darbepoetin alfa studied here was found to be effective and well tolerated, and provides a convenient dosing schedule, allowing for the possible synchronization of anemia treatment with the administration of many common chemotherapy regimens.

##### Reviewer's comments:

*Study 200030232 was conducted to evaluate the efficacy and safety of darbepoetin alfa given once every 3 weeks (Q3W) in treating anemia in subjects with non-myeloid malignancies receiving cyclic chemotherapy.*

*The patient population was heterogeneous in disease characteristics and in concomitant chemotherapy regimen.*

*The hemoglobin information following the discontinuation of chemotherapy was only followed up to 4 weeks after the last dose of chemotherapy.*

*Of note is that the tested dose regimen, Aranesp 300  $\mu$ g Q3W, in study 20030232 was not the approved dosage regimen of Aranesp, 2.25  $\mu$ g/kg, SC, QW or 500  $\mu$ g Q3W. Also of note is that the efficacy results from study 20030232 indicated a similar effect of dose regimen between the tested Aranesp 300  $\mu$ g Q3W and the approved Aranesp regimen 500  $\mu$ g Q3W in reducing RBC transfusion in anemic cancer patients receiving chemotherapy, implying that a lower Aranesp dose regimen, 300  $\mu$ g Q3W, than the currently Aranesp approved 500 $\mu$ g Q3W is similarly efficacious in reducing RBC transfusion and dose regimen probably is not critical/stringent in oncology indication.*

*No difference was observed on HRQoL outcomes between the Aranesp and the placebo groups*

*The efficacy and safety outcome of study 20030232 has no impact on the current labeling of Aranesp, except suggesting a lower Q3W dosing regimen (300  $\mu$ g Q3W) may be considered.*

*The results of study 20030232 are of limited value to address the pertinent PAS supplement issues on hemoglobin initiation level (FDA Item 3), maximum hemoglobin level (FDA Item 4), and discontinuation of ESA therapy post-chemotherapy (FDA Item 5).*

#### 5.3.7 Study 20010145

##### 5.3.7.1 Study Title, Phase, and Purpose

Title: A Randomized, Double Blind, Placebo-Controlled Study of Subjects With Previously Untreated Extensive-Stage Small-Cell Lung Cancer (SCLC) Treated With Platinum plus Etoposide Chemotherapy with or without darbepoetin alfa

Study Phase: 3

#### Study Objectives:

The primary objective of this study was to evaluate whether increasing or maintaining hemoglobin concentrations with darbepoetin alfa, when administered with platinum-containing chemotherapy in subjects with previously untreated extensive-stage SCLC, increases survival.

The secondary objective of this study was to evaluate whether darbepoetin alfa improves Functional Assessment of Cancer Therapy – Fatigue (FACT-Fatigue) subscale scores.

Other objectives were to assess the effect of darbepoetin alfa on subject symptom assessment, progression-free survival, time to progression, tumor response, duration of tumor response, RBC transfusions, and FACT-General subscale scores, and to assess the overall safety profile of darbepoetin alfa in subjects with previously untreated extensive stage SCLC.

#### 5.3.7.2 Study Design

This was a multicenter, randomized, double-blind, placebo-controlled study to assess the effect of darbepoetin alfa on survival in subjects with previously untreated extensive-stage SCLC receiving platinum and etoposide chemotherapy. Randomization was stratified by region (Western Europe, Australia/North America, and rest of world), Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2), and lactate dehydrogenase (LDH; below versus above the upper limit of normal).

Study Period: 10 December 2002 (date first subject was randomized) through 22 February 2007 (data cutoff date)

#### 5.3.7.3 Inclusion/Exclusion Criteria, Study Procedures, and Timelines

##### Inclusion:

- Subjects of legal age to give consent
- with pathologically proven extensive-stage SCLC
- planned to receive chemotherapy with carboplatin or cisplatin plus etoposide Q3W for 6 cycles
- hemoglobin concentration  $\geq 9.0$  g/dL and  $\leq 13.0$  g/dL
- an ECOG status of 0 to 2
- life expectancy of  $\geq 3$  months
- adequate liver, renal, and hematopoietic function (absolute neutrophil count  $\geq 1.5 \times 10^9/L$  and platelet count  $\geq 100 \times 10^9/L$ )

Exclusion:

- previous chemotherapy for SCLC
- previous radiotherapy (except as symptom palliation for bone or brain lesions  $\geq$  24 hours before randomization)
- 2 units of packed RBCs within 4 weeks
- any RBC transfusion within 2 weeks of randomization
- recombinant human erythropoietin or darbepoetin alfa within 4 weeks of randomization.
- brain metastases that were symptomatic or treated with steroids
- other known primary malignancies within the past 5 years (except basal cell, carcinoma, squamous cell carcinoma in situ, cervical carcinoma, or surgically cured malignancies),
- cardiac diseases, iron deficiency, or known primary hematologic disorders that could cause anemia.

Study procedures:

Eligible subjects were randomized in a 1:1 ratio to receive darbepoetin alfa or placebo throughout 6 cycles of chemotherapy and for 3 weeks after the last dose of on-study chemotherapy.

Subjects were to have follow-up visits every 3 months after their end-of-study treatment visit until death or until 496 deaths had occurred (End of Study). Those subjects still alive at the End of study entered the long-term follow-up period and were to be followed until death.

A flowchart of study procedures and assessments is copied below from the study protocol:

Appendix D. Schedule of Assessments

STUDY DAY	Screen <sup>a</sup>	TREATMENT <sup>b</sup>																		ECOST	FIU						
		Beginning of Week (W)																									
		W <sup>c</sup> 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	W 16	W 17	W 18			W 19	W 20	W 21	W 22	W 23	W 24
<b>GENERAL AND SAFETY ASSESSMENTS</b>																											
Informed Consent	X																										
Medical History, Physical Exam, Wt	X	X			X			X			X			X			X			X							
Vital Signs	X	X			X			X			X			X			X			X							
ECOG Performance Status	X	X			X			X			X			X			X			X							
Disease Staging <sup>d</sup>	X							X						X											X	X	X
Adverse Event Reporting	X																										
Subject symptom assessment, FACT-Anemia, FACT-General and EuroQOL 5 dimensions		X						X						X											X	X	X
Concomitant Medication/ Treatments (RBC transfusion)		X																									
Study Drug Administration <sup>e</sup>		X	X	X	X	X			X			X			X			X			X						
Chemotherapy <sup>f</sup>		X			X			X			X			X			X			X							
<b>LAB ASSESSMENTS</b>																											
Serum Pregnancy Test <sup>g</sup>	X <sup>h</sup>																										
Anti-darbepoetin alfa Antibody Testing <sup>i</sup>		X						X																		X	
EPO Levels		X																									
Blood Count <sup>j</sup>	X <sup>h</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Chemistry <sup>k</sup>	X	X			X			X			X			X			X			X						X	
Iron Status <sup>l</sup>	X	X																									
Folate and Vitamin B <sub>12</sub>		X																									

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a. All imaging screening tests must be performed within 21 days before randomization along with history and physical exam. Other screening procedures must be performed within 7 days before randomization.  
 b. Chemotherapy of Carboplatin or Cisplatin plus etoposide at recommended dose. See section 5.3.1 for further details.  
 c. Serum samples for all subjects must be collected before study drug administration.  
 d. Week 1 (Baseline) assessments must occur before administration of study drug (if applicable) and administration of chemotherapy. If screening chemistry/iron status are obtained within 7 days of study day 1 they may be used as baseline measurements.  
 e. Blood count to include RBC, Hct, hemoglobin, platelet count, WBC+ANC (including segmented neutrophils + bands/lymphs) + eosinophils. Blood counts to be performed weekly until 3 weeks after last dose of on-study chemotherapy.  
 f. Blood Chemistry includes creatinine, bilirubin, ALT and AST, LDH, sodium, potassium, chloride and bicarbonate. Screening/baseline samples also include total protein, albumin, random glucose, urea nitrogen/BUN/urea, uric acid and alkaline phosphatase. Blood Chemistry to be performed prior to the start of each on-study chemotherapy cycle.  
 g. Iron status determined by: serum iron, ferritin, transferrin saturation, and total iron-binding capacity.  
 h. Study drug should be administered weekly (weeks 1-4) and then Q3W (from week 5) until 3 weeks after the last dose of on-study chemotherapy. Changes to this schedule should be implemented in accordance with the dosing rules in section 5 of the protocol.  
 i. End of Study Treatment (ECOST). All subjects will have an ECOST evaluation performed 3 weeks after the last dose of on-study chemotherapy.  
 j. After completion of chemotherapy, all subjects will have disease staging by CT scan every 3 months until disease progression. Subjects experiencing disease progression will be followed every 3 months until death or the point at which all randomized subjects have completed their end of study treatment visit and 495 deaths have occurred. An additional assessment of FACT-Anemia, FACT-General and EuroQOL 5 dimensions will be performed 6 months after ECOST visit. All subjects that are still alive at the End of Study will move to long term follow-up until death.  
 k. For Female of childbearing potential.  
 l. Radiographic and CT scans performed at screening will be used as a baseline for disease response criteria. CT scans will be performed 1 week before cycles 3 and 5, two weeks after cycle 6 of chemotherapy and at the end of study treatment visit for monitoring of disease status. Additional imaging tests will be performed as medically indicated. Scheduled imaging does not need to be performed if previous imaging has confirmed disease progression as defined by the RECIST criteria.

Efficacy Endpoint:

Study 20010145 has two co-primary endpoints: Change in hemoglobin concentration from baseline to the end of the chemotherapy treatment period and survival time

The protocol specified that change in FACT-Fatigue (a subset of FACT-anemia) subscale scores from baseline to the end of study treatment as the secondary endpoint.

Safety Endpoint:

There was no pre-specified safety point. The overall survival was specified as the efficacy endpoint.

5.3.7.4 Treatment and ancillary management

Subjects were randomized in a 1:1 ratio to receive Aranesp or placebo throughout 6 cycles of chemotherapy and for 3 weeks after the last dose of on-study chemotherapy (cisplatin or carboplatin plus etoposide) (maximum of 24 weeks). Darbepoetin alfa was administered at a dose of 300 µg once weekly (QW) for the first 4 weeks, followed by 300 µg once every 3 weeks (Q3W) for the remainder of the treatment period.

During study weeks where no dose was planned, an additional weekly dose of investigational product was to be administered if a subject's hemoglobin concentration was  $< 11.0$  g/dL. Investigational product was to be withheld if a subject had a hemoglobin concentration  $\geq 14.0$  g/dL and reinstated once the concentration was  $< 13.0$  g/dL.

Treatment duration: 24 weeks

#### 5.3.7.5 Study Sites including enrollment

Six hundred patients were enrolled into the study at 69 sites in Europe, Australia, and Canada.

#### 5.3.7.6 Study populations

The analysis on overall survival was conducted on the full analysis set (FAS) consisting of all randomized subjects who receive at least one dose of chemotherapy according to the study regimen and at least one dose of study drug.

The analysis on the hemoglobin change was conducted on the primary analysis set (PAS) consisting of all randomized subjects who receive at least one dose of chemotherapy according to the study regimen and at least one dose of study drug with baseline, and at least one post-baseline hemoglobin value outside the 28 days after RBC transfusion.

Safety analysis set consists of all randomized subjects who received at least one dose of study drug. Subjects not dosed in accordance with the randomized treatment were included in the treatment received and not the randomized treatment for all safety presentations. Subjects who inadvertently receive doses of both study treatments were included in the darbepoetin alfa treatment group.

All PRO analyses were conducted on the PRO analysis set, which consists of all randomized subjects in the full analysis set who complete the PRO FACT-Fatigue subscale score at baseline and at a minimum of one follow-up visit.

#### 5.3.7.7 Patient Disposition

A total of 705 subjects were screened for participation in this study and 600 were randomized. Of these randomized subjects, 597 (99.5%) received at least 1 dose of investigational product (darbepoetin alfa or placebo) and 596 (99.3%) received at least 1 dose of investigational product and chemotherapy (Table 5.3.7.7.1). Overall, 305 subjects (51%) completed the study as determined by the investigator (50% darbepoetin alfa, 52% placebo). The most frequently reported reasons for study discontinuation were disease progression (19% darbepoetin alfa, 16% placebo) and death (16% in both treatment groups).

Table 5.3.7.7.1 Subject Disposition for Study 20010145 (copied from Amgen's submission)

**Table 8-1. Subject Disposition**

	Darbepoetin alfa	Placebo	Total
	n (%)	n (%)	n (%)
Subjects screened			705
Subjects randomized	299	301	600
<b>Investigational Product Accounting</b>			
Subjects who never received investigational product	0 (0)	3 (1)	3 (1)
Subjects who received investigational product	299 (100)	298 (99)	597 (100)
Subjects who completed investigational product	166 (56)	167 (55)	333 (56)
Subjects who discontinued investigational product	133 (44)	131 (44)	264 (44)
<b>Study Completion Accounting</b>			
Subjects who completed study	149 (50)	156 (52)	305 (51)
Subjects who discontinued study	150 (50)	145 (48)	295 (49)

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Note: Percentages based on subjects randomized

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### 5.3.7.8 Demographics, underlying disease and drug treatment

Among 596 (99.5%) patients who received at least 1 dose of chemotherapy and investigational product, 385 were men (65%) and 211 were women (35%); median age was 61 (28-, 82) (8.8) years, and all patients (596) were white (100%) (Table 5.3.7.8.1).

All patients had a diagnosis of extensive stage of small cell lung cancer and received platinum-containing chemotherapy. In general, baseline disease characteristics were similar between the darbepoetin alfa and the placebo groups. Most subjects had an ECOG performance status of < 2 (78% darbepoetin alfa, 79% placebo); most had abnormal LDH levels at baseline (58% darbepoetin alfa, 56% placebo); most subjects did not have clinically indicated head CT scans and bone scans (76% and 78%, respectively).

Table 5.3.7.8.1 Demographics for study 20010145 (copied from Amgen's submission)

**Table 8-5. Baseline Demographics by Treatment Group  
 (Full Analysis Set)**

	Darbepoetin alfa (N=298)	Placebo (N=298)	Total (N=596)
<b>Sex - n(%)</b>			
Male	187 (63)	198 (66)	385 (65)
Female	111 (37)	100 (34)	211 (35)
<b>Race - n(%)</b>			
White	298 (100)	298 (100)	596 (100)
Other	0 (0)	0 (0)	0 (0)
<b>Age - years</b>			
n	298	298	596
Mean	60.6	61.3	61.0
SD	9.2	8.3	8.8
Median	61.0	61.0	61.0
Q1, Q3	55.0, 68.0	55.0, 67.0	55.0, 67.5
Min, Max	28, 81	37, 82	28, 82
<b>Age Group - n(%)</b>			
< 65 years	192 (64)	196 (66)	388 (65)
≥ 65 years	106 (36)	102 (34)	208 (35)
<b>Geriatric Age Group - n(%)</b>			
< 75 years	283 (95)	280 (94)	563 (94)
≥ 75 years	15 (5)	18 (6)	33 (6)
<b>Geographic Region<sup>a</sup> - n(%)</b>			
Western Europe	66 (22)	66 (22)	132 (22)
Australia/ North America	10 (3)	9 (3)	19 (3)
Rest of the World	222 (74)	223 (75)	445 (75)

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<sup>a</sup>: This data is from IVRS vendor.

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 c\_keyvar.sas7bdat

### 5.3.7.9 Efficacy Outcomes

No difference in overall survival was observed between the darbepoetin alfa and placebo groups.

(b) (4)

#### 5.3.7.10 Outcome of Safety Assessments

Eighteen percent of subjects in the darbepoetin alfa group and 16% of subjects in the placebo group died during the study treatment period or within 30 days after the last dose of investigational product. Two deaths in the darbepoetin alfa group (pulmonary embolism and ischemic stroke) were considered to have a reasonable possibility of being treatment related by the investigator.

