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APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Statistical Review and Evaluation Addendum

NDA/Serial Number:	sBLA 103951/5173
Drug Name:	Aranesp ® (Darbepoetin alfa)
Indication(s):	Chemotherapy induced anemia
Applicant:	Amgen, Inc.
Date(s):	Submitted: 10/23/09
	PDUFA: 4/27/10
Review Priority:	Class 2 response to CR letter
Biometrics Division:	Division V, Office of Biostatistics (HFD-711)
Statistical Reviewer:	Yuan-Li Shen, Dr. P.H.
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Key Words: **Log-rank statistic; Cox's regression model;**

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Table of Contents

List of Tables

1 Overview

Supplement BL STN 103951/5173 for Aranesp was submitted on December 20, 2007. The supplement is proposed to revise the patient package insert labeling based on recommendations from the May 10, 2007 Oncology Advisory committee Meeting (ODAC). On October 24, 2008, FDA issued a complete response letter for this supplement. This submission is to respond to FDA's complete response letter and provide a prior approval labeling supplement for a Physician's Labeling Rule (PLR) conversion as well as revise labeling based on updated data.

This addendum will present the statistical review of the sponsor's proposed revisions. Updated data for progression free survival or overall survival used to support the proposed revision is in the following network path: \\cbsap58\M\eCTD_Submissions\STN103951\0309.

Data for demographic information, duration of exposure and transfusion rate provided to clarify the contents or respond to the agency's request is based on data submitted on 12/20/07. The network path is in: \\cbsap58\M\eCTD_Submissions\STN103951\0164\m5\datasets.

2 Summary

This statistical review presents a brief summary of the sponsor's proposed revisions of the package insert, including :

- OS results based on study 20010103 (data included long-term follow up study 20010149);
- Disease free survival (DFS) and overall survival (OS) results based on updated PREPARE data;
- Relative risk of thromboembolic events and overall survival (OS) results based (b) (4)
- A statement about the nature of the interim analysis for DAHANCA study
- Duration of exposure and demographic information for study 20010145

- Demographic information and transfusion rate for study 980297
- Demographic information and transfusion rate for study 20030231.

Conclusions and Recommendation

- For OS results based on study 20010103: (b) (4) can not be included for labeling changes.
- OS results based on study PREPARE: (b) (4) thus they can not be used for labeling changes.
- The reviewer confirms the transfusion rates for studies 980297 and 20030231 based on the crude rates.
- The revision on the adverse events session for study 20010145 and the addition of the demographic information for studies 20030231 and 980297 are acceptable.
- Based on FDA's comments against the use of meta analyses in the 2007 ODAC committee, it is recommended that (b) (4).
- It is this reviewer's view that the analysis performed in the DAHANCA study should be viewed as a planned interim analysis.

The sponsor's proposed labeling revisions and overview of the submitted items for the proposed labeling changes are summarized below:

OS results based on study 20010103 in Section 5 Warnings and Precautions

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, and were not planning to receive, chemotherapy or radiotherapy. Data on overall survival from this study are included in the Warning and Precautions, Increased Mortality and/or Tumor Progression section (5.2) of the current labeling.

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

(b) (4)

A detailed review of the study is in the statistical review of BLA123951/5173 signed off on 10/17/08. In the previous Post Approval Submission (PAS), the dataset contain the long-term follow-up data from study 20010103 and rollover study 20020149 based on cutoff date of 11/7/06. In the statistical review, the recommendation and conclusion section indicates "*Inclusion of the overall survival results based on combined data (studies 20010103 and 20020149) is not acceptable* (b) (4)

Reviewer's comment:

(b) (4)

No further revision should be made for this label.

(b) (4)

(b) (4)

Table 1 **Summary of Overall Survival (Safety Analysis set)- cutoff date 11/7/06 and** (b) (4)

Cutoff dates	**11/7/06 (20010103 only)**		(b) (4) **(combined 20010103 and 20020149)**
	Placebo (N=470)	**Darbepoetin alfa 6.75 µg/kg Q4W (N=515)**	(b) (4)
Number of Subjects with Death	216	250	
Survival Time (Weeks)			
Median (K-M)	47.0	34.7	
Q1, Q3 (K-M)	17.6, 104.9	14.6, 122.3	
HR (95% CI) (Aranesp vs. placebo)	HR=1.30 [a] (1.07,1.57)		
Nominal p-value	0.008		

* A subject dosed with placebo in 20010103 was incorrectly dosed with darbepoetin alfa in 20020149; this subject was analyzed as a placebo subject in the full clinical study report for 20010103 (before dosing data from 20020149 was available) and as a darbepoetin alfa subject in subsequent analysis.

[a] Cox proportional hazards model is stratified by all stratification factors at randomization (hemoglobin at screening, region, prior RBC transfusion, tumor type, ECOG and randomization schedule

Note: All deaths include on-study deaths and deaths occurring after the EOS visit and during the long-term follow-up period.

Time to death is counted as the number of days from the first day of investigational product administration to the date of death.

Reviewer's comment:

- *As indicated in previous review* [redacted] (b) (4) *the updated OS results based on current submission can not be included for labeling changes.*
- *It is noted that study 20020149 is a rollover study of study 20010103. Patient population from study 20020149 is a volunteer subgroup of the patients from study 20010103.*
- *It is noted that one patient receiving placebo in study 20010103 was incorrectly dosed with Aranesp in 20020149. Therefore, there is one more patient in Aranesp arm and one less patient in the placebo arm as compared with the denominators calculated from the data based on 11/7/06 cutoff date.*
- *Based on current data submission, this reviewer performed similar analysis based on Cox's model stratified by the randomization factors and included randomization schedule as an additional stratification factor, the hazard ratio* [redacted] (b) (4)

DFS and OS results based on updated PREPARE data in Section 5 Warnings and Precautions

The PREPARE study which was an open-label, randomized, multicenter, phase 3 study designed to evaluate the effects of neoadjuvant chemotherapy in subjects with breast cancer using a sequential dose-dense and dose-intensified regimen of epirubicin, paclitaxel, cyclophosphamide, 5-fluorouracil, and methotrexate compared with preoperative sequential administration of epirubicin and cyclophosphamide followed by paclitaxel, with or without darbepoetin alfa. Data on overall survival and relapse-free

survival from this study are included in the Warnings and Precautions, Increased Mortality and/or Tumor Progression section (5.2) of the current labeling.

The sponsor's red-line labeling revision is shown below:

(b) (4)

Reference was made to the statistical review signed off on 3/5/08 where a more detailed review of the study was provided. In the statistical review, the recommendation and conclusion section indicates (b) (4) *there are enough events (176 relapse events) to meet the number of events requirement. The current data submission is based on 10/30/2007 cutoff data. Based on the study protocol or SAP, it is not clear when the final analysis will be conducted."*

Reviewer's comment:

A post-meeting comment in a meeting summary letter dated 5/22/08 about the concerns that the timing of the intended final analysis of RFS has been reached was sent to the sponsor.

(b) (4)

Table 2 **Summary of Relapse Free Survival: PREPARE (cutoff dates: 10/30/07 and** (b) (4)

Cutoff date	10/30/07		(b) (4)
	EC→T or E→T→CMF No Aranesp [c] (n = 377)	**EC→T or E→T→CMF With Aranesp** [c] (n = 356)	
Patients with an event	79	97	
Stratified analysis			
Hazard ratio [a]	NA	1.33	
95% CI	NA	(0.99,1.79)	
Nominal P-value	NA	0.0587[b]	
3 year survival rate	78%	72%	

[a] Relative to arm without Aranesp. Estimated using Cox model.

[b] Nominal p-value based on the unstratified log rank test

[c] Sequential treatment (EC→ T) with Epirubicin (90 mg/m^2) dl, q21d – 4 × /cyclophosphamide (600 mg/m^2) dl, q2ld - 4 × followed by paclitaxel (175 mg/m^2) dl, q21d - 4× ;

Sequential dose-intensified treatment (E→T→CMF) with Epirubicin (150 mg/m^2) dl, q14d – 3 ×, followed by paclitaxel (225 mg/m^2) dl, q14d - 3×, followed by CMF (cyclophosphamide/methotrexate/5-fluorouracil) dl/d8, q28d - 3×;

Darbepoetin alfa 1× 4.5 µg/kg of body weight every 2 weeks with the start of the first epirubicin dose (day 1) to 14 days after the last dose of paclitaxel for EC→ T treated arm (or CMF for E→T→CMF treated arm).

(b) (4)

Table 3 Summary of Overall Survival: PREPARE (cutoff dates: 10/30/07 and [redacted]

Cutoff date	10/30/07		[redacted]
	EC→T or E→T→CMF No Aranesp [c] (n = 377)	EC→T or E→T→CMF With Aranesp [c] (n = 356)	
Patients with an event	37	50	
Stratified analysis			
Hazard ratio [a]	NA	1.42	
95% CI	NA	(0.93,2.18)	
Nominal P-value	NA	0.1020[b]	
3 year survival rate	90%	86%	

[a] Relative to arm without Aranesp. Estimated using Cox model.
[b] Nominal p-value based on the unstratified log rank test
[c] Sequential treatment (EC→ T) with Epirubicin (90 mg/m^2) dl, q21d – 4 × /cyclophosphamide (600 mg/m^2) dl, q2ld - 4 × followed by paclitaxel (175 mg/m^2) dl, q21d - 4× ;
Sequential dose-intensified treatment (E→T→CMF) with Epirubicin (150 mg/m^2) dl, q14d – 3 ×, followed by paclitaxel (225 mg/m^2) dl, q14d - 3×, followed by CMF (cyclophosphamide/methotrexate/5-fluorouracil) dl/d8, q28d - 3×;
Darbepoetin alfa 1× 4.5 µg/kg of body weight every 2 weeks with the start of the first epirubicin dose (day 1) to 14 days after the last dose of paclitaxel for EC→ T treated arm (or CMF for E→T→CMF treated arm).

Reviewer's comment:

[redacted] *thus they can not be used for labeling changes.*

Results based on study 20010145 in Section 6 Adverse Reaction

Study 20010145 was a randomized, placebo-controlled study for patients who had previously untreated extensive-stage small cell lung cancer receiving etoposide and platinum-containing chemotherapy. [redacted]

The revised label information based on study 20010145 in this PAS submission is described below:

Reviewer's comment:
The reviewer confirms the median age for patients in study 20010145 is 61 years old, ranged from 28 to 82 years and 64% were male based on safety evaluable population. The safety analysis set consisted of all randomized subjects who received at least 1 dose of investigational product. Subjects not dosed in accordance with their randomized treatment group assignment were analyzed according to the actual treatment received for all safety analyses. Subjects who inadvertently received doses of both investigational products were included in the Aranesp treatment group.

Results based on study 980297 in Section 14 Clinical Studies

Study 980297 was a double-blind, placebo-controlled, randomized study of Aranesp for the treatment of anemia in lung cancer (non-small cell and small cell) patients receiving 12 weeks of multicycle platinum-containing chemotherapy. Patients were randomized to receive once-weekly SC injections of Aranesp at a starting dose of 2.25 μg/kg/week or placebo for 12 weeks. Currently, the study description and the RBC transfusion rate results were included (indicated as the study C1) in the section 14 Clinical Studies Cancer Patients Receiving Chemotherapy. The primary efficacy endpoint is the proportion of subjects in the primary analysis set received RBC transfusions from week 5 to the EOTP. The primary analysis set is defined as all subjects who were randomized in the study who received at least 1 dose of study drug and who successfully completed the guarantee period. The guarantee period is defined as the minimum amount of time on-study that a subject had to complete to be evaluated for the primary endpoint of this study. Subjects who withdrew from the study during weeks 1 to 4 were excluded from the primary analysis set since they did not complete the guarantee period and did not have the opportunity to be evaluated for the primary endpoint. Based on the protocol, the transfusion rate was calculated based on Kaplan-Meier estimate. The agency requested to revise the transfusion rate based on the crude rate for consistency purpose across erythropoietin products.

