

FDA Briefing Document

May 4, 2004

Oncologic Drugs Advisory Committee

Safety Concerns Associated with Aranesp (darbepoetin alfa) Amgen, Inc. and Procrit (epoetin alfa) Ortho Biotech, L.P., for the Treatment of Anemia Associated with Cancer Chemotherapy

Prepared by

Harvey Luksenburg, M.D. Medical Reviewer,
Division of Therapeutic Biological Oncology Products, ODE 6/OND/CDER

Andrea Weir, Ph.D.
Division of Therapeutic Biological Oncology Products, ODE 6/OND/CDER

Ruth Wager, Ph.D., CMC Reviewer
Division of Therapeutic Proteins, OBP/OPS/CDER
Table of Contents

4037 B2 - 04 - FDA - ARANESP - PROCIT

TABLE OF CONTENTS

I. EXECUTIVE SUMMARY	Error! Bookmark not defined.
II. Erythropoietin Biology and Mechanism of Action.....	6
III. Preclinical Evidence for a Role of Erythropoietins in Tumor Progression	7
In Vitro Findings.....	7
In Vivo Findings	9
Conclusions.....	9
IV. Clinical Studies of Epogen/Procrit for the Treatment of the Anemia due to Chronic Renal Failure.....	10
Treatment of Anemia Due to Chronic Renal Failure in Patients Undergoing Dialysis	10
Treatment of Anemia Due to Chronic Renal Failure in Patients not undergoing Dialysis	11
Safety Analyses.....	12
V. The Normal Hematocrit Study of Epogen/Procrit in Patients with Chronic Renal Failure and Underlying Cardiovascular Disease.....	12
Safety Results.....	13
VI. Clinical Studies of Aranesp® (darbepoetin alfa) for the Treatment of the Anemia due to Chronic Renal Failure	14
Studies In Erythropoietin-Naïve Patients.....	15
Studies In Patients Previously Stable on Erythropoietin	15
Safety Analyses: Relation between adverse events, hemoglobin, and hemoglobin rate of rise	16
VII. Clinical Studies of Epogen/Procrit for the Treatment of the Anemia Associated with Chemotherapy of Cancer.	25
Efficacy Results	25
VIII. Post-Marketing Study to Assess for Tumor Stimulatory effects of Epogen/Procrit: Study N93-004	26
Efficacy Results	27
Safety Results.....	27
IX. Clinical Studies of Weekly Dosage Schedules of Epogen/Procrit for Treatment of Anemia Associated with Cancer Chemotherapy	30
X. Clinical Studies of Aranesp in the Treatment of the Anemia of Cancer Chemotherapy	30
Efficacy Results	31
Safety analyses.....	32
XI. Study EPO-INT-76: The Breast Cancer Erythropoietin Trial (BEST).....	38
Efficacy and Safety Results	39
Intent-to-treat	42
XII. The Henke Study.....	43
Efficacy Results	46
Safety Findings	48
Conclusions.....	48
XIII. Procrit Trials Halted by Johnson & Johnson For Excessive Thrombotic and Cardiovascular Adverse Events:	49

1. Protocol EPO-CAN-15: "A randomized, double-blind placebo controlled study to evaluate the impact of maintaining haemoglobin levels using EPREX (Epoetin alfa) in limited disease small cell lung cancer (LD SCLC) patients receiving combined chemotherapy and radiation therapy." (The LEGACY Trial)	49
2. Study PR00-03-006: "A double-blind, randomized, placebo controlled study of the efficacy and safety of epoetin alfa administered weekly in patients with gastric or rectal cancers undergoing preoperative chemoradiation followed by surgery."	53
3. Study GOG-191 (PR01-04-005): "A phase III trial to evaluate the efficacy of maintaining Hgb levels above 120 g/l with erythropoietin versus above 100 g/l without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer."	54
XIV. Additional Randomized, Controlled Trials Terminated Prematurely (not at request of Johnson & Johnson)	57
1. Protocol CAN-20: "A randomized trial of epoetin alfa in patients with advanced non-small cell carcinoma of the lung."	57
2. Rosenzweig Study: "Increased thrombotic events in a clinical trial of erythropoietin in metastatic breast cancer."	60
3. RTOG 99-03: "A randomized phase III trial to assess the effect of erythropoietin on local-regional control in anemic patients treated with radiotherapy for carcinoma of the head and neck."	61
XV. Summary/Conclusions	62

I. EXECUTIVE SUMMARY

There are two erythropoietin products currently approved in the U.S. The first approved agent was epoetin alfa, which is manufactured, distributed and marketed by Amgen, Inc. under the proprietary name EPOGEN. The same epoetin alfa product, manufactured by Amgen, Inc., is also marketed and distributed by Ortho Biotech, L.P., a subsidiary of Johnson & Johnson, under the proprietary name PROCRIT. EPOGEN/PROCRIT was licensed in June 1989, with the following indication: "treatment of anemia associated with chronic renal failure, including patients on dialysis (end stage renal disease) and patients not on dialysis." Under a contractual agreement, Ortho Biotech LP has rights to development and marketing of Procrit for any indication other than for the treatment of anemia associated with chronic renal failure. Epogen and Procrit have identical labeling information for all approved indications based on development programs conducted by Amgen or Ortho Biotech. Labeling was expanded in April 1993 to include a supplemental indication for the treatment of anemia associated with cancer chemotherapy.

The second product was darbepoetin alfa, which is manufactured and distributed by Amgen, Inc., under the proprietary name Aranesp. Aranesp was licensed in September 2001 with the following indication: "for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis". Labeling was expanded in July 2002 to include a supplemental indication for the treatment of anemia associated with cancer chemotherapy.

In this briefing document, FDA provides an overview of the pharmacologic effects of erythropoietin, a summary of the data on erythropoietin receptor distribution in normal and malignant tissues, an overview of relevant non-clinical (animal and laboratory) data suggesting a role for erythropoietin in tumor stimulation, and a summary the design and results of studies that supported the approvals of Epogen/Procrit and Aranesp for the indications of treatment of the anemia of renal failure and of anemia associated with cancer chemotherapy, as well as other selected relevant studies provided to the FDA, will be presented. The extent of the information on associations between Epogen/Procrit or Aranesp and the risks of thrombotic events, tumor progression and survival are noted in these summaries. The results of the BEST (INT-76) and Henke studies will also be summarized.

Evidence of an increased risk of thrombotic events associated with use of exogenous erythropoietin was noted in the trials that supported the original approval of Epogen/Procrit. Excessive or poorly-controlled pharmacodynamic effects of erythropoietins have the potential to precipitate cardiovascular adverse events (AEs), some severe or catastrophic. These events are thought to have, as their basis, alterations in rheologic and/or hemodynamic factors related to increasing erythropoiesis, and include accelerated hypertension, congestive heart failure, pulmonary edema, ischemic events (stroke, transient ischemic attack [TIA], acute myocardial infarction [MI], thrombosis of vascular access [TVA], peripheral ischemia/gangrene), and seizures. However, evidence

for an increased risk of fatal cardiovascular events and impaired survival associated with the administration of exogenous erythropoietin products according to a specific treatment strategy (i.e., targeting of higher hemoglobin levels than required for avoidance of transfusion) came several years after the original approval of Epogen/Procrit. As a result of the "Normal Hematocrit Study", the labeling of Epogen/Procrit was modified to include warnings regarding this increased risk and association with this treatment strategy. The labeling for Aranesp carries similar warning statements.

Impaired survival and evidence of possible tumor stimulation associated with erythropoietin products has been observed in the BEST Study (EPO-INT-76) and the study by Henke, et al, published in the Lancet in October 2003. These two studies are large, multicenter, randomized, placebo-controlled studies whose purposes were to assess the impact of supplemental erythropoietin use on survival and tumor outcomes. It is notable that these trials are larger than any conducted

The data from these two studies may not be applicable to the U.S. licensed products. Both the BEST and the Henke studies used erythropoietin products that are not available in the U.S. and both studies used treatment strategies (high target hemoglobin) that are not recommended in labeling for either Epogen/Procrit or Aranesp. However, the biochemical differences between various erythropoietin products are not associated with marked differences in the pharmacodynamic properties of the different products when used at recommended doses, thus effects observed with these non-US-licensed products may be also be associated with the U.S. licensed product. Furthermore, the presence of erythropoietin receptors on tumor and tumor vasculature and the stimulatory effect of erythropoietins on certain tumor lines suggest a plausible reason for concern. In addition, while the treatment strategies used in the BEST and Henke trials are not consistent with current labeling for the U.S. licensed products, the studies used to support labeling for treatment of anemia associated with cancer for Epogen/Procrit or Aranesp are smaller and were not of adequate design to rule out the potential for tumor stimulation or a survival decrement of a specific magnitude.

Data from non-clinical and clinical studies provide a sound basis for FDA's request for additional clinical studies to assess the safety and optimal manner for administration of erythropoietin to patients with cancer. Erythropoietin products are used as an alternative form of supportive care. In clinical studies in anemic cancer patients, treatment with an erythropoietin product can reduce the proportion of patients who receive red blood cell transfusions by approximately 35-50%, beginning about one month after initiation of treatment. It should be noted that claims of improvement in quality of life are not been supported by data submitted to the FDA and there is insufficient evidence to support such a claim from literature reports due to the lack of adequate and well-controlled trials. In discussion with both firms, FDA has requested and both firms have agreed to conduct adequately designed trials that will assess whether, when administered in accordance with current labeling, there is evidence of tumor stimulation or impairment in survival (due to tumor stimulation, thrombotic events, or any cause) with Epogen/Procrit or Aranesp. Amgen, Inc. and Ortho Biotech LP will present their proposed approach for addressing these concerns. The approach consists primarily of randomized, placebo-controlled

trials, potentially supplemented by additional preclinical studies. The FDA requests that the advisory committee comment on the adequacy of the proposed approach, in particular with regard to following:

- Study population, e.g., those with primary tumors where erythropoietin receptors (EPOr) are commonly present on tumor, EPOr commonly present and are shown to be functional, and EPOr not commonly present or when present are ordinarily not functional (to assess for effect mediated through angiogenesis rather than direct tumor stimulatory effect)
- Magnitude of decrement in time-to-progression and/or survival that studies should be powered to detect.
- Replication of results/number of different primary tumors that should be evaluated.

I. Erythropoietin Biology and Mechanism of Action

Erythropoietin is a glycoprotein whose main function is to stimulate the proliferation and differentiation of erythroid precursors in the bone marrow.^{1,2} Erythropoietin is a 165 amino acid monomeric polypeptide³ containing two intramolecular disulfide bonds. The primary sequence encodes one consensus O-linked glycosylation site, and three N-linked consensus glycosylation sites. The primary sequence of Darbepoetin alfa, an erythropoietin analog, contains two additional N-linked glycosylation sites resulting from amino acid substitutions in the peptide backbone. These additional oligosaccharide side chains increase the molecular weight of the protein from approximately 30 kDa to 37 kDa. Darbepoetin has a three-fold longer terminal half-life than erythropoietin alfa⁴, and a five-fold lower affinity for erythropoietin receptors. In addition to proliferation and differentiation of erythroid precursors, erythropoietin has also been shown to be an erythrocyte survival factor, by modulating pro- and anti-apoptotic mechanisms, and a pro-angiogenic factor⁵. Studies show erythropoietin stimulates the proliferation and migration of endothelial cells *in vitro*, and stimulates the expression of other angiogenic growth factors, namely Vascular Endothelial Growth Factor (VEGF) and Placental Growth Factor (PlGF)⁶.

Erythropoietin is produced mainly in the kidneys, though several other tissues produce lesser amounts of the growth factor^{1,2}. Erythropoietin transcription and the protein's release into the bloodstream are both induced by hypoxic conditions^{1,2}. The erythropoietin gene contains a hypoxia-responsive element. Hypoxia-inducible factor-1 (HIF-1), a transcription factor, is activated when cells are exposed to hypoxia. HIF-1 then binds the hypoxia-responsive element and up-regulates erythropoietin gene expression⁷.

There are two types of erythropoietin receptors, high affinity receptors, expressed predominantly on hematopoietic cells, with KDs of approximately 95 pM, and low affinity receptors expressed on non-hematopoietic cells, with binding affinities of approximately 16 nM. The binding affinity of an erythropoietin ligand for the

erythropoietin receptor is not only influenced by the type of receptor alone, but also by tissue-dependent receptor numbers and accessory proteins⁸. Normal non-hematopoietic cells expressing the erythropoietin receptor include those of the female reproductive tract (placental trophoblasts, cervical squamous epithelium, uterine glandular epithelium and endometrium, ovarian follicles)^{9,10,11,12}, breast (mammary epithelium)¹³, prostate (epithelium)¹⁴, vasculature (endothelium)¹⁵, nervous system (neurons, astrocytes, oligodendrocytes, microglia)^{16,17,18}, pancreas (islet cells)¹⁹, and kidney (cortex, medulla, papilla)²⁰. While the role of erythropoietin in nonhematopoietic tissues is not completely understood, the erythropoietin receptors expressed on these tissues are functional.

Upon ligand binding, the erythropoietin receptor dimerizes and triggers a variety of responses via several signaling pathways²¹. These pathways include proteins with a variety of functions, including transcription activators, protein kinases and phosphatases, nucleotide exchange factors, phospholipid modifying enzymes, and adaptor proteins. Activation of these pathways results in DNA synthesis, cell differentiation, and cell proliferation. The erythropoietin receptor activates signaling molecules common to several other growth factor receptors²¹. These signaling molecules include Jak2-STAT5²², Ras-MAP kinase²³, and PI3-kinase²⁴. Erythropoietin receptor signaling results in the down-regulation of several pro-apoptotic proteins (Fas-ligand²⁵, TRAIL²⁵, and BAD²⁶), and the up-regulation and activation of anti-apoptotic proteins (Bcl-X_L and Bcl-2)^{6,21}. No functional differences between high and low affinity receptors, in terms of downstream activities, have been elucidated. Ligand binding to either class of receptor results in cell proliferation and/or cell survival under hypoxic conditions.²⁷

In addition, the erythropoietin receptor associates with other receptors, namely the GM-CSF/IL-3/IL-5 β common chain²⁸ and c-Kit^{29,30}, the receptor for Stem Cell Factor. It is possible that erythropoietin influences a variety of cell types through this mechanism.

II. Preclinical Evidence for a Role of Erythropoietins in Tumor Progression

In Vitro Findings

A substantial body of preclinical studies demonstrates that erythropoietin receptors are present on a variety of malignant cell lines^{6,10,20,31,32,33} as well as on primary tumor cells. Primary tumor cells have been shown to respond to erythropoietin administration by proliferating and forming vasculature^{20,34,35,36}. This information, coupled with the knowledge that erythropoietin elicits anti-apoptotic effects in stem cells, and together with the results of recent clinical studies mandates the investigation of the potential role of erythropoietin in tumor progression.

Erythropoietin receptors are expressed on some primary tumor cells, but not on all. For example, neuroblastomas⁶, Ewing's sarcomas⁶, hepatoblastomas⁶, Wilm's tumors⁶, brain tumors⁶, cervical carcinomas¹⁰, mammary adenocarcinomas³³, renal carcinomas²⁰, acute monoblastic leukemia³¹, gastric carcinomas³⁴, and endometrial³⁵, cervical¹⁰, and ovarian³⁵ adenocarcinomas all have been demonstrated to express erythropoietin receptors. However, not all tumors of the same type from the same tissue of origin express

erythropoietin receptors at similar levels. The presence and levels of erythropoietin receptors may vary from patient to patient. Arcasoy, *et al.*³³ examined 26 mammary tumor biopsies. Although ninety percent of these tissue samples expressed detectable levels of erythropoietin receptors, the remainder did not.

Interestingly and importantly, erythropoietin receptor expression on primary tumors often directly correlates with disease staging^{10, 37}, which may reflect the level of hypoxic stress in more advanced and aggressive tumor masses. Thus, under these conditions, increased erythropoietin binding and signaling activity may facilitate tumor survival by initiating the increased expression of anti-apoptotic genes and the down-regulation of pro-apoptotic genes, in addition to facilitating angiogenic activities^{6, 13, 38}.

The expression of erythropoietin receptors on tumor vascular endothelial cells further suggests that erythropoietin may assist in tumor progression by promoting endothelial cell proliferation and vessel formation within the tumor^{34, 35}. In addition, erythropoietin may regulate tumor vasculature development indirectly; upon erythropoietin administration, the levels of other endothelial growth factors, namely VEGF and PlGF are upregulated⁶. Stimulation of erythropoietin receptors in vascular endothelial cells leads to cell proliferation and increased chemotaxis, providing evidence of a role for erythropoietin/erythropoietin receptors in angiogenesis^{39, 40, 41}.

In addition to the expression of erythropoietin receptors on malignant cells, some tumors also secrete erythropoietin^{6, 13, 20, 33, 35, 38}. This may allow a tumor to regulate its own growth by an autocrine pathway. It has been postulated that the local intratumor levels of erythropoietin produced through this autocrine loop may exceed the level of erythropoietin the tumor would encounter from therapeutic doses of erythropoietin. Batra, *et al.*⁶, postulate that, unlike hematopoietic tissues that respond to relatively low levels of erythropoietin, tumors might require high concentrations of erythropoietin to achieve a response. This high concentration of erythropoietin might be achieved only by local intratumoral erythropoietin production. The effect of therapeutic erythropoietin administration on tumor progression must be considered within this context as well.

Among data addressing the capacity of erythropoietin to stimulate tumor growth, the most convincing are studies demonstrating that tumor progression and tumor angiogenesis can be inhibited by the addition of agents that block erythropoietin binding or signaling: e.g. anti-erythropoietin antibodies, Jak2 inhibitors, and soluble erythropoietin receptors^{32, 33}. Yasuda *et al.* (2002)³⁵ reported that erythropoietin and erythropoietin receptor are expressed in malignant tumors of the female reproductive organs, where tumor cells and capillary endothelium showed erythropoietin receptor immunoreactivity, and that the injection of a monoclonal antibody against erythropoietin or the soluble form of erythropoietin receptor into tumors reduced capillaries and caused tumor destruction in a dose-dependent manner. Histopathologic changes including, fragmented cellular DNA, and the absence of phosphorylated Jak2 and STAT5 cells in tumors, relative to controls suggested that the tumor and capillary cell decrease resulted from apoptotic cell death. These studies support the conclusion

that erythropoietin signaling contributes to tumor survival and to the promotion of tumor growth and angiogenesis.

It should be noted that the mere presence of erythropoietin receptors on tumor cells does not necessarily confer on such cells the capacity to respond to erythropoietin. These receptors must be functional. Not only must they be able to bind erythropoietin, but they must be able to activate the downstream intracellular signaling pathways through which erythropoietin elicits its biological activities. Some *in vitro* studies on tumor cell lines have demonstrated the lack of proliferation upon exogenous erythropoietin administration, despite the presence of erythropoietin receptors on the surface of cells. Westphal *et al.*³¹ evaluated over twenty tumor cell lines, including AML, breast, pancreatic, prostate, and kidney cell lines. This study demonstrated that the proliferation rates of these erythropoietin receptor-positive cell lines were not influenced by the addition of exogenous erythropoietin. Moreover, addition of erythropoietin did not increase the tyrosine kinase activity in these cells. The presence of erythropoietin receptors on these cells was not essential for the growth of these cells in culture. A lack of proliferative response on erythropoietin receptor-positive cells was also observed by Takeshita, *et al.*⁴² when primary AML and melanoma cells were treated with exogenous erythropoietin. These studies, as opposed to the ones indicating a trophic effect of erythropoietin, beg the question as to whether the tumors that respond express the high affinity receptor versus the low, whether the levels differ, or whether the amount of endogenous erythropoietin produced by cells that fail to respond to exogenous erythropoietin renders such cells resistant to further stimulation by erythropoietin.

In Vivo Findings

While the majority of the published data supporting that erythropoietin can promote tumor growth, survival and angiogenesis was obtained in *in vitro* systems, *in vivo* data are also available. First, the direct exposure of uterine and ovarian tumor slices transplanted into nude mice to erythropoietin antagonists resulted in reduction in size. Immunohistochemical staining revealed a decrease in erythropoietin -responsive malignant and capillary endothelial cells through apoptotic cell death⁴³. Second, treatment of xenograft models of stomach choriocarcinoma and melanoma with erythropoietin antagonists inhibited angiogenesis and survival of tumor cells. In contrast, treatment of the xenograft models with an erythropoietin-mimetic peptide promoted angiogenesis and tumor survival³². Third, experiments conducted using a rat syngeneic mammary adenocarcinoma cell line implanted into the subcutaneous tissue of rats in a chamber revealed that erythropoietin antagonists delayed tumor growth³³.