Almost all subjects had at least 1 adverse event during the study (96% darbepoetin alfa, 98% placebo). The subject incidence of treatment-related adverse events was 5% in each group. Serious adverse events were reported for 46% of subjects in the darbepoetin alfa group and 41% of subjects in the placebo group; the most frequently reported serious adverse events were attributed to the underlying malignancy. The most frequently reported treatment related serious adverse event was pulmonary embolism (1% darbepoetin alfa, 0% placebo). A similar percentage of subjects discontinued the study because of adverse events (4% darbepoetin alfa, 3% placebo).

Cardiovascular and thromboembolic events occurred at higher rate in the

darbepoetin alfa group (22%) compared to the placebo group (15%), primarily due to embolism/thromboses (9% darbepoetin alfa, 5% placebo). During the study treatment period, deaths reported by the investigator as resulting from cardiovascular/thromboembolic events did not differ between treatment groups (4% darbepoetin alfa, 3% placebo).

#### 5.3.7.11 Discussion of Findings/Conclusions

##### **Amgen's Conclusions:**

Superiority of darbepoetin alfa versus placebo was not demonstrated for overall survival, with no difference observed between the treatment groups (b) (4)

In this phase 3 study, darbepoetin alfa administered as a fixed dose of 300 µg QW for 4 weeks followed by 300 µg Q3W significantly lessened reductions in hemoglobin concentrations relative to placebo in subjects with previously untreated extensive-stage SCLC receiving cytotoxic chemotherapy.

Thromboembolic events occurred at a moderately higher rate in subjects receiving darbepoetin alfa than in those receiving placebo, consistent with the known safety profile of darbepoetin alfa in chemotherapy induced anemia.

##### *Reviewer's comments:*

*Study 200010145 was conducted to evaluate whether increasing or maintaining hemoglobin concentrations with darbepoetin alfa, when administered with platinum-containing chemotherapy in subjects with previously untreated extensive-stage SCLC, increases survival.*

*The patient population was homogenous in disease characteristics (extensive stage of SCLC) and in concomitant chemotherapy regimen (platinum-containing chemotherapy). Due to the aggressiveness in disease nature of SCLC and the relatively uniform platinum-containing chemotherapy used for extensive stage of SCLC, there are limitations to generalizing the observed efficacy and safety results from study 20010145 to patients with tumors other than SCLC.*

*The tested dosing regimen, Aranesp 300 ug Q3W for 4 weeks followed by 300ug Q3w, in study 20010145 is not the approved dosage regimen of Aranesp, 2.25 ug/kg, SC, QW or 500 ug Q3W.*

*About half of the subjects enrolled in the Aranesp (50%) and the placebo (48%) arms in study 20010145 did not complete the study, limiting any conclusion or interpretation inferred from the study results.*

(b) (4)

*Though the endpoint of regulatory interest, i.e., the proportion of subjects who received RBC transfusions, was not the primary endpoint of the study 20010145, the efficacy outcome demonstrated the efficacy of Aranesp in reducing the proportion of subjects receiving RBC transfusions in patients with small cell lung cancer on chemotherapy, implying that a different Aranesp dose regimen, 300 ug Q3W for 4 weeks followed by 300 ug Q3W, from the currently approved dosing regimen, 2.25 ug/kg QW, or 500ug Q3W may be considered effective and the dosing regimen of Aranesp may be not critical/stringent in reducing RBC transfusions in the oncology indication.*

*The study results of 20010145 did not meet the pre-specified co-primary endpoint to demonstrate* (b) (4)

*No difference was observed on HRQoL outcomes between the Aranesp and the placebo groups.*

*In summary, the results of study 20010145 are of limited value to address the pertinent PAS supplement issues on hemoglobin initiation level (FDA Item 3), maximum hemoglobin level (FDA Item 4), and discontinuation of ESA therapy post-chemotherapy (FDA Item 5).*

### 5.3.8 Study 20010103

#### 5.3.8.1 Study Title, Phase, and Purpose

Title: A Multicenter, Randomized, Double-blind, Placebo-controlled Study of Darbepoetin Alfa for the Treatment of Anemia of Cancer.

Study Phase: 3

#### Study Objectives:

The primary objective of study 20010103 was to evaluate the efficacy of darbepoetin alfa given at 6.75 µg/kg every 4 weeks (Q4W) versus placebo in reducing the occurrence of red blood cell (RBC) transfusions in anemic subjects with active malignancies who were not receiving chemotherapy or radiotherapy. Additional objectives included evaluation of hemoglobin (HGB) variables and the safety profile of darbepoetin alfa.

#### 5.3.8.2 Study Design

Study 20010103 was a phase 3, multicenter, randomized, double-blind, placebo-controlled study of darbepoetin alfa in anemic subjects with active nonmyeloid malignancies who had not received within 4 weeks, or were not planning to receive, chemotherapy or radiotherapy. Subjects were randomized in a 1:1 ratio to receive darbepoetin alfa or placebo. Randomization was stratified on 5 factors: geographic region, screening HGB, recent RBC transfusion, ECOG score, and tumor type/treatment category. Upon achieving a predefined number of transfusion events, the randomization weighting was changed to 9:1 (darbepoetin alfa vs. placebo) until there was a total of 500 subjects randomized to darbepoetin alfa.

After treatment on this study, subjects were eligible to proceed into a separate but similar treatment protocol for an additional 16 weeks on their originally assigned blinded study design (study 20020149).

Study Period: 15 April 2004 through 07 November 2006 (data cutoff)

### 5.3.8.3 Inclusion/Exclusion Criteria, Study Procedures, and Timelines

#### Inclusion:

- Subjects of legal age to give consent
- with myeloid malignancy
- hemoglobin concentration  $\leq 11.0$  g/dL
- an ECOG status of 0 to 2
- life expectancy of  $\geq 4$  months
- adequate serum folate, vitamin B12 levels and adequate liver and renal functions

#### Exclusion:

- Subjects received or planned to receive cytotoxic chemotherapy or myelosuppressive radiotherapy (i.e., pelvic/spinal irradiation) during the study or within 4 weeks before randomization previous radiotherapy
- in complete remission as determined by the investigator
- chronic myeloid or acute leukemia, Burkitts's or lymphoblastic lymphoma
- other diagnoses not related to cancer which cause anemia
- documented history of pure red cell aplasia
- known history of seizure disorder, inflammatory or cardiac disorders, uncontrolled hypertension
- any RBC transfusion within 2 weeks of randomization
- recombinant human erythropoietin or darbepoetin alfa within 4 weeks of randomization.
- brain metastases that were symptomatic or treated with steroids
- other known primary malignancies within the past 5 years (except basal cell carcinoma, squamous cell carcinoma in situ, cervical carcinoma, or surgically cured malignancies)
- cardiac diseases, iron deficiency, or known primary hematologic disorders that could cause anemia

Study procedures:

Patients were evaluated during treatment, at the end-of-treatment visit (week 17), an end-of-study visit (week 19) and an additional 2 years of follow up for survival status.

A flowchart of study procedures and assessments is copied below from the study protocol.

**Appendix A. Schedule of Assessments**

	SCREEN <sup>a</sup>	TREATMENT									EOT	EOS <sup>c</sup>	LTFU	
		W 1 <sup>b</sup>	W 3	W 5	W 7	W 9	W 11	W 13	W 15	W 17				W 19
Informed Consent <sup>d</sup>	X													
Medical History/Current Treatment	X													
Disease assessment	X										X			
Survival <sup>n</sup>														X
Physical Exam <sup>e</sup>	X										X			
Vital Signs <sup>f</sup>	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X					X					X			
Adverse Events and Hospitalization		→												
Concomitant Medication		→												
Transfusions	X	→												
PRO Assessments <sup>g</sup>		X				X					X			
Planned Investigational Product Administration <sup>h</sup>		X		X		X			X					
Serum Pregnancy Test	X													
Antibody Sample Collection		X									X	X		
EPO Concentration <sup>g</sup>		X												
CBC <sup>i</sup>	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry <sup>j</sup>	X	X									X			
Iron Status <sup>k</sup>	X	X		X		X			X		X			
Folate and Vitamin B <sub>12</sub>	X													
sTfR <sup>l</sup>		X	X											
Proinflammatory Cytokines <sup>m</sup>		X		X							X			

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- (a) screening will occur ≤ 14 days of randomisation, however if screening hemoglobin is more than 7 days prior to randomisation, an additional hemoglobin concentration is required within 7 days prior to randomisation
- (b) week 1 = baseline, procedures and assessments will occur on study day 1 before administration of investigational product
- (c) the end of study is scheduled to occur at week 19, or 6 weeks post last dose for subject who terminate investigational product prior to week 13
- (d) signed informed consent must be obtained before any study specific procedures
- (e) including body weight and height at screening. At the EOT visit the subject's weight will be reassessed for subjects who complete all visits
- (f) including blood pressure
- (g) before any other assessments are performed on the same day
- (h) investigational product will be administered once every 4 weeks
- (i) complete blood count (CBC) will consist of hct, hgb, platelet count, and WBC with differential
- (j) chemistry will consist of creatinine, bilirubin, LDH, ALT, AST
- (k) iron status will consist of serum iron, TIBC, ferritin and Tsat and are required at weeks 1, 5, 9, 13 and EOT visit
- (l) soluble transferrin receptor (sTfR levels) will be collected at baseline (week 1) and week 3 at selected centers
- (m) serum cytokine levels (IL-1 and TNFα) will be collected at baseline (week 1), week 5 and EOT visit at selected centers
- (n) survival status will be assessed every 6 months for a minimum of 2 years after the end of study visit

**Study Endpoints**

Primary Efficacy Endpoint: total occurrence of RBC transfusions from week 5 to week 17.

Secondary Efficacy Endpoints: incidence of first RBC transfusion from week 5 to week 17, and

change in HGB between baseline and the end of treatment period (EOTP).

Supportive Endpoints:

- HGB response ( $\geq 2$  g/dL increase in HGB from baseline) between study day 1 and EOTP in the absence of RBC transfusions in the preceding 28 days
- HGB correction ( $\text{HGB} \geq 12$  g/dL) between study day 1 and EOTP in the absence of RBC transfusions in the preceding 28 days
- hematopoietic response (increase in  $\text{HGB} \geq 2$  g/dL from baseline or achieving  $\text{HGB} \geq 12$  g/dL) between study day 1 and EOTP in the absence of RBC transfusions in the preceding 28 days
- change in HRQoL measures between baseline and week 17 (including FACT-Fatigue subscale, FACT-General subscales, EQ-5D thermometer, BSI anxiety scale, BSI depression scale, number of caregiver hours)

Safety Endpoints:

- all adverse events, serious adverse events, survival, and incidence of neutralizing antibodies to darbepoetin alfa

Statistical Analysis Plan

Approximately 1000 subjects (500 per treatment group) were planned for this study, assuming an underlying transfusion rate of 20%, a treatment-related reduction of 40%, 90% power to detect a difference, and a significance level of 5% (2-sided). This would require approximately 145 subjects to receive at least 1 transfusion.

Analysis of the primary endpoint, total occurrence of RBC transfusions between weeks 5 and 17, was performed on the primary transfusion analysis set which consisted of subjects who received at least 1 dose of investigational product, were randomized during the period of 1:1 randomization, and completed at least 4 weeks of the study. A proportional hazards model was constructed to estimate the hazard ratio (HR) between darbepoetin alfa and placebo (darbepoetin alfa/placebo) in the occurrence of RBC transfusions. This analysis was stratified by the following variables: screening HGB concentration ( $<10$  g/dL or  $\geq 10$  g/dL); geographic region (Europe vs. Rest of World); recent RBC transfusion (yes vs. no); tumor-type treatment categories (chronic lymphocytic leukemia or low grade lymphoma vs. receiving hormonal or antibody vs. all other eligible subjects); and ECOG score (0-1 vs. 2).

Analysis of the secondary endpoint incidence of first transfusion between weeks 5 and 17 used the stratified Cochran-Mantel-Haenszel test on the primary transfusion analysis set. The distribution for the time to event was estimated by Kaplan-Meier curves with supporting summary statistics. The secondary endpoint of change in HGB from baseline to end-of-treatment was assessed by calculating a point estimate and 95% confidence interval (CI). Pre-specified sensitivity analyses were performed on the incidence of transfusions that included subjects with  $\text{HGB} \leq 8.0$  g/dL (the protocol trigger for a transfusion) as transfused regardless of whether they were transfused.

Standard tabulations were constructed for adverse events, listing preferred terms grouped by MedDRA system organ class. Summary statistics were generated for laboratory analyses, as well as demographics, baseline characteristics, study drug exposure, and other variables.

#### 5.3.8.4 Treatment and ancillary management

Subjects received darbepoetin alfa at a dose of 6.75 µg/kg or placebo SC Q4W, i.e., at weeks 1, 5, 9, and 13, for up to 16 weeks. Treatment was designed to maintain HGB at ≤12 g/dL; the dose of investigational product was withheld or reduced accordingly based on HGB monitoring throughout the study.

Treatment duration: 16 weeks

#### 5.3.8.5 Study Sites including enrollment

This study was conducted at 144 sites across multiple regions including Western Europe, North America, Australia, and Central and Eastern Europe. A total of 1473 subjects were screened for the study, of whom 989 were randomized at 144 sites and 985 received study drug.

#### 5.3.8.6 Study populations

The full analysis set (FAS) consists of all randomized subjects who receive at least one dose of investigational product. This analysis set contains both subjects enrolled in the 1:1 randomization and the 9:1 randomization period.

The efficacy analysis set (EAS) consists of subjects in the FAS that were randomized during the period of 1:1 randomization.

For the occurrence of a red blood cell transfusion from week 5 (study day 29) to the end of week 17 (study day 119), the primary statistical analysis were conducted on subjects in the efficacy analysis set (EAS) who completed at least 4 weeks of study (i.e., date of study withdrawal on or after study day 29).

The hemoglobin analysis set consists of all subjects in the EAS with baseline and at least one post baseline hemoglobin concentration.

The safety analysis set consists of all subjects who received at least one dose of investigational product.

The Health-Related Quality of Life (HRQoL) analysis set consists of a subset of the EAS where subjects have a valid baseline and at least one valid post-baseline FACT-Fatigue subscale score.

#### 5.3.8.7 Patient Disposition

Of 985 subjects who received study drug, nearly half of the subjects in both treatment groups prematurely discontinued the study; 253 (49%) in the Aranesp arm and 219 (46%) in the placebo

arm (Table 5.3.8.7.1). The most common reasons for premature study discontinuation were death, consent withdrawn, and disease progression (Table 5.3.8.7.2). There were more patients who discontinued study due to death in the Aranesp arm (116/515, 22%) than in the placebo arm (83/470, 17%). Similar numbers of subjects in both arms discontinued study due to reasons other than death. Median time on study was similar in both arms: 17.9 weeks for the darbepoetin alfa group and 18.0 weeks for the placebo group .

