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August 10, 2007

CONFIDENTIAL TREATMENT REQUESTED

VIA ELECTRONIC MAIL

The Honorable John D. Dingell
Chairman
United States House of Representatives
Committee on Energy and Commerce
Washington, DC 20515-6115

The Honorable Bart Stupak
Chairman
United States House of Representatives
Committee on Energy and Commerce
Subcommittee on Oversight and Investigations
Washington, DC 20515-6115

Re: Request to Johnson & Johnson and Ortho Biotech Products, L.P.

Dear Chairman Dingell and Chairman Stupak:

This letter is intended to supplement our April 18, 2007 submission which responded to your March 20, 2007 letter to Johnson & Johnson ("J&J") and Ortho Biotech Products, L.P. requesting certain information related to erythropoiesis-stimulating agents ("ESAs").

In our April 18, 2007 letter, we explained that J&J had not been able to identify communications to FDA about the discontinuation of study PR00-27-024. Since that time, we have learned that J&J notified FDA about the discontinuation of PR00-27-024 in a submission made on December 1, 2003.

We also wish to advise the Committee that J&J made submissions to FDA and to European health authorities on August 8, 2007 reporting a preliminary safety observation related to a study called EPO-ANE-4008. While a decision to discontinue this study has not been made, we are enclosing a copy of the August 8, 2007 submission to FDA which summarizes available information in an effort to be as forthcoming as possible with the Committee.

As always, please do not hesitate to contact me at (202) 662-5538 with any questions or comments.

Sincerely,

Lanny A. Breuer /EJA

Lanny A. Breuer

Enclosures:
August 8, 2007 Submission to FDA

Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

0 8 AUG 2007

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

BB-IND 2318
Recombinant-human
erythropoietin (EPO)

Serial No.: 1 2 8 7

General Correspondence
Safety Information

Dear Sir/Madam:

Reference is made to Investigational New Drug Application BB-IND 2318 for Recombinant-human erythropoietin (EPO).

The purpose of the communication is to inform the Agency of a preliminary safety observation in Study EPO-ANE-4008: "**A Randomized, Open-Label, Multicenter Study Evaluating Thrombovascular Events in Subjects With Cancer Receiving Chemotherapy and Administered Epoetin Alfa Once or Three Times a Week for the Treatment of Anemia.**" This communication has been sent to all Health Authorities in countries in which a J&J Operating Company markets epoetin alfa.

Study EPO-ANE-4008 is an ongoing, company-sponsored, open-label, multicenter Phase IV study, initiated as a post-approval commitment to the EU Mutual Recognition Procedure (MRP) approval for once weekly dosing in patients with cancer. In this study, subjects are randomized to receive epoetin alfa either 450 IU/kg once (QW) or 150 IU/kg three times (TIW) a week using labeled regimens for the treatment of chemotherapy-induced anemia. The primary protocol objective is to "compare the safety with respect to the incidence of clinically relevant and objectively confirmed Thrombovascular Events (TVEs) in 2 dosing regimens of epoetin alfa when used following guidelines for baseline Hb (≤11 g/dL) and target Hb (12 g/dL) to treat anemia in subjects with nonmyeloid malignancies who are receiving chemotherapy."

Secondary objectives include:

- assessment of change in Hb;
- proportion of responders to epoetin alfa;
- red blood cell (RBC) transfusion

Secondary safety objectives include:

- rate of rise in Hb;
- time to first clinically relevant and objectively confirmed TVE;
- the proportion of subjects with at least one TVE during the study;
- total number of TVEs, whether clinically relevant and objectively confirmed or not;
- time to death

A copy of the current protocol synopsis is attached (Attachment 1).

The study is currently enrolling in 10 countries (Bulgaria, France, Germany, Greece, Italy, Poland, Romania, Russia, Slovakia and UK).

As of 3 August 2007, 112 patients have been randomized, with a total of 9 deaths reported. A preponderance of these deaths occurred in the TIW arm of the study. Two of the deaths were reported more than 4 weeks after the end of epoetin alfa therapy.

Died during therapy or <4weeks after end of epoetin alfa therapy		Died >4weeks after end of epoetin alfa therapy	
QW	TIW	QW	TIW
1	6	-	2

Further information on these deaths is provided in the table in Attachment 2.

