CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103234Orig1s5166

STATISTICAL REVIEW(S)

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

ADDENDUM

BLA/STN:	103234/5166
Drug Name:	Procrit (epoetin alfa)
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Applicant:	Johnson & Johnson
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Keywords: Meta-Analysis, Epoetin alfa, labeling change

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1. Overview

This addendum to the statistical review signed on October 16, 2008 summarizes the resubmission to BLA 103234/5166 by Amgen in response to FDA's October 24, 2008 complete response letter which constitutes amendment 11 to the pending supplement.

This resubmission includes

- A response document addressing each of the FDA's comments/requests identified in the 24 October 2008 FDA complete response letter.
- Revised labeling for Epogen and PROCRIT, including an annotated redline package insert, clean package insert, redline Medication Guide, clean Medication Guide, and labeling in structured product labeling (SPL) format.

Please see the BLA 103234.5166 statistical review that was an outcome of May 10, 2007 Oncologic Drugs Advisory Committee (ODAC) meeting.

This review focuses the sponsor's labeling changes comparing with the previous labeling. The background information and the reasoning of the changes were verified and summarized.

2. Summary of Labeling Changes

Summary of Changes

- (b) (4)
- In the labeling section 6.1 Clinical Trial Experience, the sponsor summarized age, gender and race demographic information for patients administered once weekly dosing PROCRIT-treatment group based on study PR98-27-0008.
- In the labeling section 8.5 Geriatric Use, the sponsor added demographic data for age and exposure to study drug based on safety population analysis set by pooling 3 EPO studies, N93-004, J89-004, and PR98-27-008.
- In the labeling section 14.3 Cancer Patients on Chemotherapy, patient eligibility for Study C1 (PR98-27-0004) for anemia was corrected Hemoglobin levels in males <11.5 g/dL; hemoglobin levels in females <10.5 g/dL according to the study protocol.
- In the labeling section 14.3 Cancer Patients on Chemotherapy, stratification factors for Study C2 (Study PR99-11-034/044) and demographic characteristics were added according to the study protocols.

Recommendation and Conclusions

(b) (4)

The sponsor added the demographic data for age and exposure to study drug based on safety population analysis set by pooling 3 EPO studies, N93-004, J89-004, and PR98-27-008 for Geriatric section in the labeling section 8.5. Study EPO-N93-004 is a Phase 4, randomized, double-blind, parallel group, placebo-controlled trial in patients with newly diagnosed small cell lung cancer (SCLC) undergoing etoposide/cisplatin chemotherapy. Study J89-004 is a Phase 3 multicenter study that consisted of a 12-week randomized, double-blind, placebo-controlled phase, followed by a 12-week open-label phase in patients with chronic lymphocytic leukemia (CLL). Study PR98-27-008 is a phase 3 randomized double-blind study in anemic patients with cancer undergoing chemotherapy. See the statistical review of BLA103234.5166 for the detailed study information. All information in the labeling was verified.

Data Sources

Data were provided electronically, the location/names of data sets are as follows.

\\Cbsap58\M\eCTD_Submissions\STN103234\0199\m5\datasets

2.1 (b) (4)

(b) (4)

(b) (4)

Reviewer's comments:

(b) (4)

(b) (4)

2.2 (b) (4) Meta Analysis Results

(b) (4)

Previous labeling
A systematic review of 57 randomized, controlled studies (including Studies 1, 2, 5, and 7 in Table 1 *[see Warnings and Precautions (5.2)]*) evaluating 9353 patients with cancer compared

ESAs plus RBC transfusion with RBC transfusion alone for prophylaxis or treatment of anemia. In cancer patients with or without concurrent antineoplastic therapy. An increased relative risk (RR) of thromboembolic adverse reactions (RR 1.67, 95% CI: 1.35, 2.06; 35 studies and 6769 patients) was observed in ESA-treated patients. An overall survival hazard ratio (HR) of 1.08 (95% CI: 0.99, 1.18; 42 studies and 8167 patients) was observed in ESA-treated patients.

Reviewer's comments:

(b) (4)

2.3 6.1 Clinical Trial Experience

Cancer Patients on Chemotherapy

The sponsor revised this sentence by FDA request.

(b) (4)

Reviewer's comments:

The sponsor summarized age, gender and race demographic information for patients administered once weekly dosing PROCRIT-treatment group for study PR98-27-0008 in the revised label.

2.4 8.5 Geriatric Use

The sponsor added the new sentence in the labeling based on pooled 3 EPO studies, N93-004, J89-004, and PR98-27-008 in the geriatric use.

(b) (4)

[redacted]

Reviewer's comments:

The sponsor summarized demographic data for age and exposure to study drug based on safety population analysis set by pooling 3 EPO studies, N93-004, J89-004, and PR98-27-008.

The sponsor summarized the age distribution, age category of <65 versus ≥65, and age category of <75 versus ≥75 in Table 2.

Table 2: Demographics (EPO Oncology Study EPO-N93-004 EPO-J89-040 and PR98-27-008: Safety Population Analysis Set)

	Epoetin alfa (N=419)	Non-ESA control (N=359)	---- Total ---- (N=778)
AGE (YR)			
N	419	359	778
Mean (SD)	65.4 (10.71)	64.6 (11.18)	65.0 (10.93)
Median	67.0	66.0	66.0
Range	(20;88)	(24;95)	(20;95)
AGE CATEGORY (<65, ≥65)			
N	419	359	778
Category, n (%)			
<65	172 (41)	159 (44)	331 (43)
≥65	247 (59)	200 (56)	447 (57)
AGE CATEGORY (<75, ≥75)			
N	419	359	778
Category, n (%)			
<75	341 (81)	293 (82)	634 (81)
≥75	78 (19)	66 (18)	144 (19)

ESA=erythropoiesis-stimulating agent; SD=standard deviation

The median age and the number of subjects in the age categories are similar between the Epoetin alfa arm and the non-Epoetin alfa control arm.

The demographic characteristics are summarized by studyin Table 3.

Table 3: Demographics by Study (ITT population)

		All n, (%)	J89-040 n, (%)	N93-004 n, (%)	PR98-27-080 n, (%)
Sex					
Female	Epo	200/425(47)	54/142(38)	50/109(46)	96/174(55)
	Control	174/364(48)	27/79(34)	51/115(44)	96/170(56)
Male	Epo	225/425(53)	88/142(62)	59/109(54)	78/174(45)
	Control	190/364(52)	52/79(66)	64/115(56)	74/170(44)
Race					
White	Epo	392/425(92)	130/142(92)	98/109(90)	164/174(94)
	Control	315/364(87)	70/79(89)	94/115(82)	151/170(88)
Other	Epo	33/425(8)	12/142(8)	11/109(10)	10/174(6)
	Control	49/364(13)	9/79(11)	21/115(18)	19/170(12)
Age					
Median	Epo	67.0(20,88)	69.0(41,88)	66.0(35,79)	64.0(20,88)
(min,max)	Control	66.0(24,95)	68.0(47,95)	63.0(37,78)	66.0(24,86)

Majority are White for all three studies. There are more male patients than female patients in studies J89-040 and N93-004. Patients in study J89-040 are older than that of studies N93-004 and PR98-27-008.

The number of subjects for age <65 vs. ≥ 65 and age <75 vs. ≥ 75 years old is summarized by study using intent-to-treat population (ITT).

Table 4: Demographics by Study and Age category (ITT Population)

Age		All n, (%)	J89-040 n, (%)	N93-004 n, (%)	PR98-27-008 n, (%)
<65	Epo	172/419(41)	41/142(29)	46/109(42)	85/168(51)
	Control	159/359(44)	24/79(30)	60/115(52)	75/165(45)
≥65	Epo	247/419(59)	101/142(71)	63/109(58)	83/168(49)
	Control	200/359(56)	55/79(70)	55/115(48)	90/165(55)
<75	Epo	341/419(81)	104/142(73)	99/109(91)	138/168(82)
	Control	293/359(82)	61/79(77)	106/115(92)	126/165(76)
≥75	Epo	78/419(19)	38/142(27)	10/109(9)	30/168(18)
	Control	66/359(18)	18/79(23)	9/115(8)	39/165(24)

The patient population was older in study J89-040 than in studies N93-004 and PR98-27-008.

The number of transfused subjects from Day 29 to Day 90 are summarized by age <65 vs. ≥ 65 and <75 vs. ≥ 75 years old group by study using ITT population.

Table 5: Proportion of Transfused Patients After 28 Days by Study and Age Group (ITT Population)

		All n, (%)	J89-040 n, (%)	N93-004 n, (%)	PR98-27-008 n, (%)
Total	Epo Control	78/425(18) 116/364(32)	43/142(30) 40/79(51)	16/109(15) 38/115(33)	19/174(11) 38/170(22)
<65	Epo Control	31/175 (18) 49/162 (30)	13/41 (32) 13/24 (54)	6/46 (13) 23/60(38)	12/88 (14) 13/78 (17)
≥65	Epo Control	47/250 (19) 67/202 (33)	30/101 (30) 27/55 (49)	10/63 (16) 15/55 (27)	7/86 (8) 25/92 (27)
<75	Epo Control	66/346 (19) 93/296 (31)	36/104 (35) 30/61 (51)	13/99(13) 37/106 (35)	17/143 (12) 26/129 (20)
≥75	Epo Control	12/79 (15) 23/68 (34)	7/38 (18) 10/18 (56)	3/10 (30) 1/9 (11)	2/31 (6) 12/41 (29)

The overall relative risks of transfusion were fairly similar across treatments, although the overall rates were quite different among studies. The differences in transfusion rates between the epoetin alfa arm and the control arm were similar for patients' age <65 vs. ≥65 in studies J89-040 and N93-004. The transfusion rate was similar between the control arm and the epoetin alfa arm for patients' age <65 in study PR98-27-008.

The number of transfused subjects from Day 29 to Day 90 are summarized by age <65 vs. ≥ 65 and <75 vs. ≥ 75 years old group by study using safety population.

Table 6: Demographics by Study and Age Category (Safety Population)

		All n, (%)	J89-040 n, (%)	N93-004 n, (%)	PR98-27-008 n, (%)
<65	Epo Control	172/419(41) 159/359(44)	41/142(29) 24/79(30)	46/109(42) 60/115(52)	85/168(51) 75/165(45)
≥65	Epo Control	247/419(59) 200/359(56)	101/142(71) 55/79(70)	63/109(58) 55/115(48)	83/168(49) 90/165(55)
<75	Epo Control	341/419(81) 293/359(82)	104/142(73) 61/79(77)	99/109(91) 106/115(92)	138/168(82) 126/165(76)
≥75	Epo Control	78/419(19) 66/359(18)	38/142(27) 18/79(23)	10/109(9) 9/115(8)	30/168(18) 39/165(24)

There was no difference between ITT population and safety population in studies J89-040 and N93-004. There are 11 more patients (6 patients in the epoetin alfa arm and 5 patients in the control arm) in the ITT population in study PR98-27-008.

The cumulative mean of Epogen exposures are summarized for age <65 vs. ≥65 and <75 vs. ≥75 by study using safety population.

Table 7: Cumulative Mean EPO Exposure by Study and Age Group (Safety Population)

		All	J89-040	N93-004	PR98-27-008
Total	Mean SD	497264(n=743) 289647	321203(n=221) 123221	402729(n=224) 290429	698893(n=298) 253815
<65	Mean SD	516671(n=318) 283727	354517 (n=65) 137155	422714(n=106) 286175	656122(n=147) 264475
≥65	Mean SD	482743 (n=425) 293493	307322(n=156) 114560	384776(n=118) 294252	740530(n=151) 236507
<75	Mean SD	500510(n=609) 285385	336362(n=165) 127625	415226(n=205) 290287	686987(n=239) 254446
≥75	Mean SD	482508(n=134) 308973	276537 (n=56) 97184	267895(n=19) 262672	747119(n=59) 247519

The cumulative mean epoetin alfa exposure varied greatly across studies. The cumulative mean epoetin alfa exposure was the smallest in study J89-040 and the largest in study N93-004. For study PR98-27-008, the cumulative mean exposure appears to increase with age, while for studies J89-004 and N93-004, the cumulative mean exposure appears to decrease with age.