Table 5.3.8.7.1 Subject Disposition for Study 20010103 (copied from Amgen’s submission)

**Table 8-1. Subject Disposition  
 (All Screened Subjects)**

	Placebo n (%)	Darbepoetin alfa 6.75 µg/kg Q4W n (%)	Total n (%)
Subjects screened			1473
Subjects randomized	472	517	989
<b>Investigational Drug Accounting</b>			
Subjects who never received investigational drug	2 (0.4)	2 (0.4)	4 (0.4)
Subjects who received investigational drug	470 (99.6)	515 (99.6)	985 (99.6)
Subjects who completed investigational drug	303 (64.2)	320 (61.9)	623 (63.0)
Subjects who discontinued investigational drug	167 (35.4)	195 (37.7)	362 (36.6)
<b>Study Completion Accounting</b>			
Subjects who completed study	253 (53.6)	264 (51.1)	517 (52.3)
Subjects who discontinued study	219 (46.4)	253 (48.9)	472 (47.7)

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Note: Percentages based on subjects randomized

Table 5.3.8.7.2 Subject Discontinuations from Study 20010103 (copied from Amgen's submission)

Table 8-10. Subject Discontinuations from Study  
 (All Randomized Subjects)

	Placebo	Darbepoetin alfa 6.75 µg/kg Q4W	Total
	n (%)	n (%)	n (%)
Subjects randomized	472	517	989
Subjects who completed study	253 (53.6)	264 (51.1)	517 (52.3)
Subjects who discontinued study	219 (46.4)	253 (48.9)	472 (47.7)
Ineligibility Determined	9 (1.9)	5 (1.0)	14 (1.4)
Protocol Deviation	2 (0.4)	0 (0.0)	2 (0.2)
Noncompliance	6 (1.3)	2 (0.4)	8 (0.8)
Adverse Event	10 (2.1)	14 (2.7)	24 (2.4)
Consent Withdrawn	51 (10.8)	48 (9.3)	99 (10.0)
Disease Progression While on Study	39 (8.3)	48 (9.3)	87 (8.8)
Administrative Decision	1 (0.2)	3 (0.6)	4 (0.4)
Lost to Follow-up	5 (1.1)	7 (1.4)	12 (1.2)
Death	83 (17.6)	116 (22.4)	199 (20.1)
Protocol-specific Criteria	11 (2.3)	10 (1.9)	21 (2.1)
Other	2 (0.4)	0 (0.0)	2 (0.2)

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Note: Percentages based on subjects randomized.

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Program: /stat/nesp/bnc/nesp20010103/analysis/final/stat/ves/programs/tables/t\_disp.sas  
 Output: t14\_001\_002\_002\_disp\_study\_all.rtf (Date Generated: 06MAR07:16:48:15) Source Data: c\_disp, c\_norand.sas7bdat

### 5.3.8.8 Demographics, underlying disease and drug treatment

A total of 1473 subjects were screened for the study, of whom 989 were randomized at 144 sites and 985 received study drug. Most subjects were white and there were slightly more men than women; median age was 65.0 years (range: 18, 89) (Table 5.3.8.8.1). The most common malignancies were non-small cell lung, breast, prostate, colorectal, myeloma, and kidney cancers (Table 5.3.8.8.2). In general, patient demographics and baseline tumor types and disease characteristics (Table 5.3.8.8.3) were similar between the Aranesp and the placebo arms.

Table 5.3.8.8.1 Demographics from Study 20010103 (copied from Amgen's submission)

**Table 8-4. Subject Demographics  
 (Full Analysis Set)**

	Placebo (N=470)	Darbepoetin alfa 6.75 µg/kg Q4W (N=515)	Total (N=985)
<b>Sex - n (%)</b>			
Male	220 (46.8)	285 (55.3)	505 (51.3)
Female	250 (53.2)	230 (44.7)	480 (48.7)
<b>Race - n (%)</b>			
White	444 (94.5)	493 (95.7)	937 (95.1)
Black	21 (4.5)	18 (3.5)	39 (4.0)
Hispanic	2 (0.4)	3 (0.6)	5 (0.5)
Asian	3 (0.6)	1 (0.2)	4 (0.4)
<b>Age - years</b>			
n	470	515	985
Mean	64.3	64.0	64.1
SD	11.4	11.8	11.6
SE	0.5	0.5	0.4
Median	66.0	65.0	65.0
Q1, Q3	57.0, 73.0	56.0, 73.0	56.0, 73.0
Min, Max	28, 88	18, 89	18, 89
<b>Age Group - n (%)</b>			
< 65 years	213 (45.3)	247 (48.0)	460 (46.7)
≥ 65 to < 75 years	162 (34.5)	163 (31.7)	325 (33.0)
≥ 75 years	95 (20.2)	105 (20.4)	200 (20.3)

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Program: /stat/nsp/bnc/nsp20010103/analysis/final/stat/ties/programs/tablest\_demog.sas  
 Output: t14\_002\_001\_001\_demog\_fit.rtf (Date Generated: 06MAR07:10:41:30) Source Data:  
 c\_keyvar.sas7bdat

Table 5.3.8.8.2 Baseline Tumor Types from Study 20010103 (copied from Amgen's submission)

**Table 8-5. Primary Tumor Types  
 (Full Analysis Set)**

	Placebo n (%)	Darbepoetin alfa 6.75 µg/kg Q4W n (%)	Total n (%)
Number of Subjects	470	515	985
<b>Solid Tumor Type</b>			
Non-small cell lung	83 (17.7)	97 (18.8)	180 (18.3)
Breast	62 (13.2)	66 (12.8)	128 (13.0)
Prostate	49 (10.4)	54 (10.5)	103 (10.5)
Large intestine	29 (6.2)	45 (8.7)	74 (7.5)
Kidney	28 (6.0)	22 (4.3)	50 (5.1)
Cervix	21 (4.5)	19 (3.7)	40 (4.1)
Ovarian	22 (4.7)	17 (3.3)	39 (4.0)
Stomach	18 (3.8)	19 (3.7)	37 (3.8)
Other solid tumor	17 (3.6)	14 (2.7)	31 (3.1)
Small cell lung	10 (2.1)	15 (2.9)	25 (2.5)
Head & neck (squamous cell carcinoma)	12 (2.6)	11 (2.1)	23 (2.3)
Pancreas	13 (2.8)	10 (1.9)	23 (2.3)
Soft tissue sarcoma	9 (1.9)	10 (1.9)	19 (1.9)
Bladder	10 (2.1)	8 (1.6)	18 (1.8)
Melanoma	4 (0.9)	10 (1.9)	14 (1.4)
Endometrial	5 (1.1)	4 (0.8)	9 (0.9)
Uterus	4 (0.9)	4 (0.8)	8 (0.8)
Oral	3 (0.6)	4 (0.8)	7 (0.7)
Esophagus	2 (0.4)	4 (0.8)	6 (0.6)
Carcinoma of unknown primary	2 (0.4)	3 (0.6)	5 (0.5)
Testicular	1 (0.2)	2 (0.4)	3 (0.3)
Ureter	0 (0)	1 (0.2)	1 (0.1)
<b>Hematological Tumor Type</b>			
Multiple myeloma	38 (8.1)	33 (6.4)	71 (7.2)
Non-Hodgkin's lymphoma	15 (3.2)	21 (4.1)	36 (3.7)
Chronic lymphocytic leukemia (CLL)	10 (2.1)	10 (1.9)	20 (2.0)
Other hematological malignancy	2 (0.4)	6 (1.2)	8 (0.8)
Hodgkin's disease	1 (0.2)	6 (1.2)	7 (0.7)

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Note: Tumor type as indicated on the CRF.

Table 5.3.8.8.3 Baseline Disease characteristics from Study 20010103 (copied from Amgen's submission)

**Table 8-6. Baseline Disease Characteristics  
 (Full Analysis Set)**

	Placebo (N=470)	Darbepoetin alfa 6.75 µg/kg Q4W (N=515)	Total (N=985)
<b>Current disease stage - n (%)</b>			
I	11 (2.3)	10 (1.9)	21 (2.1)
II	42 (8.9)	38 (7.4)	80 (8.1)
III	104 (22.1)	115 (22.3)	219 (22.2)
IV	275 (58.5)	311 (60.4)	586 (59.5)
Other	21 (4.5)	26 (5.0)	47 (4.8)
Unknown	17 (3.6)	15 (2.9)	32 (3.2)
<b>ECOG performance status - n (%)</b>			
0	87 (18.5)	85 (16.5)	172 (17.5)
1	254 (54.0)	280 (54.4)	534 (54.2)
2	128 (27.2)	149 (28.9)	277 (28.1)
3	1 (0.2)	0 (0.0)	1 (0.1)
Missing	0 (0.0)	1 (0.2)	1 (0.1)
<b>Disease status - n (%)</b>			
Complete Response	3 (0.6)	3 (0.6)	6 (0.6)
Partial Response	34 (7.2)	33 (6.4)	67 (6.8)
Progressive Disease	193 (41.1)	225 (43.7)	418 (42.4)
Stable Disease	217 (46.2)	237 (46.0)	454 (46.1)
Unable to Evaluate	20 (4.3)	16 (3.1)	36 (3.7)
Missing	3 (0.6)	1 (0.2)	4 (0.4)
<b>Extent of disease(only if SCLC) - n (%)</b>			
	10	15	25
Extensive	7 (70.0)	11 (73.3)	18 (72.0)
Limited	3 (30.0)	4 (26.7)	7 (28.0)
<b>Grade of lymphoma(only if Non-Hodgkin's) - n (%)</b>			
	15	21	36
Low	12 (80.0)	13 (61.9)	25 (69.4)
Intermediate	1 (6.7)	6 (28.6)	7 (19.4)
High	2 (13.3)	2 (9.5)	4 (11.1)

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Program: /stat/hespi/nc/nesp20010103/analysis/final/statfiles/programs/tables1\_dischar.sas  
 Output: t14\_002\_003\_001\_dischar\_mt.tr (Date Generated: 06MAR07:16:44:36) Source Data: c\_diag,  
 c\_disrsp, c\_vitals.sas7bdat

### 5.3.8.9 Efficacy Outcomes

The primary endpoint, total occurrences of transfusions between weeks 5 and 17, was not significantly different between treatment groups, with a HR of 0.85 (95% CI: 0.62, 1.17) for darbepoetin alfa relative to placebo (p = 0.320).

In contrast, a pre-specified sensitivity analysis in which non-transfused subjects with HGB  $\leq$  8.0 g./dL were considered to have transfusion “events”, yielded a statistically significant result, with a HR of 0.72 (95% CI: 0.56, 0.92;  $p = 0.008$ ).

Subjects in the Aranesp group had a statistically significant higher incidence of protocol pre-specified HGB response, HGB correction, and hematopoietic response.

HRQOL outcomes:

No difference was observed in any HRQoL outcome between the Aranesp and the placebo arms.

The proportions of subjects who completed the required questionnaires were similar between treatment groups. Baseline scores for all of the HRQoL outcomes were also similar between groups (Median baseline FACT-Fatigue score for the placebo group was 29.6 and 30.0 for the darbepoetin alfa group).

No marked improvement or worsening was seen between baseline and end-of-treatment in any HRQoL variable. Mean change from baseline was less than 1 point in either direction in both treatment groups for FACT Fatigue, FACT-General Physical, FACT-General Emotional, FACT-General Functional, FACT-General Social/Family, EQ-5D Health State Index, Health State Index, BSI Anxiety, and BSI Depression scales—all except FACT-General Total subscale score, which decreased by a mean of 0.45 points in the placebo group and by 1.50 points in the darbepoetin alfa group.

#### 5.3.8.10 Outcome of Safety Assessments

Subjects were to receive 4 total doses of study drug, planned at study weeks 1, 5, 9, and 13. Median number of doses delivered for the placebo and darbepoetin alfa groups were 4 and 3, respectively, although the means were similar between groups (3.2 and 2.9 doses, respectively) (Table 11-2). Median duration on treatment was longer for the placebo group 17.0 weeks versus 13.0 weeks for darbepoetin alfa.

There were more deaths on study in the darbepoetin alfa group (26.4%) than in the placebo group (20.0%). In an analysis of all deaths, including those occurring during long-term follow-up, median survival times were 34.7 weeks and 47.0 weeks, respectively. The majority of deaths on study were attributed to the subjects’ underlying neoplastic disease, but causes of death in this study were not adjudicated. The HR for death in the darbepoetin alfa group relative to placebo was 1.29 (95% CI: 1.08, 1.55;  $p = 0.006$ ).

Subjects in the darbepoetin alfa group experienced higher incidences of fatal adverse events (26% versus 20%), serious adverse events (41% versus 34%), and severe, life-threatening or fatal adverse events (48% versus 41%) than those in the placebo group.

Baseline factors that were the most consistent covariates for death included gender, lung cancer, low screening HGB, European region, low ECOG, stage IV disease, and recent prior transfusion. Risk of death did not appear to be associated with a HGB  $\geq$  13 g/dL (adjusted HR = 0.55,  $p < 0.001$ ) or with a rapid rate of HGB rise (adjusted HR = 0.82,  $p = 0.05$ ) in time-varying covariate analyses.

Similar proportions of subjects in each treatment group experienced at least 1 adverse event during the study. Fatigue was the only individual adverse event that occurred in more than 10% of subjects, occurring in 13.2% of subjects receiving placebo and 11.5% of subjects receiving darbepoetin alfa. No individual event had a between-group difference greater than 5%.

Among pre-specified adverse events of interest, cardiovascular and thromboembolic events occurred at a higher rate in the darbepoetin alfa group, primarily due to arrhythmias and embolism/thrombosis. However, these adverse events did not appear to be associated with maximum HGB attained or with rate of HGB rise, and there were no between-group differences in deaths attributed to cardiovascular or thromboembolic events.

The majority of serious adverse events were attributed to neoplastic disease, with a higher incidence of serious adverse events in the darbepoetin alfa group relative to the placebo group (28.3% vs. 22.8%, respectively).

#### 5.3.8.11 Discussion of Findings/Conclusions

Amgen's conclusion:

This study did not demonstrate the effectiveness of darbepoetin alfa given at 6.75  $\mu\text{g}/\text{kg}$  Q4W in reducing the total occurrences of RBC transfusions in anemic subjects with cancer who were not receiving chemotherapy or radiotherapy. A secondary transfusion endpoint and hematologic endpoints did suggest benefit in the darbepoetin alfa group. Safety analyses demonstrated a significantly higher risk of death in the darbepoetin alfa treatment group, indicating a detrimental effect of darbepoetin alfa use in anemic cancer patients not receiving chemotherapy or radiotherapy.