Conclusions

From the regulatory perspective there are sufficient preclinical data to support the hypothesis that erythropoietin can promote tumor growth, survival, and angiogenesis. Although there are, undoubtedly, additional preclinical studies that could be conducted to further elucidate the mechanisms underlying erythropoietin's apparent effect on tumors, these studies would not be able to directly assess the clinical relevance of this effect. It is recommended that the ability of erythropoietin to promote tumor growth, survival, and

angiogenesis be assessed in an appropriately designed clinical trials in patients that have been adequately informed of the potential risk.

III. Clinical Studies of Epogen/Procrit for the Treatment of the Anemia due to Chronic Renal Failure

The results of thirteen clinical studies that included a total of 1,010 patients were used support the approval of Epogen/Procrit for treatment of anemia associated with ESRD. Four other studies were performed in patients with renal failure whose disease was not severe enough to require dialysis. Six studies were conducted in normal male volunteers (157 subjects, 108 of whom received Epogen and 49 of whom received placebo).

Treatment of Anemia Due to Chronic Renal Failure in Patients Undergoing Dialysis

The primary efficacy data were derived from two large multicenter trials. The first study was a multicenter, open-label study in which 412 subjects with end stage renal failure on dialysis received Epogen three times a week. Patients initially received one of three dose levels: one group received 300 U/kg only; one group was dosed at 300 U/kg and subsequent dose reduced to 150 U/kg; and the majority received 150 U/kg only. When a patient achieved a hematocrit of 35%, or completed 12 weeks of therapy at the initial dose, they entered the dose adjustment and long-term maintenance phase of the study.⁴⁴ 309 patients were evaluable for efficacy, and 95.5% had an increase in hematocrit of 6 points or reached the target hematocrit of 35% within 12 weeks of the initiation of therapy. Approximately 70% satisfied these criteria within the first four weeks of therapy. Following six more weeks of therapy, 97% of the evaluable patients met these criteria. The percentage of patients who responded to therapy was not significantly different between the three dosage groups: for 300 U/kg, 300 U/kg and 150 U/kg, and 150 U/kg the values were 100%, 94.5% and 95.2%, respectively.⁴⁵

When the enrolled patients achieved a hematocrit of 35%, they were entered into the dose adjustment and long-term maintenance phase, where the dose was individually adjusted to maintain the hematocrit within the target range of 32-38%. Sixty-four percent of the patients required doses of Epogen between 12.5 and 100 U/kg to maintain their hematocrit within the desired target range.

Transfusion requirements decreased within weeks after the initiation of therapy. The pre-study transfusion requirements of 0.52 units per patient per month were reduced to 0.1 units per patient per month after the first four weeks on Epoetin therapy, and to 0.04 units per patient per month or less through 14 months on study.

The second major efficacy study was the U.S. Pivotal Double-blind, Placebo-controlled (DBPC) Multicenter Study in ESRD Patients, which was conducted at three study sites. This study enrolled 100 anemic ESRD patients who were on maintenance hemodialysis. Patients were randomized to receive either placebo or 150 U/kg Epogen t.i.w. for 12 weeks. During the second 12-week study period, all patients received drug on an open-

label basis. Once a patient's hematocrit reached 35%, they were entered into the dose adjustment and long-term maintenance phase of this study.

Of the 62 patients evaluable for efficacy, 95% achieved a hematocrit of 35% or six points over baseline. Ninety-seven percent of the patients (97%) randomized to therapy achieved this efficacy criterion in the blinded phase of the study, and 93% of the patient achieved this criterion after crossover from placebo to Epogen treatment.

Two, double-blind, placebo controlled studies were conducted in Canada in ESRD patients. In a single-center trial, ESRD patients (6 patients per group) were treated IV for nine weeks with either placebo or 50 U/kg, 100 U/kg or 200 U/kg Epogen t.i.w. The rate of rise of hematocrit was dose dependent. In the larger multicenter DBPC trial, patients received placebo (n=40) or Epogen at an initial dose of 100 U/kg (n=78) for 26 weeks. The mean change from baseline for hemoglobin was 0.006 g/dl for placebo-treated patients, and 3.8 g/dl for Epogen -treated patients.

Treatment of Anemia Due to Chronic Renal Failure in Patients not undergoing Dialysis

Four clinical studies were conducted in CRF patients whose disease was not severe enough to require dialysis (non-dialysis CRF patients): two U.S. multicenter double-blind placebo controlled studies, a continuation long-term maintenance study, and a European open-label study. In the first U.S. DBPC study, non-dialysis CRF transplants received placebo (n=31) or Epogen at 50 U/kg (n=28), 100 U/kg (n=28), or 150 U/kg (n=30) intravenously t.i.w. ; patients were treated for 8 weeks, or until their anemia was corrected (hematocrits of 40% for males and 35% for females). Treatment with Epogen increased the hematocrit in a dose-dependent manner; changes of -0.01, 0.13, 0.20 and 0.26 hematocrit points per day were seen for the placebo, Epogen 50 U/kg, 100 U/kg, and 150 U/kg dosage groups, respectively. Upon completion of eight weeks of therapy or correction of anemia, whichever came first, patients in this study were enrolled in a 6-month maintenance study protocol. In the maintenance study, Epogen was administered either intravenously or subcutaneously t.i.w., and the dose was adjusted to maintain a constant elevated hematocrit. Ninety-four percent of all patients in the study corrected their hematocrit, and doses of Epogen 75-150 U/kg per week were shown to maintain hematocrits of 36-38% for up to six months.

In the second U.S. DBPC trial, non-dialysis CRF patients were administered either placebo (n=48) or 100 U/kg Epogen (n=45) t.i.w. subcutaneously for up to 12 weeks or until the hematocrit reached 38-40%, whichever occurred first. Fifty-eight percent of the Epogen-treated patients, versus 4% of the placebo-treated patients, corrected their anemia (hematocrit > 40% for males and > 35% for females) during the study period.

Safety Analyses

Analyses of safety included the data from all studies conducted in patients with chronic renal failure, including those undergoing dialysis and those not undergoing dialysis. Hypertension was the most frequently reported adverse event in both the placebo and Epogen-treated patients. In patients on dialysis, the incidence of reported hypertensive events for all Epogen-treated patients was approximately twice that for placebo-treated patients (0.69 versus 0.33 events per patient-year, respectively). In non-dialysis CRF patients, the rate of hypertension was higher, occurring at a rate of 1.70 and 3.28 events per patient-year in Epogen- and placebo-treated patients, respectively.⁴⁶ When patients in the U.S. Phase III multicenter ESRD trial were analyzed for incidence of hypertension as a function of the rate of rise in hematocrit, there was a trend towards more reports of hypertension in the first 90 days of therapy in patients who had increases in hematocrit that were greater than 0.3 points per day.

In placebo-controlled studies enrolling over 300 patients with chronic renal failure, the following adverse events occurred at a higher incidence Epogen-treatment patients as compared to placebo controls: hypertension (24% vs. 18%), headache (16% vs. 12%), arthralgias (11% vs. 6%), diarrhea (8% vs. 6%), vomiting (8 % vs. 5%), and clotted vascular access (6.8% vs. 2.3%). In US and non-US studies, the annual rates (events per patient-year) of clotted vascular access in patients receiving Epogen was 0.25 and 0.27 events/patient-year, respectively.⁴⁷

IV. The Normal Hematocrit Study of Epogen/Procrit in Patients with Chronic Renal Failure and Underlying Cardiovascular Disease

Amgen, Inc. conducted a study in 1,233 patients with chronic renal failure on dialysis⁴⁸ and clinical evidence of congestive heart failure or ischemic heart disease. Patients were randomized to an Epogen dose titrated to achieve a target hematocrit of 42% (± 3) (the “normal hematocrit group” or an epoetin dose titrated to achieve and maintain a target hematocrit of 30% (± 3) (the “low hematocrit group”). The study was designed to test the hypothesis that correction of anemia in chronic renal failure patients on dialysis with clinical evidence of congestive heart failure or ischemic heart disease would have improved survival and better exercise tolerance if treated with Epogen to obtain a higher hematocrit than had been commonly targeted in clinical practice. The primary endpoint was the length of time to death or a first nonfatal myocardial infarction.

This study was halted at the third interim analysis on the recommendation of the Data Safety Monitoring Board. At 29 months, there were 183 deaths and 19 first nonfatal myocardial infarctions in the group with a normal hematocrit and 150 deaths and 14 nonfatal myocardial infarctions in the low hematocrit group. (Figure 2) Even though these differences did not reach the prespecified statistical stopping boundary, the study was halted “because differences in mortality between the groups were recognized as sufficient to make it very unlikely that a continuation of the study would reveal a benefit

for the normal-hematocrit group and the results were nearing the statistical boundary of a higher mortality in the normal-hematocrit group.”⁴⁹

Safety Results

The incidences of non-fatal MI were 3.1% and 2.3% in the normal and low hematocrit groups, respectively. The incidences of CVA (39% versus 29%) and all other thrombotic events (22% versus 18%) were also higher in the normal hematocrit group. There was a trend to decreasing mortality with increasing hematocrit values within both groups. (Figure 1)

This study demonstrated that the aggressive use of erythropoietin to correct the hematocrit to normal values is associated with higher risks in subjects with chronic renal failure and pre-existing cardiovascular disease. As a result, a Warning was added to the Eprex and Procrit Package Inserts.

These findings also led FDA to examine the risks associated with the rate of rise of hemoglobin in the studies that were submitted to support the licensure of Aranesp for treatment of anemia in chronic renal failure (see below).

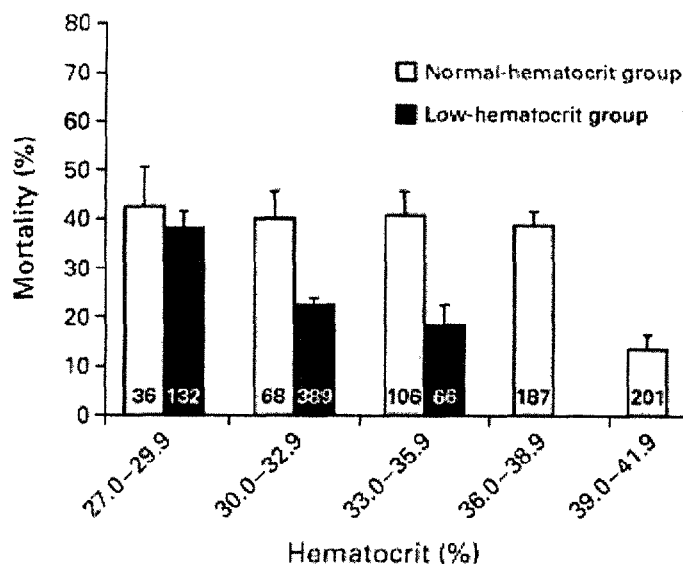


Figure 1: Mean (\pm SE) Mortality Rate as a Function of the Average Hematocrit Value in the Normal-Hematocrit and Low-Hematocrit Groups.

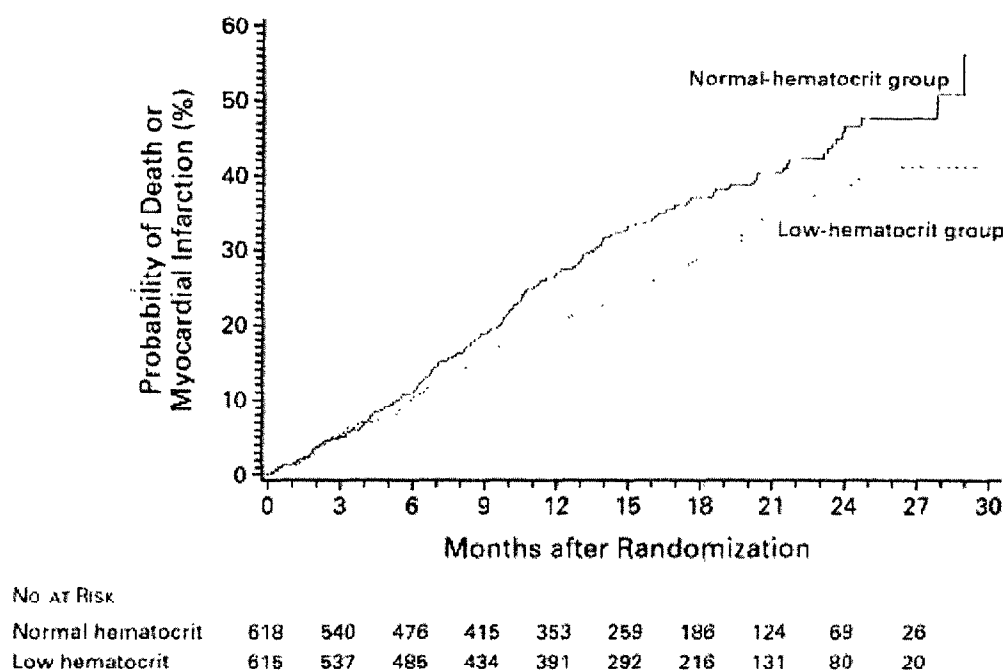


Figure 2: Kaplan–Meier Estimates of the Probability of Death or a First Nonfatal Myocardial Infarction in the Normal-Hematocrit and Low-Hematocrit Groups.

V. Clinical Studies of Aranesp® (darbepoetin alfa) for the Treatment of the Anemia due to Chronic Renal Failure

The licensure of Aranesp in subjects with chronic renal failure was based on two active controlled open-label studies in EPO naïve patients, and two randomized double-blind non-inferiority studies in patients who had previously been on a stable dose of epoetin alfa. The two studies in EPO naïve patients were Study 211: An Open-Label Randomized Study of ARANESP and Recombinant Human Erythropoietin (r-HuEPO) (EPOGEN) for Treatment of Anemia in Patients With End-Stage Renal Disease Receiving Dialysis (North American Phase 2 Study in EPO-Naïve Subjects), and Study 202: A Randomized Study of ARANESP and Recombinant Human Erythropoietin (r-HuEPO) for Treatment of Anemia in Predialysis Chronic Renal Failure Subjects (European Phase 2 Study in Pre-Dialysis, EPO-Naïve Subjects). The two studies in patients who had previously been on a stable dose of EPO were: Study 117: A Randomized Double-blind, Non-Inferiority Study of IV ARANESP Compared to IV Recombinant Human Erythropoietin (EPO) for Treatment of Anemia in Patients with End-Stage Renal Disease (ESRD) Receiving Hemodialysis, and Study 200: A Randomized, Comparative Study of ARANESP Recombinant Human Erythropoietin for Prevention of Anemia in Subjects With Chronic Renal Failure Receiving Dialysis.

Studies In Erythropoietin-Naïve Patients

In Study 211, 120 subjects with chronic renal failure, on dialysis, were randomized 3:1 to receive 0.45 µg/kg of Aranesp QW or 50 U/kg of EPO administered T.I.W. IV or s.c. for 20 weeks.

In Study 202, 160 subjects with chronic renal failure, but not receiving dialysis, were randomized in a 3:1 ratio to receive Aranesp 0.45 µg/kg QW or EPO 50 U/kg BIW s.c. for ≤ 24 weeks, with both agents to be administered subcutaneously.

For both studies, dose adjustments were to be made, if necessary to achieve a hemoglobin increase of ≥ 1.0 g/dl above baseline, to within a target range of 11-13 g/dl.

The primary efficacy endpoint in both studies was the proportion of subjects achieving a hemoglobin target, defined as a hemoglobin ≥ 1.0 g/dl from baseline and a hemoglobin concentration of ≥ 11.0 g/dl during the study. The time points for assessment of the endpoint were 20 and 24 weeks in Study 211 and 202, respectively.

Efficacy results

In Study 211 the hemoglobin target was achieved by 72% (95% CI: 62%, 81%) of the 90 patients treated with Aranesp and 84% (95% CI: 66%, 95%) of the 31 patients treated with Epoetin alfa. The mean increase in hemoglobin over the initial 4 weeks of Aranesp was 1.10 g/dl (95% CI: 0.82 g/dl, 1.37 g/dl).

In Study 202 the primary efficacy endpoint was achieved by 93% (95% CI: 87%, 97%) of the 129 patients treated with Aranesp and 92% (CI: 78%, 98%) of the 37 patients treated with Epoetin alfa. The mean increase in hemoglobin from baseline through the initial 4 weeks of Aranesp treatment was 1.38 g/dl (95% CI: 1.21 g/dl, 1.55 g/dl).

Studies In Patients Previously Stable on Erythropoietin

The objectives of both of these studies were to show that Aranesp was not inferior to EPO for the treatment of anemia in patients with ESRD receiving dialysis, and to compare the safety of the two agents.

Study 117, the North American pivotal phase 3 study, was a randomized, double-blind, active control study of Aranesp versus EPO for the maintenance of hemoglobin in subjects with ESRD receiving hemodialysis. Study 200, the European/Australian study, was similar in design, except that it was open-label, and subjects could be receiving hemodialysis or peritoneal dialysis.

The primary efficacy endpoint was the change in hemoglobin from baseline through the evaluation period (Week 21-28).

Subjects were to be on a stable regimen of Epoetin, with a baseline Hgb between 9.5-12.5 g/dl at the time of enrollment. In Study 200, subjects could be receiving Epoetin alfa or

Epoetin beta at baseline, whereas Study 117 enrolled subjects on Epoetin alfa only. After a 2-week screening and baseline periods, subjects were to be randomized 2:1 to Aranesp or Epoetin alfa or beta. Subjects assigned to Epoetin were to continue on their previous dose of Epoetin. Subjects assigned to Aranesp were to switch to Aranesp, at a total weekly starting dose that was based on the total weekly Epoetin dose at the time of randomization using the proportionality 1 µg Aranesp to 200 units Epoetin. Hemoglobin was to be maintained within a target range of -1.0 to +1.5 g/dl of the baseline hemoglobin and between 9-13 g/dl for up to 28 weeks, with dose adjustments as needed per protocol-specified algorithms.

Efficacy Results

The results of Study 117 showed that the distributions of changes in hemoglobin from baseline through the evaluation period were similar for the two treatment groups. The prospectively defined primary efficacy endpoint, the mean change in hemoglobin, adjusted for center and baseline hemoglobin concentration, was similar in the Aranesp and Epoetin arms: 0.24 ± 0.10 g/dl versus 0.11 ± 0.07 g/dl (mean \pm SEM) respectively. The difference between groups was 0.13 g/dl (95% CI: -0.08, 0.33). The lower boundary of the 2-sided 95% CI was above the protocol-specified non-inferiority margin of -1.0 g/dl, providing support that Aranesp was not inferior to Epoetin in maintaining Hgb in this study.

For Study 200, the results showed that the change (mean \pm SD) in Hgb from baseline to the evaluation period was similar in the Aranesp and Epoetin arms (0.05 ± 0.80 versus 0.00 ± 0.87 g/dL, respectively). After adjustment for covariates (center, frequency of Epoetin dosing at baseline, modality of dialysis, route of administration, and baseline Hgb concentration), the difference in the mean change in Hgb between the 2 groups was 0.03 g/dL (95% CI: -0.16, 0.21). The lower limit of the 2-sided 95% CI was above the protocol-specified non-inferiority margin of -0.5 g/dL, providing support that Aranesp was not inferior to Epoetin in maintaining the mean Hgb concentration in this study.

Safety Analyses: Relation between adverse events, hemoglobin, and hemoglobin rate of rise

The development program of Aranesp for the anemia of chronic renal failure (CRF) indication evaluated the use of Aranesp in the settings of pre-dialysis, peritoneal dialysis, and hemodialysis. In addition, it assessed two types of Aranesp use: 1) the treatment of anemia in subjects who had not been treated previously with erythropoietins (i.e., anemia "correction" studies); and 2) as maintenance therapy for patients whose anemia had been treated with a stable regimen of Epoetin alfa (EPO) prior to study enrollment (i.e., "conversion" studies). Details of FDA's safety analyses can be found in the Medical Officer's clinical review of Aranesp for anemia of CRF.⁵⁰

Overall, the safety database included 1598 Aranesp-treated subjects and 600 EPO-treated subjects, with median lengths of exposure of 24 and 28 weeks, respectively. The substantive investigations were either active-controlled studies using EPO as a

comparator, or uncontrolled studies. The vast majority of the clinical experience was unblinded.

Given the lack of placebo-controlled studies and the pattern of AEs observed, characterization of the safety of Aranesp during review of the marketing application was not straightforward. Adverse events occur frequently in the CRF patient population, and treatment emergent AEs had to be assessed against this background. Moreover, cardiovascular disease is prevalent in the CRF patient population, and cardiovascular events occur fairly commonly, yet they also constitute a primary manifestation of excessive erythropoiesis, as noted above.