We have reviewed the available data on the patient deaths. There is no safety signal related to either the overall incidence of reported deaths (which is consistent with that expected for patients with advanced cancer), or the cause of deaths (most of the deaths were due to progression of disease in subjects with advanced cancer in whom prior therapies had failed). The majority of the deaths, as per investigator assessment, were not related to epoetin alfa therapy, nevertheless, the difference in the number of deaths in the two treatment arms could be of potential concern. We, therefore, felt that it was appropriate to inform you of these preliminary observations.

The independent 5-member Steering Committee that oversees the EPO-ANE-4008 study is fully aware of the preliminary imbalance of deaths observed in the 2 treatment arms and will further evaluate the available data by Friday, 10 August.

The Company has contacted the sites to obtain more complete information on the 9 deaths in order to be able to provide further assessments. The Company believes that it is important to continue to follow the study closely to evaluate the preliminary imbalance in deaths, and we will provide an update with further details as soon as available.

This submission is being provided in electronic format. J&JPRD certifies that we have taken precautions to ensure that the submission is free of computer viruses and authorizes CDER to use antivirus software, as appropriate. The following software was run to check for viruses: McAfee VirusScan Enterprise 8.0.0, Virus definitions: 5018, copyright 1995-2004, Networks Associates Technology, Inc.

Should you have any questions and/or comments, please contact me directly at (908) 927-2228 or, in my absence, Mark Cornfeld, MD at (908) 218-6956.

Sincerely,

Brian J. Maloney

Brian J. Maloney, RPh, MS
Director, North America Regional Liaison

ATTACHMENT 1
EPO-ANE-4008: A Randomized, Open-Label, Multicenter Study Evaluating Thrombovascular Events in Subjects With Cancer Receiving Chemotherapy and Administered Epoetin Alfa Once or Three Times a Week for the Treatment of Anemia

SYNOPSIS

OBJECTIVES:

The primary objective is to compare the safety with respect to the incidence of clinically relevant and objectively confirmed thrombovascular events (TVEs) in 2 dosing regimens of epoetin alfa when used following guidelines for baseline hemoglobin (Hb) (≤11 g/dL) and target Hb (12 g/dL) to treat anemia in subjects with nonmyeloid malignancies who are receiving chemotherapy.

Clinically relevant TVEs considered as the primary endpoint for the study are defined as deep venous thrombosis (DVT) of the limbs; thromboses of other major veins, such as iliacal, caval, portal, or mesenteric vein; pulmonary embolism (PE); acute coronary syndrome (ACS) (unstable angina, myocardial infarction with or without ST elevation); ischemic stroke of arterial or cardiac origin; cerebral venous thrombosis; and arterial thrombosis.

Objectively confirmed is defined as the confirmation of the clinical diagnosis of a TVE by appropriate medical imaging studies and laboratory tests. Only TVEs that are determined by the Adjudication Committee to be clinically relevant and objectively confirmed will be counted in the analysis for the primary endpoint.

Secondary efficacy objectives include assessment of change in Hb, proportion of responders to epoetin alfa, and the use of red blood cell (RBC) transfusions. Secondary safety objectives include rate of rise in Hb; time to first clinically relevant and objectively confirmed TVE; the proportion of subjects with at least one TVE during the study and the total number of TVEs, whether clinically relevant and objectively confirmed or not; and time to death. Overall safety including adverse events, clinical laboratory values, and mortality will also be assessed.

Hypothesis

The group of subjects receiving epoetin alfa once a week and the group of subjects receiving epoetin alfa 3 times a week will have similar proportions of subjects with at least 1 clinically relevant and objectively confirmed TVE from randomization through Week 16.

OVERVIEW OF STUDY DESIGN:

This is a randomized, open-label, multicenter, postapproval safety study. Approximately 500 subjects with nonmyeloid malignancies who are receiving chemotherapy and are anemic will be enrolled.

The study is divided into 3 phases: screening, open-label treatment, and posttreatment. Following a screening phase of up to 2 weeks before randomization, eligible subjects will participate in the open-label treatment phase until 4 weeks after the last dose of chemotherapy, for a maximum of 26 weeks, followed by a 4-week posttreatment phase.