*Reviewer's comments:*

*Study 200010103 was conducted to evaluate the efficacy of Aranesp given at 6.75  $\mu\text{g}/\text{kg}$  every 4 weeks (Q4W) versus placebo in reducing the occurrences of red blood cell (RBC) transfusions in anemic subjects with active malignancies who were not receiving chemotherapy or radiotherapy.*

*The tested dosing regimen of Aranesp administered at 6.75  $\mu\text{g}/\text{kg}$  Q4W is not the approved Aranesp dosing regimen, and the patient population was not the indicated population.*

*Nearly half of the enrolled subjects in both Aranesp and placebo arms did not complete the study, raising questions on the overall study conduct and conclusions and the interpretations inferred from the study results.*

*The results from study 20010103 did not demonstrate the efficacy of Aranesp in reducing RBC transfusion rates, but demonstrated the detrimental effect of Aranesp on the increased risks for death and shortened survival, reinforcing the safety concerns of increased mortality of Aranesp use in the oncology setting, and the ineffectiveness of Aranesp use in reducing RBC transfusions in patients not receiving chemotherapy. It is this reviewer's opinion that the differences on the efficacy of Aranesp in reducing RBC transfusions between patients receiving concomitant chemotherapy or not are plausible, assuming the role of chemotherapy on the RBC transfusions patients received during the chemotherapy course. However, the safety signals on the risks of increased mortality of Aranesp observed in patients not receiving concomitant chemotherapy should not be different from patients receiving concomitant chemotherapy, and should be extrapolated into the safety concerns in patients receiving Aranesp and concomitant chemotherapy. Therefore, the safety concerns of increased mortality of Aranesp should be applicable in all patients receiving Aranesp in the oncology setting, regardless whether patients are receiving concomitant chemotherapy.*

*The study protocol did not specify whether Aranesp or other ESAs are permitted during the long term follow up period. Considering the wide off-label use of ESAs in oncology community practice, the survival results from the long term follow-up period may be influenced by the potential effect of post-study ESA use which could reduce harmful effects seen in the Aranesp arm.*

*It is of interest to note that study 20010103 did not meet the protocol specified primary endpoint for RBC transfusion, but met protocol specified endpoints on hemoglobin variables, indicating the effectiveness of Aranesp in increasing the hemoglobin values as consistently observed in other studies. Therefore, there is discordance between the effect of Aranesp on increasing hemoglobin values and the effect of Aranesp on reducing RBC transfusions observed in study 20010103, but not in other studies (e.g., 980297, 20000161, 20030232, and 20010145). This raises a question as to whether RBC transfusion practice in patients not receiving chemotherapy are less likely to be affected by individual hemoglobin values as compared with RBC transfusion practice in patients on concomitant chemotherapy. The fact that sensitivity analyses that included non-transfused subjects with HGB  $\leq$  8.0 g/dL as events yielded a statistically significant result for reduction in RBC transfusions in Aranesp treated patients lends supporting evidence to the reviewer's hypothesis that anemic patients not on chemotherapy are less likely to receive RBC transfusions as compared to anemic patients on chemotherapy. As a matter of fact, 33 out of 110 patients with RBC transfusion events in the Aranesp arm and 42 out of 144 patients with RBC transfusion events in the placebo arm had hemoglobin levels less than 8 g/dL but did not receive RBC transfusions as directed in the protocol transfusion policy. It is not clear whether inferior medical practice was observed in study 20010103 or if conventionally accepted RBC transfusion practice with hemoglobin levels less than 8 g/dL and the liberal use of RBC transfusions with hemoglobin levels greater than 8 g/dL for "anemic associated symptoms" is not warranted. If the medical practice of not prescribing RBC transfusions in patients with hemoglobin less than 8 g/dL as observed in study 20010103 is reasonable, it may be assumed that compared to patients not on chemotherapy, anemic patients on chemotherapy have higher tendency to receive RBC transfusions due to a low hemoglobin values or "anemia related" symptoms which are compounded by the concomitant chemotherapy.*

*The negative effect of Aranesp on overall survival from study 20010103 is described in the current labeling of Aranesp.*

*Though baseline hemoglobin level (< 10 g/dL versus ≥ 10 g/dL) was included as a stratification factor in study 20010103, the study was not designed to address the FDA requested items 3 on the issues of hemoglobin level for the initiation of Aranesp in the indicated population. For the same reason that patient population in study 20010103 is not the indicated population and the reasons discussed in previous review sections 5.2.2.2 and 5.2.2.3, the results from study 20010103 are of limited value to address the pertinent PAS issues on maximum hemoglobin level (FDA items 4), and discontinuation of ESA therapy post-chemotherapy (FDA item 5).*

### 5.3.9 Study 20020149

#### 5.3.9.1 Study Title, Phase, and Purpose

Title: A Multicenter, Double-blind, Placebo-controlled Rollover Study to Protocol 20010103 of Darbepoetin Alfa for the Treatment of Anemia of Cancer

Study Phase: 3

#### Study Objectives:

Study 20020149 was designed to characterize the safety profile of Aranesp over a longer period of time in allowing subjects completing study 20010103 to receive an additional 16 weeks of blinded treatment, with an emphasis on safety outcomes across a total of 32 weeks.

#### 5.3.9.2 Study Design

After 16 weeks of blinded treatment on study 20010103, subjects who completed the study were eligible to roll over into study 20020149, maintaining their blinded randomized treatment assignment for an additional 16 weeks, or a total of 32 weeks across both studies.

#### Study Period:

10 August 2004 (first subject enrolled) through 17 January 2007 (last subject completed end-of-study visit)

#### 5.3.9.3 Inclusion/Exclusion Criteria, Study Procedures, and Timelines

Successful completion of study 20010103, informed consent signed for study 20020149

#### Study procedures:

A flowchart of study procedures and assessment is copied below from the study protocol.

Appendix A. Schedule of Assessments

	20010103	20020149											
	EOT <sup>a</sup>	REGISTRATION <sup>b</sup>	TREATMENT										EOT
	W 17		W <sup>c</sup> 1	W 3*	W 5	W 7	W 9	W 11	W 13	W 15	W 17	W 19	
Informed Consent		X											
Weight <sup>e</sup>	X												
Vital Signs <sup>f</sup>	X		X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X					X					X		
Adverse Events and Hospitalization <sup>g</sup>			—————→										
Concomitant Medication <sup>h</sup>			—————→										
Transfusions <sup>k</sup>			—————→										
PRO Assessments <sup>g</sup>	X					X					X		
Planned Investigational product Administration <sup>h</sup>			X		X		X		X				
Antibody Sample Collection	X										X	X	
CBC <sup>i</sup>	X		X	X	X	X	X	X	X	X	X	X	
Chemistry <sup>j</sup>	X										X		
Iron Status	X			X		X		X		X	X		

- (a) All end of study assessments will be performed as per the 20010103 protocol before the subject is assessed for participation in the 20020149 study.  
 (b) If the subject is eligible, written informed consent must be obtained, prior to calling the IVRS to register the subject into the 20020149 study.  
 (c) The first dose of 20020149 investigational product will be administered when all 20010103 assessments have been completed.  
 (d) the end of study is scheduled to occur at week 19, or 8 weeks post last dose for subject who terminate investigational product administration prior to week 13  
 (e) only weight will be re-assessed at the 20010103 end of study visit  
 (f) including blood pressure  
 (g) before any other assessments or medical care performed on the same day  
 (h) investigational product will be administered once every 4 weeks.  
 (i) complete blood count (CBC) will consist of hct, hgb concentration, platelet count, and WBC with differential  
 (j) chemistry will consist of creatinine, bilirubin, LDH, ALT, AST  
 (k) Adverse events, concomitant medication and transfusions will be recorded on the 20010103 CRF up to the 20010103 end of study assessments are completed and will only be recorded on the 20020149 CRF once the first dose of 20020149 investigational product has been administered  
<sup>3</sup> 20010103 EOS assessments may be utilized for the 20020149 week 3 assessments.

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Study Endpoints:

Efficacy Endpoints:

- RBC transfusions
- HGB concentration and HGB change from baseline

Primary Safety Endpoint: Incidence of adverse events

Secondary Safety Endpoints:

- Formation of antibodies to darbepoetin alfa
- Survival
- Laboratory parameters
- Vital signs

Statistical Analysis Plan:

Standard tabulations were constructed for adverse events incidence, listing preferred terms grouped by MedDRA system organ class, and additionally tabulated in descending order of

incidence. Standard summary statistics were generated for laboratory analyses, vital signs, and incidence of antibody formation, as well as demographics, baseline characteristics, study drug exposure, and other descriptive variables. Survival was analyzed using the Cox proportional hazards model either stratified or adjusted for the stratification factors used at randomization, and additionally including enrollment status into study 20020149 as a time-dependent covariate to adjust for possible bias. Median survival was estimated using Kaplan-Meier curves with supporting statistics.

Subject incidence of transfusions given any time during the 32-week treatment period was expressed as a simple proportion with summary statistics; no inferential testing was employed.

Descriptive statistics were used to display HGB concentration and changes in HGB during the treatment period.

#### 5.3.9.4 Treatment and ancillary management

Subjects received darbepoetin alfa at a dose of 6.75 µg/kg or placebo SC Q4W, i.e., at weeks 1, 5, 9, and 13, with an end-of-treatment visit (week 17), an end-of-study visit (week 19) and follow-up for survival status (continuing for 2 years from the completion of study 20010103). Treatment was designed to maintain HGB at ≤ 12 g/dL; the dose of investigational product was withheld or reduced accordingly based on HGB monitoring throughout the study.

Duration of treatment: 16 weeks

#### 5.3.9.5 Study Sites including enrollment

Three hundred seventy one were enrolled into the study at 93 sites across multiple regions including Western Europe, North America, Australia, and Central or Eastern Europe.

#### 5.3.9.5 Study populations

The full analysis set (FAS) and the safety analyses set consisted of all enrolled subjects who receive at least one dose of investigational product (on or after 20020149 study day 1).

The combined full analysis set and the combined safety analysis set consist of all randomized subjects who receive at least one dose of investigational product during the combined period.

#### 5.3.9.7 Patient Disposition

A total of 371 subjects were enrolled into the study: 173 previously randomized to placebo and 198 randomized to receive darbepoetin alfa. Of these, 350 subjects received study drug during study 20020149, 165 in the placebo arm and 185 in the Aranesp arm (Table 5.3.9.7.1). The remaining 21 subjects were not dosed during extension treatment due to their HGB being > 12 g/dL; these subjects were followed for all observations and were evaluable for safety. Similar percentages of subjects (34%) in the two treatment groups did not complete the study; the most

common reasons for premature study discontinuation were death, disease progression, and consent withdrawn

Table 5.3.9.7.1 Subject Disposition from study 20020149 (copied from Amgen's submission)

Table 8-1. Subject Disposition  
 (All Subjects Enrolled in Study 20020149)

	Placebo	Darbepoetin alfa 6.75 µg/kg Q4W	Total
	n (%)	n (%)	n (%)
Subjects enrolled	173	198	371
Investigational Product Accounting			
Subjects who never received investigational product	8 (4.6)	13 (6.6)	21 (5.7)
Subjects who received investigational product	165 (95.4)	185 (93.4)	350 (94.3)
Subjects who completed investigational product	122 (70.5)	138 (69.7)	260 (70.1)
Subjects who discontinued investigational product	43 (24.9)	47 (23.7)	90 (24.3)
Study Completion Accounting			
Subjects who completed study	114 (65.9)	131 (66.2)	245 (66.0)
Subjects who discontinued study	59 (34.1)	67 (33.8)	126 (34.0)

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Note: Percentages are based on subjects enrolled.

Program: /statistics/ncsp/ncsp20020149/analysis/final/statistics/programs/tables/1\_disp.sas  
 Output: 114\_001\_002\_001\_dsp\_subject\_sas.rtf (Date Generated: 24MAY07:11:42:23) Source Data:  
 c:\dsp\sas7bdat

### 5.3.9.8 Demographics, underlying disease and drug treatment

Three hundred seventy one patients were enrolled; baseline demographics were 171 males (46%) and 200 females (54%) with a mean (SD) age of 65.3 (SD11.1), and ethnicity composition of 95% white, 4% black, and 1% others.

The most common malignancies were non-small cell lung, breast, prostate, colorectal, and kidney cancers. In general, demographics and baseline disease characteristic were similar between the two treatment groups. Median duration on treatment was 33.0 weeks for both groups.

### 5.3.9.9 Efficacy Outcomes

Among subjects who continued into extension treatment, 1 or more transfusions were received by 15.2% of subjects receiving darbepoetin alfa during the entire 32-week treatment period versus 26.0% of subjects receiving placebo. HGB in the darbepoetin alfa group increased from a pretreatment median of 9.9 g/dL to an end-of-treatment median of 11.3 g/dL, a mean increase of 1.29 g/dL. In the placebo group, median HGB increased from 10.1 g/dL to 10.5 g/dL, a mean increase of 0.5 g/dL.

### 5.3.9.10 Outcome of Safety Assessments

Thirty-two subjects (16.1%) died on-study in the darbepoetin alfa group compared with 22 subjects (12.8%) in the placebo group. The majority of deaths on study were attributed by the investigator to the subjects' underlying neoplastic disease. Overall median survival time was shorter in the darbepoetin alfa group relative to the placebo group (37.1 weeks vs. 47.0 weeks, respectively). Predictors for death included disease stage, gender, screening HGB, geographic region, recent RBC transfusion, tumor type, and ECOG score.

Serious adverse events were experienced by 30.7% of subjects in the darbepoetin alfa group vs. 32% of subjects in the placebo group. Cardiovascular/thromboembolic events occurred at a slightly higher in the darbepoetin alfa group relative to placebo (8.5% vs. 7.6%, respectively). None of these adverse events of interest (including death) appeared to be associated with maximum HGB attained or with rate of HGB rise.

The percentage of subjects who experienced 1 or more adverse events in the darbepoetin alfa group vs. placebo group was 78.9% vs. 83.7%, respectively. The most common adverse events were fatigue, constipation, dyspnea, nausea, and anorexia. Three adverse events occurred with a between-group difference greater than 5%: fatigue, headache, and anemia—all occurring at a higher incidence in the placebo group.

No notable blood chemistry or hematologic toxicities were detected. No subject in either treatment group developed neutralizing anti-erythropoietic antibodies.

#### 5.3.9.11 Discussion of Findings/Conclusions

Amgen's conclusions:

The subjects who were enrolled into study 20020149 represented the subset of subjects who successfully completed study 20010103 and who elected to continue with 16 additional weeks of blinded treatment. Continuation of treatment with darbepoetin alfa given at a dose of 6.75 µg/kg Q4W for up to 32 weeks demonstrated a safety profile for darbepoetin alfa very similar to that characterized in study 20010103. Treatment-related reductions in transfusions were seen, as well as the expected elevations in HGB that were sustained throughout treatment. A negative effect on survival persisted in the updated analysis of long-term follow-up, but otherwise the adverse event profile was as expected.

*Reviewer's comments:*

*Study 200020149 was conducted to characterize the safety profile of Aranesp over a longer period of time in allowing subjects completing study 20010103 to receive an additional 16 weeks of blinded treatment, with an emphasis on safety outcomes across a total of 32 weeks.*

*The tested dosing regimen of Aranesp administered at 6.75 µg/kg Q4W is not the approved Aranesp dosing regimen, and the population tested (patients not receiving concomitant chemotherapy) was not the indicated population.*

*The negative effect of Aranesp on overall survival from study 20010103 is described in the current labeling of Aranesp. The results from study 20020149 have no impact on the current labeling of Aranesp.*

*The results from study 20020149 are of limited value to address the pertinent issues on the hemoglobin level for the initiation of ESAs (FDA item 3), maximum hemoglobin level (FDA items 4), and discontinuation of ESA therapy post-chemotherapy (FDA item 5).*

## 6. Review of Efficacy

### Efficacy Summary

Amgen proposed labeling revisions in response to FDA requested items 3, 4, and 5 are not justified. Amgen's supporting information from the clinical study reports and datasets contained in this supplement are inadequate to address FDA requested items.

The efficacy of Aranesp in reducing the proportion of subjects receiving RBC transfusions are demonstrated in studies 980297, 20000161, 20030232 and 20010145 in patients receiving concomitant chemotherapy, indicating the effectiveness of a variety Aranesp dosing regimens in a variety of patients with different tumor types.

In addition to the efficacy in reducing RBC transfusions, the effectiveness of Aranesp in increasing hemoglobin values are also consistently demonstrated in studies 980297, 20000161, 20030232, and 20010145, indicating the effect of Aranesp on the hemoglobin values may explain the impact on the reduction in RBC transfusions.

The efficacy of Aranesp in reducing the proportion of subjects receiving RBC transfusions was not demonstrated from study 20010103 in which patients did not receive concomitant chemotherapy, indicating the futility of off-label use of Aranesp. However, the effectiveness of Aranesp in increasing hemoglobin values was observed in study 20010103, suggesting in this study there was discordance between the effect of Aranesp on the hemoglobin values and reduction in RBC transfusions in patients not receiving chemotherapy.

The results from study 20010145 did not demonstrate a survival benefit in administering Aranesp in patients with anemia and receiving chemotherapy for small cell lung cancer.

The results from study 20010103 demonstrated a detrimental effect of Aranesp on survival in patients with anemia and non-myeloid malignancies but not receiving concomitant chemotherapy.

None of the nine randomized, placebo controlled studies of Aranesp contained in this supplement demonstrated any effect of Aranesp on the HRQoL endpoints.

#### 6.1.1 Indication

Amgen submitted this postmarketing prior approval supplement with proposed labeling revisions in response to FDA's May 30 2007 action letter requesting Amgen provide data to support when to start (the appropriate hemoglobin level for the initiation of Aranesp) and when to stop (at what

hemoglobin level during the course of receiving chemotherapy and post chemotherapy) Aranesp in the indicated population (patients with anemia and non-myeloid malignancies receiving chemotherapy).

