

SYNOPSIS

<p><u>NAME OF SPONSOR/COMPANY:</u> Ortho Biotech Clinical Affairs, L.L.C.</p> <p><u>NAME OF FINISHED PRODUCT:</u> epoetin alfa</p> <p><u>NAME OF ACTIVE INGREDIENT(S):</u> epoetin alfa</p>	<p><u>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</u></p> <p>Volume:</p> <p>Page:</p>	<p><u>(FOR NATIONAL AUTHORITY USE ONLY)</u></p>
<p>Protocol No.: PR02-27-015</p> <p>Title of Study: AN OPEN-LABEL PILOT STUDY TO EVALUATE THE EFFECTS OF HIGH DOSE PROCRT[®] (EPOETIN ALFA) IN MAINTAINING HEMOGLOBIN LEVELS IN ANEMIC CANCER PATIENTS RECEIVING CHEMOTHERAPY ON A WEEKLY OR EVERY 4 WEEK REGIMEN</p>		
<p>Principal Investigator: Stephanie A. Gregory, M.D., Rush University Medical Center, Chicago, IL</p>		
<p>Publication (References): ASH 2003: Gregory SA, Williams D. Epoetin alfa 60,000 U QW followed by Q2W maintenance dosing corrects anemia and maintains hemoglobin (Hb) in anemic patients with cancer receiving chemotherapy. Blood 2003;102(11):166b (abstract 4373).</p> <p>ASCO 2004: Baltz B, Gregory SA, Ehmann WC, Williams D. Initial dosing of epoetin alfa 60,000 U qw followed by q2w maintenance for anemic patients with cancer receiving chemotherapy. Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition). Vol 22, No 14S (July 15 Supplement), 2004: abstract 8212.</p> <p>ASH 2004: Gregory SA, Baltz B, Williams D. Every-Two-Week (Q2W) maintenance dosing with epoetin alfa in anemic patients with cancer receiving chemotherapy: 60,000 U qw to target Hb 12 g/dL, followed by 60,000 U q2w. Blood 2004;104(11):144b (abstract 4233.5).</p> <p>ASH 2005: Gregory SA, Xie J, Woodman RC. Maintenance dosing with epoetin alfa every two weeks (q2w) in anemic patients with cancer receiving chemotherapy every one or four weeks: final results. Blood 2005;106(11): abstract 3770.</p>		
<p>Study Initiation/Completion Dates: 6 February 2003 to 16 February 2005</p>	<p>Phase of development: 2</p>	
<p>Objectives: The primary objective was to determine the efficacy and safety of PROCRT (epoetin alfa) at a starting dose of 60,000 Units (U) administered subcutaneously (sc) once per week (qw) to a target hemoglobin (Hb) of 12 g/dL in the Initiation Phase (IP), followed by a maintenance dose of 60,000 U once every other week (q2w) in the Maintenance Phase (MP) (to maintain Hb range 11.5 to 12.5 g/dL) in anemic cancer patients receiving chemotherapy.</p> <p>The secondary objective of the study was to determine the incidence of anti-erythropoietin antibodies (anti-EPO Ab) at baseline and at end of study/early withdrawal in patients who received a minimum of 2 or more doses of epoetin alfa over at least a 1-month period.</p> <p>Safety and tolerance of the dosing regimen was also assessed throughout the study.</p>		
<p>Methodology: This was an open-label, single-arm, multicenter pilot study. All patients were assigned the same dosing regimen. The treatment period was divided into 2 phases, IP and MP. During the IP, patients received PROCRT at a starting dose of 60,000 U administered sc qw to achieve the target Hb of 12 g/dL (within 12 weeks). Patients who did not achieve the target Hb of 12 g/dL within the 12 weeks were not eligible to proceed to the MP. Once the target Hb of 12 g/dL was reached, patients proceeded to the MP. In the MP patients received PROCRT at 60,000 U sc q2w to maintain Hb range 11.5 to 12.5 g/dL. If, at any time during the study, the Hb level rose to >13 g/dL, PROCRT therapy was withheld until the Hb fell to ≤12 g/dL, then resumed at a dose reduction of 20,000 U (i.e., from 60,000 U to 40,000 U in the IP and MP). A similar dose reduction was made if an Hb increase of more than 1.3 g/dL occurred in a 2-week period. Patients whose Hb fell below 11 g/dL during the MP dosing had a confirmatory Hb measurement performed within 24 hours. If the confirmatory Hb measurement remained below 11 g/dL, the patient was withdrawn from the study. There was a 90-day follow-up period after study completion or withdrawal. Iron: Patients received supplemental iron, ferrous sulfate 325 mg orally every day or an equivalent iron preparation, as tolerated and if not contraindicated. Patients who were not able to tolerate the oral iron preparation received an intravenous formulation of iron as prescribed by their physicians and at their physicians' discretion.</p>		