Please see the transfusion rates from Day 29 to Day 90 by baseline hemoglobin levels and study, and overall survival by baseline hemoglobin levels and study in the previous BLA 103234.5166 statistical review.

2.5 14.3 Cancer Patients on Chemotherapy

The sponsor corrected hemoglobin levels in the Study C1 (PR98-27-0004) according the study protocol by FDA's request.

<u>Study C1:</u>

Study C1 was conducted in anemic patients (hemoglobin < 11.5 g/dL for males and < 10.5 g/dL for females) with non-myeloid malignancies, receiving myelosuppressive chemotherapy. Randomization was stratified by type of malignancy (lung vs. breast vs. other), concurrent radiation therapy planned (yes or no), and baseline hemoglobin (< 9 g/dL vs. ≥ 9 g/dL); patients received PROCRIT 40,000 Units (n = 174) or placebo (n = 170) as a weekly subcutaneous

injection commencing on the first day of the chemotherapy cycle. (b) (4)

Reviewer's comments:

Patient eligibility for EPO Study, PR98-27-0004 was patients with anemia (Hemoglobin in males <11.5 g/dL; hemoglobin in females <10.5 g/dL) in the study protocol.

The sponsor provided the stratification factors for Study C2 (PR99-11-034 and PR99-11-044).

<u>Study C2:</u>

Study C2 was conducted in 222 anemic patients ages 5 to 18 receiving chemotherapy for the treatment of various childhood malignancies. Randomization was stratified by cancer type (b) (4) (b) (4)

Sixty-nine percent of patients were white, 55% were male, and the median age of patients was 12 years (range: 5 to 18 years). (b) (4)

Reviewer's comments:

Study PR99-11-034/044 was 2 separate randomized, double-blind, placebo-controlled, multicenter studies (PR99-11-034 and PR99-11-044) combined into 1 protocol study due to slow patient accrual. Study PR99-11-034 was planned for the enrollment of 220 anemic children with newly diagnosed malignant solid tumor or Hodgkin's disease, while Study PR99-11-044 was planned for the enrollment of 220 anemic children with ALL, or NHL.

Among 222 patents, 162 patients (68.5%) were white, 121 patients (54.8 %) were male, 101 patients (45.5%0 were female, and the median age was 12 years (range 5 to 18 years).

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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

BLA/STN:	103234/5166
Drug Name:	Procrit (epoetin alfa)
Indication(s):	Chemotherapy-induced anemia
Applicant:	Johnson & Johnson
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Review Priority:	Standard
Biometrics Division:	Division of Biometric V
Statistical Reviewer:	Dr. Mark Rothmann, Lead Mathematical Statistician
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1. EXECUTIVE SUMMARY

This statistical review summarizes the analyses of submission BLA 103234/5166 submitted by Amgen as a Prior Approval Supplement (PAS). This submission is an outcome of 10 May 2007 Oncologic Drugs Advisory Committee (ODAC) meeting.

This statistical review is 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 meeting for six studies (BEST, ENHANCE, EPO-CAN-20, 2001-0103, 2000-0161, DAHANCA10).

We summarized our statistical analyses results according to the sponsor's responses to hemoglobin initiation level (FDA Item 3), maximum hemoglobin level (FDA Item 4), discontinuation of ESA therapy post-chemotherapy (FDA Item 5), and other proposed label changes, as discussed below.

1.1 Conclusions and Recommendations

For hemoglobin initiation level (Item 3), it is not possible to draw a conclusion. Some studies had very few or no patients enrolled at lower baseline hemoglobin categories while other studies had very few or no patients at higher baseline hemoglobin categories, making overall conclusion difficult.

For maximum hemoglobin level (Item 4), it is hard to draw conclusions (b) (4)

For other proposed label changes, (b) (4)

For Study N93-004, the sponsor used a month as 28 days for the median month calculation. The median months were corrected using a month as 30.44 days. For study EPO-N93-004, the hazard ratio of overall survival was 1.17 (0.89, 1.55) and median overall survival were 9.7 months (95% CI: 8.5, 11.9) and 9.6 months (95% CI: 7.7, 11.8) in the epoetin alfa group and the placebo group, respectively.

1.2 Brief Overview of Submission

In this submission, the sponsor summarized the results for darbepoetin alfa in chemotherapy-induced anemia (CIA) by pooling 6 Amgen-sponsored, randomized, double-blind, placebo-controlled trials and for epoetin alfa in CIA by pooling 11 Johnson & Johnson Pharmaceutical Research & Development (J&JPRD)-conducted, randomized, double-blind, placebo-controlled studies. This review summarized the results of 11 epoetin alfa in CIA studies; Cisplatin (I88-036, OEO-U24, and OEO-U25), EPO-INT-1, EPO-INT-10, EPO-INT-2, EPO-INT-3, EPO-INT-76 (BEST), EPO-J89-040, EPO-N93-004, EPO-P-174, Non-Cisplatin (I88-037, OEO-U22, and OEO-U23), and PR98-27-008.

For Item 3, the sponsor proposed [redacted] (b) (4)

For Item 4, the sponsor proposed [redacted] (b) (4)

For Item 5, the sponsor proposed [redacted] (b) (4)

For other proposed Label changes, the sponsor proposed [redacted] (b) (4)

1.3 Statistical Issues and Findings

- The sponsor conducted analyses pooling 11 randomized, double-blind, placebo-controlled studies of epoetin alfa in CIA even though the study designs of these 11 studies' population, chemotherapy type, hemoglobin entry criteria, target of hemoglobin are different (See Dr. Mark Rothmann's review).
- [redacted] (b) (4)

(b) (4)

- (b) (4)

- For Study N93-004, the sponsor calculated one month as 28 days instead of 30.44 days. OS median survivals were 9.7 months among the epoetin alfa-treated subjects and 9.6 months among the placebo-treated subjects.

2. INTRODUCTION

2.1 Overview

This statistical review is part of the continual reassessment of the safety and potential tumor promotion of Erythropoiesis-Stimulating Agents (ESAs).

The sponsor's responses were hemoglobin initiation level (FDA Item 3), maximum hemoglobin level (FDA Item 4), discontinuation of ESA therapy post-chemotherapy (FDA Item 5) and other proposed label changes by FDA Items.

The sponsor summarized the results for darbepoetin alfa in chemotherapy-induced anemia (CIA) by pooling 6 Amgen-sponsored, randomized, double-blind, placebo-controlled trials and the results for epoetin alfa in CIA by pooling 11 Johnson & Johnson Pharmaceutical Research & Development (J&JPRD)-conducted, randomized, double-blind, placebo-controlled studies. This review was summarized the results of 11 epoetin alfa in CIA studies; Cisplatin, EPO-INT-1, EPO-INT-10, EPO-INT-2, EPO-INT-3, EPO-INT-76 (BEST), EPO-J89-040, EPO-N93-004, EPO-P-174, Non-Cisplatin, and PR98-27-008.

For Item 3, the sponsor proposed (b) (4)

(b) (4)

(b) (4)

For Item 4, the sponsor proposed (b) (4)

For Item 5, the sponsor (b) (4) summarized the results of a phase 3, randomized, double-blind, placebo-controlled Study 20010145 of subjects with previously untreated, extensive-stage small cell lung cancer (SCLC) receiving platinum chemotherapy and etoposide. See the statistical review of BLA 103951/5173 by Dr. Yuan-Li Shen for an evaluation on the Aranesp Study 20010145.

For other proposed Label changes, the sponsor proposed (b) (4)

The sponsor proposed (b) (4)

2.2 Data Sources

Data were provided electronically, the location/names of data sets are as follow.

Item 3 and Item 4

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Item 5 and for other proposed Label changes

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\\cbsap58\M\eCTD_Submissions\STN103234\0096\m5\datasets\epo-int-76\tabulations

3. SPONSOR'S SUMMARY OF CLINICAL SAFETY AND REVIEWER'S COMMENTS BY ODAC ITEMS.

Items 3 to 5 and other proposed label changes were summarized for the sponsor's results and the reviewer's results.

3.1. FDA Item 3

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

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

(b) (4)

Sponsor's results:

(b) (4)

Reviewer's comments:

(b) (4)

The effects of baseline hemoglobin on survival and the risk of VTEs by baseline hemoglobin levels which were evaluated for the pooled 11 studies in subject-level analyses data from double-blind, placebo-controlled studies of epoetin alfa are presented Figures 1 and 2 below.

Figure 1 (Sponsor's Figure) Death with Follow-up: Hazards Ratio by Baseline Hemoglobin (Placebo-controlled Epoetin alfa CIA Studies)

(b) (4)

Figure 2 (Sponsor's Figure) Clinically Relevant VTE: Hazards Ratio by Baseline Hemoglobin (Placebo-controlled Epoetin alfa CIA Studies)

(b) (4)

Sponsor's Conclusion:

The sponsor proposed (b) (4)

Reviewer's results:

(b) (4)

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It is very difficult to draw conclusions from these data. Some studies had very few or no patients enrolled at lower baseline hemoglobin categories while other studies had very few or no patients at higher baseline hemoglobin categories.

2.2. 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.

The sponsor's Results:

(b) (4)

Sponsor's Conclusion:

(b) (4)

Reviewer's Comments:

The sponsor's conclusion is based on meta-analysis results. As pointed out in the May 10, 2007 ODAC meeting, the agency provided several reasons against performing meta-analyses:

Reasons against doing a meta-analysis

- *Can obscure safety signals from individual studies*

- *Results depend on the studies included*
  - *Earlier meta-analyses suggested statistical significance on overall survival favoring ESAs*
  - *Later meta-analyses suggest statistical significance on overall survival favoring controls*
- *Cumulative meta-analyses and retrospective meta-analyses have issues on appropriate allocation of alpha*
- *Heterogeneous trials w/ variable quality, variable lengths of follow up, variable target Hgb, and heterogeneous tumor types*
- *Concentrate on the differences – e.g., longer follow-up for later studies, differences in target hemoglobin levels, and differences in patient populations*

(b) (4)

(b) (4)

2.3. FDA Item 5

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

The sponsor (b) (4) summarized the results of a phase 3, randomized, double-blind, placebo-controlled Study 20010145 of subjects with previously untreated, extensive-stage small cell lung cancer (SCLC) receiving platinum chemotherapy and etoposide.

See the statistical review of BLA 103951/5170 by Dr. Yuan-Li Shen for an evaluation on the Aranesp Study 20010145.

2.4. Other proposed Label Changes.

The sponsor summarized Amgen Study 20010103 and Study 20010145 and J& JPRD Study EPO-INT-76 and Study N93-004 (b) (4). For Amgen Study 20010103 and Study 20010145, see the statistical review of BLA 103951/5170 by Dr. Yuan-Li Shen. J& JPRD Study EPO-INT-76 and Study N93-004 are reviewed below.

2.4.1. J&JPRD Study EPO-INT-76 (BEST)

2.4.1.1. Study Design and Endpoints

Study title is "A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Impact of Maintaining Hemoglobin Using Epoetin alfa (Epoetin Alfa; RWJJPRI-22512) in Metastatic Breast Carcinoma Subjects Receiving Chemotherapy." This is a Phase III study to evaluate the impact of maintaining hemoglobin levels between 12 and 14 g/dL using epoetin alfa in 939 women with metastatic breast cancer who were receiving first-line chemotherapy (various regimens), subjects received either weekly 40,000 IU epoetin alfa or placebo for up to a year (over 54 weeks).