### 6.1.2 Methods

In this submission, Amgen submitted study reports and datasets from nine randomized, placebo controlled studies; studies 980291-schedule 1, 980291-schedule 2, 990114, 980297, 20000161, 20030232, 20010145, 20010103 and 20020249, to support the proposed labeling changes. However, as discussed in the preceding section 5.2 Review Strategy, among the above mentioned 9 studies, only five studies (studies 980297, 20000161, 20030232, 20010145 and 20010103), with adequate numbers of subjects enrolled and a uniform starting Aranesp dosing regimen within the study, were considered to be informative for efficacy and safety assessment of Aranesp use in cancer patients and were, therefore, included in the following efficacy and safety review section.

Clinical results were primarily based on Amgen's submitted clinical study reports and analyses results unless indicated otherwise. Of note, among these five randomized, placebo-controlled studies, a variety of Aranesp dosing regimens were studied in a variety of patient populations and for a variety of study endpoints. To perform any integrated efficacy analyses among these studies would be a challenge and would only provide limited information to draw any conclusion. Nevertheless, limited integrated efficacy analyses were conducted in the following sections in order to assess Amgen proposed labeling revisions pertinent to this supplement and provide additional clinical information on the efficacy of Aranesp use in these studies. However, interpretation of such analyses should be taken with caution.

### 6.1.3 Demographics

Patient demographics were similar in mean age and ethnic composition across 5 randomized, placebo controlled studies of Aranesp in patients with anemia and non-myeloid malignancies receiving chemotherapy (studies 980297, 20000161, 20030232, and 20010145) or not receiving chemotherapy (study 20010103) (Table 6.1.2.1): mean age of patients ranged from 61.0 to 64.7; the majority of patients were white. There were more male patients enrolled in studies 980297 (73%) and 20010145 (65%), likely related to underlying disease (lung cancer). There were more female patients enrolled in studies 20030232 (61%); and a similar proportion of male and female patients were enrolled in study 20000161 and study 20010103.

In general, baseline disease characteristics were similar between the Aranesp arm and placebo arm within each study (details are referred to description of individual study section 5).

Table 6.1.2.1: Summary of Demographics from 5 randomized, placebo controlled studies of Aranesp

Study ID  No of Subjects (Aranesp/Placebo)	Study Population	Chemotherapy	Male (%)	Median (range) Age	White (%)
980297  (159/161)	NSCLC and SCLC	Platinum-containing regimen	232 (73%)	62 (36-80)	320 (100%)
20000161  (176/173)	Lymphoproliferative malignancies	Heterogeneous	165 (47%)	68 (18-87)	342 (98%)
20030232  (193/193)	Non-myeloid malignancies	Heterogeneous	152 (39%)	66(20-91)	309 (79%)
20010145  (299/301)	SCLC	Platinum-containing regimen	385 (65%)	61 (28-82)	596 (100%)
20010103  (575/470)	Non-myeloid malignancies	none	505 (51%)	65 (18-89)	937 (95%)

### 6.1.3 Analysis of Primary Endpoint(s)

Primary endpoints and outcomes from 5 randomized, placebo controlled studies are summarized in Table 6.1.3.1. Regulatory agreed upon primary efficacy endpoints for Aranesp in the oncology setting, i.e. proportion of subjects who received a RBC transfusion, was only used in study 980297, which was the pivotal study originally submitted to support the initial approval of Aranesp use in oncology setting in 2001 (STN BL 103951.5001). Transfusion related primary endpoints, though not precisely consistent with efficacy endpoint, were used in studies 20030232 and 20010103. Primary endpoints related to hemoglobin change were used in studies 20000161 and 20010145. Overall survival was used as a co-primary endpoint in study 20010145.

Transfusion related primary endpoints were met in studies 980297 and 20030232, but not in study 20010103. The hemoglobin related primary endpoint was met in studies 20000161 and 20010145. However, the survival co-primary endpoint was not met in study 20010145.

Table 6.1.3.1: Summary of Primary Endpoints and Outcome from 5 Randomized, Placebo Controlled Studies of Aranesp.

Study ID  No of Subjects (Aranesp/Placebo)	Study Population	Primary Endpoint & Co-primary Endpoint	Outcome
980297  (159/161)	NSCLC and SCLC receiving platino-containing chemotherapy	proportion of subjects who received a RBC transfusion from week 5 to the EOTP	Aranesp: 21 % (95% Placebo: 51% Placebo –Aranesp 24% (95% CI: 13, 35, p < 0.001).
20000161  (176/173)	Lymphoproliferative malignancies receiving heterogeneous chemotherapy	proportion of subjects who achieved a hemoglobin response (defined as an increase in hemoglobin of $\geq$ 2.0 g/dL over baseline)	Aranesp: 58% Placebo: 16% Aranesp – Placebo 41% (95% CI: 31, 50) (p < 0.001).
20030232  (193/193)	Non-myeloid malignancies receiving heterogeneous chemotherapy	The incidence of RBC transfusion from week 5 to the EOTP	Aranesp: 24% Placebo 41% Aranesp-Placebo: -16.3 (95% CI - 25.9, -6.6, p<0.001)
20010145  (299/301)	SCLC receiving platinum-containing chemotherapy	Change in hemoglobin concentration from baseline to the end of the chemotherapy treatment period (EOCP) & survival time	Change in Hb; Aranesp –placebo: 0.84 95% CI, 0.53, 1.15, p <0.001.  Overall survival:  (b) (4)
20010103  (575/470)	Non-myeloid cancer not receiving chemotherapy	Risk of RBC transfusions from week 5 to week 17	Aranesp: 19% Placebo: 24% Hazard ratio: 0.85 (95% CI: 0.62, 1.17, p=0.320)

#### 6.1.4 Analysis of Secondary Endpoints(s)

Secondary endpoints related to transfusion or hemoglobin related endpoints and outcomes were summarized in Table 6.1.4.1. Transfusion related secondary endpoints are employed and met in studies 20000161 and 20010145, whereas hemoglobin related secondary endpoints are employed and met in studies 980297, 20030232 and 20010103.

Table: 6.1.4.1: Summary of Hemoglobin or Transfusion Related Secondary Endpoints and Outcome from 5 Randomized, Placebo Controlled Studies of Aranesp

Study ID No of Subjects (Aranesp/Placebo)	Study Population (Aranesp/Placebo)	Secondary Endpoint	Outcome
980297  (159/161)	NSCLC and SCLC receiving chemotherapy	proportion of subjects achieving a hemoglobin response	Aranesp: 48% Placebo: 18% Aranesp-placebo: 29% (95%CI 18, 40 p<0.001)
20000161  (176/173)	Lymphproliferative malignancies receiving heterogeneous chemo	proportion of subjects who received a RBC transfusion from week 5 to the EOTP	Aranesp: 29% Placebo: 50% Aranesp-placebo: -17% (95% CI: -27, -7; p < 0.001).
20030232  (193/193)	Non-myeloid malignancies receiving heterogeneous chemo	The incidence of achieving a hemoglobin concentration $\geq$ 11.0 g/dL	Aranesp: 82% Placebo: 48% Aranesp-placebo: 27.1% ( 95% CI: 17.7, 36.5 , p < 0.001)
20010145  (299/301)	SCLC receiving platinum-containing chemotherapy	The incidence and number of units of red blood cells (RBCs) transfused during study	Aranesp: 17% Placebo: 39% Hazard ratio: 0.40; 95% CI: 0.29, 0.55).
20010103  (575/470)	Non-myeloid cancer not receiving chemotherapy	Incidence of first RBC transfusion from week 5 to week 17, and change in HGB between baseline and the end of treatment period (EOTP).	Incidence of transfusion: Hazard ratio: 0.89 (95% CI 0.68, 1.17, p=0.412)  Mean Hb increase: Aranesp: 0.72 Placebo: 0.28

*Reviewer Comments:*

*Using an acceptable regulatory efficacy endpoint, Aranesp demonstrated a reduction in the proportion of subjects who received RBC transfusion in patients receiving concomitant chemotherapy (studies 980297, 20000161, 20030232, and 20010145), but not in study 20010103 in which patients did not receive concomitant chemotherapy. Of note, the efficacy of Aranesp in reducing the proportion of subjects receiving RBC transfusion was demonstrated across studies 980297, 20000161, 20030232, and 20010145 regardless of primary endpoint, patient population, Aranesp dosing regimen, and chemotherapy regimen. These results corroborate the approved indication of Aranesp use in patients with anemia and non-myeloid chemotherapy receiving chemotherapy. However, the fact that different Aranesp dosing regimen tested in studies 980297, 20000161, 20030232, and 20010145 (2.25 µg/kg QW, 300µg Q3W, and 300 µg QWx4->Q3W) have shown similar efficacy in reduction in RBC transfusions indicates that dosing regimens of Aranesp may not be critical component and that a lower dosing regimen than that currently approved Aranesp dosing (2.25 µg/kg QW and 500 µg Q3W) should be considered.*

*The study results from 20010103 did not demonstrate efficacy of Aranesp in reducing the proportion of subjects receiving RBC transfusions, indicating that off-label use of Aranesp in patients with anemia and malignancies who are not receiving chemotherapy, though common in oncology community practice, is not justified.*

*Of note, in studies using hemoglobin-related endpoints (e.g., hemoglobin response, hemoglobin correction, hemoglobin change), Aranesp has consistently shown significant increase in hemoglobin values across all five randomized, placebo controlled studies regardless of primary endpoint, patient population, Aranesp dosing regimen, and chemotherapy regimen. The results indicate a consistent finding of increased hemoglobin value and decreased RBC transfusion in patients receiving concomitant chemotherapy (studies 980297, 20000161, 20030232, and 20010145), but not in patients not receiving concomitant chemotherapy (study 20010103). Patients with anemia and non-myeloid malignancies but not receiving chemotherapy in study 20010103 were less likely to receive RBC transfusions as compared to patients on chemotherapy. Hence, this reviewer hypothesizes that a portion of anemic patients on chemotherapy received RBC transfusions triggered by symptoms, (for example, fatigues), which were related to or worsened by chemotherapy instead of symptoms arising only from anemia.*

*Of further note, the co-primary endpoint of survival was not met in study 20010145, indicating no survival benefit of administering Aranesp in patients with anemia and extensive stage of small cell lung cancer receiving chemotherapy. This reviewer considers the failure to demonstrate survival benefit of Aranesp in anemic patients with small cell lung cancer receiving chemotherapy in study 20010145 could be extrapolated and applicable to patients with other tumor types.*

### 6.1.5 Other Endpoints

Health Related Quality of Life (HRQoL) related primary endpoints and outcomes from 5 randomized placebo controlled studies are summarized in Table 6.1.5.1. Change from baseline to the end of the treatment period on the Functional Assessment of Cancer Therapy FACT-Fatigue scale score are used as major supportive endpoints in all 5 randomized, placebo controlled studies. Of note, none of the studies has shown meaningful or statistically significant difference in HRQoL related primary endpoints between Aranesp and placebo arms.

Table 6.1.5.1: Summary of HRQOL Primary Endpoints and Outcomes from 5 Randomized, Placebo Controlled Studies of Aranesp

Study ID No of Subjects (Aranesp/Placebo)	Study Population	HRQOL Primary Endpoint	Outcome
980297 (159/161)	NSCLC and SCLC receiving platinum-containing chemotherapy	change from baseline to the EOTP on FACT-F scale score	Mean change score: Aranesp: (+0.8, 95% CI: -1.0, 2.5) Placebo: (-0.6, 95% CI:-2.5, 1.3), p=0.286. Aranesp-Placebo: 1.4 (95% - 1.1, 3.9)
20000161 (176/173)	Lymphoproliferative malignancies receiving chemotherapy	change from baseline to the EOTP on FACT-F scale score	Mean change score: Aranesp: 2.7 Placebo: 0.6 Aranesp – Placebo: 2.0, (95%CI -0.2, 4.2, p=0,077)
20030232 (193/193)	Non-myeloid malignancies receiving chemotherapy	change from baseline to the EOTP on FACT-F scale score	Mean change score: Aranesp (-0.95, 95% CI: - 2.72, 0.82) Placebo (+0.94, 95% CI:-1.76, 1.92), Aranesp-Placebo: -1.03 (95% CI -3.38, 1.31)
20010145 (299/301)	SCLC receiving platinum-containing chemotherapy	change from baseline to the EOST FACT-F scale score.	Mean change score: Aranesp: 1.50 (95% CI -0.17, 3.16) Placebo: 0.70 (95% CI -1.00, 2.40) Aranesp – Placebo: 0.86 (95% CI -1.16, 2.88),
20010103 (575/470)	Non-myeloid malignancies not receiving chemotherapy	change from baseline to the week 17 for FACT -F scale score.	Mean change score: Aranesp: 0.33 (95% CI: 1.50, 2.16) Placebo: 0.58 (95% CI: -1.20,

			2.36). Aranesp –Placebo: -0.25, 95% -1.78, 1.27).
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*Reviewer comments:*

*HRQoL endpoints have been included in all of the above listed 5 randomized, placebo controlled studies of Aranesp in patients with anemia and non-myeloid malignancies receiving chemotherapy (studies 980297, 20000161, 20030232 and 20010145) and not receiving chemotherapy (study 20010103). It appears that a uniform primary HRQoL endpoint, i.e., measurement of change from the baseline to the end of treatment period for the Functional Assessment of Cancer Therapy (FACT)- Fatigue scale score was used as primary HRQoL endpoint across the above discussed 5 studies.*

*Of significant clinical importance and interest is that none of the HRQoL study results from the above discussed five controlled studies has shown any meaningful or positive effect of Aranesp administration on the patient reported outcomes such as FACT-fatigue score and other FACT-anemia related measurements. FACT-Fatigue Scale includes 13 items with total scores ranging from 0 to 52. The baseline mean FACT-Fatigue scores are very similar ranging from 27 to 31) and well balanced between Aranesp and placebo arms across all 5 randomized placebo controlled studies. Overall, patient compliance on completion of the HRQoL questionnaires was more than 80% across all 5 studies and well-balanced between Aranesp and placebo arms.*

*Particularly of interest is that across all 5 studies, significant effect of Aranesp on increased hemoglobin values in patients with anemia and non-myeloid malignancies has been consistently demonstrate; in contrast, none of the above discussed studies has shown effect of Aranesp on ascertained anemia-related HRQoL measurements such as fatigue. It appears that there is no correlation between increased hemoglobin and the expected outcome improvement on the ascertained anemia-related symptoms, calling into question the commonly perceived benefit of increased hemoglobin in an attempt to ameliorate “anemia-associated” symptoms such as “fatigue” in oncology practice. This reviewer recognizes the difficulty and the complexities involved in evaluating the effect of Aranesp on HRQoL endpoint, and offers the following hypotheses to explain why there is no observed effect of Aranesp to improve HRQoL outcome despite a consistently demonstrated effect of Aranesp on increased hemoglobin: 1) None of the above discussed studies was adequately designed to detect a meaningful effect of Aranesp on HRQoL outcome; 2) The instrument and procedures used to measure HRQoL were not valid; 3) There is no relationship between the hemoglobin and the amelioration of the commonly ascertained “anemia-related” symptoms, such as fatigue and shortness of breath if the symptoms are caused by the underlying disease and/or interventions such as chemotherapy as commonly seen in the oncology setting. The overall assessment of HRQoL outcomes in the above discussed randomized, placebo controlled studies supports the recent labeling revision action post May 10, 2007 ODAC meeting to include a statement “Aranesp use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being” in the Aranesp package insert.*

### 6.1.6 Subpopulations

This reviewer considers this section not applicable to this supplement. Therefore, no subgroup efficacy analyses were conducted on subpopulations.