FDA undertook a number of approaches in its assessment of the Aranesp safety database, beyond simple comparisons of AE rates in Aranesp- and Epoetin alfa-treated subjects and subgroups. One of these approaches involved analyses of AEs with putative mechanisms involving hemodynamic and/or rheologic factors, an approach that involved four analyses:

- A) Analysis of AEs by Hgb Concentration. FDA assessed AEs by Hgb concentration as determined on the week of the reported event. This purpose of this analysis was to provide information on potential associations between AEs and specific Hgb levels.
- B) Analysis of AEs by Hgb Rate of Rise. FDA assessed AEs by Hgb rate of rise (ROR) during the weeks preceding reported AEs. The objective of this analysis was to assess potential associations between AEs and specific rates of Hgb increase.
- C) Analysis of AEs by Hgb Rate of Decline. This complementary analysis assessed rates of AEs by Hgb rate of decline during the weeks preceding the events.
- D) Examination of Potential Interaction Between Hgb Concentration, Hgb Rate of Rise and AEs: FDA combined all AEs with putative mechanisms involving hemodynamic and/or rheologic factors, and examined the potential interactions between the rate of these AEs, Hgb concentration, and Hgb ROR.

General Methods:

Weekly Hgb values were classified by both 1-g/dL range and quintile. Ranges were defined as: ≤ 10 g/dL, >10 to ≤ 11 g/dL, >11 to ≤ 12 g/dL, >12 to ≤ 13 g/dL, >13 to ≤ 14 g/dL, and >14 g/dL. Quintiles were ascertained as: <10.1 g/dL, $\square 10.1$ to <10.8 g/dL, ≥ 10.8 to <11.4 g/dL, ≥ 11.4 to <12.2 g/dL, and ≥ 12.2 g/dL.

For each subject-week, the slope of the preceding Hgb-time relation was determined, when possible, using the following approach:

- 1). The slope of the Hgb-time relation leading up to each date was calculated using Hgb values obtained over a 2-week period (i.e., 3 Hgb values).

- 2). Missing Hgb values were not interpolated.
- 3). Hgb values were construed as having been obtained on the week indicated, i.e., the actual date was not used in calculations. Slopes were expressed as weekly change in Hgb concentration.
- 4). If <2 Hgb values were reported over a 2-week (3-value) period, such that a slope could not be calculated, an attempt was made to calculate slope over a 4-week period.
- 5). Positive and negative slopes were analyzed separately, with slopes of 0 classified with the positive slopes.
- 6). Slope (m) was classified by group, as follows:

$m > 0.2 \text{ and } \leq 0.25 \text{ g/dL/week (1 g/dL per } <5 \text{ to 4 weeks)}$
 $m > 0.25 \text{ and } \leq 0.333 \text{ g/dL/week (1 g/dL per } <4 \text{ to 3 weeks)}$
 $m > 0.333 \text{ and } \leq 0.5 \text{ g/dL/week (1 g/dL per } <3 \text{ to 2 weeks)}$
 $m > 0.5 \text{ and } \leq 1 \text{ g/dL/week (1 g/dL per } <2 \text{ to 1 week)}$
 $m > 1 \text{ g/dL/week (1 g/dL per } <1 \text{ week)}$

Each AE reported was linked, by reported week of occurrence, to its associated weekly Hgb value range, quintile, and slope. Multiple AEs were linked by pathophysiologic mechanism, e.g., fluid overload included edema, dyspnea, orthopnea and pleural effusion. Congestive heart failure (CHF), abnormal ejection fraction and pulmonary edema were grouped together. Cerebrovascular disorders included cerebral ischemia, intracranial hemorrhage (ICH), and cerebral/subarachnoid hemorrhage. Angina was grouped with coronary artery disease, myocardial ischemia, and chest pain (non-specific chest pain was not included in this category). A category representing thrombosis/ischemia (but omitting TVA) was constructed including the terms arterial occlusion, embolism, arteriosclerosis, carotid stenosis, claudication, peripheral vascular disease, ischemic necrosis, gangrene, superior vena caval syndrome, phlebitis, thrombophlebitis, arterial/venous thrombosis, intestinal ischemia, pulmonary embolism, and TIA.

Absolute Hgb Values (Table 1):

Serum Hgb was analyzed both by quintiles, and by 1-gram/dL categories. For each quintile and category, the denominator used was the number of weekly Hgb values observed that fit that particular category, divided by 1000 (i.e., the number of events per 1000 weekly Hgb observations). The Ns are given at the bottom of Table .

For Aranesp -treated subjects, there were trends suggesting possible associations between reported Hgb values >13 and seizures, hypertension (HTN), and arrhythmias, though the latter appeared to be associated with Hgb values >11 g/dL, as well. Importantly, Hgb values of >13 g/dL did not appear to be associated with increased risks of these events. Of note, for ARANESP-treated subjects, Hgb values <10 g/dL appeared to be associated with excess risks of fluid overload, CHF, pulmonary edema, acute MI and TVA, whereas these risks were not apparent at Hgb values ≥ 10 g/dL.

Table 1: FDA Analysis of Relation Between Serum Hgb and AEs With Putative Mechanism Involving Hemodynamic and/or Rheologic Factors: Combined Data (Rates are Events /1000 weekly Hgb Observations)

		Hgb	Hgb Category (g/dL)					
		unknown	<10	10 to <11	11 to <12	12 to <13	13 to <14	14 +
polycythemia	EPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	ARANESP	0.0	0.0	0.0	0.0	0.0	0.4	7.2
	Total	0.0	0.0	0.0	0.0	0.0	0.3	5.2
hypertension	EPO	8.5	9.3	11.2	11.6	10.4	10.5	12.2
	ARANESP	5.5	12.1	12.0	11.0	11.0	15.6	9.6
	Total	6.0	11.3	11.7	11.2	10.8	14.2	10.4
fluid overload edema, dyspnea, orthopnea, pleural effusion	EPO	19.1	27.9	21.1	22.9	24.9	12.9	12.2
	ARANESP	9.4	26.5	16.3	11.9	12.1	12.2	7.2
	Total	11.1	26.9	17.8	15.5	15.9	12.4	8.6
CHF, abnormal ejection fraction, pulmonary edema	EPO	0.7	4.5	2.3	1.1	1.0	1.2	0.0
	ARANESP	1.5	4.4	1.7	1.0	0.6	0.8	4.8
	Total	1.4	4.4	1.9	1.0	0.7	0.9	3.5
cerebrovascular disorder, cerebral ischemia, ICH, cerebral hemorrhage, SAH	EPO	0.0	0.3	0.8	0.4	0.7	0.0	0.0
	ARANESP	0.3	0.7	0.8	0.3	0.3	0.8	0.0
	Total	0.3	0.6	0.8	0.3	0.4	0.6	0.0
impaired consciousness, encephalopathy	EPO	0.0	1.8	0.8	0.5	1.7	0.0	0.0
	ARANESP	0.0	0.4	0.8	0.1	0.4	0.0	0.0
	Total	0.0	0.8	0.8	0.2	0.8	0.0	0.0
seizure	EPO	1.1	0.6	0.4	0.4	1.0	0.0	0.0
	ARANESP	0.3	0.6	0.5	0.5	0.3	0.8	4.8
	Total	0.4	0.6	0.4	0.5	0.5	0.6	3.5
syncope	EPO	0.7	0.9	1.2	1.1	1.7	0.0	0.0
	ARANESP	0.9	0.8	1.0	0.5	1.5	0.4	0.0
	Total	0.9	0.8	1.0	0.7	1.5	0.3	0.0
acute MI	EPO	0.7	0.9	0.8	0.4	0.3	0.0	0.0
	ARANESP	0.5	1.0	0.5	0.2	0.4	0.4	0.0
	Total	0.5	1.0	0.6	0.2	0.4	0.3	0.0
cardiac arrest	EPO	0.0	0.6	0.0	0.5	0.7	1.2	6.1
	ARANESP	0.2	0.6	0.3	0.2	0.0	0.4	0.0
	Total	0.2	0.6	0.2	0.3	0.2	0.6	1.7
arrhythmia	EPO	6.6	5.4	7.5	6.4	9.0	8.2	0.0
	ARANESP	3.7	4.9	4.9	2.6	3.1	7.6	7.2
	Total	4.2	5.1	5.7	3.9	4.8	7.7	5.2
death	EPO	0.4	0.0	0.0	0.2	0.0	0.0	0.0
	ARANESP	0.2	0.2	0.2	0.0	0.0	0.0	0.0
	Total	0.2	0.2	0.1	0.1	0.0	0.0	0.0
angina, CAD, myocardial ischemia, pain chest	EPO	2.6	4.5	4.4	2.1	2.1	0.0	12.2
	ARANESP	3.9	4.8	3.4	2.9	4.4	2.9	4.8
	Total	3.6	4.7	3.7	2.7	3.7	2.2	6.9
arterial occlusion, arteriosclerosis, carotid stenosis, claudication, gangrene, ischemic necrosis, peripheral ischemia, arterial embolism, phlebitis, thrombophlebitis, SVC syndrome, arterial thrombosis, venous thrombosis, intestinal ischemia, TIA, pulmonary embolism	EPO	1.8	4.8	2.3	1.3	2.4	1.2	12.2
	ARANESP	2.4	3.6	2.3	1.7	3.2	2.1	2.4
	Total	2.3	3.9	2.3	1.5	3.0	1.9	5.2
TVA	EPO	3.7	9.3	6.6	7.7	8.6	3.5	12.2
	ARANESP	1.6	5.1	3.2	3.9	3.5	2.5	0.0
	Total	2.0	6.3	4.3	5.1	5.0	2.8	3.5
anemia	EPO	1.5	8.7	0.8	0.0	0.0	0.0	0.0
	ARANESP	0.5	6.0	0.6	0.1	0.1	0.0	0.0
	Total	0.7	6.8	0.7	0.1	0.1	0.0	0.0
hypovolemia, hypotension, postural hypotension, dehydration	EPO	12.9	17.7	13.9	17.2	18.3	16.4	12.2
	ARANESP	9.2	11.2	15.4	16.1	14.7	18.5	9.6
	Total	9.8	13.0	14.9	16.4	15.8	18.0	10.4
Number of values (N)	EPO	2716	3329	5178	5585	2894	856	164
	ARANESP	12925	8937	11013	11395	6878	2373	415
	Total	15641	12266	16191	16980	9772	3229	579

Hgb Rate of Rise (Table 2):

Adverse events are shown for Hgb rates of increase and decrease in Table 2. Rates were determined by whole fractions of a gram of Hgb (i.e., 1.0, 0.5, 0.33, 0.25, 0.20, and 0.10 g/dL/week). The denominators used for each quintile and category were the number of weekly Hgb slopes that fit that particular category, divided by 1000 (i.e., the number of events per 1000 weekly Hgb observations, table bottom).

For Aranesp-treated subjects, there appeared to be excess risk of HTN, pulmonary edema, cardiac arrest and TVA associated with Hgb ROR >0.5 and particularly 1.0 g/dL/week. There also appeared to be an association between rapid Hgb rise and fluid overload, acute MI and seizures, although the association between Hgb rate of rise and these events was less clear.

FDA also assessed the rates of these AEs in the Aranesp treatment group, with subgroups by history of cardiovascular disease (CVD). Across Hgb and Hgb ROR categories, event rates generally followed similar patterns for subjects with and without a history of CVD, though rates were higher in CVD(+) subjects. There were 2 apparent exceptions:

- 1) CHF was strongly associated with the extremes of Hgb categories (both <10 and >14 g/dL) in the CVD(+) group, whereas there was only a weak association between CHF and Hgb <10 g/dL in the CVD(-) subgroup. A Hgb ROR exceeding 0.5 was strongly associated with CHF, both in CVD(+) and CVD(-) subgroups.
- 2) There was no clear association between angina and Hgb ROR in either subgroup; however, a Hgb <10g/dL was strongly associated with angina in the CVD(+) group.

Hgb Rate of Decline:

With respect to falling Hgb in Aranesp-treated subjects (rate of Hgb decrease preceding AEs), there were apparent associations between a >1 g/dL weekly decline in Hgb and worsened anemia, CHF, pulmonary edema, acute MI, cardiac arrest, angina, arterial occlusion, and death, though the numbers of subject-weeks and events in this category were limited.

Interaction Between Hgb Concentration, Hgb Rate of Rise, and AEs:

For the Aranesp treatment group, FDA combined all of the AEs with putative mechanisms involving hemodynamic and/or rheologic factors, and examined the interaction between the rate of these AEs, Hgb concentration and Hgb ROR. These events included: accelerated HTN, fluid overload, edema, dyspnea, orthopnea, pleural effusion, pulmonary edema, CHF, abnormal ejection fraction, angina, coronary artery disease, myocardial ischemia, chest pain (cardiac), arrhythmia, syncope, cardiac arrest, impaired consciousness, encephalopathy, seizure, cerebrovascular disorder, TIA, cerebral ischemia, ICH, subarachnoid hemorrhage, arterial occlusion, arteriosclerosis, carotid stenosis, claudication, gangrene, ischemic necrosis, peripheral ischemia, arterial embolism, phlebitis, superior vena caval syndrome, thrombophlebitis, arterial/venous thrombosis, and intestinal ischemia. Each AE was linked, by week of reported

occurrence, to its corresponding Hgb category, as well as to its appropriate Hgb ROR category.

Table 2: FDA Analysis of Relations Between Hgb ROR and Rate of Fall and AEs with Putative Mechanism Involving Hemodynamic and/or Rheologic Factors: Combined Events (Events/1000 Weekly Hgb Observations)

		Rate of Rise (g/dL/week)							Rate of Fall (g/dL/week)						
		≤0.1	>0.1 to ≤0.2	>0.2 to ≤0.25	>0.25 to ≤0.33	>0.33 to ≤0.5	>0.5 to ≤1	>1	≤0.1	>0.1 to ≤0.2	>0.2 to ≤0.25	>0.25 to ≤0.33	>0.33 to ≤0.5	>0.5 to ≤1	>1
polycythemia	EPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	ARANESP	0.1	0.0	0.0	0.0	0.5	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	0.1	0.0	0.0	0.0	0.3	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
hypertension	EPO	11.4	8.8	8.8	11.9	11.3	15.7	21.1	11.2	9.8	6.8	10.4	7.5	16.3	4.6
	ARANESP	7.5	9.9	10.4	13.8	10.2	19.9	13.1	12.0	11.5	14.9	9.6	11.5	10.5	12.4
	Total	8.6	9.5	9.9	13.3	10.6	18.7	15.2	11.7	10.9	12.3	9.8	10.2	12.2	10.2
fluid overload, edema, dyspnea, orthopnea, pleural effusion	EPO	23.0	23.9	10.1	26.4	24.3	19.3	31.6	24.6	26.1	46.4	20.8	23.8	16.3	36.5
	ARANESP	15.4	14.7	16.6	14.4	15.6	18.9	35.4	16.7	21.7	17.4	12.1	17.7	17.3	19.5
	Total	17.6	17.5	14.7	17.8	18.2	19.0	34.4	19.2	23.1	26.7	14.7	19.6	17.0	24.3
CHF, abnormal ejection fraction, pulmonary edema	EPO	2.4	1.0	1.3	1.3	3.2	1.8	0.0	1.3	1.6	1.4	1.5	1.3	6.1	4.6
	ARANESP	1.5	1.5	2.1	2.1	1.4	3.1	7.5	1.6	1.0	3.9	1.3	2.1	4.6	8.9
	Total	1.7	1.4	1.8	1.9	1.9	2.8	5.5	1.5	1.2	3.1	1.3	1.8	5.1	7.7
cerebrovascular disorder, cerebral ischemia, ICH, cerebral hemorrhage, SAH	EPO	0.3	0.5	0.0	0.0	0.0	0.9	0.0	0.9	0.5	0.0	0.0	1.9	0.0	0.0
	ARANESP	0.1	0.4	0.5	0.0	0.5	1.0	1.9	0.6	1.0	0.0	1.3	0.3	0.8	0.0
	Total	0.2	0.5	0.4	0.0	0.3	1.0	1.4	0.7	0.9	0.0	0.9	0.8	0.6	0.0
impaired consciousness, encephalopathy	EPO	1.1	0.0	0.0	1.3	0.5	1.8	0.0	0.9	0.5	0.0	1.5	1.9	2.0	0.0
	ARANESP	0.1	0.7	0.5	0.0	0.2	0.3	0.0	0.4	0.2	0.0	0.0	0.9	1.3	0.0
	Total	0.4	0.5	0.4	0.4	0.3	0.8	0.0	0.6	0.3	0.0	0.4	1.2	1.5	0.0
seizure	EPO	0.3	1.0	0.0	1.3	0.0	0.9	0.0	0.9	0.0	0.0	0.0	0.0	3.0	0.0
	ARANESP	0.4	0.4	0.5	0.5	0.2	1.0	1.9	0.4	0.7	0.0	0.0	0.3	0.4	1.8
	Total	0.4	0.6	0.4	0.8	0.2	1.0	1.4	0.6	0.5	0.0	0.0	0.2	1.2	1.3
syncope	EPO	0.5	1.0	1.3	2.6	0.0	0.0	5.3	1.7	1.6	4.1	1.5	0.6	0.0	0.0
	ARANESP	1.3	0.9	1.0	1.1	0.7	1.4	0.0	1.0	0.7	0.0	0.0	0.0	0.0	3.5
	Total	1.1	0.9	1.1	1.5	0.5	1.0	1.4	1.3	1.0	1.3	0.4	0.2	0.0	2.6
acute MI	EPO	0.8	0.0	0.0	1.3	0.5	0.0	0.0	0.0	1.1	0.0	1.5	1.3	1.0	0.0
	ARANESP	0.4	0.0	1.0	0.0	0.5	0.3	1.9	0.4	1.0	0.0	0.0	0.3	1.7	1.8
	Total	0.5	0.0	0.7	0.4	0.5	0.3	1.4	0.3	1.0	0.0	0.4	0.6	1.5	1.3
cardiac arrest	EPO	0.0	1.0	0.0	0.0	0.5	2.8	0.0	0.4	0.5	0.0	0.0	0.0	1.0	0.0
	ARANESP	0.0	0.2	0.0	0.0	0.0	1.0	1.9	0.0	0.0	0.0	0.0	0.3	2.1	0.0
	Total	0.0	0.5	0.0	0.0	0.2	1.5	1.4	0.1	0.2	0.0	0.0	0.2	1.8	0.0
arrhythmia	EPO	8.5	7.3	5.0	2.6	7.0	2.8	10.5	8.2	5.4	5.5	4.5	9.4	7.1	13.7
	ARANESP	4.5	3.9	4.2	3.2	4.2	4.9	3.7	4.1	3.2	3.2	3.8	3.8	5.9	5.3
	Total	5.6	5.0	4.4	3.0	5.0	4.3	5.5	5.4	3.9	3.9	4.0	5.6	6.3	7.7
death	EPO	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0
	ARANESP	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.6	0.0	0.0	0.4	3.5
	Total	0.0	0.0	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.6	2.6
angina, CAD, myocardial ischemia, pain chest	EPO	3.2	1.5	2.5	4.0	2.7	4.6	0.0	0.4	1.6	4.1	3.0	6.9	9.1	9.1
	ARANESP	3.4	4.6	4.7	2.7	3.9	1.7	5.6	3.7	3.7	2.6	5.1	5.0	5.1	8.9
	Total	3.3	3.6	4.0	3.0	3.6	2.5	4.1	2.6	3.1	3.1	4.5	5.6	6.3	8.9
arterial occlusion, arteriosclerosis, carotid stenosis, claudication, gangrene, ischemic necrosis, peripheral ischemia, arterial embolism, phlebitis, thrombophlebitis, SVC syndrome, arterial thrombosis, venous thrombosis, intestinal ischemia, TIA, pulmonary embolism	EPO	1.1	1.9	2.5	4.0	2.2	2.8	5.3	3.0	2.7	0.0	3.0	5.6	5.1	4.6
	ARANESP	1.7	2.6	2.1	4.8	2.1	3.8	7.5	3.1	1.7	1.3	1.3	3.8	3.8	7.1
	Total	1.5	2.4	2.2	4.5	2.1	3.5	6.9	3.1	2.0	0.9	1.8	4.4	4.2	6.4
TVA	EPO	6.1	3.9	5.0	5.3	9.7	15.7	10.5	6.9	6.0	8.2	1.5	5.6	15.2	45.7
	ARANESP	2.6	3.7	2.6	5.3	5.8	5.6	3.7	2.3	3.0	3.2	3.8	4.7	3.8	3.5
	Total	3.6	3.8	3.3	5.3	7.0	8.4	5.5	3.8	3.9	4.6	3.1	5.0	7.1	15.3
anemia	EPO	0.5	0.5	1.3	1.3	0.5	0.0	0.0	0.4	1.6	1.4	1.5	1.3	15.2	32.0
	ARANESP	0.5	0.2	0.0	0.0	0.2	1.0	3.7	0.6	1.7	0.6	3.2	2.7	2.9	28.4
	Total	0.5	0.3	0.4	0.4	0.3	0.8	2.8	0.6	1.7	0.9	2.7	2.2	6.5	29.4
hypovolemia, hypotension, postural hypotension, dehydration	EPO	13.5	19.0	10.1	14.5	18.4	24.9	26.3	13.8	14.7	23.2	17.9	20.0	15.2	22.8
	ARANESP	14.6	11.8	18.2	17.6	17.2	17.1	16.8	16.5	12.7	18.7	6.4	10.9	12.2	12.4
	Total	14.3	14.1	15.8	16.7	17.5	19.2	19.3	15.6	13.3	20.2	9.8	13.8	13.1	15.3
Number of values (N)	EPO	3777	2052	796	759	1851	1086	190	2319	1837	733	672	1597	984	219
	ARANESP	9408	4561	1924	1879	4305	2863	536	4852	4017	1548	1568	3395	2376	564
	Total	13185	6613	2720	2638	6156	3949	726	7171	5854	2281	2240	4992	3360	783

The results of this analysis are shown in Table 3. The top panel shows the numbers of subject-weeks that fulfill the criteria for Hgb and Hgb ROR categories. These data serve as the denominators (Ns) for these analyses. The middle panel shows the numbers of events for each Hgb/Hgb ROR category, and the bottom panel shows event rates per 1000 subject-weeks. Each row, representing a particular Hgb ROR category, is summed in the right-most column ("All Hgb"). Note that event rates (bottom panel) tend to be similar for all ROR categories ≤ 0.50 g/dL/week, whereas event rates for ROR > 0.50 g/dL/week tend to be higher. The individual Hgb categories are summed in the bottom row ("All Slopes"). The lowest event rates are in the >11 to ≤ 12 g/dL Hgb category. A slight increase in event rate is evident above this range, with a sharper increase in event rate below this range.