The original study protocol provided subjects who completed the 12-month double-blind phase (after 54 weeks) the option of enrolling in the open-label extension phase. Subjects who elected

to participate in the open-label phase received epoetin alfa by a subcutaneous route of administration at a starting dose of 40,000 IU each week. Treatment could begin when the subject's hemoglobin concentration measured 13 g/dL or less, and the treatment goal was to maintain hemoglobin concentration between 12 and 14 g/dL.

Stratification factors for randomization were metastatic disease category (bone metastasis only vs. other measurable metastatic lesions vs. other non-measurable metastatic lesions).

The planned **sample size** was 870 (435 per treatment group) based on assumption of 70% and 80% survival in the placebo and epoetin alfa group at the end of 12-month double-blind treatment phase.

Efficacy endpoints: The primary efficacy endpoint was survival during the first 12 months (first 54 weeks) of treatment. Secondary endpoints were hematologic effects, tumor response rates, time to disease progression (TTP), RBC transfusions, and quality of life measures (QOL).

2.4.1.2. Sponsor's Efficacy Results:

A total of 939 subjects (470 from placebo and 469 from epoetin alfa) were enrolled and randomized (ITT population).

A total of 362 of 470 (77%) subjects originally assigned to the placebo treatment and 353 of 469 (75%) subjects originally assigned to the epoetin alfa treatment had died as of the clinical cut off date (For the first 54 weeks double-blind period and open-level period (crossover allowed after 54 weeks)). The first patient was enrolled 6/23/2000 and the last patient was enrolled 6/29/2001, respectively.

- Based upon the analysis of data using the 29 April 2002 cut off date, 265 subjects (116 placebo and 149 epoetin alfa) died within the first 54 weeks of randomization (25% for placebo, 32% for epoetin alfa). The treatment difference in survival rate was associated with a nominal p value of 0.0139 based on a stratified (bone metastasis only versus other metastatic disease) log-rank test without adjustments for other prognostic factors.

- The 12-month survival rate based on Kaplan-Meier estimates was lower in the epoetin alfa group (70%) compared to the placebo group (76%). The hazard ratio of Cox's proportional hazards model stratified by metastatic category was 1.37 (1.07, 1.74) (p=0.0112). The most common cause of death in both treatment groups was disease progression, accounting for 88% of all deaths in the intent-to-treat population during the 2-month double-blind study phase. For 6 (4%) subjects in the epoetin alfa group and 3 (3%) in the placebo group, the cause of death was related to thrombotic/vascular event.

- By comparison, mean hemoglobin levels were increased after Week 4 in the epoetin alfa group and remained at or elevated above the baseline level for the remainder of the study. The observed treatment group difference in hemoglobin levels over time, based on a linear mixed model, was statistically significant (p=0.0234).

- The proportion of subjects transfused from baseline to double-blind study end was lower in the epoetin alfa group (10%) compared to the placebo group (14%) (p=0.0595). The median pre-transfusion hemoglobin level for subjects who were transfused during the study was 8.3 g/dL in both treatment groups.

- The proportion of subjects in the complete response, partial response, stable disease, and progressive disease was not statistically different between the two treatment groups (p=0.9303) (46% in the placebo group and 45% in the epoetin alfa group showed a complete or partial optimal response to first-line chemotherapy).

- The percentage of subjects who showed progressive disease was similar for the two treatment groups (18% in the placebo group, 19% in the epoetin alfa group). Among the subjects who showed progressive disease, a higher percentage of subjects in the placebo group (67%) developed new lesions compared to the epoetin alfa group (49%).

- The tumor response at the end of first-line chemotherapy was similar for the two treatment groups (placebo (26%) and epoetin alfa (27%)).

- The tumor response at the last assessment for each individual subject during the 12-month double-blind phase was similar for the two treatment groups (placebo (46%) vs. epoetin alfa (42%)).

- The time to disease progression was comparable for the two treatment groups (p=0.7059). Based on Kaplan-Meier estimates, 43.4% of subjects in the placebo group and 41.1% of those in the epoetin alfa group had evidence of disease progression by Month 12.

- From the sponsor's analyses, treatment of women with metastatic breast cancer with epoetin alfa or placebo for up to 12 months (54 weeks) had a similar effect on subjects' health-related QoL as reflected by changes in FACT-An and CLAS scores. *However, the analyses ignored that overall survival was inferior for epoetin alfa for the first 54 weeks (patients who died during the first 54 weeks were not included in the QoL analysis).*

Sponsor's Conclusion:

(b) (4)

Reviewer's comment: (b) (4)

(b) (4)

Reviewer's Results:

Overall Survival

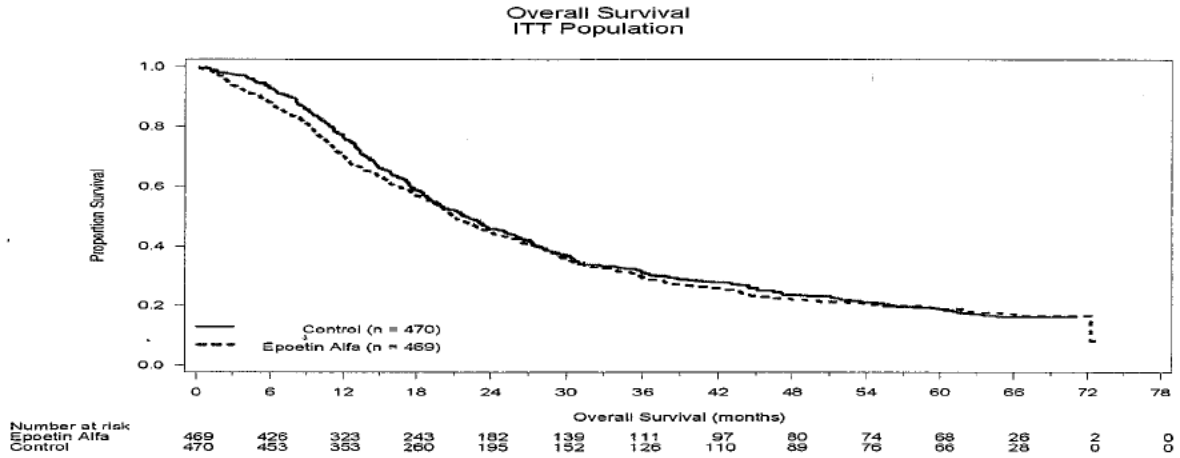
There were 715 deaths out of 939 subjects during the study in the updated data, 362 from the control group and 353 from the treatment group. The OS results for 54 weeks and for long-term follow-up in the updated data are summarized in Table 20.

Table 20. Overall Survival (BEST)

Overall Survival	Epoetin Beta N = 469	Control N = 470
First 54 weeks		
Number of Patients With OS Event	149 (31.8%)	116 (24.7%)
Number of Patients Without OS Event	320 (68.2%)	354 (75.3%)
Median Duration of OS months (95% CI)	NE	NE
Hazard Ratio (95% CI)-unstratified	1.37 (1.07, 1.74)	
P-Value (unstratified Log-Rank Test)	0.0112	
Hazard Ratio (95% CI)- stratified*	1.36 (1.06, 1.73)	
P-Value (stratified Log-Rank Test)	0.0139	
Updated data for long-term follow-up		
Number of patients with OS Event	353 (75.3%)	362 (77.0%)
Number of Patients Without OS Event	116 (24.7%)	108 (23.0%)
Median Duration of OS months (95% CI)	20.96 (19.29, 23.75)	22.05 (19.58, 25.03)
Hazard Ratio (95% CI)-unstratified	1.05 (0.90, 1.21)	
P-Value (unstratified Log-Rank Test)*	0.5370	
Hazard Ratio (95% CI)-Stratified	1.04 (0.89, 1.20)	
P-Value (Stratified Log-Rank Test)*	0.6411	

*Stratification factors are metastatic category (bone metastasis only versus other measurable metastatic lesions versus other non-measurable metastatic lesions)

Figure 3 Kaplan-Meier Curve for Overall Survival (BEST Study)



In the double blind phase (one year OS), 116 (24.7%) subjects in the placebo group and 149 deaths (31.8%) in the epoetin alfa group had died.

After the double-blind phase of 12 months 94 subjects from the epoetin alfa group and 134 subjects from the placebo group were enrolled in the open-label phase and received epoetin alfa by a subcutaneous route of administration at a starting dose of 40,000 IU each week.

The number of patients who enrolled in the open-label (OL) phase after the double-blind phase was 228 patients in the updated open label profile data set. The number of overall survival events enrolled in the open label phase was summarized in Table 21.

Table 21. Number of Deaths in the Double Blind Phase and Open Label Phase

	Double blind	*Open Label Phase (OL)*	
		Epoetin alfa (%)	*No OL (%)*
Epoetin alfa	*149/469 (31.8)*	*77/ 94 (81.9)*	*276/375(73.6)*
Placebo	*116/470 (24.7)*	*98/134 (73.1)*	*264/336 (78.6)*
Total	*265/939 (28.2)*	*175/228 (76.8)*	*540/711(75.9)*

Four patients who were counted on deaths in the original analysis, whose overall survival times changed in the updated analysis. Those four patients were dead in both analyses, but all their times decreased.

Patient ID	Treatment group	Original times to death	Updated time to death
EPO-CA-489-CDN05-1009	Epoetin Alfa	500	491
EPO-CA-489-PL06-3112	Placebo	456	453
EPO-CA-489-PL01-3159	Epoetin Alfa	309	302
EPO-CA-489-PL07-3217	Placebo	341	314

Reviewer's comments:

(b) (4)

(b) (4)

2.4.2. J&JPRD Study N93-004

2.4.2.1. Study Design and Efficacy Endpoints

This Study EPO-N93-004 is a Phase 4, randomized, double-blind, parallel group, placebo-controlled trial. This study conducted at 35 sites in the United States (U.S.). Eligible subjects were adults with histologically documented, measurable, limited- or extensive-stage, newly diagnosed SCLC who were scheduled to begin a course of chemotherapy with etoposide and cisplatin, administered every 3 weeks, for at least 3 cycles. The study consisted of a double-blind treatment phase during chemotherapy followed by 3 years of double-blind follow-up. A sample size of approximately 400 subjects was planned. **The study was terminated prematurely after 224 subjects had been enrolled (7/17/2001) due to slow enrollment.** The clinical cut-off date for inclusion of subject data into this report was May 6, 2002.

This Phase 4 study consisted of a double-blind treatment phase with up to 12 cycles of chemotherapy followed by 3 years of double-blind follow-up for assessment of survival. Subjects scheduled to begin a course of chemotherapy with etoposide and cisplatin for newly diagnosed SCLC were randomly assigned in a 1:1 ratio to receive either epoetin alfa 150 IU/kg or placebo, given subcutaneously (s.c.) three times a week (t.i.w.), until approximately 3 weeks after completing the final cycle of chemotherapy. Etoposide/cisplatin was to be administered every 3 weeks for at least 3 cycles. Approximately 3 weeks after Cycle 3 and after completion of the final cycle, the extent of measurable and evaluable disease was determined by appropriate imaging techniques. Disability ratings via ECOG scoring were assessed at baseline and at study completion/termination.

The planned sample size of 400 was determined assuming that a 15% reduction from an overall placebo response rate of 60% would be clinically significant. Given a power of 90% and a significance level of 0.05 (1-sided) so that there would be high power for detecting a specified reduction in the proportion of subjects whose tumors respond to therapy (complete response or partial response) after 3 cycles of chemotherapy.

The primary efficacy endpoint was the proportion of subjects in each treatment group who had a complete (complete absence of detectable tumor) or partial (reduction in estimated tumor mass by ≥50% and no new lesions) response to chemotherapy after the third cycle of chemotherapy.