### 6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

Currently approved dosing regimen of Aranesp in patients with anemia and non-myeloid malignancies receiving chemotherapy are 2.25 µg/kg, SC, QW and 500 µg SC, Q3W. The Aranesp 2.25 µg/kg, SC, QW dosing was used in two studies (980297 and 20000161), and various unapproved dosing regimen of Aranesp, including 300 µg Q3W, 300 µg QW x4→ 300 µg Q3W, and 6.75 µg /kg Q4W, were tested in studies 20030232, 20010145 and 20010103. The fact that Aranesp dose, 300 µg Q3W tested in study 20030232, and Aranesp dose, 300 µg QW x4→ 300 µg Q3W, tested in study 20010145 have demonstrated efficacy in reducing proportion of subjects receiving RBC transfusion to a similar extent as approved dosing regimen 2.25 µg/kg QW and 500 µg Q3W suggest that a lower Aranesp dosing regimen than the approved dosing regimen may be adequate in the oncology setting.

### 6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

Aranesp has consistently demonstrated efficacy in reducing the proportion of patients receiving RBC transfusion in patients with anemia and non-myeloid malignancies receiving chemotherapy in studies 980297, 20000161, 20030232 and 20010145, regardless of the Aranesp dosing regimen tested, underlying tumor types or chemotherapy regimen, suggesting the label indication of Aranesp use in oncology setting, i.e., for reducing RBC transfusions in patients with anemia and receiving chemotherapy. The study durations range from 12 to 24 weeks in these five studies. No analysis was conducted to evaluate the tolerance effect of Aranesp in this supplement.

### 6.1.9 Additional Efficacy Issues/Analyses

#### Issues/analyses related on Amgen's response to FDA item 3

In an attempt to address FDA requested item #3, Amgen submitted pooled analysis results on risk of transfusion by baseline hemoglobin level from seven (studies 980291-schedule 1, 980291-schedule 2, 990114, 980297, 20000161, 20030232, and 20010145) randomized, double-blind, placebo-controlled trials of Aranesp in patients with anemia and non-myeloid malignancies receiving chemotherapy (Table 6.1.9.1).

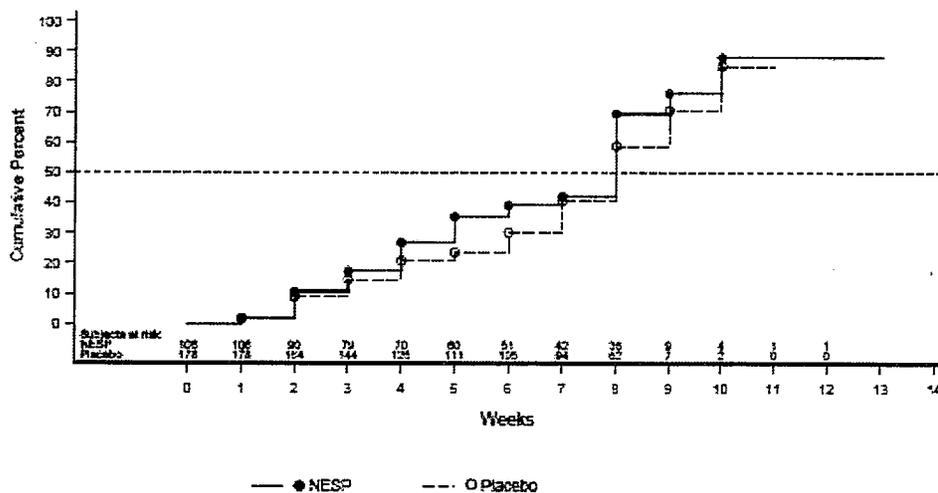
(b) (4)

Issues/analyses related to Amgen’s response to FDA item 5

In response to FDA requested item #5, i.e., *Revision of the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections to indicate that Aranesp/PROCRIPT should be discontinued following the completion of the concomitant chemotherapy regimen*, Amgen submitted the analyses on the time to hemoglobin recovery after cessation of chemotherapy observed in study 20010145, a randomized, double-blind, placebo-controlled study of subjects with previously untreated, extensive-stage SCLC receiving platinum-based chemotherapy. Amgen’s rationale for the selection of study 20010145 was that the design of this study included hemoglobin assessments for up to 12 weeks after the last dose of chemotherapy, thus providing relevant information on time to hemoglobin recovery after the cessation of chemotherapy (subjects in the Aranesp group continued to receive investigational product for only 3 weeks after the last dose of chemotherapy). Subjects entered the study with hemoglobin concentrations of  $\geq 9.0$  g/dL and  $\leq 13.0$  g/dL, and hemoglobin recovery was defined in this analysis as a value of  $\geq 11$  g/dL. The analysis of the median time to a hemoglobin level  $\geq 11$  g/dL in those patients who had a hemoglobin concentration  $< 11$  g/dL after the cessation of chemotherapy is illustrated in Figure 6.1.9.1.

Figure 6.1.9.1 (Amgen’s Figure 12 from CRS study 20010145)

**Figure 12. Study 20010145: Time to Hemoglobin  $\geq 11$  g/dL in Subjects With Levels  $< 11$  g/dL After Chemotherapy Unadjusted for Transfusions (Primary Analysis Set)**



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 Output: g\_fgl\_chemo\_unadj\_145.cpm (Date Generated: 12/UL07:11:58:04) Source Data: c\_hemad\_c\_fems.sas7deaf



(b) (4)

*Reviewer comments:*

*This reviewer strongly disagrees with Amgen's proposed labeling revisions and the supporting analyses to address FDA requested item 5 for the following reasons:*

- *There is no scientific rationale nor clinical evidence to justify Amgen's proposed approach (b) (4) after the cessation of chemotherapy to address the FDA requested item # 5, i.e., Revision of the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections to indicate that Aranesp/PROCRIT should be discontinued following the completion of the concomitant chemotherapy regimen.*
- (b) (4)
- (b) (4)
- *The study 20010145 was not designed to address FDA requested item #5. (b) (4)*
- *Most importantly, study results in the setting of patient with non-myeloid malignancies but not receiving chemotherapy (20010103) clearly demonstrated a detrimental effect of increased mortality and futility in reducing RBC transfusion rates in patients receiving Aranesp as compared to patients receiving placebo. The compelling results from study 20010103 which demonstrated serious risks of Aranesp in anemic cancer patients not receiving chemotherapy should be extrapolated and applied to patient populations after the cessation of chemotherapy course.*

*Therefore, this reviewer recommends Aranesp be discontinued immediately following the completion of the concomitant chemotherapy course and agrees with Amgen's revised text contained in the subsequent labeling supplements ( (b) (4) 103951.5195), stating that Aranesp be discontinued following the completion of a chemotherapy course.*

## 7. Review of Safety

### Safety Summary

Amgen proposed labeling revisions in response to FDA requested items 3, 4, and 5 are not justified. Amgen's supporting information from the clinical study reports and datasets contained in this supplement are inadequate to address the FDA-requested items pertinent to this supplement.

The review of safety data from studies contained in this supplement did not identify new safety signals or concerns and therefore has no impact on the current product labeling.

The safety profile of Aranesp is similar across the studies provided in this supplement in which various Aranesp dosing regimens were tested in patients with different tumor types and receiving different chemotherapy regimens.

On study deaths occurred at moderately higher incidences in the Aranesp arms in patients receiving concomitant chemotherapy (study 980297, 20000161, and 20010145) and in patients not receiving chemotherapy (20010103), corroborating the current safety concern of a negative impact Aranesp on the survival as warned and described in the product labeling.

The incidences of adverse reactions observed in study 20010103 in which patients did not receive concomitant chemotherapy are noticeably lower than those observed in studies in which patients received concomitant chemotherapy. This suggests a role for chemotherapy on the rate of reported adverse reactions in studies of Aranesp in patients on chemotherapy.

### 7.1 Methods

As discussed in the previous review sections, there is significant heterogeneity in study endpoints, patient populations, study procedures, and Aranesp dosing regimens across the nine randomized, placebo-controlled studies of Aranesp contained in this supplement. Therefore, to conduct an integrated safety analyses by pooling the safety data from these studies is not considered an optimal approach to address safety issues of Aranesp use. Instead, this reviewer chooses to briefly describe and review safety outcome for each of the nine individual studies in the review section 5, and conduct additional integrated safety analyses based on data from five selected studies in which a uniform Aranesp dosing regimen was tested. Summarized information and limited analyses on Aranesp exposure, deaths, serious adverse events, common adverse events, and adverse events of interest (e.g. thromboembolic events) in studies 980297, 20000161, 20030232, 20010145 and 20010103 are described in sections 7.2 to 7.4. Additional

review and discussion on Amgen's proposed labeling revisions and the supporting analyses and arguments in response to FDA items 3 and 4 are provided in section 7.5.

### 7.1.1 Clinical Studies Used to Evaluate Safety

Safety information provided in clinical study reports from five randomized, placebo controlled studies of Aranesp (studies 980297, 20000161, 20030232, 20010145 and 20010103) were used to evaluate safety issues, including death, serious adverse events, common adverse events, adverse events of interest (thromboembolic events), and exploratory safety analyses on the adverse events in relation to hemoglobin values.

### 7.1.2 Adequacy of Data

The data from the submitted studies are inadequate to address the issues pertinent to this supplement. Please also see discussion in section 5.2.2 Review Strategy.

### 7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Side-by-side analyses describing and comparing the incidences of on-study death, serious adverse events, and common adverse events from individual data from studies 980297, 20000161, 20030232, 20010145 and 20010103 are provided in this review. No attempt was pursued to pool data across studies to estimate and compare incidence because of the heterogeneity of the study endpoints, study populations in terms of tumor types and chemotherapy, and Aranesp dosing regimens tested.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 7.2.1 summarizes the overall exposure to Aranesp in five randomized, placebo controlled studies (980297, 20000161, 20030232, 20010145 and 20010103), including one study (20010103) in which patients did not receive concomitant chemotherapy. The median durations of treatment across five studies ranged from 12 to 16 weeks. However, there were some differences observed for average weekly Aranesp dose, ranging from 95 to 208  $\mu\text{g}/\text{week}$ , and for the average weight-adjusted Aranesp dose, ranging from 1.4 to 2.9  $\mu\text{g}/\text{kg}/\text{week}$  across the five studies (980297, 20000161, 20030232, 20010145 and 20010103). Because different Aranesp dosing regimens were used in these five studies, it is understandable that differences were observed for the average Aranesp weekly dose or average weight-adjusted dose across all five studies.

Table 7.2.1: Summary of Overall Exposure of Aranesp from 5 Randomized, Placebo Controlled Studies (980297, 20000161, 20030232, 20010145 and 20010103).

(b) (4)

The same Aranesp dosing regimen, 2.25ug/kg weekly, was used in two studies 980297 and 20000161; and there was no clinically important difference in the average Aranesp weekly dose or average weight-adjusted Aranesp dose among subjects in studies 980297 and 20000161.

The Aranesp dosing regimen of 300 µg QW for 4 weeks then followed by Q3W was used in study 20010145. The average weekly Aranesp dose among the subjects in study 20010145, 195 µg/week, was similar to the average weekly doses (190 and 208 µg/week) in studies 980297 and 20000161, in which Aranesp 2.25ug/kg dosing was used.

Similar Aranesp average weekly doses and average weight-adjusted doses were observed among subjects in study 20030232 and study 20010103; Aranesp 300 µg, Q3W was used in study 20030232 and Aranesp 6.75 µg/kg Q4W was used in study 20010103.

With the same Aranesp regimen, 2.25ug/kg weekly, similar Aranesp exposures were observed among subjects with lung cancer (980297) and lymphoproliferative diseases. (20000161). Aranesp 300 µg QWx4-> Q3W used in study 20010145 also resulted in similar patient exposures as compared subjects receiving the Aranesp dosing 2.25 µg/kg weekly. Aranesp dosing regimen of 300 µg, Q3W or 6.75 µg Q4W resulted in lower exposures among subjects as compared to Aranesp 2.25ug/kg weekly or 300 µg QWx4-> Q3W.

The incidences of dose reductions were higher in studies using an every three- or four-week dosing regimen (about 40% in studies 2003023, 20010145 and 20010103) than in studies using weekly dosing regimen (< 20% in studies 980297 and 20010161).

#### 7.2.2 Explorations for Dose Response

No exploration for dose response was conducted in this supplement.

#### 7.2.3 Special Animal and/or In Vitro Testing

No information on special animal and/or in vitro testing was submitted to this supplement.

#### 7.2.4 Routine Clinical Testing

Overall, routine clinical testing regarding to hematological values and biochemistry panel were appropriately conducted in studies during the study period.

#### 7.2.5 Metabolic, Clearance, and Interaction Workup

This section is considered not applicable to this supplement.

#### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events for drugs in this class, i.e., erythropoiesis stimulating agents (ESAs), include increased risk for mortality, thromboembolic events, and tumor progression/recurrence. Safety reviews on the available information for death (on-study) and thromboembolic events are provided in sections 7.3, 7.4, and 7.5.

## 7.3 Major Safety Results

### 7.3.1 Deaths

The incidences of on study death, defined as death occurred during the study and within 30 days after the last dose of study drug in five randomized, placebo controlled studies (980297, 20000161, 20030232, 20010145, and 20010103) are summarized in Table 7.3.1.1.

Table 7.3.1.1. Summary of incidence of on study deaths from study 980297, 20000161, 20030232, 20010145 and 20010103

Study ID	Aranesp Deaths/Total Number of subjects (%)	Placebo	Total
980297	22/155 (14%)	19/159 (12%)	41/314 (13%)
20000161	10/175 (6%)	4/169 (2%)	14/344 (4%)
20030232	17/194 (9%)	20/192 (10%)	37/386 (10%)
20010145	53/301 (18%)	48/296 (16%)	101/597(17%)
20010103	136/515 (26%)	94/470 (20%)	230/985 (23%)

As discussed in the previous review sections, patient populations (i.e., disease characteristics and concomitant therapy) aware different as were the Aranesp dosing regimens tested across the studies. Therefore, incidences of on-study deaths observed are expectedly different across the studies. Patients with a variety of advanced malignancies who were not receiving chemotherapy (study 20010103) had the highest on-study death rates (23%), followed by subjects with small cell lung cancer in study 20010145 (17%), subjects with small cell and non-small cell lung cancer in study 980297 (13%), subjects with heterogeneous malignancies in study 20030232 (10%), and subjects with lymphoproliferative malignancies in study 20000161 (4%).

In comparing death rates between Aranesp arm and placebo arm within each study and across the five studies, a slightly higher on-study death rates occurred in the Aranesp arm compared with placebo arm in four studies (980297, 20000161, 20010145 and 20010103), but not in study 20030232, in which death rate in Aranesp arm is lower than in the placebo arm (9% vs. 10%). In reviewing the reports of the investigator-attributed causes for on-study deaths, no specific safety signal for death was detected except that most of the patient deaths are attributed to disease progression. This reviewer notes the difficulties in differentiating disease progression-related deaths from adverse event-related deaths, for example, death due to thromboembolic (pulmonary embolism) or cardiovascular adverse reaction.

However, the slightly higher incidences of deaths in Aranesp arm observed in studies 980297, 20000161, 20010145 and 20010103, raise the concern that Aranesp caused increased on-study deaths, though to a modest extent, as compared to placebo, and support the warnings on the increased mortality of Aranesp use in the current labeling. The long term follow-up results from

study 20000161 and 20010103 demonstrating an increased mortality in Aranesp arms are described in the current Aranesp package insert.

This reviewer considers the findings of a statistically significantly increased deaths observed in Aranesp arm in study 20010103 is of particular clinical importance and interest in the safety assessment of Aranesp use in oncology setting. Though patients in study 20010103 did not receive concomitant chemotherapy and therefore, received Aranesp “off label”, study 20010103 enrolled the largest number of subjects (985) among the available randomized studies of Aranesp in oncology setting. The large sample size in study 20010103 permits modest safety signals to be detected, such as the modestly increased risk of mortality with Aranesp. Aranesp did not demonstrate efficacy in reducing RBC transfusion rates in patients not receiving concomitant chemotherapy, as indicated in the study results in 20010103. However, there is little scientific basis to suggest the worrisome safety signals of an increased mortality, including both on-study and post-study death rates, in patients receiving Aranesp without concomitant chemotherapy in study 20010103, are not applicable to subjects receiving Aranesp with chemotherapy.