The red-line revision of the current labeling based on study 980297 is shown below:

Reviewer's comment:

- *The labeling revision is based on the primary analysis set based on the pre-planned analysis specified in the protocol. The primary analysis set is defined as all randomized subjects who received at least 1 dose of study drug and completed weeks 1 to 4. The reviewer obtained crude rates of 50% (74/149) and 26% (39/148) for Aranesp and placebo arm, respectively, based on the primary analysis set.*
- *The reviewer confirms the median age for patients in study 980297 is 62 years old, ranged from 36 to 80 years based on the primary analysis set.*

Results based on study 20030231 in Section 14 Clinical Studies

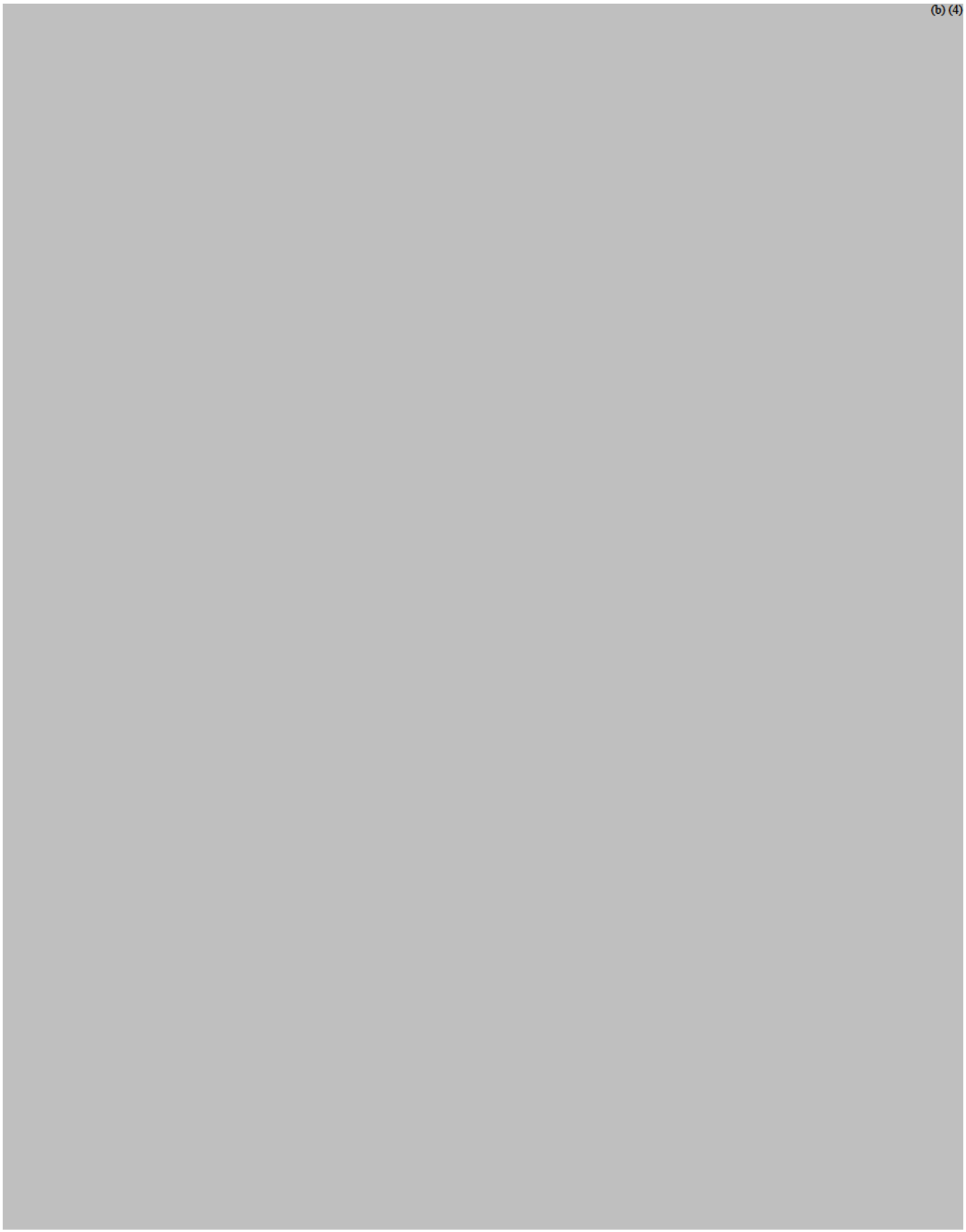
Study 20030231 was a multicenter, double-blind, double-dummy, active-controlled, randomized phase 3 study conducted in anemic patients with non-myeloid malignancies receiving chemotherapy. This study compared darbepoetin alfa 500 µg Q3W and 2.25 µg/kg QW for their effects on the incidence of RBC transfusions, hemoglobin level, and overall safety. Currently, the study description and the RBC transfusion rate results were included (indicated as the study C2) in the section 14 Clinical Studies Cancer Patients Receiving Chemotherapy. The primary efficacy endpoint was the incidence of at least one RBC transfusion from week 5 (day 29) to the EOTP. The primary efficacy analysis was based on the primary transfusion analysis set defined as all subjects who took at least one study medication and who were enrolled in the study until at least day 29, i.e., EOTP day $\geq$ day 29. Based on the protocol, the transfusion rate was calculated based on Kaplan-Meier estimate. The agency requested to revise the transfusion rate based on the crude rate for consistency purpose across erythropoietin products.

Reference was made to the statistical review for BLA103951/5097 (signed off on 2/27/06) where a more detailed review of the study was provided.

The sponsor revised labeling information based on study 20030231 is shown below:

Reviewer's comment:

- *The summary of transfusion rate was based on the primary transfusion analysis set, which included all subjects who were randomized and received at least one dose of study medication and who were in treatment until at least day 29. The numbers of patients were 337 and 335 for every week and every 3 week dose arm, respectively. The reviewer confirmed the sponsor's revision based on dataset a_eendfu.xpt : i.e. crude transfusion rates were 28% (96/337, 95% CI= [24%, 34%]) and 23% (76/335, 95% CI= [18%, 28%]) for every week and every 3 week dose arm, respectively. The observed difference in the RBC transfusion rates was -5.8% (95% CI= [-12.4%, 0.8%] calculated based on normal approximation).*
- *The reviewer confirms that among 705 patients in the ITT population, 99.9% were white, 54% were female and the median age was 60 years (ranged from 20 to 86 years). Also, there were 112 out of 705 patients had either lung (non small cell lung cancer or small cell lung cancer) or gynecologic cancer (cervix, ovarian, uterus/endometrial) based on the ITT population.*


(b) (4)

Results based on DAHANCA in Section 5 Warnings and Precautions

SE 2002-9001 (DAHANCA 10, i.e. Study 6 in section 5.2 of the labeling) is a study of the importance of Novel Erythropoiesis Stimulating Protein (Aranesp®) for the effect of radiotherapy in patients with primary squamous cell carcinoma of the head and neck. Patients were randomized to receive radiotherapy with or without Aranesp. The primary efficacy endpoint is time to locoregional failure. In the protocol, it states that one interim analysis based on all time to event endpoints will be performed after observation of half (about 150) of the estimated local failures. O'Brien and Fleming sequential design method will be used to preserve the type I error rate of the analysis.

The sponsor's revision on the labeling is shown below:

(b) (4)

[redacted]

Reviewer's comments:
According to the principle investigator's memo dated 12/1/06 for the interim analysis, it indicates that the study was temporarily stopped on 10/18/06 due to information about potential unexpected negative effects related to immunohistochemical estimation of the EPO receptor. Also, the timing is very close to the timing for the planned interim analysis. It was later decided to temporarily stop enrollment into the protocol until further decision. At the time of the analysis, among 522 patients randomized, 158 locoregional failures were observed which is close to the planned 150 locoregional failure events. Therefore, FDA considers the analysis as the formal interim analysis, (b) (4) [redacted]

3 SIGNATURES/DISTRIBUTION LIST PAGE

Primary Statistical Reviewer: **Date:** March 18, 2010

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Mathematical Statistician

Yuan-Li Shen 3-18-10

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CC:

HFD-107/ Keegan, Shastri, Patel
HFD-711/ Sridhara, Rothmann, Shen
HFD-700/Patrician

This review consists of 16 pages
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Statistical Review and Evaluation

Medical Division: Biologic Oncology Drug Products (HFD-107)
Biometrics Division: Division V, Office of Biostatistics (HFD-711)

STATISTICAL KEY WORDS:	**Log-rank statistic; Cox's regression model; Meta analysis; Analysis of Variance model**
BLA NUMBER:	**sBLA 103951/5173**
DRUG NAME:	**Aranesp® (Darbepoetin alfa)**
INDICATION:	**Chemotherapy induced anemia**
SPONSOR:	**Amgen, Inc.**
STATISTICAL REVIEWER:	**Yuan-Li Shen, Dr. P.H. (HFD-711)**
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Distribution: sBLA 103951
HFD-107/ Summers, Gootenberg, Keegan, Hughes, Fan, Shastri
HFD-711/Chakravarty, Rothmann, Shen, Lee
HFD-700/Patrician

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C:/BLA_2007/EPO-PAS/meta/Aranesp_PAS_statreview_2007.doc

Table of Contents

List of Tables

List of Figures

1. Executive Summary of Statistical Findings

Since Aranesp was approved on July 19, 2002 for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy, the agency have become aware of eight controlled clinical studies that provide evidence of increased mortality and/or poorer tumor outcomes in patients with head and neck cancer, breast cancer, non-small cell lung cancer, cervical cancer and in anemic cancer patients receiving non active anti-cancer therapy (BEST, ENHANCE, EPO-CAN-20, 2001-0103, 2000-0161, DAHANCA 10, PREPARE and GOG191). Based on the new finding and safety concerns, three Oncologic Drugs Advisory Committee (ODAC) meetings were held on May 3, 2004, May 10, 2007 and March 13, 2008.

After the May, 2007 ODAC meeting, the agency issued a letters to the sponsor (Amgen) dated 5/31/07 requesting the submission of proposals to address the points discussed by ODAC. Items 1, 2, and 6 of agency's 5/31/07 letters were addressed in revised package inserts under Change Being Effect (CBE) supplements submitted on 9/19/07 (Aranesp® STN BL 103951/5157, Sequence No. 0158) and on 9/21/07 (EPOGEN®/PROCRIT® STN BL 103234/5158 Sequence No. 0092) and were approved by the agency on 11/08/07. This submission is intended to provide rationale in support of additional labeling changes in response to items 3, 4 and 5 in the agency's 5/31/07 letter based on both individual studies and subject-level and study-level combined analyses of randomized, controlled studies of darbepoetin alfa.

1.1 Recommendations and Conclusions

Several findings based on this statistical review are summarized below:

1. The sponsor's analysis results did not support the inclusion of the statement: [redacted] (b) (4)
2. The sponsor's analysis results did not provide sufficient support for the proposal of (b) (4) [redacted]

3. The analysis results using study 20010145 data did not provide sufficient [redacted] (b) (4)

4. Inclusion of the overall survival results based on combined data (study 20010103 and 20020149) is not acceptable [redacted] (b) (4)

5. In the evaluation of the quality of life data based on the change from baseline to EOTP in FACT-fatigue sub-score, both the reviewer's and the sponsor's results did not show any favorable trend in supporting the use of Aranesp.

1.2 Brief Overview of Clinical Studies

This statistical review presents a brief summary of the sponsor's results and the reviewer's evaluation on items 3, 4, 5 based on agency's 5/31/07 letter and other proposed labeling changes based on study 20010103. Statistical evaluation for other proposed labeling changes based on study 20010145 will be presented briefly in this review. In addition, a brief summary of the quality of life analysis will be presented. Statistical review for studies EPO-INT-76 (BEST) and N93-004 will be presented in sBLA 103234/5166.

1.3 Statistical Issues and Findings

Several major statistical/data issues are summarized below:

1. The combined analysis results used to justify the starting hemoglobin level for initiation of Aranesp is inconsistent with results obtained from the individual study.
2. There are several issues related to the meta analyses :
    1) Meta analyses can obscure safety signals from individual studies.
    2) Meta analysis results depend on the studies included:
        I. earlier meta-analysis suggest statistical significance on overall survival (OS) favoring ESA;

II. later meta-analyses suggest statistical significance on OS favoring control.

3) Cumulative meta analyses and retrospective meta analyses have issues on appropriate allocation of alpha.

4) Heterogeneous trials with variable quality, lengths of follow-up, Target hemoglobin level (Hgb) and heterogeneous tumor type.

3. (b) (4)

4.

5. The analysis based on study 20010145 (SCLC) did not provide sufficient (b) (4)

6. The proposed inclusion of overall survival results in the label based on combined data from studies 20010103 (patient with non-myeloid malignancies) and the roll-over study 20020149 is not acceptable (b) (4)

7. Majority of the sponsor's quality of life analyses did not consider missing data issues or deaths. Missing data problems in QOL assessment may be non-informative, therefore, caution should be taken for the interpretation of the QOL results.

2 Introduction

This section provides an overview of the submitted items for the proposed labeling changes. More detailed description of studies 20010103 and 20010145 are included in Section 3 and abbreviated summaries for all darbepoetin alfa (Aranesp®) studies included in this review will be presented in the Appendix. Summaries of the studies for epoetin alfa will be presented in sBLA 103234/5166.

2.1 Overview of the Submission

Item 3 on agency's 5/31/07 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.

The sponsor observed that the lowest absolute risk and greatest relative risk reduction for transfusions was seen at hemoglobin levels of (b) (4) at initiation based on combined results from studies 980291, 990114, 980297, 20000161, 20010145, and 20030232. (b) (4)

(b) (4)

Item 4 in agency's 5/31/07 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)

Item 5 in agency's 5/31/07 letter

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 sponsor evaluated the time to hemoglobin recovery after cessation of chemotherapy based on data from study 20010145. The design of this study included hemoglobin assessments for up to 12 weeks after the last dose of chemotherapy, thus the sponsor indicates that it can provide relevant information on time to hemoglobin recovery after the cessation of chemotherapy (patients in the darbepoetin alfa group continued to receive investigational product for only 3 weeks after the last dose of chemotherapy). The (b) (4) analysis is to evaluate the median time to a hemoglobin level ≥ 11 g/dL in those patients who had a hemoglobin concentration < 11 g/dL after the cessation of chemotherapy.