<p><u>NAME OF SPONSOR/COMPANY:</u> Ortho Biotech Clinical Affairs, L.L.C.</p> <p><u>NAME OF FINISHED PRODUCT:</u> epoetin alfa</p> <p><u>NAME OF ACTIVE INGREDIENT(S):</u> epoetin alfa</p>	<p><u>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</u></p> <p>Volume:</p> <p>Page:</p>	<p><u>(FOR NATIONAL AUTHORITY USE ONLY)</u></p>
<p>Number of Patients (planned and analyzed): One hundred thirty (130) patients were planned and 129 were treated and included in the safety and efficacy analyses.</p>		
<p>Diagnosis and Main Criteria for Inclusion: Patients, age ≥ 18 years, who were receiving chemotherapy qw or every 4 weeks (q4w) for histologically-confirmed non-myeloid malignancies and who had a baseline Hb ≤ 11 g/dL.</p>		
<p>Test Product, Dose and Mode of Administration, Lot No.: Epoetin alfa 40,000 U solution was provided in commercially available, single-use vials and administered sc. Lot numbers were R11982 and R12492. The starting dose in both the IP and MP was 60,000 U. Doses reductions of 20,000 U were made when Hb levels rose to >13 g/dL or when Hb increased more than 1.3 g/dL in a 2-week period.</p>		
<p>Duration of Treatment: The IP lasted up to 12 weeks. The maximum duration of the study (IP and MP) was 24 weeks.</p>		
<p>Criteria for Evaluation:</p> <p>Efficacy: All efficacy analyses were independent of RBC/Whole Blood transfusions within 4 weeks (i.e., Hb values occurring within 28 days after a transfusion were not considered in the analyses). The primary efficacy endpoint was the proportion of patients with a major response during IP (up to 12 weeks post-first dose). The definitions of responses for IP (qw dosing) were:</p> <p>Major response in IP: ≥ 2 g/dL Hb increase from baseline or Hb ≥ 12 g/dL</p> <p>Minor response in IP: ≥ 1 g/dL Hb increase from baseline (i.e., up to 1.9 g/dL)</p> <p>The secondary efficacy endpoints were the proportions of patients with a minor response during the IP, a major response during the MP and a minor response during the MP. The definitions of responses for MP (q2w dosing) were:</p> <p>Major response in MP: maintenance of Hb level 11.5 to 12.5 g/dL</p> <p>Minor response in MP: maintenance of Hb level >11 g/dL (up to 11.4 g/dL)</p> <p>MP responses were calculated in two ways:</p> <p>At all weeks within phase – If every week’s Hb value was between 11.5 to 12.5 g/dL ($11.5 \leq \text{Hb} \leq 12.5$), the patient was categorized as having a major response. If every week’s Hb value was greater than 11 g/dL but at least one was less than 11.5 g/dL, the patient was categorized as having a minor response.</p> <p>Average within phase – If the MP average Hb was between 11.5 to 12.5 g/dL ($11.5 \leq \text{Hb} \leq 12.5$), the patient was categorized as having a major response. If the MP average Hb was greater than 11 g/dL and up to 11.4 g/dL, the patient was categorized as having a minor response.</p> <p>Safety: All safety analyses were performed on the Safety, Initiation Phase Only (IP Only), and MP populations. Safety evaluations included clinical laboratory tests (Hb and hematocrit), vital sign measurements (blood pressure), and incidence and severity of adverse events (AE). In addition, the incidence of anti-EPO Ab at baseline and study completion/early withdrawal was evaluated in patients who received multiple doses of PROCRIT.</p>		