Study 20010145 is the only study with survival time as a co-primary study endpoint. The study results did not demonstrate a superior survival in Aranesp arm. The hazard ratio for Aranesp versus the control arm was [REDACTED] <sup>(b) (4)</sup>, excluding more than 11% detrimental effect of increased mortality in the Aranesp arm. However, a slightly higher incidence of on-study death was observed in the Aranesp arm than in the placebo arm (18% versus 16%). In addition, the study protocol did not specify whether Aranesp or other ESAs were permitted during the follow-up period. Thus, the long term follow-up results on survival could potentially be confounded by ESA use in the control, thus masking greater toxicity in the Aranesp arm. <sup>(b) (4)</sup>

[REDACTED]

[REDACTED]

### 7.3.2 Serious Adverse Events

Subject incidences of serious adverse events, and severe, life-threatening, or fatal events reported in studies 980297, 20001061, 20030232, 20010145 and 20001013 are summarized in Table 7.3.2.1 and Table 7.3.2.2.

Higher incidences of serious adverse events in Aranesp arms compared with placebo arms within individual studies occurred in studies 980297, 20030232, 20010145, and 20010103, but not in study 20000161. Higher incidences of severe, life-threatening and fatal events in Aranesp arms also occurred in studies 980297, 20030232, 20010145 and 20001013. Therefore, in general, higher incidences of serious adverse events and severe, life-threatening, and fatal events occurred in subjects receiving Aranesp regardless of Aranesp dosing regimen, subject disease characteristics, and receiving concomitant chemotherapy or not. These findings should be weighed in considering risk and benefit of Aranesp use in the oncology setting.

Table 7.3.2.1. Summary of Subject Incidences of Serious Adverse Events in 5 randomized, placebo controlled studies (980297, 20000161, 20030232, 20010145, and 20010103).

Study ID	Aranesp SAEs/Total Number of subjects (%)	Placebo
980297	60/155 (39%)	58/159 (36%)
20000161	51/175 (29%)	63/169 (37%)
20030232	84/194 (43%)	77/192 (40%)
20010145	138/301 (46%)	121/296 (41%)
20010103	210/515 (41%)	159/470 (34%)

Table 7.3.2.2. Summary of Subject Incidences of Severe, Life-threatening and Fatal adverse events in 5 randomized, placebo controlled studies (980297, 20000161, 20030232, 20010145, and 20010103).

Study ID	Aranesp severe, life threatening or fatal AEs/Total Number of subjects (%)	Placebo
980297*	69/155 (45%)	66/159 (42%)
20000161*	59/175 (34%)	59/169 (35%)
20030232	102/194 (53%)	88/192 (46%)
20010145	181/301 (60%)	169/296 (51%)
20010103	245/515 (48%)	192/470 (41%)

\* does not include fatal events

### 7.3.3 Dropouts and/or Discontinuations

The incidences on dropouts regardless of cause, dropouts due to death, and dropouts due to adverse events (AEs) by study for the five randomized, placebo controlled studies (980297, 20000161, 20030232, 20010145, and 20010103) are summarized in Table 7.3.3.1

The overall profiles of dropouts between the Aranesp arms and the placebo arms are considered to be similar within individual study. However, there are different incidences of dropouts reported across all the five studies, with the highest dropout rates observed in study 20010103, followed by the dropout rates in study 20010145, 20030232, 980297 and 20000161, possibly reflecting differences in severity of illness in enrolled subjects in different studies. No specific cause for dropouts across the studies was identified. In general, death and disease progression are the most frequently reported reasons for dropouts across all the studies.

Of interest is that a modestly higher dropouts due to deaths in Aranesp arm than in placebo arm are reported in study 20010103 in which subjects did not receive concomitant chemotherapy, but no consistent patterns of dropouts due to death in comparing the Aranesp and the placebo arms in

studies 980297, 20000161, and 20030232. Limited conclusions on the overall profile of dropouts due to death can be drawn from the available data. However, it is of concern that a higher incidence of dropouts due to deaths in the Aranesp arm are reported in study 20010103, considering the final study reports indicated an increased mortality was observed in subjects receiving Aranesp during the 16 weeks of treatment period and for the subsequent follow up period.

Table 7.3.3.1. Summary of Dropouts in 5 randomized, placebo controlled studies of Aranesp (980297, 20000161, 20030232, 10010145, and 20010103)

Study ID Aranesp Dosing		Subjects receiving study drug (%)	Dropouts (%)	Dropouts Due to death (%)	Dropouts due to AEs (%)*
980297 2.25ug/kg QW	Aranesp (n=155)	156 (98%)	49 (31%)	14 (9%)	2 (1%)
	Placebo (n=159)	158 (98%)	52 (32%)	19 (12%)	5 (3%)
20000161 2.25ug/kg QW	Aranesp (n=176)	174 (99%)	29 (16%)	8 (5%)	5 (3%)
	Placebo (n=173)	170 (98%)	29 (16%)	3 (2%)	5 (3%)
20030232 300µg Q3W	Aranesp (n=196)	193 (98%)	58 (30%)	15 (8%)	8 (4%)
	Placebo (n=195)	193 (99%)	63 (32%)	16 (8%)	3 (2%)
20010145 300µg QWx4- >Q3W	Aranesp (n=299)	298 (99%)	150 (50%)	NA	12 (4%)
	Placebo (n=301)	299 (99%)	145 (48%)	NA	10 (3%)
20010103** 6.75 µg/kg Q4W	Aranesp (517)	515 (99.6%)	253 (49%)	(22.4%)	51 (10%)
	Placebo (n=472)	470 (99.6%)	219 (46%)	(17.6%)	43 (9%)

\*excluding death and disease progression

\*\* patients not receiving chemotherapy

### 7.3.4 Significant Adverse Events

Thromboembolic events including arterial and venous thrombotic events have been well recognized as drug-related significant adverse events and are described in the product labeling. Because different coding and reporting systems for adverse events (WHOART, MedDra version 7.0 and MedDRA version 9.0) were used across studies, it is difficult to conduct integrated analyses on the incidences of thromboembolic events across the studies. However, a summary of reported thromboembolic events from clinical study reports of studies 980297, 2000161, 20030232, 20010145, and 20010103 is attempted in Table 7.3.4.1.

Table 7.3.4.1 Summary of incidences of thromboembolic events in studies 980297, 2000161, 20030232, 20010145, and 20010103.

Study ID	Aranesp Thromboembolic AEs/Total Number of subjects (%)	Placebo Thromboembolic AEs/Total Number of subjects (%)
980297	7/155 (5%)	5/159 (3%)
20000161	9/175 (5%)	3/169 (2%)
20030232	18/194 (9%)	11/192 (6%)
20010145	26/301 (9%)	15/296 (5%)
20010103	50/515 (10%)	36/470 (8%)

The increased incidences of thromboembolic events in Aranesp arm compared with placebo arm were consistently observed in all the studies. Adverse events were coded using a modified WHOART system in study 20000161 and in 980297. MedDRA version 7.0 was used in study 20030232 and MedDRA version 9.0 was used in studied 20010145 and 20010103. Studies using a newer version of MedDRA coding system for adverse events (20030232, 20010145 and 20010103) seem to have more reported thromboembolic events. When cardiovascular and thromboembolic events are grouped in a single analysis of arterial and venous events in study 20010145, a higher rate of cardiovascular and thromboembolic events in the Aranesp arm compared to the placebo group (22% vs. 15%) is observed.

Overall, an increased risk for thromboembolic events in subjects receiving Aranesp has been consistently shown in studies regardless of Aranesp dosing regimen, background disease characteristics, or chemotherapy. The importance of these findings should be weighed in considering the risks and benefits of ESAs in the oncology setting.

### 7.3.5 Submission Specific Primary Safety Concerns

There is no additional submission related to specific primary safety concerns submitted to this supplement.

## 7.5 Supportive Safety Results

### 7.4.1 Common Adverse Events

Subject incidences of common adverse events, which include adverse events present in  $\geq 5\%$  of patients and in more subjects in Aranesp arms than in placebo arms in studies 980297, 20000161, 2003023, 20010145 and 20010103 are summarized in Tables 7.4.1.1, 7.4.1.2, 7.4.1.3, 7.4.1.4, and 7.4.1.5.

Overall, in studies in which subjects received concomitant chemotherapy, there is no distinct adverse event with clinically significant differences in the incidences between the Aranesp and the placebo arms identified.

Interestingly, in study 2001013 in which subjects not receiving chemotherapy, incidences of reported adverse events are lower than in the subjects receiving concomitant chemotherapy. For example, abdominal pain was the only adverse events with subjects incidence of  $\geq 5\%$  and in Aranesp arm and with a marginal difference as compared to the placebo arm (1%). This indicates the role of chemotherapy on the rate of patient-reported adverse reactions in studies where patients received chemotherapy.

Visual comparisons of common adverse events across studies indicates discrepancies in the incidences of similar preferred terms of adverse events, understandably attributed to different patient populations with background diseases and chemotherapy regimen. Therefore, no attempt is carried out to conduct an in depth integrated analyses of common adverse events reported in studies 980297, 20000161, 20030232, 20010145 and 20010103 or to draw any meaningful conclusion.

**Table 7.4.1.1 Study 980297:** Subject Incidence of Adverse Events ( $\geq 5\%$  and observed in more subjects in Aranesp arm than in placebo arm) Derived from Amgen's results.

Study ID 980297	Aranesp (N=155)	Placebo (N=159)
Preferred term		
Number of Subjects reporting AEs	148 (95%)	151 (95%)
Nausea	66 (43%)	60 (38%)
Vomiting	53 (34%)	46 (29%)
Asthenia	37 (24%)	31 (19%)
Constipation	26 (17%)	23 (14%)
Diarrhea	21 (14%)	14 (9%)
Dizziness	21 (14%)	11(7%)
Headache	16 (10%)	12 (8%)
Paresthesia	15 (10%)	13 (8%)
Anxiety	12 (8%)	10 (6%)
Arthralgia	12 (8%)	11 (7%)
Edema Peripheral	12 (8%)	11(7%)
Metastatic Neoplasma	12 (8%)	9 (6%)
Hypertension	9 (6%)	6 (4%)
Bronchitis	8 (5%)	2 (1%)
Somnolence	8 (5%)	5 (3%)
Vertigo	8 (5%)	5 (3%)
Edema	7 (5%)	2 (1%)

**Table 7.4.1.2 Study 20000161:** Subject Incidence of Adverse Events ( $\geq 5\%$  and observed in more subjects in Aranesp arm than in placebo arm) Derived from Amgen's results.

Study ID 20000161	Aranesp (N=175)	Placebo (N=169)
Preferred term		
Number of Subjects reporting AEs	161 (92%)	161 (95%)
Infection upper Respiratory	25 (14%)	14 (8%)
Granulocytopenia	23 (13%)	15 (9%)
Pain Abdominal	23 (13%)	18 (11%)
Pain Back	23 (13%)	19 (11%)
Arthragia	22 (13)	20 (12%0
Asthenia	19 (11%)	15 (9%)
Dizziness	19 (11%)	16 (9%)
Myalgia	19 (11%)	15 (9%)
Pain limb	18 (10%)	13 (8%)
Mucositis	15 (9%)	1 (1%)
Sore Throat	14 (8%)	5 (3%)
Hypertension	8 (5%)	5 (3%)
Hypokalemia	8 (5%)	5 (3%)
Infection	8 (5%)	2 (1%)
Rash	8 (5%)	7 (4%)

**Table 7.4.1.3 Study 20030232:** Subject Incidence of Adverse Events ( $\geq 5\%$  and observed in more subjects in Aranesp arm than in placebo arm) derived from Amgen's results.

Study ID 20030232	Aranesp (N=194)	Placebo (N=192)
Preferred term		
Number of Subjects reporting AEs	182 (94%)	182 (95%)
<b>Fatigue</b>	<b>62 (32%)</b>	<b>60 (31%)</b>
Diarrhea	44 (23%)	38 (20%)
Dysnea	44 (23%)	37 (19%)
Vomiting	39 (20%)	33 (17%)
Edema Peripheral	30 (15%)	27 (14%)
Pyrexia	30 (15%)	14 (7%)
Asthenia	25 (13%)	15 (8%)
Back Pain	24 (12%)	20 (10%)
Decreased Appetite	21 (11%)	11 (6%)
Arthralgia	20 (10%)	12 (6%)
Headache	20 (10%)	12 (6%)
Neutropenia	19 (10%)	15 (8%)
Upper Respiratory Tract Infection	17 (9%)	15 (8%)
Stomatitis	16 (8%)	9 (5%)
Bone Pain	13 (7%)	7 (4%)
Rash	14 (7%)	8 (4%)
Urinary Tract Infection	13 (7%)	8 (4%)
Deep Vein Thrombosis	9 (5%)	5 (3%)
Mucosal Inflammation	9 (5%)	6 (3%)

**Table 7.4.1.4 Study 2000145:** Subject Incidence of Adverse Events ( $\geq 5\%$  and observed in more subjects in Aranesp arm than in placebo arm) Derived from Amgen's results.

Study ID 2000145	Aranesp (N=301)	Placebo (N=296)
Preferred term		
Number of Subjects reporting AEs	288 (96%)	289 (98%)
Nausea	133 (44%)	122 (41%)
Neutropenia	112 (37%)	96 (32%)
Thrombocytopenia	60 (20%)	39 (13%)
Back Pain	21 (7%)	15 (5%)
Abdominal Pain	20 (7%)	8 (3%)
Hypokalemia	18 (6%)	15 (5%)
Pneumonia	15 (5%)	10 (3%)
Paraesthesia	14 (5%)	13 (4%)

**Table 7.4.1.5 Study 20010103:** Subject Incidence of Adverse Events ( $\geq 5\%$  and observed in more subjects in Aranesp arm than in placebo arm) Derived from Amgen's results.

Study ID 20010103	Aranesp (N=515)	Placebo (N=470)
Preferred term		
Number of Subjects reporting AEs	399 (78%)	359 (76%)
Abdominal pain	33 (6%)	22 (5%)
Chest pain	19 (4%)	10 (2%)
Confusional state	8 (2%)	3 (1%)

#### 7.4.2 Laboratory Findings

No specific information and analyses on the laboratory findings, other than hemoglobin values and related parameters, are submitted to this supplement.

#### 7.4.3 Vital Signs

There is no analysis on vital signs conducted and submitted to this supplement.

#### 7.4.4 Electrocardiograms (ECGs)

There is no information on electrocardiograms submitted to this supplement.

#### 7.4.5 Special Safety Studies

There is no information on special safety studies submitted to this supplement.

#### 7.4.6 Immunogenicity

No new information on immunogenicity was obtained during the review of this supplement.

### 7.5 Other Safety Explorations

#### Review and discussion on Amgen's proposed labeling revisions and supporting analyses on safety in response to FDA item 3

In response to FDA requested item 3, i.e., *Revision of the INDICATIONS AND USAGE section to clarify the severity of anemia for which Aranesp/PROCRIT is indicated, by inclusion of the maximum, and if appropriate minimum, pretreatment hemoglobin level on the threshold for the initiation of Aranesp*, Amgen conducted analyses on overall survival by pooling data from 7 randomized, placebo controlled studies of Aranesp in subjects receiving concomitant chemotherapy (980291-1, 980291-2, 990114, 980297, 20000161, 20030232, and 20010145). The pooled data was analyzed in subgroups defined by baseline hemoglobins. The results are illustrated in Figure 7.5.1, copied from Amgen's Summary of Clinical Safety (103951.5173, 2.7.4).