Other proposed labeling changes based on studies 20010145 and 20010103

Study 20010103

The sponsor proposes 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. :

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)

The update information is based on combined data from study 20010103 and the extension study 20020149.

Study 20010103 is a phase III, multicenter, randomized, double-blind, placebo-controlled study of Darbepoetin Alfa for the treatment of patients with active nonmyeloid malignancies who had not received within 4 weeks, and were not planning to receive chemotherapy or radiotherapy. The primary objective of this study is to evaluate the efficacy of darbepoetin alfa in reducing the occurrence of RBC transfusion.

Nine hundred eighty nine patients were enrolled at 144 sites in Europe, Australia, and North America. Majority of patients (75%) were from Europe.

Initially, patients were randomly assigned to one of the two treatment arms in a 1:1 ratio:

Group A: Darbepoetin alfa 6.75 mcg/kg (SC) Q4W
Group B: Placebo (SC) QW.

Enrollment continued until, upon a blinded review of the data, 145 patients experienced at least one RBC transfusion from study day 29 to week 17. Additional patients were enrolled and randomized in a 9:1 ratio to receive either Aranesp or placebo until 500 Aranesp patients were enrolled for the assessment of safety.

Treatment was designed to maintain hemoglobin concentrations of ≤12 g/dL. Patients received treatment every 4 weeks for 16 weeks (weeks 1,5,9,13). The end of treatment visit was on week 17 and the end of study visit was on week 19.

After treatment on this study, patients were eligible to proceed into a separate but similar treatment protocol (Study 20020149) for an additional 16 weeks, continuing on their originally assigned blinded treatment.

Randomization was stratified by the following stratification factors:

- Screening hemoglobin concentration (<10 g/dL vs. ≥10 g/dL)
- Region (central and eastern Europe vs. rest of the world)
- Whether RBC transfusion was given in the previous 12 weeks (Yes, No)
- Tumor type /treatment categories; defined as
  1) have chronic lymphocytic leukemia or low grade lymphoma as defined in the International Working Formulation Criteria vs.
  2) receiving hormonal or antibody vs.
  3) all other eligible patients.
- ECOG status (0,1 vs. 2)

Study 20010145

Study 20010145 was a randomized, placebo-controlled study was conducted in 600 patients with previously untreated extensive-stage small cell lung cancer receiving etoposide and platinum-containing chemotherapy. 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.

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) level (below versus above the upper limit of normal). This study was conducted at 69 sites in Europe, Australia and Canada.

The primary objective of this study is 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 second objective is to evaluate whether darbepoetin alfa improves FACT-Fatigue subscale scores. The other objectives are

- To assess the effect of darbepoetin alfa on subject symptom assessment, progression free survival, time to progression, tumor response, duration of tumor response, red blood cell (RBC) transfusions, and FACT-General
- To assess the overall safety profile of darbepoetin alfa in subjects with untreated extensive-stage SCL.

Subjects of legal age when consents were obtained, with pathologically proven extensive-stage SCLC, who planned to receive chemotherapy with carboplatin or cisplatin plus etoposide Q3W for 6 cycles were eligible for this study. Subjects were required to have a hemoglobin concentration ≥ 9.0 g/dL and ≤ 13.0 g/dL, an ECOG status of 0 to 2, and a life expectancy of ≥ 3 months. Subjects in the darbepoetin alfa

group continued to receive investigational product for only 3 weeks after the last dose of chemotherapy.

This study includes two co-primary endpoints : Change in hemoglobin concentration from baseline to the end of the chemotherapy treatment period and survival time.

The sponsor proposes the addition of 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)

Details of overall survival and progression free survival results will be provided in the review for (b) (4). A brief summary of the study will be provided in the appendix. The duration of time to recover to a hemoglobin level of ≥ 11 g/dL following cessation of chemotherapy will be discussed in this review.

2.2 Data Sources

Items 3 and 4

Data used to evaluate items 3, 4 and quality of life analysis is based on the sponsor provided meta-dataset in

\\cbsap58\M\eCTD_Submissions\STN103951\0164\m5\datasets\pas-meta-analysis.

Item 5 - Study 20010145

Data used for review item 5 and study 20010145 is from the electronic submission received on 12/20/07. The network path is in:

\\cbsap58\M\eCTD_Submissions\STN103951\0164\m5\datasets\20010145

Study 20010103

Data used for review of study 20010103 is from the electronic submission received on 9/17/07. The network path is in:
\\cbsap58\M\eCTD_Submissions\STN103951\0158\m5\datasets\20010103\analysis

3 Statistical Evaluation

The efficacy and safety analysis results will be presented in this section for protocols 20010103 and 20010145 and for items discussed in the sponsor's submission in section 2.7.4 Summary of Clinical Safety. More detailed statistical evaluation for study 20010145 will be presented in the statistical review for (b) (4)

3.1 Evaluation of Efficacy and Safety Endpoints

3.1.1 Introduction

Due to the nature of this submission, efficacy and safety discussion will be described simultaneously. The study design, including efficacy and safety endpoints, sample size, interim analysis and analysis methods for individual studies will be presented in the appendix. For this evaluation, in general, efficacy variables including RBC transfusion rate and safety variables including overall survival, progression free survival, etc will be discussed.

3.1.2 Safety Endpoints

Descriptions of the safety endpoints that are relevant to the proposed labeling changes and the studies involved will be presented in this section.

Item 3 in agency's 5/31/07 letter

Both OS and RBC transfusions rate were evaluated based on 6 Amgen-sponsored randomized double-blind, placebo-controlled trials of darbepoetin alfa in CIA

(890291,990114,980297,20000161,20010145 and 20030232).

Item 4 in agency's 5/31/07 letter

Both OS and a dichotomized hemoglobin level (>12 g/dL vs ≤12 g/dL) as a time-dependent covariate were evaluated based on combined studies analyses per sponsor and study 20010103 per the reviewer.

Item 5 in agency's 5/31/07 letter

Time to hemoglobin level ≥11 g/dL in patients with level <11 g/dL after chemotherapy was evaluated by the sponsor.

Study 20010103

The primary efficacy endpoint of this study is the risk of RBC transfusion from week 5 (day 29) to week 17. The safety endpoints of this study include adverse events, overall survival, etc.

Study 20010145

This study includes two co-primary endpoints : Change in hemoglobin concentration from baseline to the end of the chemotherapy treatment period and survival time.

The secondary endpoint includes the change in FACT-Fatigue (a subset of FACT-Anemia) subscale scores from baseline to the end of study treatment.

3.1.3 Quality of Life Endpoints

Functional Assessment of Cancer Therapy - Anemia Questionnaire (FACT-An)

The FACT-Anemia includes 20 questions evaluating the impact of anemia on cancer patients with various tumor types who were receiving chemotherapy. Two domains were included in this instrument: the domain of fatigue (FACT-Fatigue Scale, 13 items) and the domain of distinct anemia symptoms (FACT-Anemia Symptoms Scale, 7 items). Fatigue scale scores range from 0 to 52, and anemia symptom scale scores range from 0 to 28, with a higher score indicating less fatigue or fewer anemia symptoms.

3.1.4 Sponsor's Results and Statistical Reviewer's Findings/Comments

In this section, the sponsor's rationale and analyses as well as the reviewer's analyses

and comments will be discussed.

Demogrphic Information and Baseline Characteristics for Study 20010103

The first subject was randomized on 4/15/2004 and the data cutoff for the clinical study report is 11/07/2006.

Among 989 patients randomized, 517 and 472 patients were randomized to Aranesp and placebo arm, respectively. Two patients in each treatment arm never received study treatment, therefore, they were not included in both efficacy and safety analyses. Approximately 52% of patients completed 19 weeks study period. The mean age for patients in this study was 64 years old. There are more male (55%) in the Aranesp arm compared with those in the placebo arm (47%). Majority of the patients were Whites (95%).

Table 1 Sponsor's Summary of Demographic information and Baseline Characteristics - study 20010103

	Placebo n (%)	**Darbepoetin alfa 6.75 µg/kg Q4W n (%)**
Sex - n (%)		
Male	220 (46.8)	285 (55.3)
Female	250 (53.2)	230 (44.7)
Race - n (%)		
White	444 (94.5)	493 (95.7)
Black	21 (4.5)	18 (3.5)
Hispanic	2 (0.4)	3 (0.6)
Asian	3 (0.6)	1 (0.2)
Age - years		
n	470	515
Mean	64.3	64.0
SD	11.4	11.8
SE	0.5	0.5
Median	66.0	65.0
Q1, Q3	57.0, 73.0	56.0, 73.0
Min, Max	28, 88	18, 89
Age Group - n (%)		
< 65 years	213 (45.3)	247 (48.0)
≥ 65 to < 75 years	162 (34.5)	163 (31.7)
≥ 75 years	95 (20.2)	105 (20.4)

There were about 25 different primary tumor types identified in this study. The most common cancers were solid tumors including non-small cell lung (18-19%), breast (13%), and prostate (10-11%). The most common hematologic malignancies were multiple myeloma (6-8%) and Non-Hodgkin's lymphoma (NHL, 3-4%). Most subjects had stage III or IV disease (82%) and an Eastern Cooperative Oncology Group status of 0 or 1 (72%). Mean baseline hemoglobin was 9.5 g/dL in each group. However, the darbepoetin alfa arm had more patients who had received prior cytotoxic chemotherapy (74% versus 66%).

Table 2 Sponsor's Summary of Primary Tumor Type - Study 20010103

	Placebo n (%)	Darbepoetin alfa 6.75 µg/kg Q4W n (%)
Number of Subjects	470	515
Solid Tumor Type		
Non-small cell lung	83 (17.7)	97 (18.8)
Breast	62 (13.2)	66 (12.8)
Prostate	49 (10.4)	54 (10.5)
Large intestine	29 (6.2)	45 (8.7)
Kidney	28 (6.0)	22 (4.3)
Cervix	21 (4.5)	19 (3.7)
Ovarian	22 (4.7)	17 (3.3)
Stomach	18 (3.8)	19 (3.7)
Other solid tumor	17 (3.6)	14 (2.7)
Small cell lung	10 (2.1)	15 (2.9)
Head & neck (squamous cell carcinoma)	12 (2.6)	11 (2.1)
Pancreas	13 (2.8)	10 (1.9)
Soft tissue sarcoma	9 (1.9)	10 (1.9)
Bladder	10 (2.1)	8 (1.6)
Melanoma	4 (0.9)	10 (1.9)
Endometrial	5 (1.1)	4 (0.8)
Uterus	4 (0.9)	4 (0.8)
Oral	3 (0.6)	4 (0.8)
Esophagus	2 (0.4)	4 (0.8)
Carcinoma of unknown primary	2 (0.4)	3 (0.6)
Testicular	1 (0.2)	2 (0.4)
Ureter	0 (0)	1 (0.2)
Hematological Tumor Type		
Multiple myeloma	38 (8.1)	33 (6.4)
Non-Hodgkin's lymphoma	15 (3.2)	21 (4.1)
Chronic lymphocytic leukemia (CLL)	10 (2.1)	10 (1.9)
Other hematological malignancy	2 (0.4)	6 (1.2)
Hodgkin's disease	1 (0.2)	6 (1.2)

Demogrphic Information and Baseline Characteristics for Study 20010145

The first subject was randomized on 12/10/2002 and the data cutoff for the clinical study report is 2/22/2007.

Among 600 randomized patients, 3 patients in placebo arm did not receive study treatment (darbepoetin alfa or placebo). Fifty-six percent and 55% in darbepoetin alfa and placebo arm, respectively completed investigational product.

Fifty percent and 52% in darbepoetin alfa and placebo arm, respectively, completed study.

Sponsor also provided subject enrollment by country and center for all randomized subjects. The highest-enrolling country was the Czech Republic (25%), followed by Poland (16%), and Hungary (14%). Enrollment was well distributed between the sites, with no site enrolling more than 8% of subjects.

The distribution of the patients in each demographic category is well balanced. The study came from all white patient population. More than 60% of patients were male. The mean age is 61 years old.