Table 3: Interaction Between Hgb Concentration, Hgb Rate of Rise, and AEs – ARANESP Group

		N = # Subject-Weeks Fitting Criteria (Denominator)						
		Hgb Category (g/dL) →	≤ 10	>10 to ≤ 11	>11 to ≤ 12	>12 to ≤ 13	>13 to ≤ 14	>14
Slope (g/dL/week)	≤ 0.1	1090	1857	1873	1127	374	36	6357
	>0.10 to ≤ 0.20	536	965	1149	716	245	37	3648
	>0.20 to ≤ 0.25	237	376	482	359	128	19	1601
	>0.25 to ≤ 0.33	191	309	441	323	123	28	1415
	>0.33 to ≤ 0.50	390	735	1009	782	321	71	3308
	>0.50	269	411	593	522	303	129	2227
All Slopes		2713	4653	5547	3829	1494	320	18556

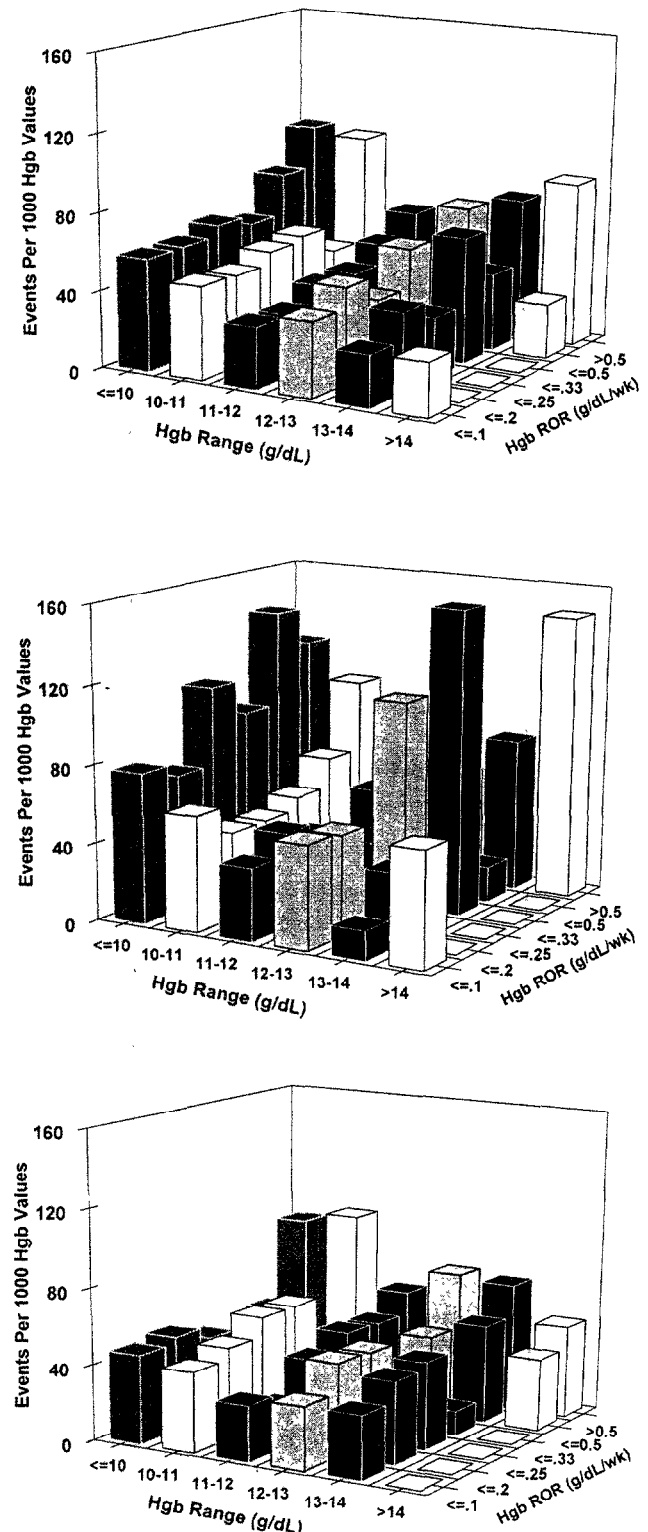
		Numbers of Events						
		Hgb Category (g/dL) →	≤ 10	>10 to ≤ 11	>11 to ≤ 12	>12 to ≤ 13	>13 to ≤ 14	>14
Slope (g/dL/week)	≤ 0.1	66	97	65	44	11	1	284
	>0.10 to ≤ 0.20	32	50	36	38	10	0	166
	>0.20 to ≤ 0.25	16	20	19	14	4	0	73
	>0.25 to ≤ 0.33	11	18	17	19	8	0	73
	>0.33 to ≤ 0.50	33	31	49	32	14	2	161
	>0.50	27	41	36	36	23	12	175
All Slopes		185	257	222	183	70	15	932

		Event Rates Per 1000 Subject-Weeks						
		Hgb Category (g/dL) →	≤ 10	>10 to ≤ 11	>11 to ≤ 12	>12 to ≤ 13	>13 to ≤ 14	>14
Slope (g/dL/week)	≤ 0.1	61	52	35	39	29	28	45
	>0.10 to ≤ 0.20	60	52	31	53	41	0	46
	>0.20 to ≤ 0.25	68	53	39	39	31	0	46
	>0.25 to ≤ 0.33	58	58	39	59	65	0	52
	>0.33 to ≤ 0.50	85	42	49	41	44	28	49
	>0.50	100	100	61	69	76	93	79
All Slopes		68	55	40	48	47	47	50

Figure 3 (top) displays these event rates graphically. A general trend towards higher event rates for the lowest Hgb categories (≤ 10 ; >10 to ≤ 11) is apparent at the left side of the graph. Event rates are higher in the row corresponding to a Hgb ROR >0.5 g/dL/week. The middle panel shows the event rates for the subset of subjects with a reported history of cardiovascular disease. Rates are generally higher for this subgroup. Of note, higher event rates appear to be associated with the lowest Hgb class (<10 g/dL), and the highest ROR class (>0.5 g/dL/week). For the subset of subjects without a reported history of cardiovascular disease (lower panel), the event rates tend to be lower, but the trends are similar. Importantly, therefore, even subjects without overt cardiovascular disease appear to incur excess risk with Hgb ROR in excess of 0.5 g/dL/week.

In summary, FDA's exploratory analyses suggested that higher Hgb concentration, per se, is not associated with increased rates of events that involve hemodynamic or rheologic mechanisms. Importantly, however, the hemoglobin rate of rise appears to be particularly relevant with respect to these events. Specifically, a hemoglobin rate of rise in excess of 0.5 g/dL/week appears to be associated with increased event rates, irrespective of the presence or absence of overt cardiovascular disease. This finding provided the basis for the Warning on cardiovascular events in the Aranesp package insert.

Figure 3: Relations Between Hgb, Hgb ROR, and AEs With Hemodynamic/Rheologic Mechanisms – ARANESP Group. Top panel – all subjects; middle panel CVD(+) subjects; bottom panel CVD(-) subjects



VI. Clinical Studies of Epogen/Procrit for the Treatment of the Anemia Associated with Chemotherapy of Cancer.

In April 1993, Epogen/Procrit was approved for the indication of treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. The data supporting this supplemental indication was based on pooled data from six randomized, placebo-controlled, double-blind, trials, in a total of 131 anemic cancer patients. 72 of these patients were treated with concomitant chemotherapy regimens that did not contain cisplatin, and 59 patients were treated with regimens that contained cisplatin. Patients were randomized to Procrit 150 units/kg or placebo subcutaneously t.i.w. for 12 weeks.⁵¹

Efficacy Results

Proportion of Patients Transfused During Chemotherapy (Efficacy Population)^a

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

^aLimited to patients remaining on study at least 15 days.

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

^cLimited to patients remaining on study beyond week 6 and includes only transfusions during weeks 5-12.

^dUnadjusted 2-sided $p < 0.05$.

Data were not systematically collected on tumor response, tumor progression, or survival. The reviewer noted that "Based in part on the percentage of Epoetin alfa and placebo-treated patients who discontinued therapy due to death, disease progression or adverse experiences (22% and 13% respectively, $p = 0.25$) the clinical outcome in Epoetin alfa and placebo-treated patients appeared to be similar.

FDA noted that Procrit could potentially serve as a growth factor for malignant tumors, however the pivotal studies that had been used to support supplemented approval were not designed to examine tumor response rate, time to progression or overall survival. Because of this concern, Amgen agreed to the following post-marketing commitment to conduct a study to assess:

“The effect of Epoetin alfa on initial response rate and response rate at the completion of chemotherapy, site of first relapse and overall survival will be investigated in a randomized, double-blind, placebo-controlled phase IV study in patients with limited stage small cell lung cancer.”⁵²

VII. Post-Marketing Study to Assess for Tumor Stimulatory effects of Epogen/Procrit: Study N93-004

Protocol, Study N93-004, “The Effect of r-HuEPO in Patients with Small Cell Cancer (SCLC): A Randomized, Double blind, Placebo-controlled Trial” to FDA on January 7, 1993. In July 2001, Amgen and Ortho Biotech LP notified FDA of its intention to prematurely terminate the study after accrual of 225 subjects, (instead of the planned accrual of 400), due to slow accrual rates. FDA stated that the results of than study should be submitted and, based on review of the data, a determination would be made as to whether additional studies would be required.

Study N93-004 was a randomized, double-blind placebo-controlled trial conducted at 35 sites in the United States. The primary objective was to determine the effect of Procrit on tumor response in SCLC in patients receiving treatment with etoposide and cisplatin. The primary endpoint was determination of the objective response rate (defined as partial response plus complete response) after 3 cycles of chemotherapy. The secondary endpoints were: effects of Procrit on survival, hemoglobin, and transfusion rates. Eligible subjects were those with newly diagnosed limited or extensive stage small cell carcinoma of the lung. Subjects were randomized to receive chemotherapy with etoposide and cisplatin every 3 weeks for 3 cycles with either Procrit 150 IU/kg t.i.w. or placebo. Subjects continued to receive study medication until approximately 3 weeks after the final cycle of chemotherapy. No target hemoglobin was specified, but the study medication was to be held if the hemoglobin rose above 16 g/dl and restarted at a 50% dose reduction when the hemoglobin fell to less than 14 g/dl.

The study was designed with a sample size of 400 (200 patients/arm). The sample size was selected in order to be able to exclude, with 90% power, an absolute decrement in overall response rate of 15% in the Procrit-treated arm as compared to placebo, based on the 95% confidence interval around the observed difference in response rate. The assumed response rate in the placebo arm was 60%.

In the intent-to-treat population of 224 subjects, there were 115 in the placebo and 109 in the Procrit arm. There were no differences between the two groups in baseline demographics or other baseline entry variables (including baseline hemoglobin), with the exception of a slightly higher proportion of subjects in the Procrit arm had extensive stage SCLC than in the placebo arm (66% versus 59%). In both arms, 72% received at least 3 cycles of chemotherapy. The median number of cycles was 4 for both arms. The

median doses of both etoposide and cisplatin were not significantly different between the groups.

Efficacy Results

For the primary endpoint, the tumor response (CR + PR) after 3 cycles of chemotherapy, the results were as follows (intent-to-treat population):

	Placebo (n=115)	Procrit (n=109)
No. having CR/PR	77	79
Tumor response rate	67%	72%
95% CI around observed response rate	58-67%	64-81%
95% confidence interval around observed difference in ORR	-6% to 18%	

The observed difference in tumor response rates between the Procrit and placebo arms was 6% (95% CI: -6% to 18%). The lower bound of the 95% confidence interval around the difference in response rates was -6%, indicating that in this trial, the response rate observed in the Procrit arm would not be more than 6% lower than that of the placebo arm. The methods used to collect data on tumor response and patient follow-up did not permit the determination of time to progression.

Safety Results

Thrombotic Vascular Events:

Twenty-two percent of the subjects in the Procrit arm and 23% of the subjects in the placebo arm expired at least one thrombotic vascular event. The incidences of specific subtype of thrombotic vascular event were generally similar between the two treatment arms with the exceptions of chest pain, which was reported by 14% of placebo treated subjects as compared to 7% of Procrit-treated subjects, and vascular (extracardiac) disorders, which was reported in 4% of placebo patients and 10% of Procrit-treated patients.

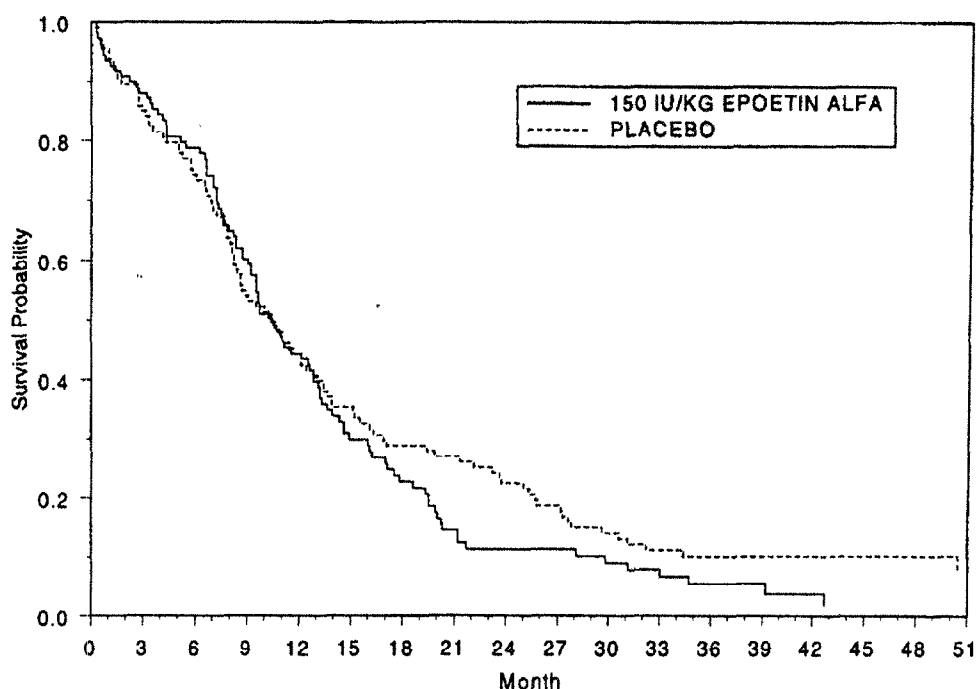
**Incidence of Thrombotic Vascular Events
In Study N93-004**

Preferred Term	Placebo N=115	Procrit N=109
Chest pain	16 (14%)	8 (7%)
Chest pain substernal	0 (0)	1 (1%)
Vascular (extracardiac)	5 (4%)	11 (10%)
Cerebrovascular disorder	2 (2%)	3 (3%)
Phlebitis	1 (1%)	3 (3%)
Thrombophlebitis, deep	1 (1%)	2 (2%)
Thrombophlebitis	1 (1%)	1 (1%)
Peripheral ischemia	0 (0)	1 (1%)
Phlebitis, superficial	0 (0)	1 (1%)
Platelet, bleeding, and clotting	7 (6%)	5 (5%)
Thrombosis	3 (3%)	2 (2%)
Pulmonary embolism	2 (2%)	2 (2%)
Thrombosis venous arm	2 (2%)	1 (1%)
Thromboembolism	0 (0)	1 (1%)
Myo-, endo-, pericardial- and valve	1 (1%)	2 (2%)
Myocardial infarction	0 (2)	2 (2%)
Angina	1 (1%)	0 (0)
Heart rate and rhythm	0 (0)	1 (1%)
Cardiac arrest	0 (0)	1 (1%)

Survival⁵³

A total of 201 of the 224 subjects enrolled in this study died at some time during the study treatment period or 3 year follow-up. The overall mortality rate in the Procrit arm (100 of 109 subjects, 92%) was similar to that in the placebo arm (101 of 115 subjects, 88%). The median duration of survival (based on Kaplan Meier estimates) was 10.5 months among Procrit-treated subjects compared with 20.4 months among placebo-treated subjects.

Summary of Survival Over Time in N93-004 (Intent-to-treat Population)



The FDA biostatistical reviewer confirmed the sponsor's survival analysis, presented in the table below (Sponsor's Table 17)⁵⁴:

Sponsor's ITT Survival Analysis in Months*
(Table 17)

	PLACEBO			PROCRIT		
	Estimate	95% CI		Estimate	95% CI	
Quartile		Lower	Upper		Lower	Upper
75%	5.9	3.5	7.7	6.6	4.3	7.6
Median	10.4	8.3	12.9	10.5	9.2	12.9
25%	23.3	15.3	27.3	17.1	14.0	20.1

* Note: To convert days to months, the sponsor used a divisor of 28 days rather than the more usual 30.437 days, which takes into account leap year.

A total of 201 out of 224 subjects enrolled in this study died at some time during the study treatment period or during the 3-year follow-up. A somewhat higher proportion of subjects assigned to the Procrit arm had extensive stage disease at diagnosis (66%) compared to the placebo arm (59%). Since stage of disease (limited vs. extensive) was a stratification factor, the FDA statistical reviewer examined the descriptive stratified Kaplan-Meier analysis provided by the sponsor. Kaplan-Meier survival plots were comparable in the Procrit and placebo arms through Months 17 to 18 after study start. As

for the overall ITT population, the variability after study completion along with the small number of subjects in the two extent of disease subgroups does not permit any conclusive statement to be made.

Tumor Outcomes

Response duration was not calculated. No data were provided for date of tumor response.

Time to disease progression (TTP) could not be accurately calculated. In Protocol N93-004 subjects were allowed to withdraw early for progressive disease. In these cases, the date of discontinuation was captured and not the actual date of progression. For the 25 subjects who were discontinued from the study for disease progression, the progression date was on or before the date of discontinuation.”

VIII. Clinical Studies of Weekly Dosage Schedules of Epogen/Procrit for Treatment of Anemia Associated with Cancer Chemotherapy

The recommended starting dose of Epogen/Procrit in cancer patients receiving chemotherapy in the package insert is 150 Units/kg t.i.w. However, many community oncologists administer Epogen/Procrit at a dose of 40,000 Units once a week. FDA is currently reviewing the results of a study⁵⁵, in which 344 patients with cancer receiving chemotherapy were randomized to receive either placebo or Epogen/Procrit 40,000 U/week. The patient population consists of anemic patients with a variety of malignancies, who were receiving standard therapy. Given the heterogeneity of the population and cancer treatments, no comparative assessments are possible regarding tumor outcomes (response rates, time-to-progression) or survival. Analyses of adverse events, including incidence of thrombotic vascular events is in progress.