The secondary endpoints included survival rate, the proportion of subjects with a complete or partial response after the final chemotherapy cycle, changes in hemoglobin levels over time, red blood cell (RBC) transfusion rates on-study, and the ECOG performance status scores at baseline and the final visit. Survival was defined as the time from the date of the first dose of chemotherapy of Cycle 1 to the date of death.

Among 224 subjects (intent-to-treat population), 109 subjects treated with epoetin alfa and 115 subjects were treated with placebo. The first patient was enrolled 7/15/1993 and the last patient was enrolled 7/11/2000, respectively.

Sponsor's results:

- The overall tumor response rate after 3 cycles of chemotherapy was 72% (79 of 109 subjects) for the epoetin alfa treatment group and 67% (77 of 115 subjects) for the placebo group with 6% observed difference (95% CI: -6%, 18%).

- The overall tumor response rates after all chemotherapy cycles were similar for the epoetin alfa (60%) and the placebo (56%) treatment groups with 4% observed difference (95% CI: -9%, 17%).

- Two hundred one of the 224 subjects were died prior to the end of the 3-year follow-up. The overall mortality rates were 92% in the epoetin alfa and 88% in the placebo groups as was median survival, which was reached in 10.5 months among epoetin alfa-treated subjects and in 10.4 months among placebo-treated subjects.

Median overall survival was 9.7 months in the epoetin alfa group and 9.6 in the placebo group.

- At the time of median exposure to study drug (94 days; 13 weeks) the mean change from the baseline hemoglobin was -2.9 g/dL in the placebo group and -0.2 g/dL in the epoetin alfa group. For the observed difference in hemoglobin levels over time, fewer subjects in the epoetin alfa treatment group required a transfusion during the study treatment period (24%) compared with the placebo group (37%).

- ECOG performance status showed that the majority of subjects in the epoetin alfa (78%) and in the placebo (81%) treatment groups had an ECOG score of 0 to 2 at the end of the double-blind treatment period.

Sponsor's Conclusion:

(b) (4)

[redacted]

Reviewer's Results:

Among 224 subjects, 57 subjects (25.4%) were not followed for 3 years.

Tumor response

There were 82 overall response subjects (ORR: 75.2%) (18 complete response (CR) subjects and 64 partial response (PR) subjects) in the epoetin alfa group and 79 overall response subjects (ORR: 68.7%) (17 CR subjects and 62 PR subjects) in the placebo group.

Overall Survival

There were 201 deaths out of 224 subjects during the study, 101 from the control group and 100 from the treatment group. The results are summarized in Table 22.

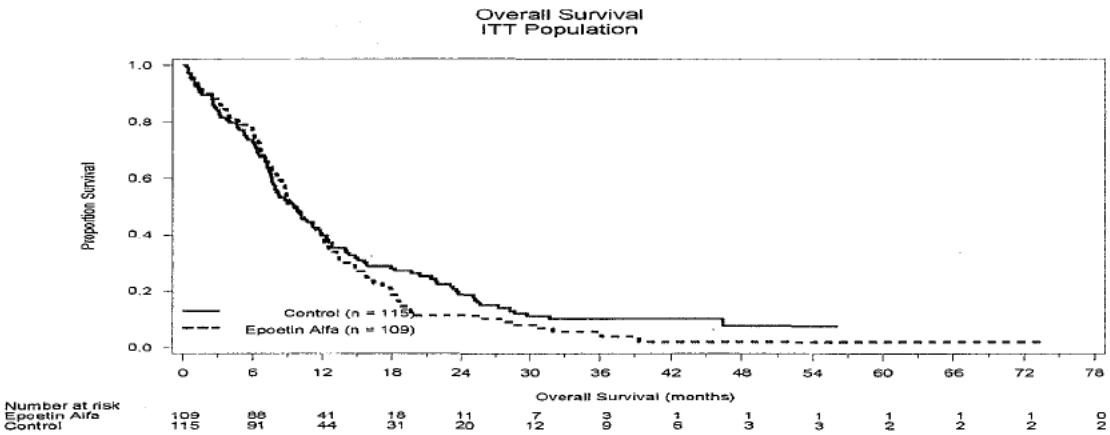
Table 22. Overall Survival (EPO-N93-004)

Overall Survival	Epoetin Beta N = 109	Control N = 115
Number of Patients With OS Event	100 (91.7%)	101 (87.8%)
Number of Patients Without OS Event	9 (8.3%)	14 (12.2%)
Median Duration of OS months (95% CI)	9.69 (8.51, 11.9)	9.56 (7.66, 11.8)
Hazard Ratio (95% CI)-unstratified	1.17 (0.89, 1.55)	
P-Value (Unstratified Log-Rank Test)	0.2648	

Survival was defined as the time from the date of the first dose of chemotherapy of Cycle 1 to the date of death. The sponsor's OS median survival were 10.5 months among epoetin alfa-treated subjects and 10.4 months among placebo-treated subjects. The discrepancy of the median survival was that the sponsor calculated one month as 28 days and this reviewer calculated one month as 30.44 days.

There were 91 deaths (83.5%) and 85 deaths (73.9%) in the epoetin alfa group and the placebo group, respectively, due to disease. The numbers of death from other causes were 9 subjects (8.3%) and 16 subjects (13.9%) in the epoetin alfa group and the placebo group, respectively. Two patients (in each arm) were lost-follow-up for overall survival.

Figure 4 Kaplan-Meier Curve for Overall Survival (EPO-N93-004 Study)



Reviewer's comments:

Table 10 in the page 43 **(2.7.4 – Summary of Clinical Safety)** *was incorrect (25th and 75th percentiles were reversed). The table below was updated.*

Table 23. Quartiles for Duration of Survival (Months) (EPO-N93-004: Intent-to-Treat Population)

Quartile	Placebo			Epoetin Alfa		
	Point Estimate	95% CI		Point Estimate	95% CI	
		Lower	Upper		Lower	Upper
75%	21.4	14.1	25.1	15.8	12.5	18.5
50%	9.6	7.7	11.8	9.7	8.5	11.9
25%	5.4	3.2	7.1	6.1	4.0	7.6

(b) (4)

3. CONCLUSION AND RECOMMENDATIONS

For Items 3, drawing conclusions from such data is very difficult. Some studies had very few or no patients enrolled at lower baseline hemoglobin categories while other studies had very few or no patients at higher baseline hemoglobin categories.

For item 4, it is hard to draw conclusions (b) (4)

For other proposed label changes, (b) (4)

For Study N93-004, the sponsor used a month as 28 days for the median month calculation. The median months were corrected using a month as 30.44 days. For study EPO-N93-004, the hazard ratio of overall survival was 1.17 (0.89, 1.55) and median overall survival were 9.7 months (95% CI: 8.5, 11.9) and 9.6 months (95% CI: 7.7, 11.8) in the epoetin alfa group and in the placebo group, respectively.

4. APPENDICES

1. Study Cisplatin (I88-036, OEO-U24, OEO-U25)

Study Cisplatin (I88-036-MR92013) was a double-blind, placebo-controlled study to determine the safety and the efficacy of epoetin alfa, administered subcutaneously, in patients with anemia secondary to advanced cancer and cisplatin chemotherapy.

The planned sample size was 72 patients (36 each) based on 7.8 to 4.8 units of a reduction in the mean number of unit blood transfused with a 80% power. A total of 59 patients (3 protocols) undergoing cisplatin-containing chemotherapy every three to four weeks were randomly assigned to one of two treatment groups, 26 patients to epoetin alfa 150 U/kg and 31 patients to placebo. All patients completing the double-blind phase of the study were eligible to enter the open-label phase during which all patients received epoetin alfa at a dose titrated to maintain hematocrit between 38-40%.

Among 72 enrolled patients, 35 received epoetin alfa and 37 received placebo. Two patients were excluded from the efficacy analyses because these two patients had less than 15 days treatment.

Majority was female (70.8%) and Caucasian (81.9%) patients with the mean age of 61.5 years old (641. years old for epoetin alfa and 59.1 years old for placebo).

The primary endpoints of this study were weekly hematocrit on-study, change in the level of hematocrit from baseline (Day 1) to the end of the double-blind phase, proportion of patients who achieved a hematocrit of 38% or greater unrelated to transfusion, the proportion of responders (subjects with a 6% increase in hematocrit), transfusion rate, change in quality-of-life assessment, investigator's global evaluation at the end of the double-blind phase.

Planned Analysis: ANOVA for primary endpoints (hematocrit response and transfusion requirements).

The first patient was enrolled 10/25/1988 and the last patient was enrolled 5/11/1990, respectively.

Sponsor's Results:

- Hematocrit levels were increased from a baseline mean of 27.7% to a maximum mean value of 35.1% by Week 12 of treatment in the epoetin alfa group and a baseline mean of 29.4% to a maximum mean value of 31.1% by Week 12 of treatment in the placebo group. Mean final values for hematocrit were 35.3% for epoetin alfa and 30.7% for placebo ($p<0.001$).
- The number of patients who achieved a hematocrit of 38% or greater unrelated to transfusion were 15 (44.1%) out of the 34 epoetin alfa-treated patients and 1 (2.8%) out of the 36 placebo-treated patients ($p<0.001$). Mean times to correction (38%) to treatment of hematocrit were 58.5 days for the epoetin alfa-treated patients and 81.3 days for the placebo–treated patients.
- The number of patients who responded to therapy (subjects with a 6% increase in hematocrit unrelated to transfusion) were 21 (61.8%) and 4 (11.1%), for the epoetin alfa-treated group and the placebo-treated group, respectively ($p<0.001$). Mean times to response to therapy were 41.days and 79.0 days, for the epoetin alfa-treated group and the placebo-treated group, respectively.

- The mean transfusion rates for baseline and cumulative on-study were 2.65 units/patient/3 months for the epoetin alfa-treated patients and 2.08 units/patient/3 months at baseline and 2.69 units/patient/3 months on study for the placebo-treat patients. There was no statistically significant difference between the two groups.
- The number of patients who required transfusion during the study was 15 (44.1%) and 16 (44.4%), for the epoetin alfa group and the placebo group, respectively. There was no statistically significant difference between the two groups. The proportions transfused in Month 3 were 4.5% (1 out of 25) and 28.1% (9 out of 32) and there was statistically significant difference between the two groups.
- There were no statistically significant differences in QoL measures (energy level, daily activity and overall quality) between the two groups. The changes in energy level for the epoetin alfa-treated patients (n=28) and the placebo-treated patients (n=29) were 11.25 and 5.52, respectively. The changes in daily activity for the epoetin alfa-treated patients and the placebo-treated patients were 7.86 and 5.72, respectively. The changes in overall quality for the epoetin alfa-treated patients and the placebo-treated patients were 2.46 and 5.48, respectively.

The sponsor did not provide appendices which include study protocols (I88-036, OEO-U24, OEO-U25) in the submission.

The first patient was enrolled 10/25/1988 and the last patient was enrolled 5/11/1990 for Study I88-036, respectively. The first patient was enrolled 12/16/1988 and the last patient was enrolled 5/10/1990, respectively for Study OEO-U24 and the first patient was enrolled 7/31/1989 and the last patient was enrolled 5/08/1990, respectively for Study OEO-U25.

2. Study EPO-INT-1 (2574-P-416)

Study EPO-INT-1 was randomized, double-blind study on the effect of epoetin alfa in subjects with ovarian cancer receiving cyclic platinum based chemotherapy regimens (PROTOCOL CC 2574-P-416; PHASE 3).

This study was conducted in Czechoslovakia, Italy, Poland, Spain, United Kingdom, Austria, Germany, Hungary, France, Bulgaria, Greece, the Netherlands, Portugal, Israel, Sweden, Yugoslavia, and Finland.