Table 3 Sponsor's Summary of Demographic Information (Full Analysis Set) -- Study 20010145

	Darbepoetin alfa (N=298)	Placebo (N=298)
Sex - n(%)		
Male	187 (63)	198 (66)
Female	111 (37)	100 (34)
Race - n(%)		
White	298 (100)	298 (100)
Other	0 (0)	0 (0)
Age -years		
n	298	298
Mean	60.6	61.3
SD	9.2	8.3
Median	61.0	61.0

Q1, Q3	55.0, 68.0	55.0, 67.0
Min, Max	28, 81	37, 82
Age Group - n(%)		
< 65 years	192 (64)	196 (66)
≥ 65 years	106 (36)	102 (34)
Geographic Region a - n(%)		
Western Europe	66 (22)	66 (22)
Australia/ North America	10 (3)	9 (3)
Rest of the World	222 (74)	223 (75)

3.1.4.1 Endpoint Evaluation

3.1.4.1.1 ITEM 3 in the agency's 5/31/07 letter

The sponsor provides some analysis results to support a hemoglobin initiation level (b) (4) and proposed an addition of the following text to the INDICATIONS AND USAGE section:

(b) (4)

(b) (4)

Sponsor's summary and conclusion

(b) (4)

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(b) (4)

[redacted]

3.1.4.1.2 ITEM 4 in the agency's 5/31/07 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)

[redacted]

Sponsor's analysis

(b) (4)

[redacted]

Figure 2 Sponsor's meta analysis for Overall Death for CIA Studies (including 3 Radiotherapy/Chemotherapy Studies*) by Threshold Hemoglobin

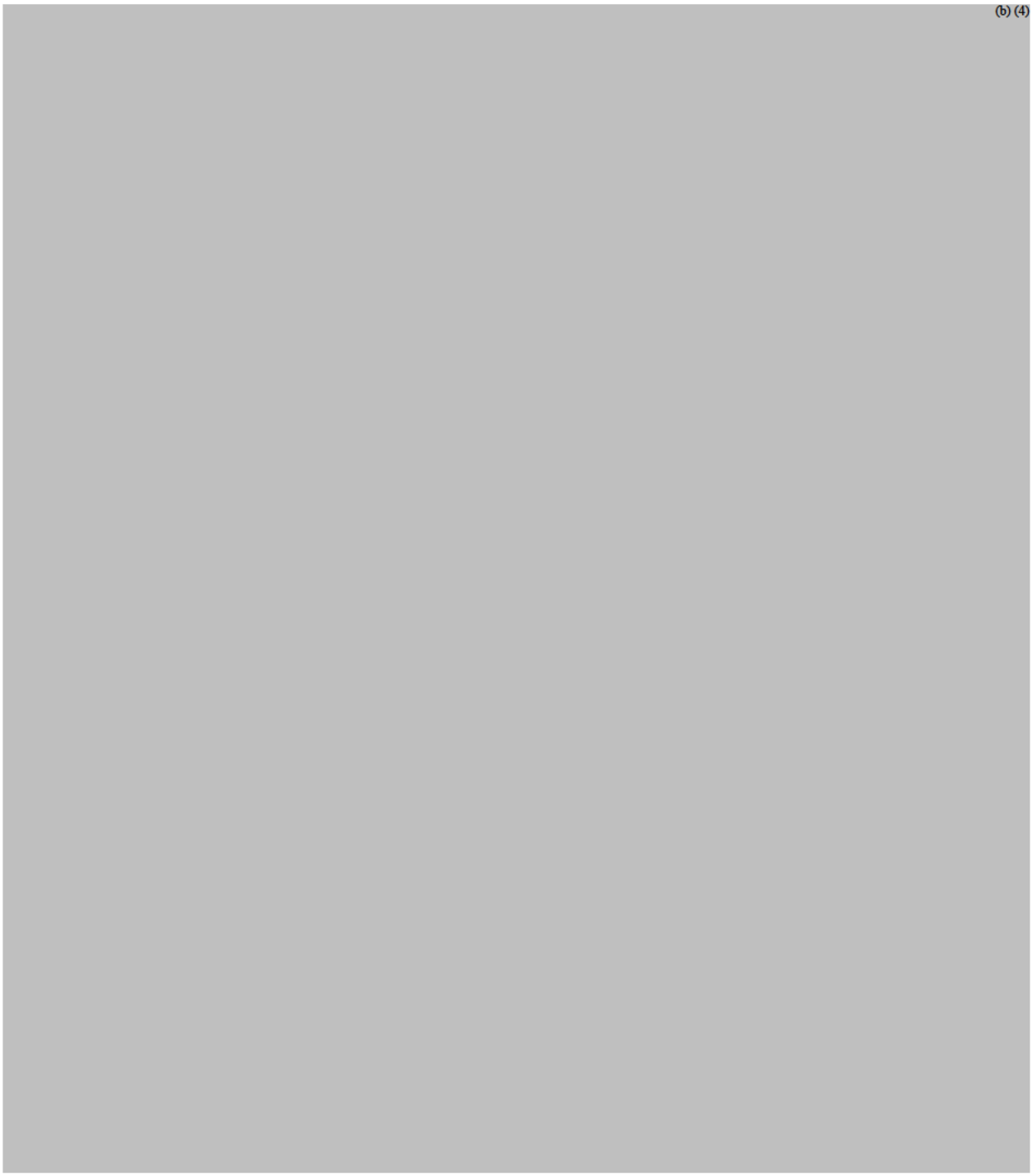


Figure 3 **Sponsor's Analysis using Hazard Ratio Based on a Time-dependent Covariate: Hemoglobin > 12 g/dL (Darbepoetin alfa Placebo-controlled CIA Studies, Randomized Group)**

Based on these analyses, the sponsor proposes that (b) (4)

Reviewer's comment:

- *The reviewer was not able to confirm the meta analysis for overall death for CIA studies by threshold hemoglobin. However, several issues related to meta analyses should be re-iterated:*
  1) Meta analyses can obscure safety signals from individual studies.

2) *Meta analysis results depend on the studies include*
   - *earlier meta-analysis suggest statistical significance on overall survival (OS) favoring ESA;*
   - *later meta-analyses suggest statistical significance on OS favoring control.*
3) *Cumulative meta analyses and retrospective meta analyses have issues on appropriate allocation of alpha.*
4) *Heterogeneous trials with variable quality, lengths of follow-up, target hemoglobin level (Hgb) and heterogeneous tumor type.*

- (b) (4)

- *In addition to the concern of meta analyses, there are several issues about the analyses based on time-dependent covariate :*

(b) (4)

- *It was noted that the targeted hemoglobin level may not be equivalent to the achieved hemoglobin level. For studies that showed decreased overall survival , many of them did not have **achieved** median hemoglobin levels over 12 g/dL any time during the treatment period. Summaries of the median and the 25 and 75 percentiles of the hemoglobin level overtime for study 20010103 and 20000161 were presented in the following table :*

Table 10 Reviewer's Summary of Median Hemoglobin Level Overtime – Study 20010103

	Placebo		Aranesp	
Week	N	Median[a] (25%, 75%)	N	Median[a] (25%, 75%)
0	425	9.7(4.5,11.2)	462	9.8(3.1,14.5)
2	395	9.7(5.2,12.3)	439	9.9(3.4,13.5)
4	422	9.8(4.7,14.1)	459	10.5(3.0,14.6)
6	384	10.0(4.4,13.8)	409	10.6(4.9,14.5)
8	375	10.0(4.7,14.3)	399	10.9(3.8,14.6)
10	326	10.3(4.8,15.2)	355	11.1(2.4,15.5)
12	325	10.3(5.4,15.3)	345	11.0(2.7,14.9)
14	286	10.5(4.0,15.5)	308	10.9(3.1,15.4)
16	272	10.4(4.5,15.5)	274	11.3(3.2,14.7)

[a] Median of the average hemoglobin values (per patient) at each week

Table 11 Reviewer's Summary of Median Hemoglobin Level Over Time – Study 20000161

	Placebo		Aranesp	
Week	N	Median[a] (25%, 75%)	N	Median[a] (25%, 75%)
0	150	9.8(9.2,10.4)	157	9.8(8.9,10.5)
2	169	9.8(9.1,10.4)	171	9.7(9.1,10.6)
4	165	9.8(9.0,10.5)	169	10.2(9.0,11.3)
6	164	9.9(9.1,10.7)	167	10.6(9.3,11.9)
8	159	9.9(9.1,10.7)	166	11.0(9.5,12.3)
10	158	10.1(9.2,10.9)	159	11.4(9.7,12.8)
12	151	10.0(9.4,10.9)	151	11.7(9.9,13.4)
14	144	10.3(9.4,11.0)	146	11.8(10.2,13.3)
16	141	10.3(9.5,11.1)	140	11.4(9.9,12.8)

[a] Median of the average hemoglobin values (per patient) at each week

3.1.4.1.3 ITEM 5 in the agency's 5/31/07 letter

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 sponsor indicates that the time necessary for bone marrow recovery after cessation of chemotherapy can vary widely based on individual patient factors such as age, type of chemotherapy, type and extent of disease, prior radiotherapy to marrow-producing areas, general inanition, and nephrotoxocity of the chemotherapy on renal endocrine function. After cessation of chemotherapy, serum hemoglobin returns to normal in most patients, and ESA treatment should be discontinued at the cessation of a chemotherapy course based on the current prescribing information. However, the sponsor feels that the inclusion of a revised statement on discontinuation (b) (4)

(b) (4)

[redacted]

Sponsor's analysis

Data from study 20010145 was used to evaluate the time to hemoglobin recovery after cessation of chemotherapy. (b) (4)

[redacted]

(b) (4)

[redacted]

Figure 4 Cumulative percent of time to Hemoglobin ≥11.0 g/dL in subjects with levels <11 g/dL after Chemotherapy Unadjusted for Transfusions (Study 20010145)

Based on the above discussion, the sponsor added the following item in the BOX WARNINGS section:

(b) (4)

The sponsor also proposes the following statements for inclusion in the DOSAGE AND ADMINISTRATION section:

(b) (4)

Reviewer's comment:

- *Sponsor's analysis based on time to hemoglobin ≥11.0 g/dL analysis in subjects who had a hemoglobin concentration <11 g/dL after the cessation of chemotherapy can not justify* (b) (4)

3.1.4.1.4 Study 20010103

In this section, the sponsor proposes 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 this PAS submission, the dataset contain the long-term follow-up data from study 20010103 and rollover study 20020149. However, the result based on combined analyses (b) (4) In this statistical review, the evaluation will be based on the data with a cutoff date of 11/7/06. A summary of the combined analysis results will be provided, however, a detailed evaluation based on combined data will not be performed.

The study dataset was submitted (submission number #158, dated 9/19/07) as a CBE (change being affected) supplement submission for BLA103951. The data cutoff date for the clinical study report is 11/7/06.

Sponsor's Analysis

Based on the 11/7/06 cutoff date, the results show that the Darbepoetin alfa arm has shorter median survival time as compared to the placebo arm. The hazard ratio was 1.29 in favor of the placebo arm (95% CI=[1.08, 1.55]).

The analyses are based on the 985 patients who received at least 1 study medication – 515 patients in the Aranesp arm and 470 patients in the control arm. The first patient was enrolled 4/15/04 and the last patient was enrolled 5/23/2006. The most common baseline tumor types were non-small cell lung (19%), breast (14%) and prostate (10%). Overall, 57% had hemoglobin at randomization < 10 g/dL.

Table 12 Sponsor's Summary of Overall Survival (Safety Analysis Set)- study 20010103

	Placebo (N=470)	Darbepoetin alfa 6.75 µg/kg Q4W (N=515)	Summary results
Number of Subjects with Death	216	250	
Survival Time (Weeks)			HR=1.29 [b] (Aranesp vs placebo) 95% CI (1.08,1.55) Nominal p-value =0.006
Median (K-M)	47.0	34.7	
Q1, Q3 (K-M)	17.6, 104.9	14.6, 122.3	
Min, Max	0.9, 104.9	0.4, 122.3	
Follow-up Time (Weeks)[a]			
n	470	515	
Mean	32.3	27.6	
SD	26.7	24.7	
Median	19.9	18.1	
Q1, Q3	13.4, 44.4	10.4, 42.1	
Min, Max	0.9, 125.3	0.1, 122.6	

[a] Follow-up time is calculated as the time from study day 1 to the last known follow-up status date as of data cutoff.

[b] Cox proportional hazards model is stratified by all stratification factors at randomization (hemoglobin at screening, region, prior RBC transfusion,

Note: All deaths include on-study deaths and deaths occurring after the EOS visit and during the long-term follow-up period.

Time to death is counted as the number of days from the first day of investigational product administration to the date of death.