IX. Clinical Studies of Aranesp in the Treatment of the Anemia of Cancer Chemotherapy

Aranesp (darbepoetin alfa) received supplemental approval “for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy” in July 2002.⁵⁶

The data supporting this supplemental indication was based on the results of Protocol 980297: A Double-blind, Placebo-Controlled, Randomized, Study of NESP for the Treatment of Anemia in Lung Cancer Receiving Multicycle Platinum Containing Chemotherapy. This was a multicenter, multinational study in which 320 patients were enrolled and randomized 1:1 to receive either Aranesp 2.25 µg/kg QW (treatment arm) or placebo. Eligibility criteria included lung cancer (either small cell carcinoma or non-small cell carcinoma) a cancer treatment plan of at least 12 additional weeks of platinum-

containing chemotherapy, and anemia (hemoglobin ≤ 11 g/dl). The primary endpoint was the estimated Kaplan-Meier proportion of subjects who received RBC transfusions between week 5 and the end of the treatment phase (EOTP). Week 5 was specified since hematologic responses to Aranesp are not observed until 3-6 weeks after the initiation of therapy.

Efficacy Results

The primary efficacy analysis was conducted in patients who had completed the first 4 weeks of study. In this analysis, patients who withdrew or discontinued from the study after week 4 for death or disease progression were censored, while those who withdrew for any other reason were imputed to be transfused (treatment failures for primary endpoint).⁵⁷ The Kaplan-Meier proportion of patients transfused was 51% for the patients in the placebo arm versus 21% in the Aranesp arm. The same analysis was also performed in the intent-to-treat dataset, which included patient information across all 12 weeks on. The comparable figures were 60% for the Kaplan-Meier proportion of transfused patients in the placebo arm versus 26% in the Aranesp arm.

Proportion of Patients Transfused in Weeks 5 through End-of-Treatment In Protocol 980297

	Placebo arm N=149	Aranesp arm N=148
Number of patients transfused	74	39
Kaplan-Meier estimated proportion	51%	21%
95% CI	43, 60	15, 28

Secondary analysis

Proportion of Patients Transfused Between Entry and End-of-Treatment In Protocol 980297

	Placebo arm N=158	Aranesp arm N=156
Number of patients transfused	89	53
Kaplan-Meier proportion	60%	26%
95% CI	52, 68	20, 33

Safety analyses

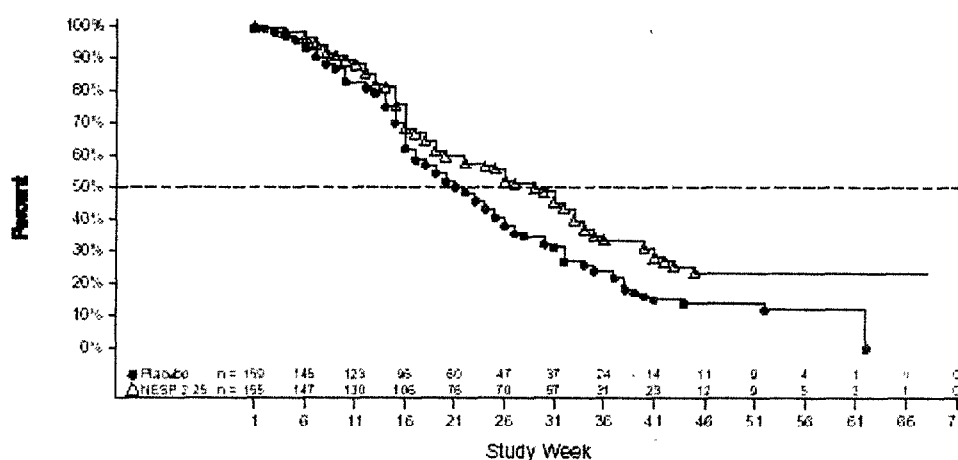
There were 314 protocol 980297 patients who received study drug; 156 were randomized to Aranesp and 158 to placebo. A single patient randomized to the Aranesp arm failed to receive the study drug. In the efficacy analyses, he remained in the Aranesp arm to which he had been randomized but for Safety studies he was switched to the placebo arm. Thus safety data are provided for 155 Aranesp-treated patients and 159 placebo-treated patients.

Time to Progression

In the long-term follow-up to the pivotal, phase 3 study (NESP 980297), the median observation period was 12 months for disease progression and 11 months for survival. Long-term follow-up analyses were based on the subjects included in the safety analysis set of Aranesp disease progression. All 314 subjects in the safety analysis set are included in the analysis of disease progression, death, and disease progression or death.

Ninety-four subjects (61% of the safety analysis set) in the Aranesp group and 110 subjects (69%) in the placebo group had disease progression either during NESP 980297 or during the long-term follow-up period evaluated. The hazards ratio for disease progression comparing the Aranesp group to the placebo group was 0.70 (95% CI: 0.53, 0.92) based on the Cox-proportional hazards model that includes only treatment group as an independent variable and was 0.71 (95% CI: 0.54, 0.94) after adjusting for tumor type and region. Figure 1 shows the Kaplan-Meier curve for time to disease progression by treatment group for subjects in the safety analysis set. The median time to disease progression in the NESP group was 29 weeks compared with 22 weeks in the placebo group.⁵⁸

Figure 1. Kaplan-Meier Curve of Time to Disease Progression
(Safety Analysis Set of NESP 980297)



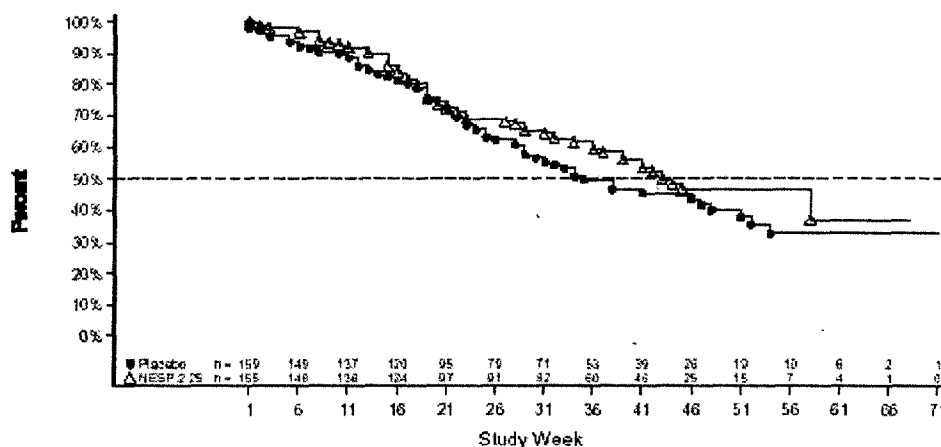
The median time to Disease Progression was 22 weeks for placebo and 29 weeks for NESP.
The hazards ratio (95% CI) adjusting for tumor type and region of NESP to Placebo was 0.71 (0.54, 0.94).
NESP dose is in units of $\mu\text{g/kg/week}$.

Program: statkmpcncn980297anal/strata/strata/program/plotting/time_to_sas
Output: g_time_to_sas.ojm (Date Generated: 12/01/2007 15:36)

Survival

“Sixty-six subjects (43%) in the NESP group and 78 subjects (49%) in the placebo group died within 30 days of the last dose of study drug or during the long-term follow-up period evaluated. The hazards ratio was calculated as 0.80 (95% CI: 0.58, 1.11) based on the Cox-proportional hazards model that includes only treatment group as an independent variable and after adjusting for the effects of tumor type and region. Figure 2 shows the Kaplan-Meier curve for time to death by treatment group for subjects in the safety analysis set. The median time to death in the NESP group was 43 weeks compared with 35 weeks in the placebo group.”⁵⁹

Figure 2. Kaplan-Meier Curve of Time to Death
(Safety Analysis Set of NESP 980297)



The median time to Death was 35 weeks for placebo and 43 weeks for NESP.
The hazards ratio (95% C.I.), adjusting for tumor type and region, of NESP to Placebo was 0.80 (0.58, 1.12).
NESP dose is in units of $\mu\text{g/kg/wk}$.
Program: statshespcn/nesp980297/analysis/statfiles/programs/graphing/time_tup.sas
Output: g_time_tup_dsgm (Date Generated: 03/04/2007 15:53)

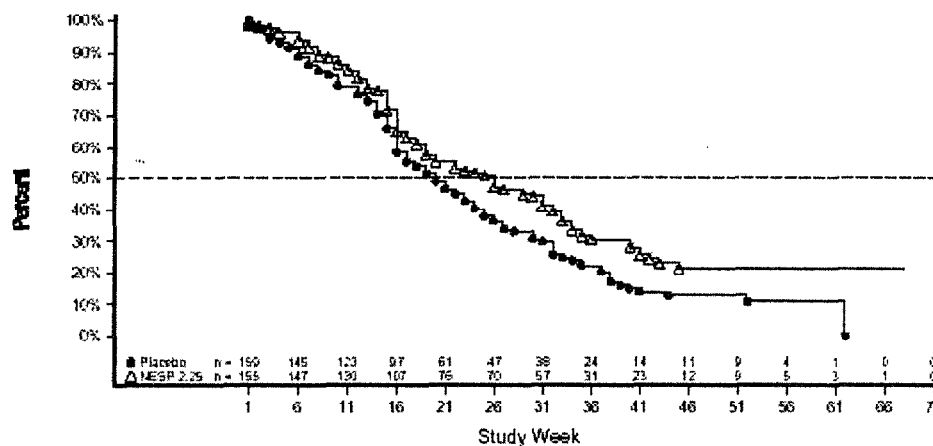
Progression-free Survival

“One hundred five subjects (68%) in the NESP group and 120 subjects (75%) in the placebo group had disease progression or died within 30 days of the last dose of study drug or during the long-term follow-up period evaluated. The hazards ratio was calculated as 0.73 (95% CI: 0.56, 0.95) based on the Cox-proportional hazards model that includes only treatment group as an independent variable and was 0.74 (95% CI: 0.57, 0.97) when adjusted for tumor type and region. This indicates that, on average, subjects in the placebo group had a 35% higher odds of either disease progression or death (i.e., $1 / 0.74$) as compared with subjects in the NESP group.”

“The Kaplan-Meier plot of time to either disease progression or death for all subjects in the safety analysis set by treatment group is shown in Figure 3. The Kaplan-Meier plot is very similar to that for time to disease progression, with an apparent prolonged time to either disease progression or death observed in the NESP group compared with the placebo group. The median time to disease progression or death was 26 weeks for the

NESP group and 20 weeks for the placebo group.⁶⁰

**Figure 3. Kaplan-Meier Curve of Time to Disease Progression or Death
(Safety Analysis Set of NESP 980297)**



The median time to Disease Progression or Death was 20 weeks for placebo and 26 weeks for NESP. The hazards ratio (95% C.I.), adjusting for tumor type and region, of NESP to Placebo was 0.74 (0.57, 0.97). NESP dose is in units of $\mu\text{g/kg/week}$.

Program: stat/nsp/nsp980297/analyze/tables/tables/graphs/g_time_surv.sas
Output: g_time_surv_00000001.pdf (Date Generated: 03/01/2001 15:51)

Exploratory Analyses of Relationships between Rate of Rise of Hemoglobin and Cardiovascular/Thrombotic Events in the Aranesp Integrated Summary of Safety (ISS)

The ISS consisted of 873 patients from 6 major studies who received Aranesp, 115 patients who received Epogen/Procrit in the active-control arms, and 221 patients who received placebo. All patients also received concomitant chemotherapy. The mean observation period for the majority of subjects was 12 weeks on treatment plus 4 succeeding weeks off treatment.

INCIDENCE OF AEs ASSOCIATED WITH EPOETIN ALFA

	ISS			Protocol 980297	
	Aranesp	Placebo	Procrit	Aranesp	Placebo
	n=862	n=217	n=113	n=155	159
Hypertension+	3.7%	3.2%	2%	9 (6%)	6 (4%)
Convulsions**	0.6%	0.5%	1%	0	1 (1%)
Thrombotic events\$	6.2%	4.1%	1%	7 (5%)	5(3%)

+ Hypertension included preferred terms Hypertension and Hypertension aggravated

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

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

When the incidence for all of the Preferred Terms are combined there was no major difference in the incidence of thrombotic events between study arms. This was attributable to the large variety of types of venous adverse events. Notably, pulmonary emboli and related thromboembolism were restricted entirely to the Aranesp subjects. There was also a trend toward higher incidences of thrombophlebitis thrombophlebitis deep, and thrombosis in Aranesp-treated patients. The incidences of adverse event by specific preferred terms across the treatment groups in the ISS are displayed in the following table.

Incidence of Thrombotic Events By Preferred Term

Preferred term	rHuEPO N= 115	Aranesp N=873	Placebo N=221
Embolism, pulmonary	0	11	0
Thromboembolism	0	1	0
Thrombophlebitis	0	4	0
Thrombophlebitis , deep	0	2	1
Thrombosis, venous	1	8	2
Thrombosis, venous deep	3	27	6
Thrombosis	0	5	0
Total # AEs	4 (4.7%)	58 (7.4%)	9 (4.1%)
Total pts with AEs	85	781	221

The FDA requested that Amgen provide an analysis exploring the correlations between rate of rise of hemoglobin (ROR) and the following: death, hypertension, cerebrovascular events (seizures, TIAs, "strokes"), cardiovascular events (myocardial infarction, CAD, arrhythmia, angina, CHF, cardiac failure, cardiac arrest), thrombotic events, ischemic and peripheral vascular disease and pulmonary edema. For comparison, the results of a similar analysis using Aranesp-treated patients enrolled in Amgen-sponsored studies for treatment of chronic renal failure were also provided. .

Adverse event/week per 1000 events⁶¹ as a function of Rate of Rise of Hgb

Adverse Event Term	Patients with CRF N=1598			Patients with Cancer N=873		
	Rate of rise in hgb/week			Rate of rise in hgb/week		
	< 0.1	0.5 to 1.0	1.0 or >	< 0.1	0.5 to 0.67	0.67 or >
Hypertension	7.5	19.9	13.1	2.1	1.8	5.2
Seizures	0.4	1.0	1.9	1.1	0	1.3
Vascular*	1.7	3.8	7.5	1.1	7.1	3.9
Fluid overload	15.4	18.9	35.4	25.6	26.5	29.5
Cardiac arrest	0.0	1.0	1.9	0	0	0
Myocardial infarction, acute	0.4	0.3	1.9	0	0	0
Pulmonary edema	1.5	3.1	7.5	0	0	0

*thrombosis, ischemia, infarction

The analysis provided suggests that the incidences of hypertension and vascular events are increased in patients with higher ROR compared to those who had less rapid ROR.⁶²

The ISS database was also used to examine for a possible relationship between the hemoglobin value at the time of an event and the incidence of specific adverse events, possibly or probably associated with Aranesp. The FDA reviewer concluded that: "The major events of interest were death, hypertension, cardiac events, cerebrovascular events, and thrombotic events. There did not appear to be a relationship between increasing hemoglobin concentration and increased risk of adverse event across any the adverse event groups evaluated. Death (n=18) was the only event group in which the highest event rates for Aranesp and Procrit were in the category representing the highest hemoglobin increase (> 0.667 g/dl/week hemoglobin slope). Of these 18 subjects, 12 received Aranesp, 4 received placebo, and 2 received Procrit. The death rate was 13.6 per 1000 subject weeks and 7.8 per 1000 subject weeks for the Procrit and Aranesp groups, respectively. Of the 18 subjects how died in this slope category, 13 died of disease progression, 3 died of sepsis, and 2 died of clinically suspected but not objectively confirmed pulmonary embolisms."⁶³

**Incidence of Selected Adverse Events Occurring
Within 14 days of Rapid Rise of Hgb⁶⁴**

	Placebo n=221	Procrit N=115	Aranesp N=873
Number of patients with hypertension (%)	5 (2.2%)	0	12 (1.3%)
Number of patients with Convulsions (%)	0	0	2 (0.2%)
Number of Patients with Thrombosis (%)	5 (2.2%)	2 (1.7%)	14 (1.6%)

Because the combined term "thrombosis" included a small number of specific thrombotic events that were clearly increased in the Aranesp-treated group (notably pulmonary

emboli), an assessment was made of the clinical course of these subjects. The displayed in the following table summarizes the dose, schedule, and clinical treatment course of patients who suffered pulmonary emboli.

Assessment of ROR and Maximum Hemoglobin Levels in Relationship to the Development and Time of Onset of Pulmonary Emboli in Aranesp-Treated Patients

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

The protocol permitted maximum hemoglobin thresholds of 14.0 g/dl for women and 15.0 g/dl for men. An analysis was performed in which the number and percentage of adverse events occurred in each study population in patients who exceeded the maximum hemoglobin threshold, if the event happened within 14 days of the time the threshold was exceeded.

Adverse event By Treatment Assignment in Patients Exceeding Maximum Hgb Threshold⁶⁵

	Placebo N=221	Procrit N=115	Aranesp N=873
Number patients exceeding maximum threshold (%)	4/221 (2%)	15/115 (14%)	114/873 (13%)
Number patients with hypertension within 14 days	0	0	4
Number Pts with convulsions within 14 days	0	0	0
Number Pts with Thrombosis within 14 days	1	0	3

Incidence of Specific Adverse events in Patients Exceeding Maximum hemoglobin Threshold Regardless of Study Arm and Regardless of Time of Occurrence⁶⁶

Adverse Event Term	Maximum threshold not reached (n=1074)	Maximum threshold reached (n=134)
Hypertension	33 (3%)	8 (6%)
Arrhythmia	85 (8%)	7 (5%)
Coronary artery disease	18 (2%)	3 (2%)
CHF	22 (2%)	2 (1%)
CVA	9 (1%)	1 (1%)
Cardiac arrest	2 (<1%)	0
Fluid overload	388 (36%)	42 (31%)
Myocardial infarction	5 (<1%)	0
Seizures	5 (<1%)	1 (1%)
Vascular thrombosis & ischemia/infarction	67 (6%)	5 (4%)

- The FDA reviewer concluded: “No major disparities are noted. It is noted that hypertension was higher in the Aranesp population.”⁶⁷

In these exploratory analyses, there was no clear association between risk of cardiovascular or thrombotic adverse events and either maximum hemoglobin levels achieved or the rapidity of the rate of rise in hemoglobin.

X. Study EPO-INT-76: The Breast Cancer Erythropoietin Trial (BEST)

The Breast Cancer Erythropoietin Trial (BEST), designed by Johnson & Johnson, was conducted to extend and possibly confirm the results of an earlier trial (Study EPO-INT-10) EPO-INT-10⁶⁸ was a randomized, placebo-controlled trial that had enrolled 375 subjects. The patients had either solid or non-myeloid hematologic malignancies and hemoglobin levels of either ≤ 10.5 g/dl or between 10.5 and 12.0 g/dl after a hemoglobin decrease of at least 1.5 g/dl per cycle since starting chemotherapy. Patients received study drug for 12 to 24 weeks. No specific target hemoglobin was given, however, the dose of EPREX was to be held if the hemoglobin was greater than 15 g/dl, and restarted at 12 g/dl. The trial was not powered for survival, but there was a trend in overall survival favoring the EPREX arm (log rank test $p=0.13$; Cox regression analysis hazards ratio of 1.309 ($p=0.052$)). At 12 months, the Kaplan-Meier estimate of survival was 60% for the EPREX arm and 49% for the placebo arm. The median survival times were 17 months with EPREX and 11 months with placebo. An additional basis for initiation of EPO-INT-76 was the supposition that use of an erythropoietin to increase hemoglobin levels might improve survival given the literature suggesting a link between low hemoglobin levels (as a marker for tumor hypoxia), poorer response to treatment (both radiation and chemotherapy), and worsening survival.⁶⁹

Study EPO-INT-76 was designed to test the hypothesis that maintaining hemoglobin in the range of 12 to 14 g/dl via the administration of EPREX would improve survival and quality of life in patients with metastatic breast cancer receiving chemotherapy. The study was conducted at 139 sites in 20 countries (Western and Eastern Europe, Canada, Australia, South Africa). Eligible patients were women with breast cancer who were receiving first-line chemotherapy for metastatic disease. Randomization was stratified by the following three variables: disease restricted to the skeleton; extraskkeletal measurable disease, extraskkeletal nonmeasurable disease.