Enrollment was restricted to subjects whose hemoglobin level had fallen substantially (≥1.5 g/dL when baseline prior to chemotherapy was <14 g/dL; ≥2 g/dL when baseline prior to chemotherapy was ≥14 g/dL) since the beginning of their current course of chemotherapy or those who had a low baseline hemoglobin level (<11 g/dL). Subjects were randomized into two groups with 2:1 ratio:
1. 300 IU/kg epoetin alfa or comparable volume of placebo (2:1)
2. 150 IU/kg epoetin alfa or comparable volume of placebo (2:1)

The first patient was enrolled 4/2/1993 and the last patient was enrolled 4/3/1996.

Transfusions could be administered as needed during the trial; however, every effort was made not to transfuse subjects with hemoglobin concentrations >8 g/dL. In order to minimize bias, individuals making decisions about transfusion requirements were not informed of the reticulocyte count.

The primary efficacy endpoints were the proportion of subjects transfused during Months 2 and 3 (stratified by baseline transfusion status and overall) with both the intent-to-treat and efficacy populations; For the intent to-treat population, subjects who were on study for less than two months were counted as treatment failures, i.e., transfused. The Secondary efficacy endpoints were additional transfusion variables, change in hemoglobin concentration, hematocrit level, quality-of-life assessments, performance score, and the physician's global assessment with both for the efficacy population and for the intent-to-treat population;

Two hundred forty-six women who were at least 18 years old, had documented ovarian cancer, and were being treated with a cyclic platinum-based (cisplatin or carboplatin) chemotherapeutic agent were enrolled in this study in the 49 sites in 17 countries.

Eighty subjects were randomly assigned to receive epoetin alfa 300 IU/kg, 85 to receive epoetin alfa 150 IU/kg, and 81 to receive placebo (38 to receive 300 IU/kg placebo; 43 to receive 150 IU/kg placebo). The study initiated date and completed dates were April 2, 1993 and February 13, 1997, respectively.

The mean age was 57.8 years. Mean baseline hemoglobin levels were the same for the three groups (9.9 g/dL). The mean serum erythropoietin level at baseline was higher in the 300 IU/kg epoetin alfa group (122 mU/mL) compared with levels in both the 150 IU/kg epoetin alfa and placebo groups (79 mU/mL and 78 mU/mL, respectively).

Sponsor's Results:

- There was no statistically significant difference in the proportion of transfused during study Months 2 and 3, among subjects who were transfusion-dependent at baseline, treated with epoetin alfa 300 IU/kg versus with placebo (15.4% (2 out of 68) versus 42.9% (6 out of 77) of subjects in the efficacy population treated with epoetin alfa 300 IU/kg and placebo, respectively). With ITT population, the proportion of transfused during Months 2 and 3 were 35.3% (6 out of 80), 53.8% (7 out of 85) and 42.9% (6 out of 81), for epoetin alfa 300 IU/kg, epoetin alfa 150 IU/kg, and placebo, respectively.
- Regardless of prestudy transfusion status, the proportion of transfused during study Months 2 and 3 were 28.8% (23 out of 80), 23.5% (20 out of 85) and 22.2% (18 out of 81), for epoetin alfa 300 IU/kg, epoetin alfa 150 IU/kg, and placebo, respectively (ITT) (16.2% (11 out of 68), 15.6% (12 out of 77) and 18.2 % (14 out of 77)-for efficacy population). There was no statistically significant difference between epoetin alfa 300 IU/kg and placebo.
- There were no significant differences in the proportion of subjects transfused or having hemoglobin levels less than 8 g/dL or in the proportions of subjects becoming transfusion-independent after being transfusion-dependent at baseline among treatment groups.

- The time to the first transfusion after the first month of the study (i.e., excluding transfusions that occurred during Month 1) tended to be longer for epoetin alfa-treated subjects than for placebo-treated subjects. However, the difference between the epoetin alfa 300 IU/kg group and the placebo group analyzed by the log-rank test was not statistically significant (p=0.08).
- There was a significant difference in cumulative transfusion rates during Months 2 and 3 among subjects who were transfusion-dependent at baseline were lower for subjects in the epoetin alfa 300 IU/kg group (0.82 units for epoetin alfa 300 IU/kg and 2.97 units for placebo) than for those in the placebo group (p=0.047).
- The change in hemoglobin levels from baseline to last value on study were 2.5, 1.8, and 0.5 for the epoetin alfa 300 IU/kg group, the epoetin alfa 150 IU/kg group, and the placebo group, respectively. The change in hematocrit levels from baseline to last value on study were 7.8, 5.8, and 1.8 for the epoetin alfa 300 IU/kg group, the epoetin alfa 150 IU/kg group, and the placebo group, respectively. Both epoetin alfa groups were statistically significant greater changes in hemoglobin and hematocrit levels from baseline to last value on study as compared to the placebo group ($p<0.05$).
- There were no significant differences with regard to improvements in Eastern Cooperative Oncology Group (ECOG) Performance Scores by investigator assessment among the treatment groups. However, the responses for physicians indicated an "excellent" or "very good" global effect were 22.1% and 27.9%, respectively, of subjects in the epoetin alfa 300 IU/kg group and 16.9% and 27.3%, respectively, of subjects in the epoetin alfa 150 IU/kg group, as compared with 2.6% and 10.4%, respectively, of subjects in the placebo group. Based on the physician's global assessment, the effect of study medication on subjects who received either dose of epoetin alfa was significantly ($p<0.001$) better than on those who received placebo.
- Overall, 39% (96 out of 246) of subjects received carboplatinum chemotherapy, 41% (102 out of 246) received cisplatinum chemotherapy, and 20% (48 out of 246) received both carboplatinum and cisplatinum chemotherapy regimens. In addition, 23% (56 out of 246) of all subjects received iron supplementation during the study.

The sponsor did not provide appendices which include study protocols. The first patient was enrolled 4/2/1993 and the last patient was enrolled 4/3/1996.

3. Study EPO-INT-10 (EPO-C111-457)

This study was a double-blind, placebo-controlled study to assess the effect of early intervention and/or treatment with epoetin alfa on anemia in cancer patients receiving non-platinum containing chemotherapy. Subjects who had either a low baseline hemoglobin level (≤10.5 g/dL) at any time during chemotherapy or to those subjects whose hemoglobin had fallen substantially (≥1.5 g/dL per cycle or per month) since the beginning of the current course of chemotherapy such that it dropped to ≤12 g/dL, thought to be at high risk for the development of transfusion-dependent anemia were enrolled in the study.

Stratification factors are tumor type (solid or hematological) and hemoglobin level (≤10.5 g/dL and >10.5 g/dL) based on hemoglobin at the time of screening.

The sample size calculation was based on the ability to detect an odds ratio of 2 between success and treatment, where success is defined as the absence of any transfusion after the end of the first four weeks of treatment. The following assumptions on success rates per stratum and treatment arm (placebo:epoetin alfa) were to be made:

_ Solid tumors - hemoglobin level ≤10.5 g/dL: 0.50/0.67
_ Solid tumors - hemoglobin level >10.5 g/dL: 0.55/0.71
_ Hematologic tumors - hemoglobin level ≤10.5 g/dL: 0.45/0.62
_ Hematologic tumors - hemoglobin level >10.5 g/dL: 0.50/0.67

Based on the Cochran-Mantel-Haenszel test, the sample size of 360 was calculated to detect a power of 90% at the 0.05 significance level (one-sided) with a treatment assignment of 2:1 ratio (120 in the placebo-treated group and 240 in the epoetin alfa-treated group).

Study drug was blinded for identity (epoetin alfa or placebo) but not for dose level (150 or 300 IU/kg after the initial four weeks), and was administered subcutaneously (s.c.).

The protocol recommended that blood transfusions be performed as necessary during the study, but every effort should be made not to transfuse subjects with a hemoglobin level above 8 g/dL. If, at any time during the study, the hemoglobin level exceeded 15 g/dL, study drug was to be withheld until the hemoglobin level fell below 12 g/dL, and was to be restarted at a dose level approximately 25% below the dose level that was previously being administered. If the hemoglobin level was rising at a rate ≥2 g/dL per month or ≥2 g/dL per cycle, the dose of study drug was to be reduced by approximately 25% to maintain the rate of rise of hemoglobin to <2 g/dL per month (<2 g/dL per cycle).

Three hundred seventy-five subjects with non-myeloid malignancies receiving non-platinum-containing chemotherapy were enrolled into the study and were randomly assigned by double-blind randomization in a 2:1 ratio. Two hundred fifty one subjects were assigned to receive 150 IU/kg epoetin alfa and 124 subjects were assigned to receive placebo three times weekly.

Three hundred seventy-five subjects were enrolled at 73 sites in 15 countries, and approximately half of the subjects were enrolled in Germany (21%), the Netherlands (16%), and Great Britain (10%).

The primary efficacy endpoint was the proportion of subjects not transfused (successes) after the first four weeks (>28 days) of treatment. The secondary endpoints were changes in hemoglobin levels, hematocrit levels, reticulocyte counts, testing predictive algorithms for response, quality-of-life parameters and subject burden and work loss.

Survival data (i.e., survival/death, date of death, whether or not death was caused by disease progression) were to be collected for the post-study period ending three months after the last subject completed the study (November 15, 1998) and also for the post-study period ending 12 months after the last subject completed the study (August 15, 1999).

The mean age was 58.7% and women were 67%, and the majority was Caucasian (96%).

Overall, 54% of the subjects had solid tumors and 46% had hematological tumors (included non-Hodgkin's and Hodgkin's lymphoma). Eighty-five percent of all the subjects were stratified to a hemoglobin ≤10.5 g/dL and 15% were stratified to a hemoglobin >10.5 g/dL.

The first patient was enrolled 8/3/1996 and the last patient was enrolled 2/6/1998, respectively.

Sponsor's results:

- The primary endpoint, the proportion of subjects transfused after Day 28 was lower in the epoetin alfa group with 62 out of 251 subjects (24.7%) than in the placebo group with 49 out of 124 subjects (39.5%) (P=0.0057, logistic regression, ITT population). With efficacy population, the rates were 23.0% (56 out of 244 subjects) and 35.7% (41 out of 115 subjects), for epoetin alfa and placebo, respectively.
- The proportion of subjects transfused after Day 28 by tumor type (solid or hematological) and hemoglobin level (≤10.5 g/dL or >10.5 g/dL) were 33 out of 136 (24.3%), for solid tumor, 29 out of 115 (25.2 %) for hematological tumor, 59 out of 209 subjects (28.2%) for ≤10.5 g/dL hemoglobin, and 3/42 (7.1%) for >10.5 g/dL hemoglobin, respectively, in the epoetin alfa group and 24 out of 66 subjects (36.4%) for solid tumor, 25 out of 58 subjects (43.1%) for hemotogogic tumor, 46 out of 109 subjects (42.2%) for ≤10.5 g/dL hemoglobin, and 3 out of 15 subjects (20.0%) for >10.5 g/dL hemoglobin, respectively, in the placebo group. There were no statistically significant differences in the transfusion rates by tumor type, and hemoglobin stratum between the two treatment groups.
- The secondary efficacy endpoint, the proportion of subjects transfused or with a hemoglobin below 8 g/dL after Day 28 was significantly lower in the epoetin alfa group with 61 out of 244 subjects (25.0%) than in the placebo group with 52 out of 115 subjects (45.2%) (p=0.0002). This proportion by tumor type was not statistically significant between the two treatment groups (solid tumor; 29/131 (22.1%) vs.25/61 (41.0%), for epoetin alfa vs. placebo; hematological tumor; 32/113 (28.3%) vs. 27/54 (50.0%), for epoetin alfa vs. placebo), but this proportion by the effect of hemoglobin stratum was statistically significant (≤10.5 g/dL: 59/203(29.1%) vs. 2/41(4.9%) for epoetin alfa vs. placebo: >10.5 g/dL; 48/100(48.0%),4/15(26.7%) for epoetin alfa vs. placebo).
- The cumulative transfusion rate was calculated as the number of units transfused per subject per three months on study. The median baseline transfusion rate for subjects who were transfusion dependent at baseline was 2.0 units per three months prior to study for both groups, but the median cumulative transfusion rate was lower in the epoetin alfa group (3.8 units per three months on study) than in the placebo group (4.7 units per three months on study).
- Hemoglobin levels rose a mean of 2.2 g/dL in the epoetin alfa group from baseline to last value as compared with only a slight mean increase of 0.5 g/dL in the placebo group and this difference between the treatment groups was statistically significant (p<0.001).
- Hematocrit levels rose a mean of 7.3% in the epoetin alfa group over the course of the study compared with a mean increase of 1.1% in the placebo group and this difference between the treatment groups was statistically significant (p<0.001).
- There was also a greater mean increase from baseline to last value in reticulocyte counts (manually or automatically assessed) for the epoetin alfa group (0.5%) compared with the

placebo group (0.1%) and this difference between the treatment groups was statistically significant (p=0.037).