Reviewer's comment:

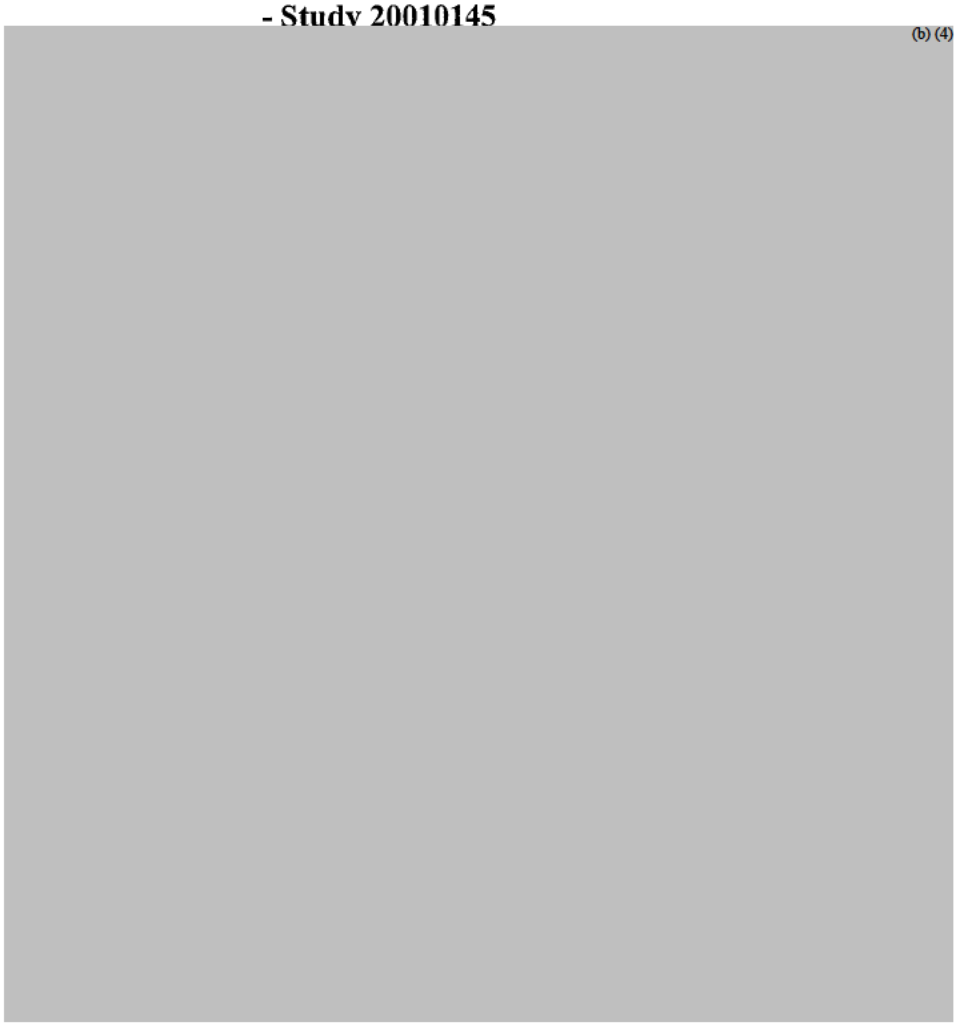
- (b) (4) [redacted]
- *It is noted that randomization ratio was changed from 1:1 to 9:1 after 145 patients had the first transfusion. To maintain the fairness of randomization, the analysis must be stratified by the randomization ration. This reviewer performed similar analysis based on Cox's model and included randomization schedule as an additional stratification factor, the hazard ratio estimate and the 95% CI did not change much (HR=1.295, 95%CI= [1.07, 1.568]; Median survival was 243 days and 329 days for the Aranesp and placebo arms, respectively). Overall, 46% (216/470) on the placebo arm and 49% (250/515) on the Aranesp arm died on study or in long term follow-up.*
- *Using the sponsor's analysis (the Cox's proportional hazards model stratified by the stratification factors at randomization) based on study 20010103 alone, this reviewer obtained a hazard ratio estimate of 1.29 and the 95% CI=(1.068, 1.559) (nominal p-value=0.0083).* (b) (4) [redacted]
- *The sponsor integrated data from studies 20010103 and 20020149 to update the overall survival result for the labeling change. The revised results appear to* (b) (4) [redacted]

3.1.4.1.5 Study 20010145

Based on the sponsor's analysis for overall survival, the hazard ratio for Aranesp versus the control arm was (b) (4) [redacted] in which the statistical difference was not demonstrated.

Table 13 Sponsor's Summary of Overall Survival (Full Analysis Set) - Study 20010145

(b) (4)



Reviewer's comments:

- (b) (4)

Based on the proposed labeling, the sponsor indicates that based on the (b) (4)

However, based on the 8/22/07 report, the results are different (see below):

Table 14 Sponsor's Summary of Progression Free Survival (Full Analysis Set) - Study 20010145

(b) (4)

Reviewer's comments:

- *The results in the previous table were based on data from the 2/22/07 cutoff date* (b) (4)
- *Using the full analysis set and the 2/22/07 data cutoff date, the reviewer obtained a hazard ratio* (b) (4) *for PFS based on stratified log rank test) which is slightly different from the sponsor's proposed results in the labeling.*

3.1.4.2 Quality of Life Endpoint Evaluation

The sponsor did not present quality of life analysis in this submission. However, the sponsor submitted a quality of life analysis meta-datasets.

Since the change from baseline in FACT-fatigue subscale score was used in almost all studies when quality of life evaluation was mentioned in the protocol, the evaluation will focus on the FACT-fatigue subscale. In this evaluation, the sponsor's results based on a few study reports (submitted previously) will be briefly summarized and analyses will be performed based on the sponsor's derived datasets from studies 20000161, 20010103, 20010145, 20030204, 20030232 and 980297.

In study 20010145, the change in FACT-fatigue subscale score from baseline to end of study Treatment (EOST) is the major secondary endpoint. [redacted] for Aranesp and placebo arm, respectively. The difference in the [redacted] which did not show significant difference in the change in the FACT-fatigue subscale score from baseline between treatment arms.

In study 20000161, the means for the change in the FACT-fatigue subscale score from baseline were [redacted] for the Aranesp and placebo arms, respectively. The weighted mean difference was [redacted] stratified by region, tumor type and prior chemotherapy which was not statistically significant different.

In study 980297, for the primary HRQOL endpoint, FACT-F change from baseline, the mean change score at the EOTP [redacted] in the Aranesp and control arms, respectively. The weighted mean difference (stratified by region and tumor type) between treatment groups was [redacted]

In study 20010103, the sponsor indicates that no marked improvement or worsening was seen between baseline and end-of-treatment in any HRQoL (Health related quality of life) variable. Mean change from baseline was [redacted] both treatment groups for FACT-Fatigue. It is noted that deaths by end of treatment [redacted] for control and Aranesp arm, respectively). The sponsor's quality of life analysis did not take mortality into account.

Reviewer's comment:

In most study reports, it indicates that the last available assessment up to EOST was used for computing the change in FACT-fatigue (Functional Assessment of Cancer Therapy-Fatigue) score from baseline. [redacted] (b) (4)

[redacted] *There is no specific definition of EOST from analyses for other studies.*

This reviewer performed analyses of the change of FACT-fatigue subscale score from baseline based on an ANOVA model. It is noted that all upper bounds of the 95% CIs were above 0 which confirms the sponsor's results that there was no significant difference between the Aranesp and control arms observed.

Table 15 Reviewer's Summary of the Change from Baseline in FACT-Fatigue subscale

PROTOCOL	Placebo N	Placebo LS Mean [a] (95% CI)	Aranesp N	Aranesp LS Mean [a] (95% CI)	Difference in LS Means [a] (95% CI)	Nominal P-value [a]
20000161	[redacted] (b) (4)					
20010103						
20010145						
20030232						
980297						

[a] The least square means are obtained from the ANOVA model including treatment as a class variable; p-values are from F-test based on the ANOVA models.

Reviewer's comment :

There are several issues for the quality of life analyses:

[redacted] (b) (4)

- (b) (4)
- [redacted]

4 Summary and Conclusions

4.1 Summary of Collective Evidence

In item 3 about the inclusion of the maximum and if appropriate, pretreatment hemoglobin level, the results of the submitted meta-analysis should be taken with caution (See the statistical comments in section 3.1.3.2.1 for further details and the reviewer's comments about meta-analysis in section 3.1.3.2.2). (b) (4) [redacted] the sponsor's analysis results did not support the inclusion of the statement : (b) (4) in the label.

In item 4 about including a lower maximum hemoglobin level (ie, hemoglobin level less than 12 g/dL), (b) (4) [redacted] Based on the analyses, the sponsor did not provide sufficient support for the proposed claim (b) (4) [redacted]

section 3.1.3.2.2).

In item 5 about the duration of administration of ESA following the completion of the concomitant chemotherapy region, the sponsor's analysis shows that (b) (4) [redacted] The analysis results using study 20010145 data did not provide sufficient evidence to support (b) (4) [redacted]

In the proposed label changes based on study 20010103, the sponsor proposed the inclusion of the overall survival results based on data from long-term following-up from study 20010103 and rollover study 20020149. (b) (4) [redacted]

In the evaluation of the quality of life data based on the change from baseline to EOTP in FACT-fatigue sub-score, both the reviewer's and the sponsor's results did not show any favorable trend in supporting the use of Aranesp.

4.2 Summary of Statistical Issues

The major statistical/data issues are summarized as follows:

1. The combined analysis results used to justify the starting hemoglobin level for initiation of Aranesp is inconsistent with results obtained from the individual study.
2. There are several issues related to the meta analyses :

1) Meta analyses can obscure safety signals from individual studies.
2) Meta analysis results depend on the studies include
   I. earlier meta-analysis suggest statistical significance on overall survival (OS) favoring ESA;
   II. later meta-analyses suggest statistical significance on OS favoring control.
3) Cumulative meta analyses and retrospective meta analyses have issues on appropriate allocation of alpha.
4) Heterogeneous trials with variable quality, lengths of follow-up, Target hemoglobin level (Hgb) and heterogeneous tumor type.

3. (b) (4)

4.

5. The analysis based on study 20010145 (SCLC) did not provide sufficient (b) (4)

6. Shortened survival for the Aranesp arm was demonstrated for study 20010103.

The proposed inclusion of overall survival results in the label based on combined data from studies 20010103 (patient with non-myeloid malignancies) and the roll-over study 20020149 is not acceptable (b) (4)

7. Majority of the sponsor's quality of life analyses did not consider missing data issues or deaths. Missing data problems in QOL assessment may be non-informative, therefore, caution should be taken for the interpretation of the QOL results.

4.3 Conclusions and Recommendations

Based on this statistical evaluation, here are summaries of a few findings :

1. The sponsor's analysis results did not support the inclusion of the statement : (b) (4) in the label (b) (4)
2. The sponsor's analysis results did not provide sufficient support for the proposal (b) (4)
3. The analysis results using study 20010145 data did not provide sufficient (b) (4)
4. Inclusion of the overall survival results based on combined data (study 20010103 and 20020149) is not acceptable (b) (4)
5. In the evaluation of the quality of life data based on the change from baseline to

EOTP in FACT-fatigue sub-score, both the reviewer's and the sponsor's results did not show any favorable trend in supporting the use of Aranesp.

5 Appendix

5.1 Protocol Synopsis for Study 20010103

Study 20010103 was a phase III, multicenter, randomized, double-blind, placebo-controlled study of Darbepoetin Alfa for the treatment of patients with active nonmyeloid malignancies who had not received within 4 weeks, and were not planning to receive chemotherapy or radiotherapy. The primary objective of this study is to evaluate the efficacy of darbepoetin alfa in reducing the occurrence of RBC transfusion.

Patients were enrolled at 144 sites in Europe, Australia, and North America. Majority of patients (75%) were from Europe.

Patients were randomly assigned to one of the two treatment arms in a 1:1 ratio:

Group A: Darbepoetin alfa 6.75 mcg/kg (SC) Q4W
Group B: Placebo (SC) QW .

Efficacy assessments schedule
All assessment occurred prior to administration of study medication. During treatment period (weeks 1 to 16), Complete blood count (CBC) was evaluated at baseline and every 2 weeks during treatment period. .

Transfusion policy
It is recommended that a RBC transfusion be given in the event that the hemoglobin concentration decrease to ≤ 8.0 g/dL or as medically indicated.

After end of the study, patients were followed up for an additional 2 years for survival status.

Primary Efficacy Endpoint
The primary endpoint of this study is the risk of RBC transfusion from week 5 (day 29) to week 17.

Note : Patients who withdraw from investigational product treatment prematurely were

followed for red blood cell transfusions until week 17.

Secondary Efficacy Endpoint:

- Change in hemoglobin concentration measured from baseline to EOTP.

  The baseline hemoglobin concentration is the value measured on study day 1 before first administration of study medication. The EOTP hemoglobin concentration is defined as the last hemoglobin concentration during the treatment period that is not within a 28 day window following a RBC transfusion.

Safety Endpoint

The pre-specified safety endpoints include:

- Adverse events;
- Serious adverse events;
- Survival (deaths on study and deaths in long term follow-up period).

Primary Efficacy Analysis Method :

The primary statistical analysis of efficacy will be conducted on the primary transfusion analysis set. The primary transfusion analysis set was defined as all randomized patients who were randomized during the period of 1:1 randomization and who complete at least 4 weeks of study (i.e. their date of study withdrawal is on or after study day 29). Sensitivity analyses will be performed on the efficacy analysis set (see definition in the Secondary Efficacy Analysis section) to evaluate the robustness of the study results, particularly to assess the effect of dropout and other potential confounding factors.

Unless otherwise specified, analyses for the primary and secondary efficacy endpoints will be stratified by Screening hemoglobin concentration (<10 g/dL vs. ≥ 10 g/dL), region (central and eastern Europe vs. rest of the world) and whether RBC transfusion was given in the previous 12 weeks (Yes, No).

The primary efficacy analysis will be based on the risk of RBC transfusion from week 5 (day 29) to week 17, which will be estimated using a proportional hazards model (Andersen and Gill, 1982). The hazard ratio estimate and significance test will be calculated using a stratified model using the previously mentioned stratification factors and treatment will be the only explanatory variable. Proportional hazard plots (Grambsch and Therneau, 1994) will be used to assess deviation from the proportional

hazards assumptions for each event.

Kaplan-Meier plots for the time to occurrence of red blood cell transfusions will be presented for individual event numbers (1^{st}, 2^{nd}, etc., RBC transfusions).

Patients who withdrew due to disease progression or death, the transfusion status at the time of withdrawal was used. Patients withdrawing due to other reasons were considered transfused at the time of withdrawal.