Subjects were randomly assigned to receive either 40,000 IU EPREX or placebo subcutaneously QW. Study drug was administered once a week to maintain hemoglobin in the range of 12 to 14 g/dl for 12 months. The choice of chemotherapy or hormonal therapy was left to the discretion of the investigator. Study drug was to be initiated only when the hemoglobin was 13 g/dl or lower. The study drug was withheld if the hemoglobin rose above 14 g/dl.⁷⁰

The primary endpoint was survival at 12 months after randomization. Secondary endpoints included assessment of hematologic effects, tumor response rates to chemotherapy, time to progression, transfusion requirements, and quality of life determinations.

The planned enrollment was 870 (435/treatment group). A total of 939 subjects (470 on placebo and 469 on EPREX) were enrolled and analyzed in the intent-to-treat (all randomized) population. The sample size was based on the assumption of 70% survival in the placebo arm and 80% in the EPREX arm at the end of the 12-month double-blind treatment phase. This assumption took into consideration an estimate that 25% of the study population comprised subjects who had bone only metastases. The primary statistical objective was to detect a minimum absolute 10% improvement (i.e., 80% survival). A 100% follow-up was anticipated with respect to 12-month survival status. Based on these assumptions and a 2-sided significant level of 0.05, a planned total of 870 subjects (435/arm) yielded greater than 90% power for testing the null hypothesis of an equal 12-month survival rate between the two treatment arms.

Efficacy and Safety Results

939 patients were enrolled. The study was initiated in June 2000, and the last subject was enrolled in June 2001. In January 2002, an Independent Data Monitoring Committee was established at the request of the Ethics Committees of Germany and the United Kingdom. In April 2002, the IDMC reviewed the available data from 938 subjects. The Committee expressed concern over an unexpected excess mortality observed in the EPREX-treated arm. At the time of this interim analysis, there were 179 deaths, 101 in the EPREX-treated arm and 78 in the placebo arm. On April 24, 2002, the IDMC asked Johnson & Johnson to discontinue administration of the study drug to all participating subjects. The J&J also commissioned an outside consulting firm to conduct a medical chart review, in which the primary documents were reviewed in a blinded manner in an attempt to "collect additional information concerning factors of prognostic significance for breast cancer and potentially fatal medical conditions". This latter review was conducted in

August 2002. The results in the tables below contain data from the "Clinical Trial Database" which was derived from the Case Report Forms (CRFs) submitted by the investigators at each site; and the "Medical Chart Review Database" that was based on a chart review by an outside consulting firm.

The results of the unplanned interim analysis of this study are as follows:

- The Kaplan-Meier estimates for 12-month survival in the intent-to-treat population was shorter in the EPREX arm (70%) compared with the placebo arm (76%). This difference was statistically significant ($p=0.0117$, relative risk=1.359).
- At 4 months after randomization, there was different evidence of increased early in mortality in patients randomized to EPREX; among 57 subjects who died within the first 4 months, 41 (72%) were in the EPREX arm and 16 (28%) were in the placebo arm.
- Twice as many patients in EPREX arm experienced disease progression as in the placebo arm: 28 (6%) versus 13 (3%).
- There was also an increased incidence to thrombotic vascular and cardiovascular adverse events: 2.3% in the EPREX arm versus 0.4% in the placebo arm.
- The overall response rate (complete and partial responses) was 46% in the placebo arm and 45% in the EPREX arm.
- Patients in the EPREX arm received study drug for an average of 30.4 weeks versus 36.9 weeks for the placebo arms.
- In the EPREX arm, 59% of hemoglobin determinations were within the target range (12-14 g/dl). In the placebo arm, this value was 45%.⁷¹ Of note, the median baseline hemoglobin was 12.8 g/dl in both arms.

Causes of Death Among Subjects Who Died Within the First 4 Months After Randomization (Study EPO-INT-76: Intent-to-treat Population)
Data Source: Clinical Trial Database⁷²

	Placebo (N=470)	EPREX (N=469)
No. (%) died within 4 months	16 (3)	41 (9)
No. (%) alive at 4 months	454 (97)	428 (91)
Cause of death within 4 months, no. (%)		
Chemotherapy toxicity	1 (0)	3 (1)
Disease progression	13 (3)	28 (6)
Missing	0	1 (0) ^a
Thrombotic vascular event	1 (0)	5 (1)
Other ^b	1 (0)	4 (1)

**Cardiovascular/Thrombotic/Vascular Deaths
(Study EPO-INT-76: All Randomized Subjects)**
Data Source: Medical Chart Review Database

	Placebo (n=468)	EPREX (n=469)
	N (%)	N (%)
Cardiovascular/TVE death in the first 4 months after study randomization	2 (0.4%)	11 (2.3%)
Cardiovascular/TVE death more than 4 months after study randomized	7 (1.5%)	3 (0.6%)
Total	9 (1.9%)	14 (3.0%)

^a Cause of death was unknown. Subject died suddenly on Study Day 36.

^b Other causes include: fatty embolism, ischemic colon perforation, pulmonary edema, unknown.

**Causes of Death in Subjects Dying During the 4 Months After Study Randomization
(Study EPO-INT-76: All Randomized Subjects)
Data Source: Medical Chart Review Database**

	Placebo N=468	EPREX N=469
	N (%)	N
Disease Progression	10 (2%)	21 (4%)
Adverse event ^a	1 (<1%)	10 (2%)
Other ^b	5 (1%)	10 (2%)
Total	16 (3%)	41 (9%)

^a placebo: 1 sepsis; epoetin alfa: 7 sudden death/cardiac/TVE, 1 hepatotoxicity/heart failure, 1 unknown, 1 multiorgan failure.

^b placebo: 1 fatty embolism, 2 cardiac/TVE, 1 unknown, 1 pneumonia; epoetin alfa: 4 sudden death/cardiac/TVE; 1 pancytopenia, 3 unknown, 1 pneumonia, 1 hepatorenal syndrome.

Survival

Primary Efficacy Variable: 12-Month Survival Rate⁷³

	Placebo	EPREX	Hazard ratio (95% CI) p value ^a
Intent-to-treat	N=470	N=469	1.37 (1.37,1.74) 0.0117
Died ^b	115 (24%)	148 (30%)	
Survived ^b	355 (76%)	321 (70%)	
Efficacy ^c	N=456	N=448	1.35 (1.05,1.74) 0.0189
Died ^b	109(23%)	137 (29%)	
Survived ^b	347 (77%)	311 (71%)	

^a Based on Cox's model stratified by metastatic category

^b Percentage of subjects who survived or died within 12 (+ 2 week window) of randomization are based on Kaplan-Meier estimates.

^c Efficacy population comprised only of subjects who received study drug.

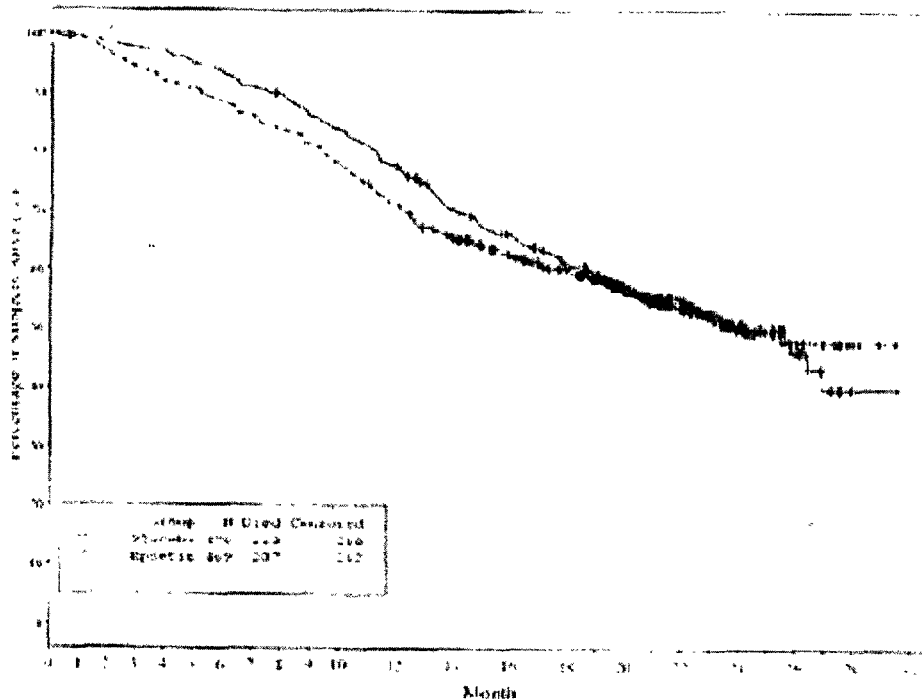


Figure 4: Kaplan-Meier Curves of Survival (August 2003⁷⁴)

The results of this study have not been published. However, Dr. Leyland-Jones, the principal investigator of the study, did publish an article describing the results in Lancet Oncology. He criticized the design and conduct of the study: “the study was not designed to prospectively collect data on many potential prognostic survival factors that might have affected the study outcome.” “The study design suffered from a lack of standard assessment and documentation of important prognostic factors for survival including: definition of disease site; initial prognosis and specific assessment of tumor response at predefined intervals; and type duration and dose of chemotherapy”. He stated “it is not currently possible to account for the observed difference in survival by referral to differences in prognostic indicators between treatment groups or to rule out the possibility of an adverse treatment effect”.

However, he concluded, “the study findings do not support the use of erythropoietin as an adjunct to first-line chemotherapy for patients with metastatic breast cancer who have normal hemoglobin concentrations”.

XI. The Henke Study

Previous studies indicated that the results of radiotherapy for malignant disease are less effective when anemia is present⁷⁵. Henke et al conducted a study to test the hypothesis that correction of anemia in subjects receiving radiation therapy for the treatment of head and neck carcinoma could possibly improve tumor control.

In a study published in The Lancet in October 2003, Henke et al⁷⁶ reported a double-blind, placebo controlled trial in subjects with squamous cell carcinoma of the head and neck who were undergoing treatment with radiation therapy, and were randomized to receive either epoetin beta or placebo. Eligibility criteria included anemia (Hgb < 12.0 g/dl for women and < 13.0 g/dl for men), advanced stage disease (T3, T4 or nodal involvement), and were scheduled to receive either definitive treatment with radiotherapy or postoperative radiotherapy.

Patients were stratified according to tumor resection status: stratum 1: postoperative radiation of complete (R0) resection; stratum 2: postoperative radiation of incompletely resected disease, stratum 3: primary definitive radiotherapy. Either placebo or epoetin beta (300 IU/kg) was administered subcutaneously three times a week. The study drug was started 10 to 14 days before radiotherapy and was continued throughout the radiation treatments. Study drug was discontinued when the target hemoglobin exceeded 14.0 g/dl for women or 15.0 g/dl for men.

Patients were seen for first follow-up 6 weeks after the end of radiotherapy, and thereafter every 3 months for assessment of locoregional control and survival.

The primary endpoint was locoregional progression-free survival, defined as the time to locoregional tumor progression or death, whichever occurred first.⁷⁷ The primary analysis was to be performed in the intent-to-treat population. The study power was set at 80% to detect a 32% risk -reduction in locoregional progression-free survival at 220 events. The authors also included a "radiotherapy-correct population" that consisted of patients who received radiation according to protocol and presented on at least one follow-up visit; and a "per-protocol population" that included all the radiotherapy-correct population except those who received less than 80% of the scheduled studied medicine administrations. (see Figure 5, below).

Three hundred and fifty one patients in 23 sites were enrolled.

Table 1. Baseline characteristics

Characteristics	Placebo (n=171)	Epoetin β (n=180)
Male sex	145 (85%)	158 (88%)
White patients	171 (100%)	179 (99%)
Median (range) age (years)	57 (36-87)	58 (35-81)
Median (range) weight (kg)	65.5 (40-113)	67 (42-115)
Current smoker	91 (53%)	118 (66%)
Median (range) haemoglobin concentration (g/L)	118 (6.9-14.6)	117 (8.5-14.4)
Median (range) serum erythropoietin concentration (U/L)	11 (3.3-168.1)	11 (11-446.2)
Relapse at entry	13 (8%)	18 (10%)
Tumour location		
Oral cavity	36 (21%)	43 (24%)
Oropharynx	74 (43%)	72 (40%)
Hypopharynx	43 (25%)	40 (22%)
Larynx	39 (23%)	41 (23%)
AJCC stage		
I	2 (1%)	2 (1%)
II	0	6 (3%)
III	46 (27%)	37 (21%)
IV	123 (72%)	135 (75%)
Treatment stratum		
1	94 (55%)	102 (57%)
2	38 (22%)	39 (22%)
3	39 (23%)	39 (22%)
Resection status		
R0	94 (71%)	102 (72%)
R1	33 (25%)	33 (23%)
R2	5 (4%)	6 (4%)

AJCC=American Joint Cancer Committee. Values n (%) unless marked otherwise.

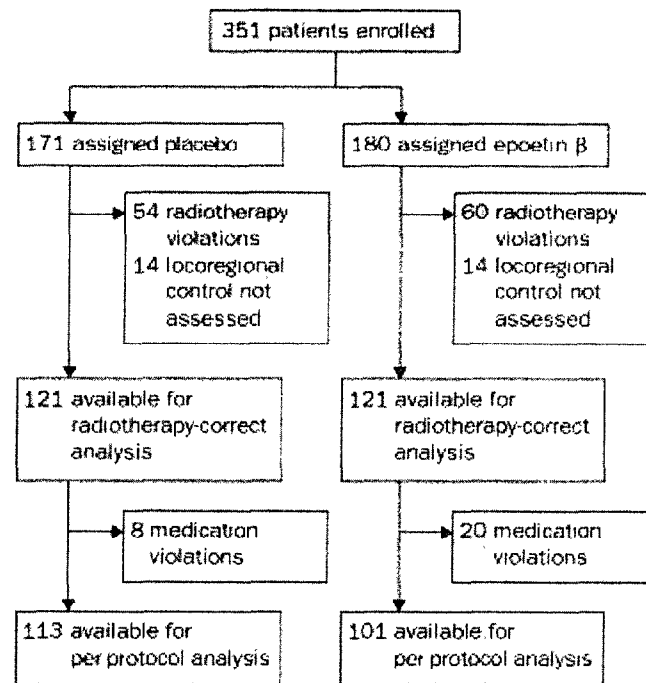


Figure 5.

Efficacy Results

The major findings in this study (Table 2 and Figure 6, below):

- The stage-adjusted and stratum-adjusted relative risk for locoregional progression-free survival was 1.62 for epoetin beta (95% CI 1.22-2.14, $P=0.0008$) (table 2).
- The corresponding Kaplan-Meier estimate showed a median locoregional progression-free survival of 745 days for placebo versus 406 days for epoetin beta ($p=0.04$, figure 2).
- For locoregional progression the relative risk was 1.69 (95% CI 1.16-2.47, $P=0.007$).
- In the actuarial analysis, patients in the placebo arm had an estimated median survival of 928 days compared with an estimated median survival of 605 days in the epoetin beta arm ($p=0.09$).
- The mean hemoglobin concentrations after 4 weeks of treatment were 12.3 g/dl for the placebo arm and 14.8 g/dl for epoetin beta arm.

“In the intent-to-treat population, locoregional tumor progression occurred in 49 placebo- and 65 epoetin beta-treated patients, with 122 and 115 censored observations, respectively. The adjusted relative risk for locoregional progression was 1.69 (95% CI 1.16-2.47, $p=0.007$). The univariate Kaplan-Meier estimate showed a difference in time to progression favouring placebo (median not reached versus 280 days, $p=0.09$). In the

same population, 89 placebo and 109 epoetin beta patients died (82 and 71 censored). The adjusted relative risk of death was 1.39 for epoetin beta patients (95% CII 1.05-1.84, $p=0.02$). In the actuarial analysis, patients treatment with placebo survived a median of 928 days compared with 605 days in the epoetin beta group ($p=0.09$).⁷⁸

Exploratory Analyses by Randomization Stratum:

“According to stratum, locoregional tumor progression or death occurred in 41 placebo and 47 epoetin beta patients in radiotherapy stratum 1, and the Kaplan-Meier estimate for locoregional progression-free survival was 1152 and 1049 days, respectively, ($p=0.9$). By contrast, 16 placebo and 30 epoetin beta patients in stratum 2 experienced locoregional progression or died, and median locoregional progression-free survival was 1791 and 377 days, respectively ($p=0.001$, Figure 2, below). Similarly, in stratum 3, 35 Phase 1 and 39 epoetin beta patients had locoregional tumor progression or died and the Kaplan-Meier analysis showed a favourable outcome for placebo (207 versus 141 days, $p=0.006$, Figure 2).” “Multivariate analysis, including treatment stratum, tumor stage, baseline smoking, and relapse status, tumor site, hemoglobin concentration, transferrin saturation, and days between start of drug administration and radiotherapy supported the finding that epoetin beta treatment is associated with unfavourable outcome (relative risk 1.26 [95% CI 0.93-1.7], $p=0.13$). “

Table 2. Effect of epoetin- β treatment on study endpoints

Population and outcome	Relative risk (95% CI)	p
Intention to treat		
Locoregional progression-free survival	1.62 (1.22-2.14)	0.0008
Locoregional progression	1.69 (1.16-2.47)	0.007
Survival	1.39 (1.05-1.84)	0.02
Radiotherapy correct		
Locoregional progression-free survival	1.42 (1.01-2.01)	0.04
Locoregional progression	1.38 (0.88-2.14)	0.15
Survival	1.22 (0.86-1.73)	0.26
Per protocol		
Locoregional progression-free survival	1.35 (0.94-1.95)	0.11
Locoregional progression	1.41 (0.87-2.27)	0.16
Survival	1.13 (0.78-1.64)	0.52

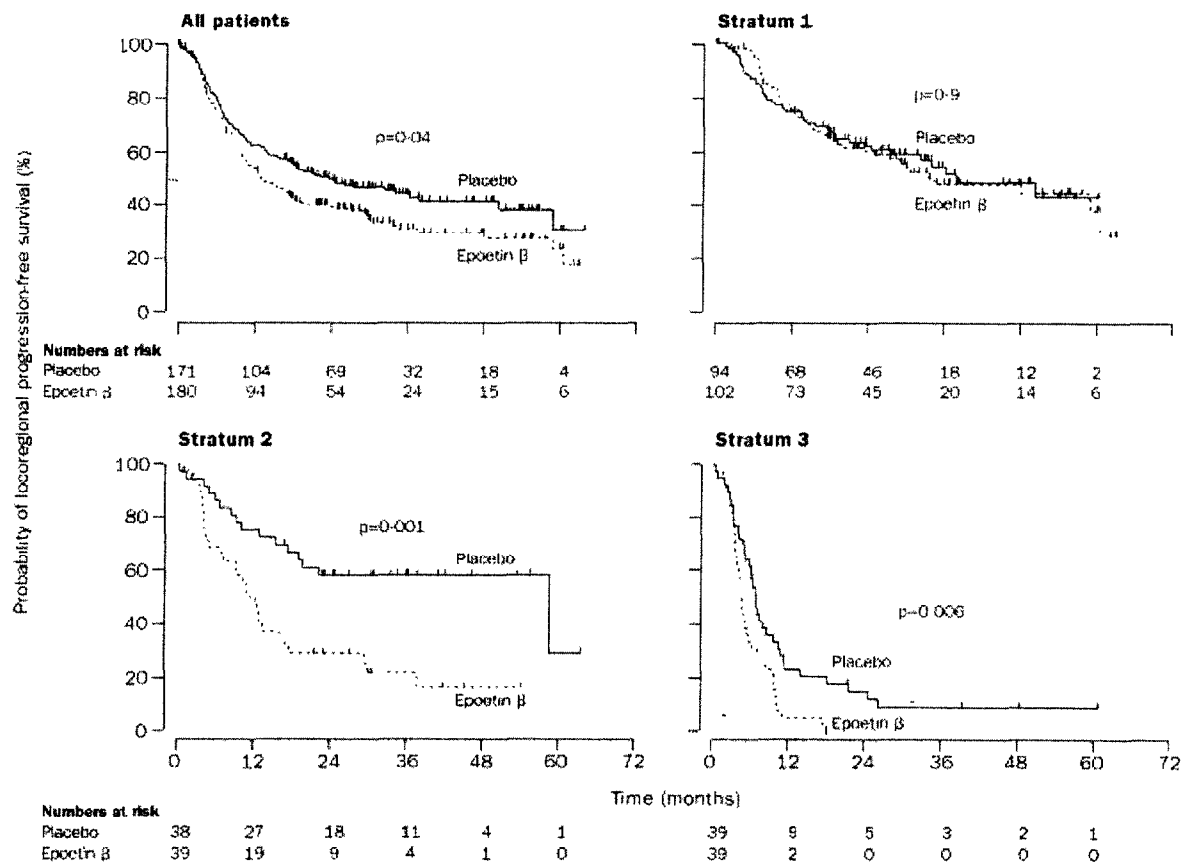


Figure 6: Probability of Locoregional Progression Free Survival

Safety Findings

Vascular disorders (hypertension, hemorrhage, venous thrombosis/pulmonary embolism, CVA) developed in 5% of the placebo group and in 11% of the epoetin beta arm.