- There were significantly (p<0.001) more responders (172/244(70.5%)) in the epoetin alfa group than in the placebo group (22/115(19.1%)).
- There were significantly (p<0.001) more correctors (165/244 (67.6%)) in the epoetin alfa group than in the placebo group (18/115(15.7%)).
- The SF-36 physical and mental component scales did not indicate any detrimental effects due to the administration of epoetin alfa on overall physical and mental quality of life with the mean change score for both scales favoring epoetin alfa but failing to reach statistical significance (p-values, adjusted for multiple comparisons: 0.0512 and 0.0952, respectively). Total FACT-G still favored epoetin alfa but was no longer statistically significant.

4. Study EOP-INT-2 (CC2574-P-467)

Epo-int-2 study was a placebo-controlled study on the effect of epoetin alfa in subjects with multiple myeloma followed by an open-label extension (protocol cc 2574-p-467 / epo-int-2; phase 3). Enrollment was restricted to at high risk subjects for the development of transfusion-dependent anemia, who had a low baseline hemoglobin value (<11 g/dL) and who were receiving chemotherapy starting at least six months previously.

The sample size of 134 was calculated based on two strata with a power of 80% at the 0.025 significance level (two-sided); subjects who received prestudy transfusions was taken to be 50% for the epoetin alfa-treated group and 90% for the placebo-treated group and the proportions in the stratum without prestudy transfusions was taken to be 5% for the epoetin alfa-treated group and 25% for the placebo-treated group.

One hundred forty-five subjects (69 in epoetin alfa and 76 in placebo) with multiple myeloma were enrolled into this study. Subjects were stratified into two groups depending on whether or not they received at least one blood transfusion within the previous three months.

The subjects were randomly assigned to receive 150 IU/kg epoetin alfa or placebo, s.c. three times weekly. If, after four weeks of therapy, a subject's hemoglobin level had increased by less than 1 g/dL above baseline, the dose was to be adjusted to 300 IU/kg three times weekly. Treatment was to continue for 12 weeks. Subjects (epoetin alfa-treated and placebo-treated) who completed this 12-week double-blind portion of the study were eligible to receive epoetin alfa for an additional 12 weeks in an open-label extension to the study.

The primary endpoint was the proportion of subjects transfused during months 2 or 3.
The secondary efficacy endpoints were the time to first transfusion after the first month on study, the cumulative on-study transfusion rates, changes in hemoglobin levels, hematocrit levels, reticulocyte counts, serum erythropoietin levels, and quality-of-life parameters.

The first patient was enrolled 2/17/1994 and the last patient was enrolled 5/20/1996.

Sponsor's Results:

- The proportion of subjects transfused during Months 2 or 3 was 14 out of 69 subjects (56.0%) in the epoetin alfa–treated group and 22 out of 76 subjects in the placebo-treated group (78.6%) (p=0.006). With efficacy population, 12 out of 66 subjects (52.2%) in the epoetin alfa–treated group and 16 out of 66 subjects in the placebo-treated group (72.7%) (p=0.028) were transfused during Months 2 or 3.
- After 12 weeks, the percentage (Kaplan-Meier estimates) of subjects who were not transfused was 50 out of 66 subjects (76%) in the epoetin alfa-treated group and 40 out of 66 subjects (61%) in the placebo-treated group (p=0.053) (efficacy population).
- The cumulative on-study transfusion rates were higher among placebo-treated subjects than among epoetin alfa-treated subjects, but the differences were not statistically significant. Among subjects who were transfusion independent at baseline, a mean of 1.09 units was transfused during the study among placebo-treated subjects compared with only 0.57 units among epoetin alfa-treated subjects (ITT). Among subjects who were transfusion dependent at baseline, a mean of 4.37 units was transfused during the study among placebo-treated subjects compared with 3.21 units among epoetin alfa-treated subjects (efficacy population).
- Hemoglobin levels rose a mean of 1.8 g/dL over the course of the double-blind phase of the study in the epoetin alfa-treated subjects, compared with no change in the placebo-treated subjects (p<0.001).
- Hematocrit levels rose a mean of 6.0 percentage points over the course of the double-blind phase of the study in the epoetin alfa-treated subjects, compared with essentially no change (0.2 percentage points) in the placebo-treated subjects (p<0.001).
- A increase in reticulocyte counts was 0.6 percentage points among epoetin alfa-treated subjects compared with 0.1 percentage points among placebo-treated subjects (p=0.025).
- The effect of epoetin alfa on hemoglobin levels was significantly more correctors (hemoglobin ≥12 g/dL reached) and responders unrelated to transfusions (≥2 g/dL hemoglobin change from baseline) in the epoetin alfa treated group than in the placebo-treated group (45.5% vs. 3.0% correctors, respectively, p<0.001; 57.6% vs. 9.1% responders, respectively, p<0.001), with a mean time to correction or response of approximately seven weeks in the epoetin alfa-treated group.
- No significant differences were observed between the two treatment groups with regard to Week 12 change in quality-of-life scores during the double-blind phase.

5. Study EPO-INT-3

Epo-int-3 study was a placebo-controlled study on the effect of epoetin alfa in patients with malignancy receiving chemotherapy (protocol cc-2574-p-034/epo-int-3; phase 3).

This was a multicenter, double-blind, placebo-controlled study conducted in four countries (Sweden, Norway, Denmark, and Iceland), followed by an open-label extension. Enrollment was restricted to high risk for the development of transfusion-dependent anemia subjects whose hemoglobin level had fallen substantially (≥1.5 g/dL) since the beginning of the current course of

chemotherapy or who had a baseline hemoglobin level (<12 g/dL) and who were predicted to receive chemotherapy for at least three more months.

The sample size of 167 subjects was calculated based on transfusion rates of 10% in the epoetin alfa-treated group and 27% in the placebo-treated group with a power of 80% at the 0.05 significance level and a treatment assignment of 2:1 ratio. The sample size was increased by 20% to a total of 201 subjects to accomplish the analysis for the evaluable subjects.

Two hundred one subjects (as planned) with various malignancies receiving chemotherapy were enrolled into the study. Subjects were randomly assigned in a 2:1 ratio to receive either 150 IU/kg epoetin alfa or placebo three times weekly. If, after four weeks of therapy, a subject's hemoglobin had increased by less than 1 g/dL above baseline, the dose was doubled to 300 IU/kg three times weekly. Treatment was to continue for 12 weeks. Subjects (epoetin alfa-treated and placebo-treated) who completed the 12-week double-blind portion of the study were eligible to receive epoetin alfa for an additional 12 weeks in an open-label extension to the study.

Among 201 subjects (enrolled at 28 sites in four countries), 136 subjects were randomly assigned to receive epoetin alfa and 65 subjects were randomly assigned to receive placebo. Twenty-eight subjects in the epoetin alfa group (21%) and eight subjects in the placebo group (12%) were not included in the efficacy population, either because they were treated for 28 days or less or because they did not receive chemotherapy. Overall, 80% of intent-to-treat subjects completed the double-blind phase of the study, 77% of subjects in the epoetin alfa group and 86% of subjects in the placebo group.

The primary efficacy endpoint was the proportion of subjects in the intent-to-treat population who were transfused during Months 2 or 3 of the double-blind phase of the study. The secondary efficacy endpoint was the proportion of subjects transfused analyzed for the efficacy population. Stratification factors were 1) non-platinum versus platinum chemotherapy, 2) tumor type (solid versus hematologic), and 3) subject pre-study transfusion-dependence.

The majority of subjects (80%) were enrolled in Sweden. The mean age was 58.3 years. Mean age was comparable in the epoetin alfa and placebo groups (58.7 and 57.3 years, respectively), but the median age was slightly higher in the epoetin alfa group (61.5 years) than in the placebo group (55.0 years). Most subjects (72%) were female. There were slightly more men in the epoetin alfa group than in the placebo group (30% versus 23%).

Twenty-eight (21%) of 136 subjects in the epoetin alfa group and 8 (12%) of 65 subjects in the placebo group were not evaluable for efficacy. Nineteen (14%) subjects in the epoetin alfa group and 6 (9%) subjects in the placebo group did not receive chemotherapy

The first patient was enrolled 2/08/1995 and the last patient was enrolled 12/01/1997, respectively.

Sponsor's Results and Conclusions:

- Significantly less (p=0.0018) epoetin alfa-treated subjects received transfusions during Months 2 or 3 compared with placebo-treated subjects (21 out of 136 subjects (15.4%) of epoetin alfa-treated and 23 out of 65 subjects (35.4%) of placebo-treated subjects).
- Among subjects who were transfusion-dependent at baseline, 6 out of 29 (20.7%) of epoetin alfa-treated subjects and 5 out of 9 (55.6%) of placebo-treated subjects remained transfusion-dependent during the trial.
- Four out of 79 (5.1%) from epoetin alfa-treated subjects and 14 out of 48 (29.2%) from placebo-treated subjects who were not transfusion dependent at baseline became transfusion-dependent during the trial.
- Among subjects who were receiving platinum containing chemotherapy, 3 out of 29 (10.3%) of epoetin alfa-treated subjects and 9 out of 15 (60.0%) of placebo-treated subjects required transfusions.
- Among those receiving non-platinum containing chemotherapy, 7 out of 79 (8.9%) of epoetin alfa-treated subjects versus 10 out of 42 (23.8%) of placebo-treated subjects required transfusions.
- In those solid tumor, 6 out of 68 (8.8%) of epoetin alfa-treated subjects versus 15 out of 37 (40.5%) of placebo-treated subjects required transfusions.
- In those with hematologic malignancies, 4 out of 40 (10.0%) of epoetin alfa-treated and 4 out of 20 (20.0%) of placebo-treated subjects required transfusions.
- The cumulative transfusion rate was defined as the number of units transfused during Months 2 and 3 of the double-blind phase (or to the end of the double-blind phase), excluding the first month. For all subjects who were transfused during Months 2 to 3, the median cumulative transfusion rate was 3.1 units in the epoetin alfa group and 3.3 units in the placebo group. For subjects who were transfusion dependent at baseline and who remained transfusion dependent on study, the median cumulative transfusion rates during Months 2 to 3 were 3.3 units for the epoetin alfa group and 5.3 units for the placebo group.
- The time to first transfusion requirement after Day 28 was significantly longer (p=0.0001) for subjects in the epoetin alfa group than for subjects in the placebo group.
- Pretransfusion hemoglobin values (ignoring hemoglobin values within 14 days after a transfusion) were defined as the hemoglobin value recorded immediately preceding a transfusion. The median transfusion-independent pretransfusion hemoglobin levels during Months 2 and 3 were similar in the two treatment groups (8.4 for 20 out of 108 epoetin alfa treated subjects and 8.2 for 22 out of 57 placebo treated subjects).
- There were significantly (p<0.001) more responders among epoetin alfa-treated subjects (76 out of 108 (70.4%)) than among placebo-treated subjects (11 out of 57 (19.3%)).
- There were significantly (p<0.001) more correctors among epoetin alfa-treated subjects (80 out of 108 (74.1%)) than among placebo-treated subjects (15 out of 57 (26.3%)).
- For quality-of-life assessments, subjects treated with epoetin alfa experienced a significant improvement in Fatigue while placebo-treated subjects experienced a significant decline in Physical Functioning, as measured by the respective scales of the EORTC-QLQ-C30 questionnaire. In between-group analysis, there was a significant decline in Physical Functioning in the placebo group compared with the epoetin alfa group.