Secondary Efficacy Analysis Method

The secondary efficacy analysis will be based on efficacy analysis set which consist of all randomized patients who receive at least one dose of investigational product and were randomized during the period of 1:1 randomization.

Model-adjusted mean change in hemoglobin concentration during the treatment period will be assessed after adjusting for the stratification factors using ANOVA method. A 2-sided 95% confidence interval for the adjusted mean difference between the treatment groups will be constructed. If the assumptions of the model are violated, a stratified Wilcoxon test will be conducted to assess the robustness of the primary model.

A close testing procedure will be used to test the secondary endpoint. If the p-value for the primary endpoint is ≤ 0.05, then testing will be performed on the secondary endpoint. Otherwise, the evaluation will be stopped.

Note: For patients who complete the treatment period, the EOTP corresponds to study week 17. For patients who do not complete the treatment period, this corresponds to the final evaluation.

A patient who ends treatment earlier than scheduled may consent to an observational period after study medication has ended to follow RBC transfusions to extend the observation period to the planned 17 week length. The RBC transfusion endpoints will include the observational period.

Safety Analysis

Adverse event, laboratory data, vital sign and concomitant medication were summarized descriptively for safety analyses.

5.2 Protocol Synopsis for Study 20010145

Study 20010145 was a randomized, placebo-controlled study was conducted in 600 patients with previously untreated extensive-stage small cell lung cancer receiving etoposide and platinum-containing chemotherapy. 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.

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) level (below versus above the upper limit of normal). This study was conducted at 69 sites in Europe, Australia and Canada.

The primary objective of this study is 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 second objectives are to evaluate whether darbepoetin alfa improves FACT-Fatigue subscale scores. The other objectives are

- To assess the effect of darbepoetin alfa on subject symptom assessment, progression free survival, time to progression, tumor response, duration of tumor response, red blood cell (RBC) transfusions, and FACT-General
- To assess the overall safety profile of darbepoetin alfa in subjects with untreated extensive-stage SCL.

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. Subjects in the darbepoetin alfa group continued to receive investigational product for only 3 weeks after the last dose of chemotherapy.

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 ≥ 14.0 g/dL and reinstated once the concentration was < 13.0 g/dL.

Sample Size Calculation

The sponsor indicates that a total of 600 patients will provide greater than 95% power to detect a 1 g/dL difference in the change in hemoglobin concentration between the 2

treatments.

The median survival time for patients with extensive-stage small-cell lung cancer in recent clinical trial is estimated to be approximately 9 months. Assuming an exponential distribution for the time to death, an increase of 3 months in median survival time for the Aranesp treated group corresponds to a hazards ratio (Aranesp vs. placebo) of 0.75. A logrank test based on a 0.049 2-sided significance level and 496 events will have 89% power to detect the hazard ratio of 0.75. Under the assumption of constant accrual over a 3 year period, the 496th death is expected to occur 1 year after the last subject is randomized.

Interim Analysis

The critical value across the boundary will be determined by the methods of Lan and DeMets with asymmetric boundaries (O'Brien & Fleming and Pocock boundaries) for the survival endpoint, and symmetric O'Brien & Fleming boundaries for the change in hemoglobin.

The sponsor indicates that for the change in hemoglobin, the amount of information available at each interim analysis depends on the accrual rate, hence the precise alpha at each analysis cannot be pre-specified. If 1/3 and 2/3 of the total information were available at each interim analysis, then the O'Brien and Fleming boundaries for the interim and final analyses would be 0.0002, 0.0120, 0.0463 for testing the difference in the change in hemoglobin. At each analysis, if the hemoglobin endpoint is statistically significant based on the O'Brien and Fleming boundaries then the survival endpoint will be tested at the nominal alpha levels given by Pocock's and O'Brien & Fleming boundaries. The asymmetric boundaries are given in the following table :

Table 1 Group sequential Boundaries for survival endpoint

Time	Upper	Nominal Upper Alpha [A]	Lower	Nominal Lower Alpha [B]
0.33	3.7307	0.0001	-2.289	0.01103
0.55	2.9692	0.00149	-2.289	0.01103
1.00	1.9687	0.02449	-2.289	0.01103

[A] O'Brien & Fleming given by Lan-DeMets Group Sequential Boundaries

[B] Pocock's given by ADDPLAN, Version 2

Analysis of survival endpoint will be performed at every analysis for safety concern, even if the change in hemoglobin is not statistically significant. The study may be

stopped if the Pocock boundary is crossed regardless of the results from the change in hemoglobin analysis.

Primary Efficacy Endpoint

This study includes two co-primary endpoints : Change in hemoglobin concentration from baseline to the end of the chemotherapy treatment period and survival time.

The change in hemoglobin concentration from baseline to the end of chemotherapy period will be based on the last hemoglobin concentration measured up to 3 weeks after the last dose of on-study chemotherapy, up to 6 cycles. Post-baseline hemoglobin concentrations measured within 28 days after RBC transfusion will be excluded. All subjects in the primary analysis set with baseline and at least one post-baseline hemoglobin values outside the 28 days after RBC transfusion were included in the analysis.

For survival endpoint, subjects who have not died until end of study, or are lost to follow-up were censored at their last contact date. Subjects who withdraw consent for follow-up were censored on the date of withdrawal.

Secondary Efficacy Endpoint

Change in FACT-Fatigue (a subset of FACT-Anemia) subscale scores from baseline to the end of study treatment was specified as the secondary endpoint.

Safety Endpoints

There was no pre-specified safety endpoint. The overall survival was specified as the efficacy endpoint. However, it will be evaluated as safety endpoints for the purpose of this statistical review.

Primary Efficacy Analysis

The primary efficacy endpoint will be performed based on "full analysis set" (defined as all randomized patients who receive at least one dose of chemotherapy according to the study regimen and at least one dose of study drug).

The sponsor also defined "primary analysis set" as all randomized patients 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.

The primary efficacy endpoint, change in hemoglobin concentration from baseline to the end of the chemotherapy treatment period, will be compared using a generalized Cochran-Mantel-Haeszel statistic. The stratification factors include region, ECOG performance status and LDH. This analysis will be performed on primary analysis set.

Adjusted means and 95% confidence interval will be provided based on an analysis of variance (ANOVA) model including treatment groups, and the stratification factors in the model.

The stratified logrank test (stratified by region, ECOG performance status and LDH) will be used to compare the two treatment groups for overall survival. This analysis will be performed on full analysis set.

Confidence intervals for Kaplan-Meier quartiles will be calculated by the methods described in Brookmeyer & Crowley, 1982. Confidence intervals for Kaplan-Meier rates at particular time points will be calculated by the methods described in Collett, 1994.

The stratified Cox proportional hazards model including treatment arms and all 3 stratification factors (region, ECOG and LDH) will be used for presenting estimated hazard ratio and its corresponding 95% confidence interval.

Adjustment for the multiple comparisons of the co-primary endpoints will be made based on closed testing procedure (described in the interim analysis section): general CMH test based on the change from baseline in hemoglobin concentration will be performed first; if the result is significant at 0.049 significance level, logrank test based on survival endpoint will be performed.

If any region, ECOG performance status and LDH stratum for either treatment group contains less than 10 subjects per treatment group or the K-M proportion for the survival endpoints is 0 or 1, strata will be pooled before analysis. The pooling strategy is described bellows:

1. Combine Western Europe with Australia/North America;
2. Combine across all regions.

Any pooling of strata that is needed for the analysis of survival time will be applied to the analyses of all of the other endpoints.

Secondary Efficacy Analysis

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, was used for PRO analyses.

The change in the FACT-Fatigue subscale score from baseline to end of study treatment was summarized for the PRO analysis set by an ANCOVA model including the 3 stratification factors and baseline FACT-Fatigue subscale score.

For the proportion of subjects with hemoglobin $\geq$ 12 g/dL, the estimated proportions (based on K-M estimate stratified by region, ECOG performance status and LDH level) for each treatment at each stratum were combined across strata weighted by the inverse of the variance, estimated by using Greenwood's formula. The pooling strategy over strata similar to the primary efficacy endpoint analyses was applied here.

For the amount of time (weeks) that subjects in each group spend with a hemoglobin value greater than 12 g/dL and proportion of subjects in each group that have hemoglobin greater than 12 g/dL for at least 50% of the entire treatment period, summary statistics were provided by treatment group. Note: for this summary, if subjects has no hemoglobin concentration in a week, subjects were considered as having hemoglobin <12 g/dL.

A stratified log rank test was used to analyze progression free survival. Other time to event endpoints such as time to progression, time to first RBC transfusion during the treatment phase and time to tumor response were summarized descriptively based on the K-M method. K-M method was also used in estimate the proportion of RBC transfusion from study day 1 to EOST. Crude estimates of the proportion (i.e. number of events divided by the number of subjects available in the analysis set) were used to present the incidences of RBC transfusions, best overall response and objective tumor response. Summary statistics were provided for the number of standardized units administered and total number of days of RBC transfusions for the study day 1 through EOST. Progression free survival, time to progression, time to first RBC transfusion during the treatment phase, best overall response and objective tumor response were analyzed based on full analysis subset.

Safety Analysis

Adverse event, laboratory data, vital sign and concomitant medication were summarized

descriptively for safety analyses.

5.3 Other Randomized, Double-blind, Controlled Studies of Aranesp

Other randomized double-blind, controlled studies for Aranesp that were used in this sBLA review are summarized in the following table:

Table 16 Randomized, Double-blind, Controlled Studies of Darbepoetin alfa

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	Primary endpoints
980291 (n = 249[a]) (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 **solid tumors receiving multicycle chemotherapy**	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)	Safety (dose limiting toxicity; AE incidence; Antibody formation)
980291 (n = 156[a]) (6/30/1999- 7/30/2001)	Schedule 2: A randomised, double-blind, placebo-controlled, dose-finding study of novel erythropoiesis stimulating protein (NESP) administered by subcutaneous (SC) injection for the treatment of anaemia in subjects with **solid tumours receiving multicycle chemotherapy**	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)	Safety (dose limiting toxicity; AE incidence; Antibody formation; concomitant **med; lab, vital signs, # days** Hospitalized)
990114 (n = 66[a]) (11/2//1999- 7/18/2000)	A multi-centre, blinded, placebo-controlled, randomised, dose-finding study of novel erythropoiesis stimulating protein (NESP) administered by subcutaneous injection in subjects with **lymphoproliferative malignancies receiving chemotherapy**	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	% of patients with sustained hemoglobin response (defined as an increase in hgb of ≥2 g/dL from BL for >28 days)

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

Table 18 Randomized, Double-blind, Controlled Studies of Darbepoetin alfa (continued)

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	Primary endpoint
980297 (n = 314[a]) (9/14/1999-(11/8/2000)	A double-blind, placebo-controlled, randomized study of novel erythropoiesis stimulating protein (NESP) for the treatment of anaemia in **lung cancer subjects receiving multicycle platinum-containing chemotherapy**	2.25 µg/kg QW (N: 159 vs. 161)	Hgb ≤ 11 g/dL /Hgb 15g/dL (men) or 14g/dL (women)	12 weeks	Proportion of RBC Transfusion (W5-EOP)
20000161 (n = 344[a]) (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 **lymphoproliferative malignancies receiving chemotherapy**	2.25 µg/kg QW (N : 176 vs. 173)	Hgb ≤ 11 g/dL /Hgb 15g/dL (men) or 14g/dL (women)	12 weeks	Proportion of Hb response (defined as increase in Hb ≥ 2 g/dL over baseline)
20000103 (n = 985) (4/15/1004-11/7/2006)	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	Proportion of RBC Transfusion
20030232 (n = 386[a]) (2/20/2004-3/3/2005)	A randomized, double-blind, placebo-controlled study of darbepoetin alfa for the treatment of anemia in subjects with **non-myeloid malignancy receiving multicycle chemotherapy**	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	Proportion of RBC Transfusion (W5-EOP)

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

Table 18 Randomized, Double-blind, Controlled Studies of Darbepoetin alfa (continued)

Study Number /Study duration	Study Design/	Aranesp Dose (N per ITT : NESP vs placebo)	Hgb/Hct Entry Criteria Upper Hgb/Hct Limit on Study /	Treatment Duration	Primary Endpoint
20010145 (n = 596[a]) (12/10/2002-2/22/2007) (see review for for sBLA 103951 /5173)	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	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	Change in Hb; Overall survival
DE20010033 "PREPARE" (n=736[a]) (6/2/3003-10/30/2007) (see review for for sBLA 103951 /5170)	A randomized phase III, open label trial for comparison of a preoperative, dose intensified, interval-shortened, preoperative, dose intensified, interval-shortened, sequential chemotherapy with Epirubicin and Cyclophosphamide followed by Paclitaxel in standard dosage ± darbepoetin alfa in patients with primary breast cancer.	4.5 µg/kg of Q2W (N: 377 vs 356)	Hgb<13 g/dL / Hgb 12.5 – 13 g/dL	26 weeks	Relapse Free Survival ; Overall survival
SE 2002-9001 (DAHANCA 10) (n=522[a]) (6/1/2002-10/2006)	Randomized phase III, for comparison between radiotherapy vs. radiotherapy+Aranesp in patients with head and neck cancer	150 mg QW (Data not available)	Hgb<14 g/dL /Hgb14g/dL(women) Hgb15.5 g/dL (men)	8-10 weeks	Local Regional Control