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immediately following this page

To summarize, no definitive or meaningful conclusion can be drawn from the exploratory analyses on the survival impact of Aranesp by baseline hemoglobin levels (< 9 g/dL versus  $\geq$  9 g/dL, or by < 10g/dL versus  $\geq$  10 g/dL). However, the findings that a shorter median survival time in the Aranesp arm in subjects with baseline hemoglobin levels  $\geq$  10 g/dL in both study 20000161 and 20010103 in which an increased mortality was seen in the overall Aranesp arms as compared to the placebo arms warrant the safety concerns of an increased mortality in patients with baseline hemoglobin levels  $\geq$  10 g/dL, providing supporting evidence for the current revised labeling statement that Aranesp should not be initiated in patients with baseline hemoglobin levels of  $\geq$  10 g/dL (103951.5195) ✓

Review and discussion on Amgen's proposed labeling revisions and supporting analyses in response to FDA item 4

In response to FDA requested item 4: *Revision of the DOSAGE AND ADMINISTRATION section to specify a lower maximum hemoglobin level (i.e., hemoglobin level less than 12 g/dL) at which dosing should be suspended or terminated*, Amgen proposes (b) (4)



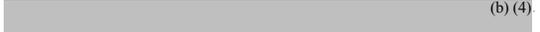
**7.5.2 Amgen's meta analysis for Overall Death for CIA Studies (including 3 Radiotherapy/Chemotherapy Studies\*) by Threshold Hemoglobin**



**Figure 7.5.3 Amgen's Analysis using Hazard Ratio Based on a Time-dependent Covariate: Hemoglobin > 12 g/dL (Darbepoetin alfa Placebo-controlled CIA Studies, Randomized Group)**



*Reviewer's comments:*

*This reviewer does not agree with Amgen's proposal*  (b) (4)



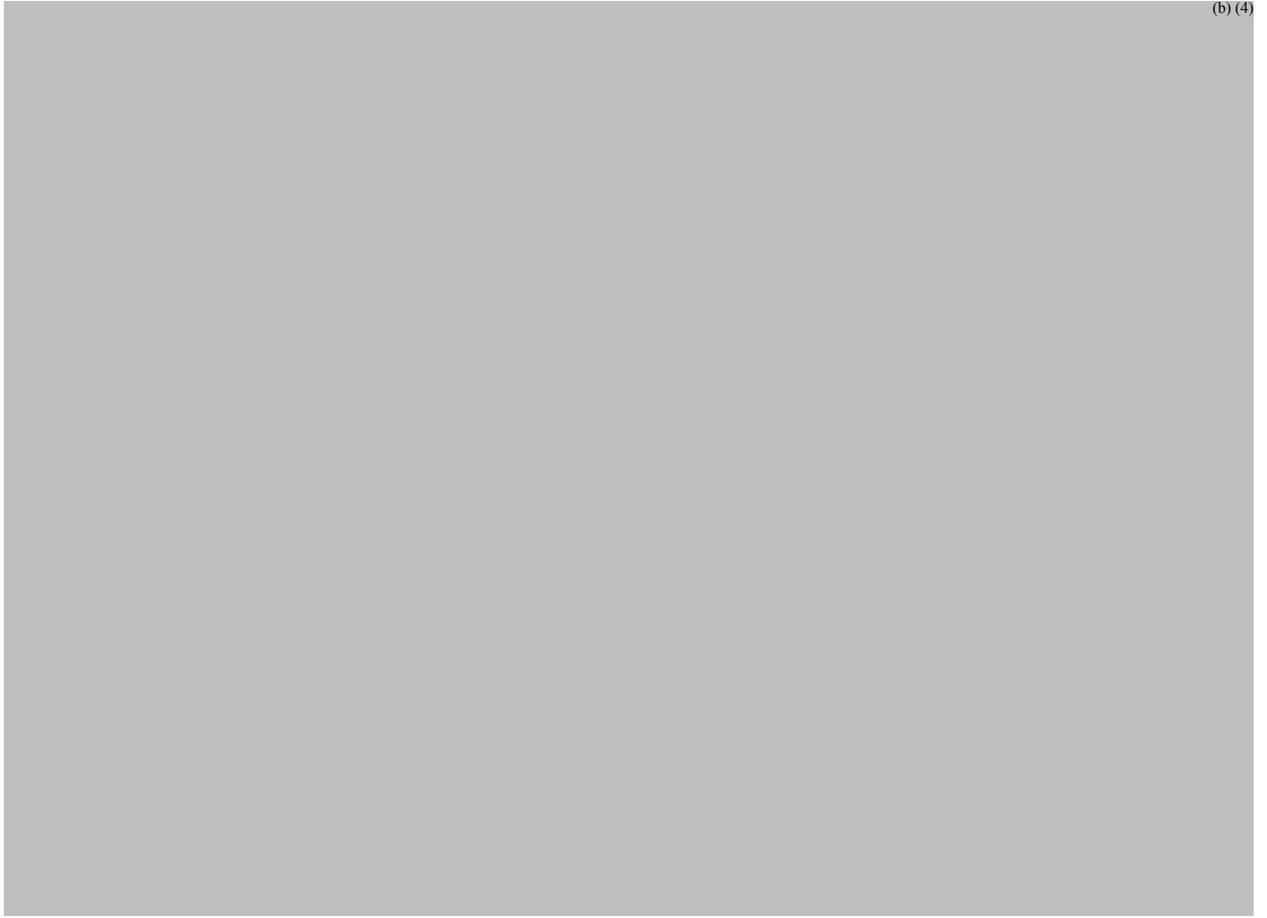
*for the following reasons:*



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(b) (4)



(b) (4)



*In summary, no perspective study was conducted to address the FDA requested item 4, nor the available information are adequate to give directions as to when ESAs should be withheld in terms of hemoglobin level. Due to heterogeneity and complexities involved in the patient populations in terms of their individual disease status, chemotherapy and co morbidity, the risk for RBC transfusion and the benefit of receiving ESAs have to be weighed on an individual basis.*

(b) (4)

*Therefore, this reviewer disagrees with Amgen's proposed response to FDA item 4 in this submission and agrees with Amgen's further revised labeling statements in the subsequent labeling submission (103951.5195) "For both dosing schedules, the dose should be adjusted for each patient to maintain the lowest hemoglobin level sufficient to avoid RBC transfusion" and "If the hemoglobin exceeds a level needed to avoid transfusion, Aranesp® should be temporarily withheld until the hemoglobin approaches a level where transfusions may be required".*

this is in fpl of  
103951/5195

## 7.6 Additional Submissions

There are no additional submissions to this supplement.

## 8. Postmarketing Experience

This supplement was submitted in response to FDA's requested action as a result of safety concerns which were raised in postmarketing studies and triggered three ODAC meetings in 2004, 2007 and 2008 as described in the review Section 5. No further information on the postmarketing experience is available since ODAC May 10, 2008.

## 9. Appendices

### 9.1 Literature Review/References

No other literature review is conducted for this supplement.

### 9.2 Labeling Recommendations

This reviewer recommends the approval of this labeling supplement when final agreed upon labeling is reached.

Amgen's most recent labeling supplement submitted on August 5, 2008 contains labeling revisions pertinent to the main issues triggering the submission of this supplement. Therefore, this reviewer considers that Amgen's revised labeling revisions contained in the most recent supplement (103951.5195) should trump and replace Amgen's earlier d labeling revisions contained in this supplement. Major labeling recommendations pertinent to this supplement, other than issues related to PLR format conversion, are made in the sections of Boxed Warnings, Dosage and Administration, and Adverse and Adverse Reactions and are summarized as follows:

Boxed Warning section:

In the Boxed Warning section, the most recent Aranesp labeling supplement (103951.5195) contains the following proposed revisions:

**WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR and THROMBOEMBOLIC EVENTS, and INCREASED RISK OF TUMOR PROGRESSION OR RECURRENCE**

**Renal failure:** Patients experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.

**Cancer:**

- **ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in some clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers (see WARNINGS: Table 1).**
- **To decrease these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion.**
- **Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.**
- **ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.**
- **Discontinue following the completion of a chemotherapy course.**

(See **WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events, WARNINGS: Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION.**)

The last bullet statement "**Discontinue following the completion of a chemotherapy course**" appropriately addressed the FDA requested item #5: *Revision of the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections to indicate that Aranesp/PROCRIT should be discontinued following the completion of the concomitant chemotherapy regimen. The statement "Discontinue (Aranesp) following the completion of chemotherapy" should replace Amgen's earlier version of proposed language* (b) (4)

DOSAGE AND ADMINISTRATION section:

In the *DOSAGE AND ADMINISTRATION* section under *Cancer Patients Receiving Chemotherapy*, the most recent Aranesp labeling supplement (103951.5195) contains the following proposed revisions:

✓ **Therapy should not be initiated at hemoglobin levels  $\geq 10$  g/dL. For both dosing schedules, the dose should be adjusted for each patient to maintain the lowest hemoglobin level sufficient to avoid RBC transfusion.** If the rate of hemoglobin increase is more than 1 g/dL per 2-week period or when the hemoglobin reaches a level needed to avoid transfusion, the dose should be reduced by 40% of the previous dose. **If the hemoglobin exceeds a level needed to avoid transfusion, Aranesp<sup>®</sup> should be temporarily withheld until the hemoglobin approaches a level where transfusions may be required.** At this point, therapy should be reinitiated at a dose 40% below the previous dose.

For patients receiving weekly administration, if there is less than a 1 g/dL increase in hemoglobin after 6 weeks of therapy, the dose of Aranesp<sup>®</sup> should be increased up to 4.5 mcg/kg.

**Discontinue Aranesp<sup>®</sup> if after 8 weeks of therapy there is no response as measured by hemoglobin levels or if transfusions are still required.**

**Discontinue Aranesp<sup>®</sup> following the completion of a chemotherapy course (see BOXED WARNINGS: *Cancer*).**

✓ The highlighted texts contained in the latest labeling supplement (103951.5199) adequately addressed the main issues which triggered the submission of this supplement and should replace Amgen proposed language contained in the current labeling supplement (103951.5173).

Specifically, the statement “**Therapy should not be initiated at hemoglobin levels  $\geq 10$  g/dL**” appropriately addressed the FDA requested item 3: *Revision of the INDICATIONS AND USAGE section to clarify the severity of anemia for which Aranesp/PROCRIT is indicated, by inclusion of the maximum, and if appropriate minimum, pretreatment hemoglobin level on the threshold for the initiation of Aranesp (FDA item3).* This statement “**Therapy should not be initiated at hemoglobin levels  $\geq 10$  g/dL**” should replace Amgen’s earlier version of proposed language (b) (4)

✓ Furthermore, the statements “**For both dosing schedules, the dose should be adjusted for each patient to maintain the lowest hemoglobin level sufficient to avoid RBC transfusion**” and “**If the hemoglobin exceeds a level needed to avoid transfusion, Aranesp<sup>®</sup> should be temporarily withheld until the hemoglobin approaches a level where transfusions may be required**” are appropriate to address the FDA requested item 4: *Revision of the DOSAGE AND ADMINISTRATION section to specify a lower maximum hemoglobin level (i.e., hemoglobin level less than 12 g/dL) at which dosing should be suspended or terminated.* Amgen’s earlier version of the proposed language containing (b) (4) and “

(b) (4).” implying a safe limit of targeting hemoglobin to 12 g/dl are not justified and unacceptable.

In addition, a statement in the **Boxed Warning** section “**Discontinue Aranesp® following the completion of a chemotherapy course**” was reemphasized in the *Dosage and Administration* section in response to FDA requested item 5 and should replace Amgen’s earlier version of response proposed as (b) (4).®

Furthermore, a revised statement “Discontinue Aranesp® if after 8 weeks of therapy there is no response as measured by hemoglobin levels or if transfusions are still required” should replace Amgen’s earlier version of proposed language (b) (4). because the revised language provide clearer direction in the referred context.

ADVERSE REACTION in the PLR conversion:

In the Adverse Reaction section, Amgen proposed adverse reactions based on pooled data from 7 randomized, placebo controlled studies of Aranesp in patients with anemia and receiving chemotherapy (study 980291-1, 980291-2, 990114, 980297, 20000161, 20030232, and 20010145.) This reviewer recommends data from a randomized, placebo controlled study of Aranesp in a patient population with relatively homogeneous tumor type, i.e., extensive small cell lung cancer) receiving homogenous platinum-containing chemotherapy be used to characterize the adverse reactions observed in patients receiving Aranesp as compared with patients receiving placebo. The following table on adverse reactions with clinical significance and occurring in higher incidence in Aranesp arm than in placebo arm based on data from study 20010145 is proposed to be inserted under section 6. ADVERSE REACTIONS



On Amgen’s proposed labeling update on study 20010103

 not the same as in fpl

Regarding Amgen’s proposed labeling revisions to include an update to clinical information on Study 20010103 (Cancer Study 8) in the WARNINGS AND PRECAUTIONS, Increased

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Mortality and/or Tumor Progression section (5.2) of the label in Physician Labeling Rule (PLR) format, this reviewer agrees with FDA's statistical reviewer's opinion that inclusion of the overall survival results on combined data (study 20010103 and the roll-over study 20020149) is not appropriate [REDACTED] (b) (4) [REDACTED]. Therefore, no update information on the study 20010103 will be included in the final approved labeling.

### 9.3 Advisory Committee Meeting

No advisory committee meeting is planned for this supplement.

## CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

Yes	No	N/A	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>			
✓			1. On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?
✓			2. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?
✓			3. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?
✓			4. Are all documents submitted in English, or are English translations provided when necessary?
✓			5. On its face, is the clinical section of the application legible so that substantive review can begin?
<b>LABELING</b>			
✓			6. Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56 <sup>1</sup> and 201.57, current divisional and Center policies, and the design of the development package?
<b>SUMMARIES</b>			
✓			7. Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?
✓			8. Has the applicant submitted the integrated summary of safety (ISS)?
✓			9. Has the applicant submitted the integrated summary of efficacy (ISE)?
✓			10. Has the applicant submitted a benefit-risk analysis for the product?
<b>DOSE</b>			
✓			11. If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?
<b>EFFICACY</b>			
✓			12. On its face, do there appear to be the requisite number of adequate and well controlled studies in the application?
✓			13. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?
<b>SAFETY</b>			
✓			14. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?
✓			15. Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?
✓			16. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?

*provided in ISS*

<sup>1</sup> [http://www.access.gpo.gov/nara/cfr/waisidx\\_01/21cfr201\\_01.html](http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html)

<b>OTHER STUDIES</b>				
17. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	✓			
18. For an Rx-to-OTC switch application, are the necessary special OTC studies included (e.g., labeling comprehension)?		✓		
<b>PEDIATRIC USE</b>				
19. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		✓		
<b>ABUSE LIABILITY</b>				
20. If relevant, has the applicant submitted information to assess the abuse liability of the product?		✓		
<b>FOREIGN STUDIES</b>				
21. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		✓		
<b>DATASETS</b>				
22. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	✓			
23. Has the applicant submitted datasets in the format agreed to previously by the Division?	✓			
24. Are all datasets for pivotal efficacy studies available and complete for all indications requested?	✓			
25. Are all datasets to support the critical safety analyses available and complete?	✓			
26. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?	✓			
<b>CASE REPORT FORMS</b>				
27. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	✓			
28. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			✓	
<b>FINANCIAL DISCLOSURE</b>				
29. Has the applicant submitted the required Financial Disclosure information?	✓			
<b>GOOD CLINICAL PRACTICE</b>				
30. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	✓			
<b>CONCLUSION</b>				
31. From a clinical perspective, is this application fileable? If "no", please state why it is not?	✓			

Signature Page

Chaocong Fan 2/11/08

Reviewer Signature/Date

 Sum

Concurrence by Team Leader: Signature/Date