The numbers of patients who died from “cardiac disorders” also differed: five placebo-treated patients as compared to ten epoetin beta-treated patients.

Conclusions

In his discussion Henke called the poorer progression-free survival in the epoetin treated patients an “unexpected finding”. In Letters to the Editor in *The Lancet*⁵⁰⁻⁵² this study has been criticized for imbalance in the groups: there was a higher proportion of current smokers and relapsed disease in the epoetin beta group. Information concerning performance status and TNM staging was not provided. Chemotherapy was not part of the treatment for incompletely resected or stage IV patients. In addition the survival data

in this study was lower than comparable studies in head and neck cancer.⁷⁹ The inclusion of subjects with postoperative completely resected tumors was criticized, since “assuming that erythropoietin was given to correct tumour hypoxia, complete resection would mean that there was no hypoxic tumour left to treat”.⁸⁰

Henke responded to these criticisms⁸¹ by stating that chemotherapy was not part of standardized treatment when the study was initiated. As for the poor outcome of the patients in this study, “we deliberately selected patients with low hemoglobin concentrations for whom the outcome was dismal. The comparator studies cited . . . enrolled non-anaemic patients with better prognoses.” He disagreed with the contention that patients irradiated after complete resection should not have been studied: “Prognosis correlates particularly closely with hemoglobin concentration in adjuvant radiotherapy”.

He admitted to not assessing the performance status of all patients “however it was evenly distributed between placebo and erythropoietin patients in the largest recruiting center”.

XII. Procrit Trials Halted by Johnson & Johnson For Excessive Thrombotic and Cardiovascular Adverse Events:

On November 27, 2003, the New York Times reported that Johnson & Johnson had halted four clinical trials “because of unexpected levels of blood clotting”.⁸²

Ortho Biotech LP, through Amgen, has submitted the following details concerning the studies that have been closed.⁸³

1. Protocol EPO-CAN-15: “A randomized, double-blind placebo controlled study to evaluate the impact of maintaining haemoglobin levels using EPREX (Epoetin alfa) in limited disease small cell lung cancer (LD SCLC) patients receiving combined chemotherapy and radiation therapy.” (The LEGACY Trial)

Objective: The objective of this study is to evaluate the impact of maintaining Hgb in the range of 14 to 16 g/dl on disease progression-free survival using EPREX (Epoetin alfa)/Procrit or placebo in limited disease small cell lung cancer subjects receiving combined modality chemoradiation therapy.

This double-blind, randomized, placebo-controlled multicenter trial that was designed to enroll 620 limited disease SCLC subjects scheduled to receive a platinum-based plus etoposide chemotherapy regimen plus concurrent thoracic radiotherapy. Patients could receive between four and six cycles of chemotherapy. Subjects were randomized in a 1:1 ratio to either EPREX/Procrit 40,000 IU or matching placebo. Study drug was administered once weekly by subcutaneous injection to maintain Hgb levels between 14 and 16 g/dl for the duration of the given chemotherapy plus concurrent radiation treatment and prophylactic cranial irradiation (if given). Both groups received RBC transfusions if clinically necessary. Subjects who met the entry criteria were randomized and study drug was administered when the Hgb was ≤ 14 g/dl. Subjects completed all

follow-up assessments until disease progression (i.e. disease relapse) was confirmed, or death occurred. Subsequent to confirmed disease progression, subjects were followed for overall survival status.

The primary efficacy endpoint was duration of disease progression-free survival. One interim analysis, was planned six months after randomization of the 310th subject.

Secondary efficacy endpoints were:

- Tumor response to first line chemotherapy plus concurrent radiation treatment.
- Median and overall survival.
- Local disease progression.
- Hgb over time (baseline to study completion).
- Proportion of subjects receiving RBC transfusions.
- Quality of life change scores between EPREX/Procrit and placebo groups.

Meeting of the Data Safety Monitoring Board, October 1, 2003:

Johnson & Johnson requested that the IDMC review the safety data from this study on Sept. 12, 2003. J&J was notified Sept 19, 2003 by the IDMC of an increased frequency of TVE's in the EPREX/Procrit arm as compared to the placebo arm (12/53 versus 2/53, per IDMC). J&J suspended enrollment on Sept. 29, 2003. There were 106 patients on the trial as of Sept. 29, 2003.

Letter to Investigators, October 1, 2003. (from Cathy Lau, Senior Director—Medical Affairs, Ortho Biotech and Richard K. Plante, Project Manager—Medical Affairs, Ortho Biotech):

“The overall incidence of TVE's [thrombovascular events] in the treatment group in these trials is higher than would be expected based on prior controlled clinical trials.”

“Ortho Biotech is thus temporarily suspending enrollment in certain company-sponsored investigational trials in patients with cancer treated to hemoglobin levels > 130 g/L, including the LEGACY trial, pending a full analysis of this and other available data.”

From: “Preliminary Analyses of Thrombotic Vascular Events in Oncology Studies”, submitted by Ortho through Amgen, Jan. 19, 2004.⁸⁴

“The study population was to include 620 subjects. A total of 106 subjects (53 placebo, 53 epoetin alfa t) were enrolled at the time the study was suspended. Of these 106 patients, 3 (6%) placebo and 18 (34%) epoetin alfa -treated subjects had a thrombotic vascular event reported. After adjusting the bias for early termination of the study the odds ratio (epoetin alfa versus control) was 7.74.”

Safety Analyses

**Incidence of Thrombotic Vascular Events to Date:
Odds Ratio and 95% Confidence Interval (Study EPO-CAN-15)**

Placebo		EPREX/Procrit		Odds ratio	
N	TVE	N	TVE	Estimate	95% CI
53	3 (6%)	53	18 (34%)	7.74	[1.65, 44.41]

**Preliminary Listing of Subjects With Thrombotic/Vascular Events
(Study EPO-CAN-15)**

Treatment Subject ID	Age	Preferred Term	Relationship to Study Drug	Day of Onset	Total Days of Therapy
Placebo					
1148	64	TIA/mini stroke	Doubtful	28	26
1217	54	CVA (visceral arterial ischemia)	Not related	29	0
1245	66	Cardiac ischemia/infarction	Not related	29	28

**Preliminary Listing of Subjects With Thrombotic/Vascular Events
(Study EPO-CAN-15 -continued)**

Treatment Subject ID	Age	Preferred Term	Relationship to Study Drug	Day of Onset	Total Days of Therapy
EPREX/Procrit					
1052	42	Hemorrhagic cerebral infarction and thrombosis	Doubtful	8	7
1112	63	DVT	Not related	39	38
1129	56	Acute arterial embolism	Not related	15	13
1132	63	Dyspnea, cardiac arrest	Not related 3	3	3
1133	67	DVT	Possible	16	7
1140	70	Cardiac ischemia, death	Not related	19	19
1142	62	Inferior myocardial infarction	Doubtful	41	19
15	65	Acute coronary syndrome	Not related	1	0
1155	65	Cardiac ischemia/infarction	Doubtful	49	48
1170	60	Cerebrovascular ischemia	Doubtful	6	6
1174	47	Peripheral arterial ischemia	Possible	53	51
1183	70	Thrombosis	Not related	25	0
1194	67	Myocardial infarction	Not related	60	18
1195	58	Cerebrovascular ischemia	Possible	27	26
1200	74	Dyspnea, pulmonary embolism	Possible	197	197
1206	41	Thrombosis/embolism	Possible	83	5
1265	63	Pulmonary edema, death	Not related	3	1
1284	65	Left femoral embolism	Not related	9	0

“Results of preliminary analysis showed that 14 of 18 epoetin alfa treated subjects with thrombotic vascular events had a hemoglobin concentration greater than 13 g/dl within the 28 days prior to the thrombotic vascular event; 2 of these subjects did not receive study drug prior to the thrombotic vascular event.”

Hemoglobin (g/dl) Concentrations Within the 28 Days Prior to the Event in Subjects With Thrombotic Vascular Events (Study EPO-CAN-15)

	Placebo	EPREX/Procrit
Total	3	18
Hgb \geq 13 g/dl	2	14
Hgb < 13 g/dl	1	3
Unknown	0	1

2. Study PR00-03-006: “A double-blind, randomized, placebo controlled study of the efficacy and safety of epoetin alfa administered weekly in patients with gastric or rectal cancers undergoing preoperative chemoradiation followed by surgery.”

Design: randomized (stratified by: type of primary disease (gastric or rectal cancer), by presence (Hgb \leq 13 g/dl) or absence (Hgb > 13 g/dl) of anemia, and by study center), double-blind, US multicenter trial.

Patient population: 184 patients with histologically confirmed gastric or rectal cancer for whom the treatment plan is preoperative chemoradiation followed by surgery. Baseline Hgb was required to be \geq 10 g/dl and < 15 g/dl.

Treatment: PROCIT 40,000 IU subcutaneous qw versus placebo for a total of 16 weeks or up to 4 weeks after surgery, whichever comes first. Study drug was to be held if \geq 15 g/dl; resumed if Hgb \leq 14.0 g/dl at a 50% dose reduction.

Primary endpoint: Proportion receiving RBC transfusions 4 weeks after start of study drug up to end of study.

Secondary endpoints: Hgb response, transfusion, QoL, local tumor response, pathological response post-surgery to assess the curative response to the combined modality treatment.

Follow-up: Safety follow-up for 90 days post-study.

From “Preliminary Analyses of Thrombotic Vascular Events in Oncology Studies”, submitted by Ortho through Amgen, Jan. 19, 2004.⁸⁵

“A total of 60 subjects out of a projected 184, had been enrolled when the trial was suspended. Thirty-one were in the placebo arm, and 29 in the epoetin alfa arm. Of these 60 subjects, 2 (6%) placebo-treated, and 7 (24%) epoetin alfa treated subjects had a thrombotic vascular event. After adjusting for bias due to early suspension of the study, the odds ratio (epoetin alfa versus control) was 3.79.”

**Incidence of Thrombotic Vascular Events to Date:
Odds Ratio and 95% Confidence Interval (Study PR00-03-006)**

Placebo		Procrit		Odds ratio	
N	TVE	N	TVE	Estimate	95% CI
31	2 (6%)	29	7 (24%)	3.79	[0.66,32.22]

**Preliminary Listing of Subjects With Thrombotic/Vascular Events
(Study PR00-03-006)**

Treatment & Subject ID	Age	Investigator Term	Relationship to Study Drug	Day of Onset	Total Days of Therapy
Placebo					
2008	50	Chest pain	Not related	N/A	N/A
		Chest pain	Not related	N/A	N/A
2150	71	DVT	Doubtful	139	104
Procrit					
2016	58	DVT	Possible	87	70
2019	57	DVT	Not related	195	105
2066	68	Chest pain	Not related	N/A	N/A
2141	71	DVT	Possible	67	67
2142	76	DVT	Possible	56	22
2154	71	DVT	Possible	87	22
2210	40	Thrombosis	Possible	14	19

“Results of preliminary analysis showed that 5 of 7 epoetin alfa treated subjects with thrombotic vascular events had a hemoglobin concentration greater than 13 g/dl within the 28 days prior to the thrombotic vascular event.”

Hemoglobin (g/dl) Concentrations Within the 28 Days Prior to the Event in Subjects With Thrombotic Vascular Events (Study PR00-03-006)

	Placebo	Procrit
Total	2	7
Hgb \geq 13 g/dl	0	5
Hgb < 13 g/dl	1	1
Unknown	1	1

- Study GOG-191 (PR01-04-005): “A phase III trial to evaluate the efficacy of maintaining Hgb levels above 120 g/l with erythropoietin versus above 100 g/l without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer.”

Design: 1:1 randomized, US/Canada cooperative group (GOG, NCIC) trial.

Patient population: 460 subjects with primary, previously untreated, histologically confirmed invasive squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix Stage IIB, IIIB, or IVA were to be enrolled. Patients were required to have baseline Hgb < 14 g/dl.

Treatment: Procrit 40,000 IU subcutaneous weekly versus transfusion prn. Procrit dose was to be titrated to maintain Hgb \geq 13 gm/dl. Treatment was continued for the duration of radiation treatment Primary endpoint: Progression-free survival.

Secondary endpoints: Overall survival, local control.

Follow-up: Followed for progression and survival.

Enrollment statistical: 111/460.

Trial suspended effective Sept. 12, 2002.

Letter, from Philip Disaia, M.D. Chairman GOG., dated Sept. 22, 2003.

“As you are aware, it was noted on 9/15/03 that there appeared to be an increased number of cardiovascular events (compared to historical experience) on this study. I was notified of this finding and recommended to you that accrual be suspended pending investigation and you concurred . . .”

“A review of GOG protocol 165 (Radiation plus Chemotherapy in a similar patient population) revealed an incidence of grade 3 or 4 cardiovascular events of 5%. The incidence of grade 3 or 4 cardiovascular events in GOG Protocol 191 (79 evaluable patients) is 13.9% with Regimen P being 7.9% and regimen Q being 19.5%. Review of each case confirmed the events.”

“The DMC discussed the findings in great detail and the salient points of that discussion are that while the events do not reach statistical significance (between the two arms), the trend does raise concern. The recommendations of the DMC are as follows:

1. The DMC does not recommend than study be closed.
2. The DMC recommends the consent form be changed to clarify the potential of increased cardiovascular events.
3. The DMC recommends that all investigators be informed by mail of the potential increased risk and that they be encouraged to consider anti-thrombosis prophylaxis if, in their judgment, such prophylaxis is not contraindicated.
4. The cardiovascular events on this study be closely monitored and the protocol should be reevaluated by the DMC at the January 2004 GOG meeting.”

Memo from GOG Administrative Office, Sept. 26, 2003:

To: All Principal Investigators.

“In response to the concerns of Ortho Biotech, this study will continue to be suspended to patient accrual, effective Sept. 12, 2003.

Effective immediately, patients currently on therapy can continue treatment but **erythropoietin must be discontinued.**”.

From “Preliminary Analyses of Thrombotic Vascular Events in Oncology Studies”, submitted by Ortho through Amgen, Jan. 19, 2004.⁸⁶

“A total of 113 subjects (55 control, 58 epoetin alfa) were enrolled when the study was terminated. Of these 113 subjects, 3 (5%) control and 9 (16%) epoetin alfa treated subjects had a thrombotic vascular event reported. After adjusting for a bias due to early termination of the study, the odds ratio (epoetin alfa versus control) was 2.65.”

**Incidence of Thrombotic Vascular Events to Date:
Odds Ratio and 95% Confidence Interval (Study PR01-04-005)**

Placebo		Procrit		Odds ratio	
N	TVE	N	TVE	Estimate	95% CI
55	3 (5%)	58	9 (16%)	2.65	[0.47, 16.90]

“Results of preliminary analyses showed that 5 of the 9 epoetin alfa treated subjects with thrombotic vascular events had a hemoglobin concentration greater than 13 g/dl within the 28 days prior to the thrombotic vascular event.”

**Hemoglobin (g/dl) Concentrations Within the 28 Days Prior to the Event in Subjects
With Thrombotic Vascular Events (Study PR01-04-005)**

	Placebo	Procrit
Total	3	9
Hgb \geq 13 g/dl	1	5
Hgb < 13 g/dl	2	2
Unknown	0	2

**Preliminary Listing of Subjects With Thrombotic/Vascular Events
(Study PR01-04-005)**

Subject ID	Age	Investigator Term	Relationship to Study Drug	Total Days of Therapy
Standard of Care (SOC)				
046-191-002	51	DVT	Not related	SOC
56-191-005	70	DVT	Not related	SOC
56-191-007	60	DVT	Not related	SOC
Epoetin alfa				
002-191-002	38	Pulmonary embolism	Possible	42
020-191-008	49	Pulmonary embolism	Possible	21
034-191-002	46	Cerebral infarct	Not related	42
047-191-001	52	Thromboembolus	Unrelated	35
056-191-004	44	Pulmonary embolism	Possible	42
076-191-006	75	Cardiac arrest	Not related	42
083-191-006	52	DVT	Not related	28
85-191-004	37	Pulmonary embolism	Related	49
85-191-018	37	Intracranial hemorrhage	Possible	14

XIII. Additional Randomized, Controlled Trials Terminated Prematurely (not at request of Johnson & Johnson)

1. Protocol CAN-20: "A randomized trial of epoetin alfa in patients with advanced non-small cell carcinoma of the lung."

Design: 1:1 randomized, double-blind, placebo-controlled multicenter Canadian trial.

Patient population: 300 planned locally advanced, metastatic, or recurrent, non-small cell lung cancer subjects who are to receive radiation treatment plus or minus non-platinum chemotherapy. Patients were required to have entry Hgb \leq 12 g/dl.

Primary endpoint: Change in quality of life (FACT-An Anemia scale) from baseline to week 12.

Secondary endpoints: quality of life measures at baseline, weeks 4, 8, 12 and 16 weeks; Hgb and Hct levels at baseline; weeks 4, 8, 12, and 16 weeks, transfusion requirements).

Treatment: 40,000 IU qw versus placebo for 12 weeks.

Follow-up: 4 week post-study quality of life plus up to two months post study drug follow-up (descriptive only).

Termination of the Trial:

Trial terminated, at the recommendation of the DMC.

Letter, dated Nov. 27, 2003, from Dr. Jim Wright, PI "Suspension of EPO-CAN-20"⁸⁷:

"Recently, information from other trials that epoetin alfa is associated with a higher than expected risk of thrombotic events, prompted the external DSMB for the OCOG [Ontario Clinical Oncology Group] EPO-CAN-20 trial to review the accumulated data collected by the OCOG Coordinating and Methods Centre. This was an unplanned analysis. The DSMB examined thrombotic events and, because of the results of the EPO- INT-76 trial, mortality was also investigated."

"The Steering Committed for the EPO-CAN-20 trial met Nov. 24, 2003 to review the analysis prepared by the DSMB."

"Preliminary results of their analysis revealed that:

1. The rates of thrombosis were low in both treatment groups and there was no increase in thrombosis associated with epoetin alfa.
2. A large proportion of patients on the trial had completed the 12 week QoL assessment (the primary outcome measure), due to high rates of mortality.
3. Patients on the active arm of the trial appear to have higher rates of mortality when compared to the placebo arm of the trial."

[Letter then goes on to quote the results of the Henke trial in head and neck cancer.]

"Based on this information, the EPO-CAN-20 Steering Committee has decided to suspend recruitment for this study. Hence no further patients should be randomized at this time and all patients should stop taking study medication. We will, however, continue to collect all scheduled follow-up and QoL [quality of life] data as outlined in the protocol."

"It is important to note that the EPO-CAN-20 trial is a QoL study and was not set up to capture very detailed information on cancer treatment or potentially confounding variables that may have influenced survival. In an attempt to better understand this situation, we plan to examine patient records in more detail focusing on each patient's cancer and treatment for the cancer. Therefore, a more complete analysis of survival is required before there can be any discussion on whether to continue the study."

2. Protocol EPO-GBR-7⁸⁸: “Open-label randomized, comparative group evaluation of the effect of epoetin alfa on local disease-free survival and quality of life in head and neck cancer patients receiving radical radiotherapy.”

Design: Phase 3, open-label, multicenter study in subjects with head and neck cancer for which radical radiotherapy with curative intent was imminent. Subjects were required to have no previous chemotherapy or surgical intervention for the malignancy pertaining to the study. Hgb at entry required to be ≤ 15 g/dl

Planned sample size was 800 patients.

Subjects were to be randomized 1:1 to receive either standard radiotherapy alone (Observation Group) or standard radiotherapy plus epoetin alfa (Epoetin Alfa Group). Subjects assigned to the active treatment group were to receive treatment immediately after randomization if their radiotherapy was scheduled to start in 2-4 weeks; or 4 weeks after randomization if their radiotherapy was to start in more than 4 weeks. : Treatment was to be titrated to achieve and be maintained a hemoglobin between 12.5 g/dl and 15 g/dl during the treatment phase.

Endpoints: “To evaluate the effect of treatment with epoetin alfa on length of local disease-free survival, local tumor control, and quality of life in subjects receiving radical radiotherapy with curative intention of head and neck cancer”.