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

6 SIGNATURES/DISTRIBUTION LIST PAGE

Primary Statistical Reviewer: **Date:** October 17, 2008

Yuan-Li Shen, Dr. P.H.
Mathematical Statistician

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Director, Division of Biometrics V

CC:

HFD-107/ Gootenberg, Keegan, Fan, Shastri, Hughes
HFD-711/Chakravarty, Rothmann, Shen, Lee
HFD-700/Patrician

This review consists of 52 pages
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION OF META-ANALYSES ON OVERALL SURVIVAL

BLA/STN:	103951/5173
Drug Name:	Aranesp
Indication(s):	Chemotherapy-induced anemia
Applicant:	Amgen
Date(s):	Received December 27, 2007
	PDUFA date: October 25, 2008
Review Priority:	Standard
Biometrics Division:	Division of Biometric V
Statistical Reviewer:	Dr. Mark Rothmann, Lead Mathematical Statistician
Concurring Reviewers:	Dr. Aloka Chakravarty, Division Director, Division of Biometrics V
Medical Division:	Division of Biologic Oncology Products
Clinical Team:	Dr. Kaushillumar Shastri, clinical reviewer
	Dr. Chaohong Fan, clinical reviewer
Project Manager:	Ms. Monica Hughes

Keywords: Meta-Analysis, collective evidence

Table of Contents

1. EXECUTIVE SUMMARY

This submission is cross-listed with the submission of sBLA 103234/5166 (Procrit). This statistical review is a part of the continual reassessment of the safety and potential tumor promotion of Erythropoiesis-Stimulating Agents (ESAs). The issues regarding decreased overall survival, increased tumor promotion, and increased thromboembolic events (TVE) were discussed at a May 2004 Oncology Drugs Advisory Committee meeting for the BEST and ENHANCE studies, and at a May 2007 Oncology Drugs Advisory Committee (ODAC) meeting for six studies (BEST, ENHANCE, EPO-CAN-20, 2001-0103, 2000-0161, DAHANCA10). Based on the results from the PREPARE (neo-adjuvant breast cancer) and the GOG191 (cervical cancer) studies, an additional ODAC meeting was held on March 13, 2008.

These sBLA submissions are outcomes of the May 10, 2007 ODAC meeting.

The primary statistical reviewers are Dr. Yuan-Li Shen (sBLA 103951/5173) and Dr. Kyung Yul Lee (sBLA 103234/5166). Please see their reviews for the general statistical evaluation of these submissions. This review is a team leader secondary statistical review that should be considered in conjunction with Drs. Shen's and Lee's reviews.

This review will primarily cover a type of meta-analysis that has presented by the sponsor in this submission and also in their briefing documents for the May 10, 2007 and March 13, 2008 ODAC meetings.

1.1 Conclusions and Recommendations

I concur with the conclusions and recommendations of Drs. Lee and Shen. I will provide my conclusions and recommendations as it applies to the topic of this review.

(b) (4)

It is my determination that the sponsor's analyses of the "odds ratio of death" and the "relative risk of death" are not valid. See Section 1.3 Statistical Issues and Findings for further details.

1.2 Brief Overview of the clinical studies

This submission utilizes the results from 23 controlled clinical trials given below:

- 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

Descriptions of these studies can be found in the statistical reviews of sBLA 103951/5173 (Aranesp) by Dr. Yuan-Li Shen and sBLA 103234/5166 (Procrit) by Dr. Kyung Yul Lee. The sponsor addresses items 3, 4, 5 of the May 31, 2007 letter from the FDA and has additionally proposed to include results or updated results from the EPO-INT-76, N93-004 and 20010103 studies.

1.3 Statistical Issues and Findings

I have no major disagreements with the statistical reviews of Drs. Kyung Yul Lee and Yuan-Li Shen. The major issues and findings that I will focus on are summarized below.

- Use of long term overall survival data from the BEST study is inappropriate. (b) (4)
- The results from studies (e.g., DAHANCA 10) prospectively identified by the sponsor at ODAC in May 2004 for the purpose of evaluating the safety/tumor promotion potential of Aranesp were not included in the meta-analyses except for the head and neck subgroup analyses. (b) (4)
- (b) (4)

(b) (4)

2. INTRODUCTION

2.1 Overview of the submission

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.

For FDA item 3, the sponsor provided pooled analyses across studies of the RBC transfusion rates, the time to first RBC transfusion, survival, "Overall Death," embolism/thrombosis and clinical relevant TVE (Thrombovascular events) by baseline hemoglobin categories.

FDA Item 4:
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.

For FDA item 4, the sponsor provided pooled analyses across studies of "Overall Death" by threshold hemoglobin level, hazard ratios for the time-dependent covariate of achieved hemoglobin (status on whether a $\geq$ 12 g/dL hemoglobin level has yet to be achieved).

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.

For FDA item 5, the sponsor provided results from the 20010145 studies for the

- Time to Hemoglobin ≥ 11 g/dL in Subjects With Levels < 11 g/dL After Chemotherapy Unadjusted for Transfusions,
- Time to Hemoglobin ≥ 12 g/dL in Subjects With Levels < 11 g/dL After Chemotherapy Unadjusted for Transfusions, and
- Time to Hemoglobin ≥ 11 g/dL or 12 g/dL in Subjects With Levels < 11 g/dL After Chemotherapy Unadjusted for Transfusions

For the EPO-INT-76 and 20010103 studies, updated survival analyses were included (intended as an update for labeling). For the N93-004 study overall survival analyses were included, which were originally reviewed in the submission of sBLA 103234/1015 (see the review by Clare Gnecco dated July 31, 2003).

2.2 Data Sources

Items 3 and 4
Data used to evaluate items 3, 4 and quality of life analysis is based on the sponsor provided meta-dataset in
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\\cbsap58\M\eCTD_Submissions\STN103234\0096\m5\datasets\pas-meta-datasets\tabulations

Item 5
Data used for review item 5
\\cbsap58\M\eCTD_Submissions\STN103951\0164\m5\datasets\20010145

Study 20010103
Data used for review of study 20010103 is from the electronic submission received on 9/17/07. The network path is in:

\\cbsap58\M\eCTD_Submissions\STN103951\0158\m5\datasets\20010103\analysis

EPO-INT-76 study
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N93-004 study
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3. STATISTICAL EVALUATION

3.1 Evaluation of Overall Survival

3.1.1 Collective Evidence of Overall Survival

At the time of the May 10, 2007 Oncology Drugs Advisory Committee meeting there were six studies that have demonstrated inferior overall survival or locoregional failure for the ESA-containing arm (see Table 1 below). To date there is no study known to the FDA that has demonstrated superior overall survival or progression-free survival for the ESA-containing arm.

Table 1. Randomized, controlled trials with decreased survival and/or decreased locoregional control

Study/Tumor/ (n)	Hemoglobin Target	Achieved Hemoglobin (Median Q1, Q3)	Primary Endpoint	Adverse Outcome for ESA-containing Arm
Chemotherapy				
BEST (EPO-INT-76) Study Metastatic breast cancer (n = 939)	12-14 g/dL	12.9 g/dL 12.2, 13.3 g/dL	12-month overall survival	Decreased 12-month survival
20000161 Study Lymphoid malignancy (n = 344)	13-15 g/dL (M) 13-14 g/dL (F)	11.0 g/dL 9.8, 12.1 g/dL	Proportion of patients achieving a hemoglobin response	Decreased overall survival
Radiotherapy Alone				
ENHANCE Study Head and Neck cancer (n=351)	> 15 g/dL (M) >14 g/dL (F)	Not Available	Locoregional progression-free survival	Decreased 5-year locoregional progression-free survival Decreased overall survival
DAHANCA 10 Head and neck cancer (n =522)	14-15.5 g/dL	Not available	Locoregional disease control	Decreased locoregional disease control
No Chemotherapy or Radiotherapy				
EPO-CAN-20 Non-small cell lung cancer (n =70)	12-14 g/dL	Not available	Quality of Life	Decreased overall survival
20010103 Study Non-myeloid malignancy (n=989)	12-13 g/dL	10.6 g/dL 9.4, 11.8 g/dL	RBC transfusion	Decreased Overall Survival

Prior to the March 13, 2008 Oncology Drugs Advisory Committee, two addition studies were identified by the FDA as having safety concerns and detrimental impact on overall survival (see Table 2 below.

Table 2. Randomized, controlled trials with detrimental impact on overall survival

Study/Tumor/ (n)	Hemoglobin Target	Achieved Hemoglobin (Median Q1, Q3)	Primary Endpoint	Adverse Outcome for ESA-containing Arm
Chemotherapy				
GOG-150 Cervical Cancer (n=114)	12-14 g/dL	12.7 g/dL 12.1, 13.3 g/dL	Progression-free and overall survival and locoregional control	Decreased 3 yr. progression-free and overall survival and locoregional control
PREPARE Early breast cancer (n=733)	12.5-13 g/dL	13.1 g/dL 12.5, 13.7 g/dL	Relapse-free and overall survival	Decreased 3 yr. relapse-free and overall survival

Meta-analysis and meta-analytic approaches

Earlier meta-analyses in the literature suggested statistical significance on overall survival favoring ESAs. Later meta-analyses suggest statistical significance on overall survival favoring the controls. Many early studies were not designed and did not have long-term follow-up of patients for overall survival. In many instances only on study deaths and/or follow-up was recorded. Many later studies were conducted for targeted hemoglobin levels above what was used for the studies that led to the approval of Aranesp and Procrit. The patient populations were also different due to the cancer type and/or the cause of anemia (e.g., radiotherapy, cancer-related). (b) (4)

Reasons against doing a meta-analysis in this setting include that meta-analysis can obscure safety signals from individual studies; the results depend on the studies included in a meta-analysis and on the "event" or circumstance that triggers a retrospective meta-analysis. Again, earlier meta-analyses suggested statistical significance on OS favoring ESAs, while later meta-analyses suggest statistical significance on OS favoring controls. In addition, cumulative meta-analyses and retrospective meta-analyses have issues on appropriate allocation of alpha. Also, due to the heterogeneity among the trials in their quality, lengths of follow up, target hemoglobin levels and tumor types, the results of a meta-analysis would not be applicable to any situation. Furthermore, patients with small cell lung cancer or head and neck cancer would be over represented in the meta-analysis compared to practice. Thus, the results would not apply to the then practice of ESAs in Oncology. It would also be easy in the future to manipulate the results of a meta-analysis by conducting studies in situations where safety signals may be less likely to occur (e.g., a study of small cell lung cancer patients where the targeted hemoglobin level is low).

3.1.2 Sponsor's meta-analyses

Many meta-analyses are provided in this submission along with the sponsor's briefing documents for the May 10, 2007 and March 13, 2008 Oncologic Drugs Advisory Committee meetings. The meta-analyses include

- A pooled analyses of patient-level data
- A study-level meta-analyses of clinical trials

This review concentrates on some of the study-level meta-analyses.

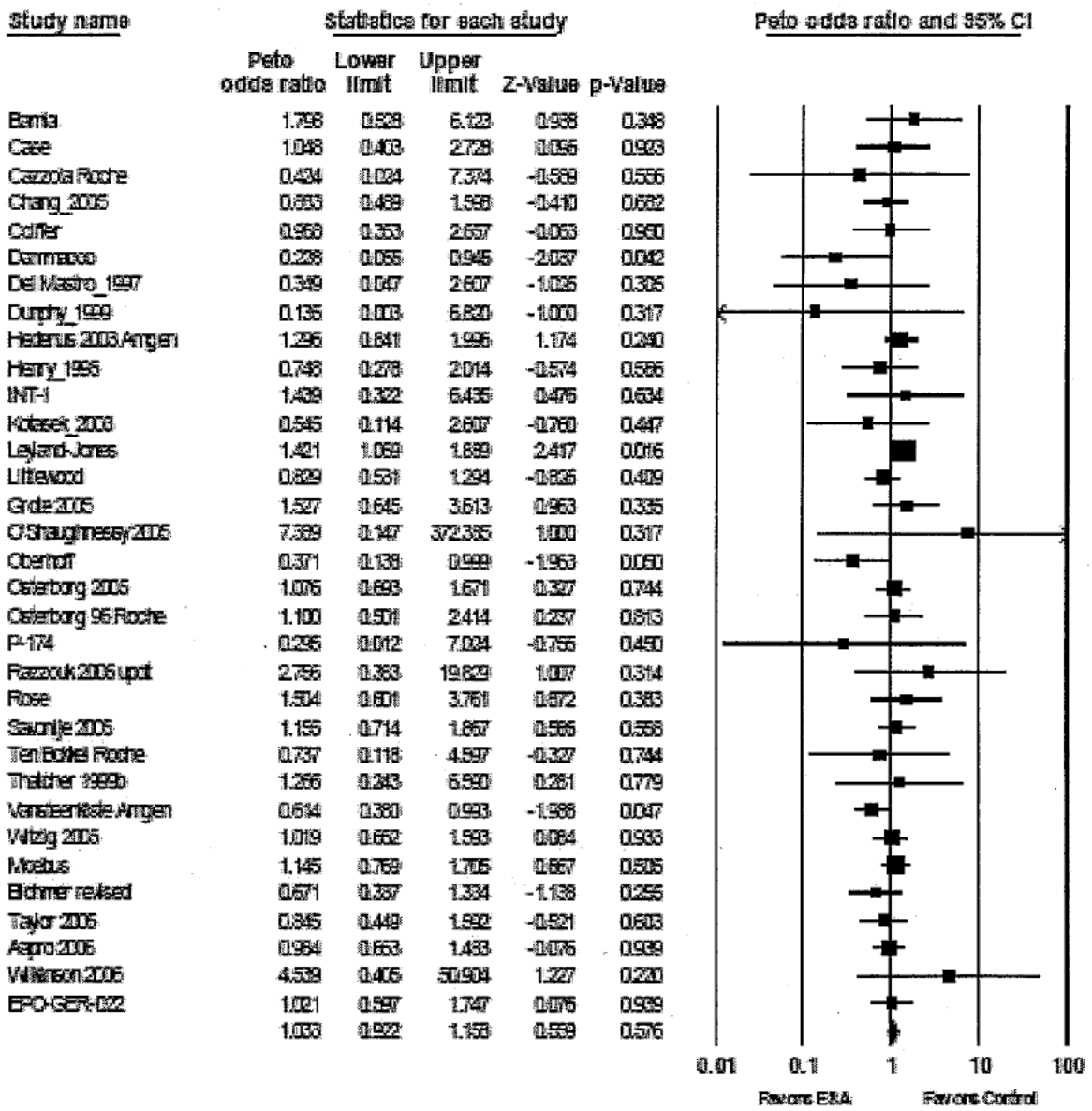
3.1.2.1 Peto's odds ratio of death and related analyses