Before any study-related procedure can be performed, subjects must sign an informed consent form. On Day 1 of the open-label treatment phase, eligible subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio to receive epoetin alfa at an initial dosage of either 450 international units (IU)/kg once a week (Group 1) or 150 IU/kg 3 times a week (Group 2) by subcutaneous injection until 4 weeks after the last dose of chemotherapy, for a maximum of 26 weeks. Epoetin alfa treatment will be initiated after randomization, and the first dose should be administered preferably on a Monday, with subsequent administrations on Wednesday and Friday for Group 2. Randomization will be stratified by study center and Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus 2). Randomization will be by means of an Interactive Voice Response System (IVRS).

Subjects may receive chemotherapy before or after randomization as long as blood has been drawn for Hb analysis. In any case, a blood sample for Hb should be taken before the start of chemotherapy. For

subjects receiving cyclic chemotherapy, the start of epoetin alfa treatment should coincide with the first day of a chemotherapy cycle.

All subjects whose calculated transferrin saturation (TSAT) drops to <20% while on epoetin alfa treatment will be considered to have functional iron deficiency and will be required to receive iron supplementation during the study.

Dosing adjustments of study drug, based on Hb values, will be permitted according to the protocol guidelines and the summary of product characteristics (SmPC) for epoetin alfa. Subjects will have Hb values measured weekly before administration of epoetin alfa to monitor the effect of epoetin alfa treatment and to determine the need for dose adjustments, interruption, or resumption of epoetin alfa therapy.

Subjects who do not respond to epoetin alfa treatment after dose escalation (nonresponders) will discontinue study drug at Week 8. Subjects who prematurely discontinue study drug (epoetin alfa) before or at Week 12 will have study assessments performed at Weeks 12 and 16. Subjects who discontinue study drug after Week 12 but before or at Week 16 will undergo Week 16 assessments as well as final study assessments 4 weeks after the last dose of study drug. Subjects who discontinue study drug after Week 16 will undergo final study assessments 4 weeks after the last dose of study drug.

Subjects who no longer respond to therapy after a first response should be appropriately evaluated for etiology. If the causative factor for this loss of effect (LOE) cannot be corrected, the subject should discontinue study drug.

In case of suspected TVE, subjects will undergo specific laboratory and medical imaging studies for confirmation of the diagnosis. All study-related diagnostic medical imaging studies used for determination and assessment of TVEs will be reviewed by an independent Adjudication Committee. An independent Steering Committee will also be established to periodically assess the safety in this study. Separate charters will be developed for both of these committees that describe their policies, procedures, and timing of reviews.

STUDY POPULATION:

Men or women 18 years of age or older who have a histologically confirmed nonmyeloid malignancy and a baseline Hb ≤11 g/dL, and who are expected to receive at least 12 weeks of chemotherapy after the start of epoetin alfa therapy. Subjects must meet all of the specific inclusion criteria and none of the exclusion criteria outlined in the protocol.

DOSAGE AND ADMINISTRATION:

Eligible subjects will be randomly assigned in a 1:1 ratio to 1 of the following 2 treatment groups:

- Group 1: epoetin alfa at an initial dosage of 450 IU/kg once a week
- Group 2: epoetin alfa at an initial dosage of 150 IU/kg 3 times a week

All subjects will receive epoetin alfa by subcutaneous injection until 4 weeks after the last dose of chemotherapy, for a maximum of 26 weeks.

Epoetin alfa will be administered after all other scheduled study assessments for that visit have been performed. Hemoglobin values will be checked weekly before study drug administration. The first dose of epoetin alfa treatment for each week should be administered preferably on a Monday, with subsequent administrations on Wednesday and Friday for Group 2.

Dosing adjustments of study drug, based on Hb values, will be permitted according to the protocol guidelines and the SmPC for epoetin alfa.

Investigators should consider treating subjects with packed RBC transfusions if Hb decreases to ≤8 g/dL, or if subjects develop signs and symptoms of anemia.

Iron supplementation should be initiated at any time that the calculated TSAT is <20% and continued until TSAT is between 30% and 50%.