Termination of the study:

“Due to slow accrual, study enrollment was terminated in 2002 after 301 subjects had been recruited across 21 sites. Per protocol, the study treatment phase has been completed and the 5 year follow-up phase continues at this time.”

Efficacy Endpoints:

Local Tumor Response 12 Weeks After Radiotherapy

“At the time of the interim analysis, Week 12 local tumor response data were available for 110 (74%) of the subjects in the observation group and 115 (76%) in the epoetin alfa group. Based on those who had such data available, 95% of the subjects had complete response and 4% had partial response to radiotherapy on the primary tumor sites in both treatment groups. Similar results were also seen in response on lymph nodes.”

Local Tumor Evidence:

Local tumor evidence was assessed at weeks 1, 4, and 8, and Years 1, 2, 3 and 5 after completion of radiotherapy. Since this trial is still ongoing, not all subjects had reached all the assessment time points; and in particular no subject had had the Year 5 assessment at the time of the interim analysis. Based on the data available at this time, epoetin alfa treatment appeared to have no effect on the outcomes of these assessments”.

Local Tumor Recurrence at Study Completion/Discontinuation:

“Forty-two (28%) of the subjects in the observation group and 38 (25%) in the epoetin alfa group were reported to have local tumor recurrence within the irradiated volume at their completion or discontinuation. Relapse outside the irradiated volume was reported in 21 (14%) of the subjects in the observation group and 20 (13%) in the epoetin alfa group. Again, epoetin alfa treatment did not seem to have an effect on the outcome of this assessment.”

Overall Survival:

“At the time of the interim analysis, the Kaplan-Meier estimate of the overall survival time showed a non-significant trend ($p=0.535$, logrank test) toward a longer survival in the observation group than in the epoetin alfa group. The Kaplan-Meier estimate of the one year survival rate was 85% (95% confidence interval 79% to 91%) for the observation group and 81% (95% confidence interval 74% to 87%) for the epoetin alfa group.”

Safety (Thrombotic Vascular Events):

“At the time of the interim analysis, 1 (1%) of the subjects in the observation group and 5 (3%) in the epoetin alfa group were reported to have experienced at least one thrombotic vascular event. Reported clinically relevant events (cardiac arrest, angina, and pulmonary embolism) were all in the epoetin alfa group.”

3. Rosenzweig Study⁸⁹: “Increased thrombotic events in a clinical trial of erythropoietin in metastatic breast cancer.”

ASCO Abstract (2002):

Rosenzweig, M., et al., University of Pittsburgh School of Medicine: Increased thrombotic events in a clinical trial of erythropoietin in metastatic breast cancer.

“100 women with metastatic breast cancer with Hgb < 12.0. Patients were randomized to receive usual care (G1) or usual care plus EPO (G2). EPO was given at 40,000 IU sq qw. At 4 weeks, dose was increased to 60,000 IU sq qw without a > 1.0 g/dl Hgb increase and discontinued at 8 weeks if Hgb improvement was < 1.0 g/dl.

“*Results:* This study was terminated early ($n=27$, $G1=13$, $G2=20$), when 4/14 (28.5%) subjects in G2 developed thrombotic events (1 DVT, 1 DVT + pulmonary embolism, 1 DVT + pulmonary embolism 1 month after EPO discontinuation, 1 brachial vein thrombosis). In all 4 patients the Hgb was normal at the time of the event.. No patient in G1 developed a thrombotic event. The historic incidence (Jan. 99 to June 01) of

thrombotic events in the UPCI MBC population was 5.5%. The incidence of thrombotic events in G2 was significantly greater than the historic incidence ($p < 0.05$)."

4. RTOG 99-03⁹⁰: "A randomized phase III trial to assess the effect of erythropoietin on local-regional control in anemic patients treated with radiotherapy for carcinoma of the head and neck."

Design: 1:1 randomized, open-label, US, cooperative group (RTOG) trial.

Patient population: 372 patients with head and neck cancer. Baseline Hgb criterion: males ≥ 9 g/dl, to 13.5 g/dl. females ≥ 9 to 12.5.

Treatment: epoetin alfa 40,000 IU subcutaneous qwk for 8-9 weeks or until completion of XRT versus no epoetin alfa. Epoetin alfa doses were held if Hgb ≥ 16 in males or ≥ 14 in females; dosing resumed when Hgb ≤ 13.5 in males and ≥ 12.5 in females, at a dose reduction of 30,000 IU.

The primary endpoint was improvement in local-regional control rate, while secondary endpoints included survival and site of first failure.
Enrollment status at termination: 147/372

Trial suspended.

Memo to RTOG Investigators, from Joseph Aisner, M.D. RTOG Monitoring Committee Chair, November 19, 2003.

"On Oct. 28, 2003, the RTOG DMC met to discuss the recently published Lancet article [Henke] and the disposition of RTOG 99-03. ... This study had a design and patient population similar to RTOG 99-03. The RTOG DMC reviewed the above information alone with results of a rapidly compiled (unplanned) interim analysis of RTOG 99-03. The interim analysis of results from RTOG 99-03 showed no statistically significant differences, but non-significant trends towards lower local-regional control and lower survival in the epoetin alfa arm. The RTOG DMC concluded that RTOG 99-03 should be permanently closed to accrual."

RTOG Analysis for DMC Telephonic Conference, Oct. 24, 2003.

Preliminary analysis of time to local-regional failure and survival for RTOG 9903. This data is not yet mature, as the median follow-up for patients still alive is only 8.7 months and only 22/117 patients have died.

148 patients have been entered in to RTOG 9903, one is ineligible and 30 have no follow-up, leaving 117 for analysis.

XIV. Summary/Conclusions

Recombinant Erythropoietin Products and Thrombotic/Cardiovascular Events:

The Normal Hematocrit Trial in patients with chronic renal failure demonstrated an increased risk of cardiovascular adverse events and death occurs using a dosing strategy in which a higher target hematocrit than in the currently approved labeling is sought. Subsequent analyses of the studies that supported the use of Aranesp (darbepoetin alfa) in chronic renal failure identified a rate of rise in hemoglobin of greater than 0.5 g/dl/week correlating with an increased risk of hypertension, pulmonary edema, cardiac arrest and CVA. A similar risk associated with an increased rate of rise was not clearly seen in the studies that supported the oncology indication for Aranesp, although a suggestion both of increased risk of serious thrombotic events, and of more rapid ROR in patients suffering pulmonary emboli suggest that a relationship may also exist in this setting.

There have been three randomized, placebo-controlled trials where a population of patients with the same histological type of malignancy was administered epoetin alfa or epoetin beta with the aim of achieving a target hemoglobin of greater than 12 g/dl. In the N93-004 trial, performed in subjects with SCLC receiving chemotherapy, there was a higher incidence of vascular (extracardiac) adverse events in the group receiving Procrit. In the EPO-INT-76 trial, in a population of women with metastatic breast cancer, at four months, there was a higher incidence of cardiovascular/thrombotic vascular events in the group who received EPREX (1.4% in the placebo arm versus 2.3% in the EPREX arm). In the Henke trial, where the population consisted of subjects with head and neck carcinoma who were to receive radiotherapy, the incidence of "vascular disorders" (hypertension, hemorrhage, venous thrombosis/pulmonary embolism, CVA) was 5% in the placebo arm and 11% in the epoetin beta arm. The numbers of patients who died from "cardiac disorders" also differed: 5 placebo and 10 epoetin beta subjects.

Finally, the three oncology studies stopped by Johnson & Johnson in September 2003, were all designed with the intention to achieve target hemoglobin levels at normal or greater than normal levels: EPO-CAN-15 (EPREX/Procrit), where a target Hgb of 14-16 g/dl was used, PR01-04-005 (Procrit), where a target hemoglobin of > 13 g/dl was used, and PR00-03-006 (Procrit), where a hemoglobin of up to 15 g/dl was allowed. All three of these studies were halted because of an excessive incidence of thrombotic vascular events in the arms receiving an erythropoietin product. There is as yet no analysis available on the effect of rate of rise of hemoglobin on the incidence of thrombotic vascular events.

It is clear from this data that both the rate of rise in hemoglobin and a target hemoglobin of greater than 12.0 g/dl may contribute to an increased risk of cardiovascular/thrombotic events in patients with chronic renal failure on dialysis. The data from major efficacy study that supported the supplemental approval for Aranesp for treatment of the anemia of cancer chemotherapy demonstrated a rapid rate of rise in hemoglobin (more than 0.5 g/dl/week) was associated with an increased incidence of hypertension, vascular thrombosis, ischemia and infarction.

The Agency considers studies conducted using target hemoglobin levels of greater than 12 g/dl to potentially unsafe; studies employing such strategies should be conducted under IND. In addition, such studies should be specifically designed to detect an impact on survival as well as the impact on thrombotic event rates. With regard to clinical practice, clinicians should adhere to the dose adjustments governing the rate of rise of hemoglobin that have been incorporated into the Aranesp and Procrit/Epogen package inserts.⁹¹

Recombinant Erythropoietin and the Risk of Tumor Promotion

There is now a body of literature consisting of studies in cell lines and in animal models that supports the possibility that erythropoietin may have a role to play in the growth of certain tumors. There are also other studies that suggest that erythropoietin has no such role. The question of whether EPO does or does not function as a growth factor for tumors (and/or vasculature) now has more immediacy, because of the results of the clinical studies outlined in this document.

Four multicenter, randomized, placebo controlled clinical trials have been conducted thus far, the N93-004 (Procrit), NESP 980297 (Aranesp), EPO-INT-76 (EPREX), and the Henke (epoetin beta) study, which were designed to measure tumor outcomes or survival in homogenous populations of tumors. In two of the four studies, which also happen to be the two largest studies, there was evidence of a tumor promotion effect in the arm that received recombinant erythropoietin. In EPO-INT-76, there was also a detrimental effect on 12-month survival. While aspects both of these studies have been criticized, the size of the two trials that showed evidence of tumor promotion (929 subjects in the EPO-INT-76 trial, 351 in the Henke trial), the size and design (randomized, placebo-controlled) of both trials and the consistency in results provide data that in the opinion of the FDA, warrant further investigation.

The basis for the adverse effects of erythropoietin on malignancy/tumor stimulation is uncertain, however, it seems reasonable that an effect could be mediated through binding to erythropoietin receptors on both tumor and vascular cells. The three studies were performed in three different primary tumor types: small cell carcinoma of the lung, metastatic breast cancer, and carcinoma of the head and neck. A tumor promotion effect was seen in the breast cancer and head and neck studies, but not in the small cell lung cancer study. This may indicate heterogeneity of malignancies, such as differences in erythropoietin receptor distributions between types of malignant tumors.

Future studies that investigate the effect of erythropoietic growth factors on tumor promotion should incorporate the following features into their design:

- Homogenous primary tumor .
- Homogenous chemotherapy and/or radiation regimens.
- Randomized, placebo-controlled.

- Data collection that will allow the systematic acquisition of information of tumor response, time to progression, and survival.
- Target hemoglobin values of no greater than 12.0 g/dl, with prespecified rules for dose adjustment.
- Prespecified definitions for cardiovascular and thrombovascular events.
- A Data Safety Monitoring Board with a charter that states criteria for halting the study in the event of a prespecified number of cardiovascular or thrombotic adverse events occurs.
- Collection of data regarding the erythropoietin receptor status of primary tumor sites.
- Studies on tumor populations with high, low, and intermediate quantities of erythropoietin receptors.

XV. References

- ¹ Krantz, S.B. (1991) *Blood* 77:419-434
- ² Jelkmann, W. (1992) *Physiol. Rev.* 72:449-489
- ³ Lin, F.K. et al., (1985) *Proc. Natl. Acad. Sci. USA* 82:7580-4
- ⁴ Egrie, J.C. and Browne, J.K. (2001) *Br. J. Cancer* 84:Suppl-10
- ⁵ Masuda, S. et al., (2000) *Int. J. Hematol.* 70:1-6
- ⁶ Batra, S. et al., *Laboratory Investigation* (2003) 83:1477-87
- ⁷ Michel, G. et al., (2002) *Biochim. Biophys. Acta* 1578(1-3):73-83
- ⁸ Masuda, S. et al., (1993) *J. Biol. Chem.* 268:11208-16
- ⁹ Benyo, D.F. and Conrad, K.P. (1999) *Biology Reproduction* 60:861-70
- ¹⁰ Acs, G. et al. *Am. J. Pathol.* (2003) 162:1789-806
- ¹¹ Yasuda, Y. et al., (2001) *Br. J. Cancer* 84:836-43
- ¹² Yokomizo, R. et al., (2002) *Mol. Hum. Reprod.* 8(5):441-6
- ¹³ Acs, G. et al., (2002) *Cancer* 95 (5):969-98114.
- ¹⁴ Brower, V. *The Lancet Oncology* (2003) 4:69
- ¹⁵ Anagnostou, A. et al., (1990) *Proc. Natl. Acad. Sci. USA* 87:5978-82
- ¹⁶ Nagai, A. et al., (2001) *J. Neuropathology and Exper. Neurology* 60:386-92
- ¹⁷ Morishita, E. et al., (1997) *Neuroscience* 76:105-16
- ¹⁸ Siren, A.L. et al., (2001) *Proc. Natl. Acad. Sci. USA* 98:4044-9
- ¹⁹ Fenjves, E.S. et al., (2003) *Transplant.* 75:1356-60
- ²⁰ Westenfelder, C. and Baranowski, R.L., *Kidney Int.* (2000) 58:647-57
- ²¹ Wojchowski, D.M., et al., *Experimental Cell Research* (1999) 253:143-156
- ²² Penta, K. and Sawyer, S.T. (1995) *J. Biol. Chem.* 270:31282-7
- ²³ Mori, M. et al., (2003) *J. Cell Physiol.* 195:290-7
- ²⁴ Mayeux, P. et al., (1993) *Eur. J. Biochem.* 216:821-8
- ²⁵ Zamai, L. et al., (2000) *Blood* 95:3716-24
- ²⁶ Kashii, Y. et al., (2000) *Blood* 96:941-9
- ²⁷ Sasaki, R. et al., (2000) *Biosci. Biotechnol. Biochem.* 64(9):1775-93
- ²⁸ Jubinsky, P.T. et al., (1997) *Blood* 90:1867-73
- ²⁹ Wu, H. et al., (1997) *Proc. Natl. Acad. Sci. USA* 94:1806-10
- ³⁰ Broudy, V.C. et al., (1998) *Blood* 91:898-906
- ³¹ Westphal, G. et al. *Tumori.* (2002) 88: 150-9
- ³² Yasuda, Y. et al., *Carcinogenesis* (2003) 24:1021-9
- ³³ Arcasoy, M.O. et al., *Laboratory Investigation* (2002) 82:911-918
- ³⁴ Ribatti, D., et al., *Histopathology* (2003) 42(3):246-50
- ³⁵ Yasuda, Y. et al., *Carcinogenesis* (2002) 23(11):1797-1805
- ³⁶ Bahlmann, F.H. et al., (2003) *Kidney Int.* 64(5):1648-52
- ³⁷ Ribatti, D., et al., *J Hematother Stem Cell Res* (2003) 12(1):11-22
- ³⁸ Acs, G. et al., (2001) *Cancer Res.* 61:3561-3565
- ³⁹ Ribatti D, et al (2003). *Eur. J. Clin. Invest.* 33: 891 – 896.
- ⁴⁰ Anagnostou A, et al (1990). *Proc. Natl. Acad. Sci.* 87: 5978 – 5982.
- ⁴¹ Carlini RG, et al (1995). *Kid. Intl.* 47: 740 – 745.
- ⁴² Takeshita, A. et al., (2002) *Leuk. Lymphoma* 43:261-4
- ⁴³ Yasuda Y, et al (2001). *Br. J. Can.* 84(6): 836 – 843.
- ⁴⁴ Ibid, p. 9.
- ⁴⁵ Ibid, p. 9.
- ⁴⁶ Ibid, p. 16.
- ⁴⁷ Ibid, p. 19.
- ⁴⁸ Besarab A, et al., *New England Journal of Medicine*, 339: 584, 1998.
- ⁴⁹ Ibid.
- ⁵⁰ <http://www.fda.gov/cder/biologics/products/darbamg091701.htm>
- ⁵¹ Document: Summary for Basis of Approval, Epoetin alfa (Amgen), March 31, 1993.
- ⁵² Ibid, p. 5.

-
- ⁵³ Final Study Report, Protocol N93-004, Johnson & Johnson, October 25, 2002.
- ⁵⁴ Luksenburg H., Gnecco C. FDA Clinical Review of sBLA STN 103234.5033, Amgen, Inc., Procrit (epoetin alfa), October 11, 2002.
- ⁵⁵ Final Study Report PR98-27-008, Johnson & Johnson, ?Date.
- ⁵⁶ STN BL 103951/5001 Approval Letter, July 19, 2002.
- ⁵⁷ Litwin, S. Clinical Review of BLA STN 103951/5001, Amgen, Inc., Darbepoetin alfa (Aranesp) for Oncologic Patients, September 20, 2001.
- ⁵⁸ Ibid, p. 59-60.
- ⁵⁹ Ibid, p. 60.
- ⁶⁰ Ibid, p. 60-61.
- ⁶¹ Ibid, p. 53.
- ⁶² Ibid, p. 53.
- ⁶³ Ibid, p. 85.
- ⁶⁴ Ibid, p. 54.
- ⁶⁵ Ibid, p. 55.
- ⁶⁶ Ibid, p. 55.
- ⁶⁷ Ibid, p. 55.
- ⁶⁸ Littlewood TJ, et al. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: Results of a randomized, double-blind, placebo-controlled trial. *JCO* 19: 2865, 2001.
- ⁶⁹ Albain, KS, et al. *JCO* 9:1618, 1991; Ohlhauser C, et al. Obermair A, et al. *Cancer* 83, 726, 1998.; Fein DA, et al. *JCO* 133:2077, 1995.
- ⁷⁰ Clinical Expert Report on INT-76, submitted by Johnson & Johnson Pharmaceutical Research and Development, April 23, 2003, p. 11.
- ⁷¹ Ibid, p. 12.
- ⁷² Ibid, p. 104.
- ⁷³ Ibid, p.75.
- ⁷⁴ Leyland-Jones, B and the BEST Investigators and Study Group. *Lancet Oncology* 4:459, 2003.
- ⁷⁵ Grogan M, et al. *Cancer* 86: 1528, 1999; Glaser CM, et al. *Int J Radiat Oncol Biol Phys* 50: 705, 2001.
- ⁷⁶ Henke et al. *Lancet* 362:1255, 2003.
- ⁷⁷ Ibid
- ⁷⁸ Ibid.
- ⁷⁹ Kaanders J, van der Kogel A, *Lancet* 363:78, 204, Haddad R, Posner M. *Lancet* 363:79, 2004; Leyland-Jones B, Mahmud S. *Lancet* 363: 80, 2004.
- ⁸⁰ Haddad R, Posner M. *Lancet* 363:79, 2004.
- ⁸¹ Henke M. et al. *Lancet* 363:81, 2004.
- ⁸² "Drug Company Halts Trials of Procrit", *New York Times*, Nov. 27, 2003.
- ⁸³ Johnson & Johnson Pharmaceutical Research & Development, L.L.C.. Medical Report: Preliminary Analysis of Thrombotic Vascular Events in Oncology Studies. January 16, 2004.
- ⁸⁴ Ibid, p. 26, 30-1.
- ⁸⁵ Ibid, p. 24-25, 28.
- ⁸⁶ Ibid, p. 25-26, 29-30.
- ⁸⁷ Ibid, p. 54-56.
- ⁸⁸ Ibid, p. 57-69.
- ⁸⁹ Rosenzweig M, et al. ASCO 2002 Meeting, abstract 1522.
- ⁹⁰ Information Package submitted to the FDA by Ortho Biotech through Amgen, for Procrit (epoetin alfa), December 2, 2003.
- ⁹¹ Aranesp® (Amgen, Inc.) package insert, DOSAGE AND ADMINISTRATION, Dose Adjustment: "the dose should be adjusted for each patient to achieve and maintain a target hemoglobin not to exceed 12 g/dl. Increases in dose should not be made more frequently than once a month. If the hemoglobin is increasing and approaching 12 g/dl, the dose should be reduced by approximately 25%. If the hemoglobin continues to increase, doses should be temporarily withheld until the hemoglobin begins to decrease, at which point therapy should be reinitiated at a dose approximately 25% below the previous dose. If the hemoglobin increases by more than 1.0 g/dl in a 2 week period, the dose should be decreased by approximately 25%."