This review will primarily focus on the various meta-analyses that the sponsor performed based on the "Peto's odds ratio of death" that appeared in their briefing documents for the 2007 and 2008 Oncologic Drugs Advisory Committee meetings and this sBLA submission. The breakdown for this section is as follows:

- Some of the sponsor's analyses on the "Peto's odds ratio of death" that appeared in their briefing documents for the 2007 and 2008 Oncologic Drugs Advisory Committee meetings and this sBLA submission ("enumerated" by capital letters, A, B, ...).
- Reviewer comments with additional details including the method of calculation of the "Peto's odds ratio of death."

A. Sponsor's 2007 briefing document: Figure 1 is the summary from the sponsor's briefing document (Figure 4 on page 37) of the Peto's odds ratios of death in chemotherapy-induced anemia studies used for the sponsor's meta-analysis. Compared with the 2005 Cochrane analysis, this analysis updates results for the Savonije study and adds results for 6 studies (Aapro, Blohmer, Taylor, Wilkinson, EPO-GER-022 and Möbus). Additionally, results for the Razzouk study were updated and the study was reclassified as a chemotherapy-induced anemia study. The ESA vs. no ESA meta-analytic Peto odds ratio was 1.03 (95% CI: 0.922, 1.158). A sensitivity analysis using the Mantel-Haenszel risk ratio gave an ESA vs. no ESA risk ratio of 1.02 (95% CI: 0.958, 1.079). The details of the Mantel-Haenszel analysis were not provided.

Figure 1. Sponsor's Meta-analysis of Peto odds ratios of death in chemotherapy-induced anemia studies



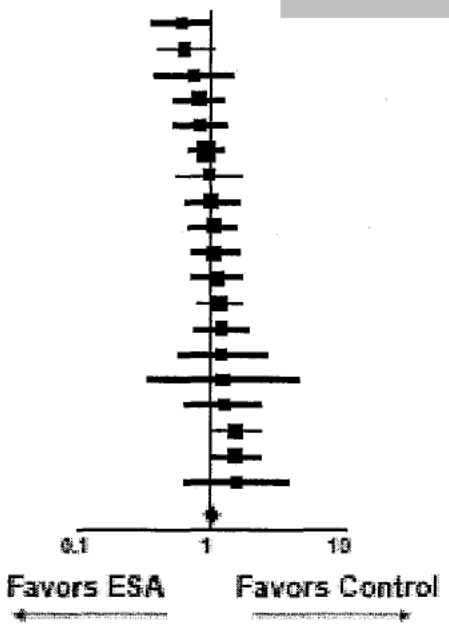
B. Sponsor's 2008 briefing document: Figure 2 is the another summary from the sponsor's briefing document (Figure 5 on page 47) of the Peto's odds ratios of death in chemotherapy-induced anemia studies used for the sponsor's meta-analysis. The ESA vs. no ESA meta-analytic Peto odds ratio was 1.00 (95% CI: 0.89, 1.12) based on a random effects model. Results were similar based on a fixed effects meta-analysis (odds ratio 1.00 with 95% CI of 0.89, 1.11). When 12-month mortality was used for the BEST study instead of the long-term follow-up, the ESA vs. no ESA meta-analytic Peto odds ratio was 1.04 (95% CI: 0.92, 1.19) based on a random effects model and 1.06 (95% CI: 0.95, 1.18) based on a fixed effects model. The sponsor provides an

analogous analysis of "Progression-related Endpoints" (Figure 6 on page 49) that will not be summarized here.

Figure 2. Sponsor's Meta-analysis of Peto's odds ratios of death in chemotherapy-induced anemia studies (Including 3 Chemotherapy/Radiotherapy studies) with Long-term Follow Up

Best Available Copy

Study name	Odds ratio	95% CI Lower limit	95% CI Upper limit
* EPO-GER-022	0.58	0.35	0.96
Vansteenkiste (AMG 960297)	0.62	0.38	1.01
* Blohmer (AGO-NOGGO)	0.73	0.37	1.44
Pirker(AMG 20010145)	0.79	0.52	1.21
Littlewood	0.81	0.52	1.29
Leyland-Jones (BEST ITT updt)	0.91	0.67	1.23
Chang 2005 (EPO-CAN-17)	0.97	0.55	1.73
Witzig 2005	0.98	0.62	1.55
Aapro 2006 (BRAVE)	1.02	0.67	1.53
Mobus	1.05	0.70	1.57
Osterborg 2005	1.08	0.69	1.67
Milroy (INT-45)	1.16	0.79	1.72
Savonije 2005	1.18	0.73	1.90
* Thomas (GOG-0191)	1.19	0.55	2.56
Engert 2007 (HD 15 IA)	1.21	0.32	4.55
Prozanto (INT-47)	1.23	0.63	2.38
Hedenus 2003 (AMG 20000161)	1.48	0.97	2.27
PREPARE	1.50	0.95	2.36
Groin 2005 (NS3-004)	1.54	0.64	3.72
Random Effects Model	1.00	0.89	1.12



Figures 8-11 in the sponsor's 2008 briefing document provide study-level meta-analyses of the Peto's odds ratio of death by disease type (respectively, breast cancer, lung cancer, lymphoid malignancies, and head and neck cancer). The results of their analyses using random effects models are summarized in the bullets below:

- Breast cancer
  - using long term follow-up from the BEST study: ESA vs. no ESA odds ratio of death is 1.04 (95% CI 0.88, 1.24)
  - using 54 week survival from the BEST study instead: ESA vs. no ESA odds ratio of death is 1.22 (95% CI 1.03, 1.45)
- Lung cancer: ESA vs. no ESA odds ratio of death is 0.86 (95% CI 0.67, 1.11)
- Lymphoid malignancies: ESA vs. no ESA odds ratio of death is 1.20 (95% CI 0.93, 1.55)
- Head and neck cancer (DAHANCA-10 study included): ESA vs. no ESA odds ratio of death is 1.18 (95% CI 0.95, 1.47)

Reviewer's comment: It is not appropriate to use long term overall survival data from the BEST study in analysis intending to draw conclusions on the safety of ESAs. (b) (4)

5 pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

At the time of the May 10, 2007 Oncology Drugs Advisory Committee meeting there were six studies that have demonstrated inferior overall survival or locoregional failure for the ESA-containing arm. Prior to the March 13, 2008 Oncology Drugs Advisory Committee, two addition studies were identified by the FDA as having safety concerns and detrimental impact on overall survival. To date there is no study known to the FDA that has demonstrated superior overall survival or progression-free survival for the ESA-containing arm.

I have no major disagreements with the statistical reviews of Drs. Kyung Yul Lee and Yuan-Li Shen. The major issues and findings that I will focus on involve the sponsor's meta-analyses on survival and are summarized below.

- Use of long term overall survival data from the BEST study is inappropriate. (b) (4) y [redacted].
- The results from studies (e.g., DAHANCA 10) prospectively identified by the sponsor at ODAC in May 2004 for the purpose of evaluating the safety/tumor promotion potential of Aranesp were not included in the meta-analyses except for the head and neck subgroup analyses.
- (b) (4) [redacted]

4.2 Conclusions and Recommendations

I concur with the conclusions and recommendations of Drs. Lee and Shen. I will provide my conclusions and recommendations as it applies to the topic of this review.

(b) (4) [redacted]

It is my determination that the sponsor's analyses of the "odds ratio of death" and the "relative risk of death" are not valid. See Sections 1.3 and 3.1.2.1 for further details.

SIGNATURES/DISTRIBUTION LIST

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Dr. Mark Rothmann, Ph. D.
Lead Mathematical Statistician
Date: October 16, 2008

Concurring Reviewer(s):

Alaka Chakravarty 10/16/08
Biometrics 5 Division Director: Dr. Aloka Chakravarty, Ph. D.

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HFD-107/Dr. Keegan
HFD-711/Dr. Lee
HFD-711/Dr. Shen
HFD-711/Dr. Rothmann
HFD-711/Dr. Chakravarty
HFD-700/Ms. Patrician

C:\A_DB5\Review\ESA\The PAS\TL review

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y) N	
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Clinical overview [2.5]	(Y) N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y N	
❑ Biopharmaceutics and associated analytical methods	Y N	NA
❑ Clinical pharmacology [includes immunogenicity]	Y N	NA
❑ Clinical Efficacy [for each indication]	(Y) N	
❑ Clinical Safety	Y N	NA
❑ Synopses of individual studies	(Y) N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	(Y) N	
Tabular Listing of all clinical studies [5.2]	(Y) N	
Study Reports and related information [5.3]	Y N	
❑ Biopharmaceutic	Y N	NA
❑ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y N	NA
❑ Pharmacokinetics (PK)	Y N	NA
❑ Pharmacodynamic (PD)	Y N	NA
❑ Efficacy and Safety	(Y) N	
❑ Postmarketing experience	Y N	NA
❑ Case report forms	Y (N)	
❑ Individual patient listings (indexed by study)	Y N	NA
○ electronic datasets (e.g. SAS)	(Y) N	
Literature references and copies [5.4]	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y) N	
❑ legible	(Y) N	
❑ English (or certified translation into English)	(Y) N	
❑ compatible file formats	(Y) N	
❑ navigable hyper-links	(Y) N	
❑ interpretable data tabulations (line listings) & graphical displays	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
❑ summary reports reference the location of individual data and records	(Y) N	
❑ protocols for clinical trials present	(Y) N	
❑ all electronic submission components usable	(Y) N	
statement for each clinical investigation: ❑ conducted in compliance with IRB requirements	Y N	NA
❑ conducted in compliance with requirements for informed consent	Y N	NA
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y N	NA
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N	NA
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	Y N	NA
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	Y N	NA
drug interaction studies communicated as during IND review as necessary are included	Y N	NA
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y N	NA
comprehensive analysis of safety data from all current world-wide knowledge of product	Y N	NA

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	Y N	NA
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y) N	
adequate characterization of product specificity or mode of action	Y N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y N	NA
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y N	NA
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y) N	

List of Clinical Studies (protocol number)	Final study report submitted?	Financial disclosure or certification submitted?	SAS & other electonic datasets complete & usable?	BiMo sites identified?	
980291 sch 1	(Y) N	Y N NR	(Y) N	Y N NR	
980291 sch 2	(Y) N	Y N NR	(Y) N	Y N NR	
990116	(Y) N	Y N NR	(Y) N	Y N NR	
980297	(Y) N	Y N NR	(Y) N	Y N NR	
20010145	(Y) N	Y N NR	(Y) N	Y N NR	
20020149	(Y) N	Y N NR	(Y) N	Y N NR	No raw dat
20030232	(Y) N	Y N NR	(Y) N	Y N NR	
	Y N	Y N NR	Y N	Y N NR	
	Y N	Y N NR	Y N	Y N NR	
	Y N	Y N NR	Y N	Y N NR	

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

There is no SAS programs submitted for analysis or derived datasets.

Is clinical site(s) inspection (BiMo) needed?

NA

Is an Advisory Committee needed?

NA

Recommendation (circle one): File RTF

For BLA and Efficacy BLS: Were any potential review issues identified? Yes No

Reviewer: [signature] 2/11/08 Type (circle one): Clinical Clin/Pharm (Statistical)
(signature/ date)

Concurrence:

Branch Chief: _____ Division. Director: Alaka Chakravarty 2/11/08
(signature/ date) (signature/ date)