PRIMARY ENDPOINT EVALUATIONS/CRITERIA (THROMBOVASCULAR EVENTS):

Clinically relevant TVEs are defined as DVT of the limbs; thromboses of other major veins, such as iliacal, caval, portal, or mesenteric vein; PE; ACS (unstable angina, myocardial infarction with or without ST elevation); ischemic stroke of arterial or cardiac origin; cerebral venous thrombosis; and arterial thrombosis. Upon suspicion of a clinically relevant TVE, appropriate medical imaging studies and supporting coagulation tests will be performed. External review by the Adjudication Committee in a blinded fashion of relevant clinical data and medical imaging studies for confirmation of a TVE will be performed.

The primary endpoint is the proportion of subjects with at least 1 clinically relevant and objectively confirmed TVE from randomization through Week 16.

SECONDARY EFFICACY ENDPOINT EVALUATIONS/CRITERIA:

Efficacy evaluations are performed throughout the study and consist of collection of detailed information on RBC transfusions and weekly determination of Hb levels. The secondary efficacy endpoints are change in Hb from baseline to each postbaseline time point through the end of the study; proportion of subjects achieving a ≥1 g/dL Hb increase from baseline through 4 weeks of therapy; proportion of responders (i.e., subjects achieving a ≥2 g/dL Hb increase or reaching a target Hb of 12 g/dL by the end of the study); proportion of subjects receiving 1 or more RBC transfusions; and number of units of RBC transfused per subject.

SECONDARY SAFETY ENDPOINT EVALUATIONS/CRITERIA*:

Safety evaluations are performed throughout the study and consist of weekly determination of Hb levels and collection of mortality data, including the date and cause of death. Secondary safety endpoints are rate of rise in Hb during each 2-week period; time to occurrence of first clinically relevant and objectively confirmed TVE; the proportion of subjects with at least one TVE during the study and the total number of TVEs, whether clinically relevant and objectively confirmed or not; and time to death.

OVERALL SAFETY EVALUATIONS*:

The study will also include the following evaluations of overall safety and tolerability: adverse events according to National Cancer Institute - Common Toxicity Criteria for Adverse Events (NCI - CTCAE), CBC, serum chemistry (limited panel), 12-lead electrocardiograms (ECGs), physical examinations, and blood pressure.

STATISTICAL METHODS:

Sample Size Determination

Based on historical data, it is expected that the rate of clinically relevant TVEs in Group 2 will be approximately 6% and that the TVE rate in Group 1 will be similar. Based on this assumption, a sample size of 500 subjects (250 subjects per arm) will provide at least 80% power (with 2-sided type I error of 0.05) to rule out an absolute difference of 6.0% in TVE rates between the 2 groups, and would be, from a clinical perspective, sufficiently large to provide a reasonably precise estimate of the safety of Group 1 compared with Group 2. In addition, this sample size will allow for an operationally feasible study.

Primary Endpoint Analysis

The primary endpoint is the proportion of subjects with at least 1 clinically relevant and objectively confirmed TVE from randomization through Week 16.

The primary analysis will be based on an estimate of the difference of the clinically relevant TVE rates between Groups 1 and 2, together with a 2-sided 95% confidence interval (CI) for the difference. In addition, logistic regression will be used to compute the estimated odds ratio of TVE between the 2 treatment groups. This test will be stratified by ECOG performance status (0 or 1 versus 2) and study center.

Secondary Efficacy Analyses

Absolute values by time point and change from baseline to each postbaseline time point for Hb will be presented. The proportion of subjects achieving a ≥1 g/dL Hb increase from baseline will be presented by week through Week 4. The proportion of responders will be summarized by treatment group.

The proportion of subjects who received at least 1 RBC transfusion will be presented, as well as the number of transfusions per subject and the cumulative number of units received per subject.

Secondary Safety Analyses

The rate of rise in Hb will be determined within each 2-week time period for each subject using linear regression with Hb as the dependent variable and time (unit of 2-week) as the independent variable. The proportion of subjects with a rise in Hb $\geq$1 g/dL for each 2-week period will be presented. The proportion of subjects with at least 1 TVE (whether clinically relevant and objectively confirmed or not) will be presented, as well as the total number of TVEs (whether clinically relevant and objectively confirmed or not) in each treatment group.

Kaplan-Meier estimates of both the TVE rate and the mortality rate at the end of study will be presented by treatment group.