6. Study EPO-J89-040

Study J89-040 was to evaluate the effect of subcutaneous epoetin alfa in patients with chronic lymphocytic leukemia: results from North America.

This was a Phase 3 multicenter study (50 study centers in North America) that consisted of two treatment phases: a 12-week randomized, double-blind, placebo-controlled phase, followed by a 12-week open-label phase. Approximately 216 CLL patients whose hematocrit was less than 32% were to be enrolled and randomly assigned to receive 150 IU/kg or a comparable volume of placebo three times weekly by subcutaneous injection for 12 weeks during the double-blind phase of the study, or until the patient's hematocrit reached the target of 38% to 40%. The study drug was blinded for identity during the double-blind phase, and the patients were randomized in a 2:1 fashion. Patients who completed the double-blind phase were eligible to enter the open-label phase, during which all patients received epoetin alfa at a dose titrated to maintain hematocrit within the target range of 38% to 40%.

A sample size of 216 patients for this study was calculated to be able to detect statistically significant differences in the various quality-of life parameters.

The primary efficacy endpoint was the percent change in hematocrit from baseline to the completion of the double-blind phase or to early withdrawal. Secondary evaluations included transfusion requirements (cumulative transfusion rate, the proportion of patients becoming transfusion-independent, and the proportion of patients transfused on-study), the proportion of patients achieving a hematocrit of 38% to 40% (correctors) at any time during the study (unrelated to transfusion), the proportion of patients achieving a six percentage point increase in hematocrit (responders) at any time during the study (unrelated to transfusion), and the change in quality-of-life parameters.

A total of 221 patients were enrolled in the study: 142 patients randomized to receive treatment with epoetin alfa and 79 patients randomized to receive placebo. In the epoetin alfa group, 25 (17.6%) patients discontinued therapy prematurely, and 117 (82.4%) patients completed the double-blind phase of the study. In the placebo group, 10 (12.7%) patients discontinued, and 69 (87.3%) patients completed the double-blind phase of the study. Twenty-six (18.3%) patients in the epoetin alfa group completed the double-blind phase of the study early by reaching the target hematocrit of 38% to 40%.

For the intent-to-treat group of patients, a comparison between the epoetin alfa treatment group and the placebo group showed that a majority of the patients were male (62% and 66%, respectively) and Caucasian (92% and 89%, respectively), and that the groups had a mean age of 68.3 years and 68.1 years, respectively.

In the epoetin alfa group, 25 (17.6%) patients discontinued therapy prematurely, and 117 (82.4%) patients completed the double-blind phase of the study. In the placebo group, 10 (12.7%) patients discontinued, and 69 (87.3%) patients completed the double-blind phase of the study.

Among subjects who were randomly assigned to treatment and received at least 15 days of therapy with epoetin alfa were 137 patients and there were 78 patients in placebo. The second efficacy subpopulation consisted of those patients (a total of 164) who were randomized to treatment and received at least 71 days of therapy with epoetin alfa were 95 patients and there were 69 patients in placebo.

The sponsor did not provide appendices which include study protocol in the submission. The first patient was enrolled 11/5/1990 and the last patient was enrolled 11/5/199, respectively.

Sponsor's Results:

- The change in hematocrit was significantly different between the two treatment groups, 6.16% for epoetin alfa and 2.07% for placebo (n=221, p=0.0001, ITT) and within two classifications of baseline chemotherapy usage. Treatment mean differences were significant for patients in the cytotoxic chemotherapy without fludarabine subgroup (7.4% points epoetin alfa versus 0.7% points placebo, p=0.0001) and at the level of no cytotoxic chemotherapy (5.8% points epoetin alfa versus 1.7% points placebo, p=0.017), but not for fludarabine chemotherapy (5.2% points epoetin alfa versus 3.7% points placebo, p=0.337).
- There was no significant difference in the mean units of blood transfused between the epoetin alfa group (9.6 units) and the placebo group (11.0 units) for the on-study (Day 1 through Day 84) cumulative transfusion rate.
- There was no significant difference in the number of patients transfused on-study (65 out of 142 subjects (45.8%) in the epoetin alfa group, 47 out of 79 subjects (59.5%) in the placebo group; p=0.068).
- The mean cumulative transfusion rates were lower in the epoetin alfa group (a mean rate of 3.02) as compared to the placebo group (a mean rate of 5.29 transfusions) and the difference between the two treatment groups was not significant overall (p=0.24).
- Seventy-five (54.7%) patients in the epoetin alfa group and 33 (42.3%) patients in the placebo group were not transfused during baseline. A comparison of the on-study cumulative transfusion rate among patients who were not transfused during baseline showed no significant difference in the mean units.
- Sixty-seven out of 142 (47.2%) patients in the epoetin alfa group and 13 out of 79 (16.5%) patients in the placebo group responded to treatment with a hematocrit increase of at least six percentage points, unrelated to transfusion.
- Forty-six out of 142 (32.4%) patients in the epoetin alfa group and six out of 79 (7.6%) patients in the placebo group achieved a hematocrit of at least 38%, unrelated to transfusion.
- Overall, a modest treatment effect of epoetin alfa on quality-of-life variables was observed among CLL patients with anemia, particularly among patients who did not receive fludarabine. For the total cohort, seven of the 13 mean quality-of-life change scale scores showed a statistically significant increase ($p<0.05$) at Week 12 within the epoetin alfa group, while only one quality-of-life scale increased significantly within the placebo group.

7. Study Non-Cisplatin (I88-037, OEO-U22, OEO-U23)

This was a multicenter, double-blind, parallel group, placebo-controlled, randomized study of the safety and efficacy of subcutaneous administration of epoetin alfa in the treatment of anemia secondary to advanced cancer and aggressive cyclic chemotherapy. A total of 157 subjects were enrolled in the three studies and 81 received epoetin alfa and 76 received placebo. Four patients (two epoetin alfa and two placebo) who were on therapy less than 15 days were excluded in the efficacy analyses. All patients were evaluable for safety.

Thirty one patients (18 epoetin alfa. 13 placebo) discontinued double-blind treatment prematurely and the reason for discontinuation were as follows: adverse experiences (11), death (3), Disease progression (7), protocol violation (4), physician/sponsor decision (three) and personal reasons (three).

The planned sample size was 72 patients (36 each) based on 5.8 to 2.8 units of a reduction in the mean number of unit blood transfused with a 80% power and 5% significance level (2-sided). A total of 72 patients were enrolled in the three protocols. Thirty five patients received epoetin alfa and 37 received placebo.

The efficacy endpoints are increase in hematocrit, achievement of the target hematocrit (38%) unrelated to transfusion. Increase in hematocrit of ≥ six percentage points unrelated to a transfusion. Change in quality of life score from baseline to last value. Better rating on Physicians Global Evaluation of Study Medication and improvement in Energy Level in those patients reaching a hematocrit of ≥ 38%.

A majority of patients enrolled were female (60.5%) and 87.9% were Caucasian and the mean age was 62.5 years.

The first patient was enrolled 10/31/1988 and the last patient was enrolled 3/15/1990, respectively, for Study I88-037. The first patient was enrolled 11/22/1988 and the last patient was enrolled 10/4/1989, respectively, for Study OEO-U22 and the first patient was enrolled 5/03/1989 and the last patient was enrolled 3/30/1990 for Study OEO-U23, respectively.

Sponsor's Results:

- There was statistically significant ($p<0.05$) hematocrit increase from baseline for epoetin alfa-treated patients as compared to placebo-treated patients with mean increase of 6.9 % (28.6% from baseline to maximum mean value of 35.0% by Week 12) in the epoetin alfa group and mean increase of 1.1% (29.4% from baseline to maximum mean value of 30.4% by Week 12 of treatment) in the placebo group.
- Thirty-two (40.5%) of the 79 epoetin alfa treated patients versus 3 (4.1%) of the 74 placebo-treated patients reached the target hematocrit of ≥ 38% unrelated to transfusion ($p<0.05$).
- There were 46 (58.2%) out of 79 patients who responded to therapy with greater than or equal to a six percentage point increase in hematocrit unrelated to transfusion in the epoetin alfa-treated group and 10 (13.5%) out of 74 patients in the placebo group ($p<0.01$).

- There was no statistically significant (p=0.083) difference in overall quality of life measure changes from baseline between the two groups with 5.68 change in the epoetin alfa group (n=63) and -1.1 change in the placebo group (n=61).
- There was a statistically significant difference in (p<0.05) Physicians' Global Evaluation, with 44 (57.9%) out of 76 from the epoetin alfa treated patients rated as having good, very good, or excellent responses versus 24 (32.9%) out of 73 placebo-treated patients.
- There was no statistically significant difference in mean transfusion rates at baseline (2.34 and 2.11, for epoetin alfa and placebo, respectively) or on-study (3.88 and 4.15, for epoetin alfa and placebo, respectively) between the two groups (p>0.05).
- There was no statistically significant difference (p>0.05) in the proportion of patients transfused on study between the two groups with 32 transfused patients out of 79 (40.5%) epoetin alfa treated patients and 36 transfused patients out of 74 (48.65) placebo treated patients. The number of patients transfused study months 2 and 3 was 20 out of 70 (28.6%) in the epoetin alfa group and 25 out of 68 in the placebo group (p=0.0561).

8. Study PR98-27-008 (NCCTG-97-92-53)

Study PR98-27-008 is a phase 3 randomized double-blind study of epoetin alfa versus placebo in anemic patients with cancer undergoing chemotherapy. This was a multicenter, randomized, double-blind, placebo-controlled, study conducted at NCCTG centers in the North Central United States and Saskatchewan, Canada. Three hundred thirty subjects with anemia who were receiving myelosuppressive, cytotoxic chemotherapy for advanced cancer were to be enrolled. Eligible patients were randomized in a 1:1 ratio to epoetin alfa or placebo treatment. Stratification factors were center (investigator), type of primary cancer (lung, breast, or other), planned concurrent radiation therapy (yes or no), and degree of anemia (hemoglobin <9 g/dL or ≥9 g/dL) using the dynamic allocation procedure of Pocock and Simon.

The double-blind treatment was administered for a maximum of 16 weeks, after which the subjects were followed for one year from the time of randomization for event monitoring (death, new primary malignancies, and long-term toxicities).

The dose of double-blind study medication (40,000 IU of epoetin alfa or corresponding placebo) was to be administered by s.c. injection, once weekly. If after 4 weeks of therapy hemoglobin concentrations had not increased by >1g/dL or if the subject had received a transfusion during the first 4 weeks of therapy, the weekly dose of study drug was to be increased to 60,000 IU once weekly. If, at any time during the study, the hemoglobin concentration exceeded 15 g/dL, the hemoglobin concentration was to be determined 1 week later. If the hemoglobin concentration exceeded 15 g/dL, study drug was to be withheld and the hemoglobin concentration was to be determined weekly until it fell below 13 g/dL. Study drug was then to be restarted at a dose level 25% less than that previously administered.

The planned sample size was 300 subjects based on difference between the QoL tests as measured by the 2-sided t-tests with a 5% type I error rate. This provided to have a 80% power to detect a difference of 0.33 standard deviations between the epoetin alfa group and the placebo group average scores.

The primary efficacy endpoint was the percentage of subjects in the ITT population who were transfused after Day 28 (i.e., from Day 29 to end of study), using the imputation that subjects who withdrew from the study after Day 28, with no transfusion after Day 28, would be assumed to be transfused for purposes of analysis.

The secondary endpoints were the change in hemoglobin concentrations from baseline, hemoglobin over time, incidence of hemoglobin concentrations below 9.0 g/dL, number of transfusion units per day alive in the study, prediction of response to epoetin alfa treatment, incidence of nephrotoxicity, tumor response, and quality of life.

The safety and efficacy data of this study were monitored by a Data Monitoring Committee (DMC) with an interim analysis performed every six months. The interim analyses included looking at differences in changes in QOL, overall survival, and toxicity. The study used a conservative interim bound of 0.001 for the p-value without adjustment in the overall experimental Type I error rate.

A total of 344 subjects (ITT population-174 in the epoetin alfa arm and 170 in the placebo arm) were registered and randomized into the study at 14 NCCTG study centers (13 in the United States and 1 in Canada). The first subject was enrolled on December 4, 1998, and the study was closed to further enrollment on September 28, 2001.

The mean age was 63.6 years, and mean weight was 74.3 kg. Slightly more women (56%) than men (44%) were enrolled, and the majority (92%) of the subjects were white non-Hispanic. Overall, 183 (53%) of the subjects had received previous chemotherapy and 127 (37%) had received previous radiotherapy. The baseline tumor response was "stable" for 186 (54%) of the subjects. Sixty-nine percent of the subjects had mild anemia (hemoglobin ≥9 g/dL) rather than severe anemia (hemoglobin <9 g/dL). Overall, 28% of the subjects had lung malignancies, 16% had breast malignancies, and 56% had "other" malignancies.

The first patient was enrolled 1/08/1999 and the last patient was enrolled 9/27/2001, respectively.

Sponsor's Results:

- The primary efficacy endpoint of percentage of subjects who received any RBC transfusion after Day 28 (i.e., from Day 29 to end of study) was 49.4% (84 out of 170) in the placebo group and 39.7% (69 out of 174) in the epoetin alfa group based on a crude transfusion rates. There was no statistically significant difference between the two groups (p=0.0687, logistic regression). With the last observation carried forward methods, the transfusion rates were 28.2% (48 out of 170) in the placebo group and 14.4% (25 out of 174) in the epoetin alfa group and there was statistically significant difference between the two groups (p=0.0017, logistic regression).
- The time to first transfusion after Day 28 was also significantly delayed in the epoetin alfa group compared to the placebo group (p=0.0016, log rank test) with 32.7% Kaplan-Meier estimates of transfusion rates in the placebo group versus 16.3% in the epoetin alfa group.

- The mean number of cumulative RBC units transfused per subject in the placebo group was 1.5 units versus 0.7 units in the epoetin alfa group. Adjusted for each subject's time on study, the mean number of RBC units transfused per 100 subject-days was significantly higher in the placebo group compared to the epoetin alfa group (1.54 vs. 0.76, $p<0.0001$).
- The mean change in hemoglobin from baseline was 0.9 g/dL in the placebo group (n=164) and 2.8 g/dL in the epoetin alfa group (n=166) and the difference between the two groups was statistically significant ($p<0.0001$). The study days on which the last hemoglobin value was obtained were similar in the two groups, with the mean study day being Day 91.8 in the placebo group and Day 91.9 in the epoetin alfa group.
- The rate of hemoglobin increase (the slope estimate) was 0.064 g/dL per week in the placebo group as compared to 0.201 g/dL per week in the epoetin alfa group. The difference between the two groups was highly significant ($p<0.0001$).
- After Cycle 1, 29.5% (44 out of 149) of subjects treated with placebo had hemoglobin values of <9 g/dL compared to 11.1% (17 out of 153) of subjects treated with epoetin-alfa ($p= <0.0001$).
- The survival curves were similar with 119 deaths in the placebo arm and 121 deaths in the epoetin alfa arm, with median survival times of 10.4 months (where 1 month = 30.44 days) in the placebo arm and 10.2 months in the epoetin alfa arm. The difference between the two groups was not statistically significant (HR=1.16 (95% CI; 0.90, 1.50), $p>0.1$ by the log rank test).
- At study completion, 47 subjects (28%) in the placebo group and 41 subjects (24%) in the epoetin alfa group had a complete or partial response, or tumor regression
- The statistical analysis of the FACT-An Fatigue subscale (i.e., the QoL scale specified in the SAP as the primary QoL analysis) failed to show a statistically significant difference between the two treatment groups.

9. Study EPO-CAN-15

This study was designed as a Phase III, randomized, double-blind, placebo controlled, multi-centre study. Eligible limited disease small cell lung cancer (LD SCLC) patients who were scheduled to receive a chemotherapy regimen containing a platinum based agent plus etoposide (plus possible additional non-investigational chemotherapeutic agents), together with concurrent thoracic radiotherapy, were randomly assigned with 1:1 ratio to epoetin alfa 40,000 IU once weekly (qw) or placebo to match qw. The study was designed to maintain subjects in the epoetin alfa treatment group at a hemoglobin level of between 14 g/dL and 16 g/dL.

Following randomization, and at the time the hemoglobin level was ≤14 g/dL, epoetin alfa or placebo was to be administered once a week for the duration of the chemotherapy regimen and was planned to be continued until the last week of the final chemotherapy cycle, or through to the completion of PCI for those subjects who receive PCI treatment, whichever was later. Both groups could receive blood transfusions when deemed clinically necessary.

This study design was overlapped two phases. The first phase was a Double-Blind Phase, which consisted of the period of time necessary to record 480 primary efficacy events defined by statistical requirements (i.e. primary events defined as disease progression or death) followed by

a Long-Term Survival Follow-up Phase, which was designed to capture the extended long-term survival status follow-up of subjects spanning up to 5 years from the time of randomization.

The planned sample size was to enroll 620 subjects, with 310 subjects per treatment group randomized in a 1:1 ratio. With 620 subjects, the specified enrollment rate and length of follow-up, and the assumed median survival times of 16 and 21 months for the placebo and epoetin alfa groups (85% power at α=0.025 (one-sided), respectively), approximately 435 deaths in total were calculated at the end of the double-blind phase. In this case, a power of 80% with a 2-sided type I error rate of 0.05 would be achieved for analysis of the overall survival.

One interim analysis to test efficacy was planned 6 months after randomization of the 310 th subject. The study terminated after only 104 subjects randomized on trial (52 subjects per group). Subjects with a confirmed diagnosis of LD SCLC who were scheduled to start a four to six cycle of platinum based, plus etoposide chemotherapy with concurrent radiotherapy were considered for participation in the study. Additional non-investigational chemotherapy agents, as per the centre's normal practice were allowable.

The mean age was 60.50 years in the epoetin alfa group and 61.28 years in the placebo group. There were more male patients (32 out of 52 (61.5%) from epoetin alfa and 28 out of 52 (53.8%) from placebo. The majority were Caucasian (88.5% from epoetin alfa and 96.2% from placebo).

The first patient and the last patient were randomized on August 22, 2001 and September 29, 2003, respectively.

Sponsor's results:

- At the end of the final cycle, the overall tumor response rate among 39 available subjects was 82.1% (32 subjects) in the epoetin alfa group (30.8% complete response and 51.3% partial response). The overall tumor response rate was 72.5% (29 subjects) (30.0% complete response and 42.5% partial response) among 40 available subjects in the placebo group.
- There was no significant difference in the Kaplan-Meier estimates of the time to disease progression (TTP) between the treatment groups based on a Log-Rank test for equality over treatment strata for all subjects (P=0.633). Median TTP in the epoetin alfa group was 15.8 months (95% CI: 11.3, 28.0) and 16.5 months (95% CI: 14.6, 23.3) in the placebo group. The hazard ratio for TTP in the epoetin alfa group relative to the placebo group was not significant [HR 1.13, 95% CI: 0.68, 1.88 (P=0.634)].
- At the cutoff date of May 2005, there were 57 deaths reported overall from the last subject follow-up: 28 deaths (53.8%) in the epoetin alfa group and 29 deaths (55.7%) in the placebo group. The majority (75% of the deaths (21) in the epoetin alfa arm and 86% of the deaths (25) in the placebo arm) of these subjects in both treatment groups, died due to disease progression. Median OS were 23.5 months (95% CI: 13.6, NE) in the epoetin alfa group and 24.0 months (95% CI: 17.3, 30.7) in the placebo group (P=0.644). The hazards ratio for OS in the epoetin alfa group relative to the placebo group was not significant [HR 1.13, 95% CI: 0.67, 1.90 (P=0.645)].

- No definitive relationship between hemoglobin variables (i.e. Hgb at the time of study drug initiation, Hgb over time) and the development of TVEs was observed.
- The number of RBC transfused during the course of study was 9 subjects (17.3%) in the epoetin alfa group and 27 subjects (51.9%) in the placebo group and there was statistically significant difference between the two groups ($p<0.0001$). Mean number of units were 2.38 units for the epoetin alfa group and 5.26 units for the placebo group.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Dr. Kyung Yul Lee Kyung Yul Lee
Date: 10/16/2008

Concurring Reviewer(s):

Statistical Team Leader: Dr. Mark Rothmann Mark Rothmann
10/16/2008

Biometrics Division Director: Dr. Aloka Chakravarty Aloka Chakravarty
10/16/08

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HFD-711/ Dr. Rothmann
HFD-711/ Dr. Lee
HFD-711/ Dr. Chakravarty
HFD-711/ Dr. Shen
HFD-700/ Ms. Patrician
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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	
◻ Clinical pharmacology [includes immunogenicity]	Y N	
◻ Clinical Efficacy [for each indication]	Y N	
◻ Clinical Safety	Y N	
◻ 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	
◻ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y N	
◻ Pharmacokinetics (PK)	Y N	
◻ Pharmacodynamic (PD)	Y N	
◻ Efficacy and Safety	Y N	
◻ Postmarketing experience	Y N	
◻ Case report forms	Y N	
◻ Individual patient listings (indexed by study)	Y N	
o electronic datasets (e.g. SAS)	Y N	
Literature references and copies [5.4]	Y N	

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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 ◻ protocols for clinical trials present ◻ all electronic submission components usable	Y N Y N Y N	
statement for each clinical investigation: ◻ conducted in compliance with IRB requirements ◻ conducted in compliance with requirements for informed consent	 Y N Y N	
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	
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	
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	
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	
drug interaction studies communicated as during IND review as necessary are included	Y N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y N	
comprehensive analysis of safety data from all current world-wide knowledge of product	Y N	

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Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	Y N	
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	
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	
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?	
CC 2574-PI	Y N	Y N NR	Y N	Y N NR	
epo-CAN-15	Y N	Y N NR	Y N	Y N NR	
epo-INT-1	Y N	Y N NR	Y N	Y N NR	
epo-INT-2	Y N	Y N NR	Y N	Y N NR	
epo-INT-3	Y N	Y N NR	Y N	Y N NR	
epo-INT-10	Y N	Y N NR	Y N	Y N NR	
epo-INT-26	Y N	Y N NR	Y N	Y N NR	individual data set
i88-036-MR 92013	Y N	Y N NR	Y N	Y N NR	→ No protocol
i88-038-MR 92014	Y N	Y N NR	Y N	Y N NR	→ No protocol
i88-040	Y N	Y N NR	Y N	Y N NR	

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

i93-004 Y Y

PR-27-008 Y Y

No raw data

No individual data

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 are no SAS programs and no raw data

Study 188-036-MR92013 } → No protocols
" MR92014 }

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

Is an Advisory Committee needed?

Recommendation (circle one): File RTF

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

Reviewer: Kyung Yul Lee 2/11/08 Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)

Concurrence:

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