ATTACHMENT 2
STUDY EPO-ANE-4008: PATIENT LEVEL INFORMATION ON DEATHS

Country	Germany	Germany	Italy	Rumania	Russia	Germany	Poland	Germany	Germany
Patient ID/Gender	1003/Male	1004/Male	1068/Male	1067/Female	1088/Female	1053/Male	1175/Female	1055/Male	1080/Male
Age	57	77	71	51	71	85	61	77	71
Treatment Group	QW	TIW	TIW	TIW	TIW	TIW	TIW	TIW	TIW
Type of Malignancy	SCLC with bone metastases in Nov.2005.Brain meta's in 2006	NSCLC March 06	Gastr-pancreatic cancer	Head &Neck	Multiple Myeloma diagnosed in Febr.03	NHL diagnosed in 1999 Acute leukemic episode in Jan.07	Ovarian cancer	NSCLC with bone metastases diagnosed in June 06	Epitheloid Pleura Mesothelioma diagnosed on 24.01.07
Prior therapy	Ended Cisplatin in April 06 and radiotherapy in June 06	Ended previous chemotherapy in June 06 (1 regimen)	Total gastrectomy/splenectomy cholecystectomy in April 06. End of chemotherapy Sept06	No	Thalidomide from 06.08.06 till 26.04.07	Bendamustine started in Sep 02	Hysterectomy and adnexectomy in August 05 Second look laparatomy in March 06 Ended last chemo on 11.04.07	Last chemotherapy ended in October 06 (5 cycles)	No
Disease stage	Metastatic	Adv/Metast lung, adrenal glands	Metastatic, peritoneum	Oropharyngeal cancer with cervical adenopathies	Bone Marrow	Mediastinum, infiltration bone marrow, secondary kidney lymphoma	Metastatic: tumors spread in peritoneal cavity with peritoneal effusion	Advanced/lung Metastases: bone	Advanced/Pleura
ECOG status	Grade 1	Grade 1	Grade 0	Grade 1	Grade 1	Grade 2	Grade 2	Grade 1	Grade 1
Current Chemo	Topotecan every 4w, start oct06	Pemetrexed started Oct 06	Epirubicin,carboplatin from 03.03.07 till 14.03.07 On 14.03.07 pump infusion with 5-Fu	Neo-adjuvans with 5-Fu, Cisplatin every 3w from 07.03.07 till May 07, followed by carboplatin till 15.06.07 Radiotherapy from 22.05.07 till 03.06.07	Cyclophosphamide started 03.05.07	Bendamustine and prednisone every 4 weeks from Sep 02 till 15 March 07 Fludarabin evry 4 weeks from 16.04.07 till 21.05.07	Gemcitabine every 3 weeks started 14.05.07	Started Gemcitabine/vinorelbine every 3 weeks on 24.01.07	Started Cisplatin, Pemetrexed every 3 weeks on 9.02.07
Date start epo	04.12.06	4.12.06	14.03.07	28.03.07	19.04.07	15.02.07	11.06.07	15.02.07	23.03.07
Duration epo treatment	8 weeks	one week	5 weeks	11 weeks	3 weeks	8 weeks (non-responder)	3 weeks	21 weeks	One week
Date of last epo dose	24.01.07	08.12.06	23.04.07	14.06.07	12.04.07	12.04.07	04.07.07	16.07.07	04.04.07
Date of death	07.02.07	29.12.06	26.04.07	15.06.07	14.05.07	31.05.07		31.07.07	15.05.07
Cause of death	worsening general condition: PD	worsening general condition, pneumonia with septic development, anuria and multi-organ failure due to PD	Acute hepatic failure due to PD	Aplasia with grade 4 thrombocytopenia due to cancer treatment toxicity	Sudden death at home (some chest pain in the previous hour)	Acute renal failure due to PD	in PD and final cardio-pulmonary failure	Progressive lung cancer with lymphangiosis carcinomatosis and atypical pneumonia	Unknown Note: patient withdrew consent on 07.05.07
Investigator causality assessment	Not Related	Not related	Not related	Not related	Possibly related	Not related	Possibly related (investigator would not exclude causality between epo treatment and cardio-pulmonary failure)	No related	Not related