<u>NAME OF SPONSOR/COMPANY:</u> Ortho Biotech Clinical Affairs, L.L.C.	<u>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</u>	<u>(FOR NATIONAL AUTHORITY USE ONLY)</u>
<u>NAME OF FINISHED PRODUCT:</u> epoetin alfa	Volume:	
<u>NAME OF ACTIVE INGREDIENT(S):</u> epoetin alfa	Page:	

Statistical Methods: The Intent-to-Treat (ITT) population was defined as all patients enrolled and treated with at least 1 dose of study medication. All analyses were performed using the ITT population and using the following subgroup populations: **IP Only population**, defined as patients receiving at least 1 dose during IP and not proceeding to the MP, and **MP population**, defined as patients receiving at least 1 dose during MP. The **Safety population** was defined the same as the ITT population.

All efficacy endpoints and the corresponding 95% confidence intervals (CI) were calculated for the ITT population. For continuous variables, the CI was based on a t-distribution. For categorical variables, the CI was based on a binomial distribution. All statistical tests were 2-sided.

The median time and 95% CI to first major response in IP were summarized using Kaplan-Meier estimates; patients who did not have a major response in the IP were considered censored based on their last Hb assessment date.

Safety data were summarized descriptively; statistical tests were not performed.

In addition to the planned analyses, post hoc analyses were performed in order to determine if an association existed between Hb level >13 g/dL or Hb rate of rise (RoR) >1 g/dL within a 2-week period and the occurrence of a thrombovascular event (TVE) or clinically relevant TVE (CRTVE). These analyses included patients who received at least one dose of study drug and who had at least one post-dose Hb measurement. During study conduct, dose titrations for Hb RoR were based on the labeled recommendations in place at that time (i.e., >1.3 g/dL rise in a 2-week period). Subsequent post hoc TVE analyses also included the currently accepted and labeled Hb rate of rise of >1 g/dL within a 2-week period.

SUMMARY - CONCLUSIONS

BASELINE ASSESSMENTS: The ITT population included 129 patients with 44 (34.1%) of those being men. The mean age of patients was 62.6 years. One hundred six (82.2%) patients were Caucasian, and 17 (13.2%) patients were black. Most patients were rated as ECOG performance status of 0 (29.5%) or 1 (54.3%) at baseline. Mean Hb at baseline was 10.0 g/dL. Of the 127 patients who received at least 1 chemotherapy administration on or after Study Day 1, 37 (29.1%) were receiving platinum-based chemotherapy regimens. Most patients had solid tumor types (119 [92.2%]), with gastrointestinal being the most common primary site (33 patients [25.6%]). The next most common sites were breast and lung (26 patients [20.2%] each). Thirteen (10.1%) patients had a diagnosis of a non-myeloid hematologic malignancy.

EXTENT OF EXPOSURE AND DOSE ADJUSTMENTS: The mean cumulative dose over the course of the study was 441,240 U, with a range of 60,000 U to 1,020,000 U. The mean duration of exposure over the course of the study was 72.0 days, with a range of 1 to 186. The mean duration in the IP was 5.2 weeks and mean duration in the MP was 11.2 weeks. Sixty patients (46.5%) had at least 1 dose reduction during the study. In the IP, 14 (10.9%) patients had a dose reduction and, in the MP, 47 (36.4%) patients had a dose reduction. Sixty patients (46.5%) had at least 1 dose withheld during the study. In the IP, 8 (6.2%) patients had a dose withheld and, in the MP, 53 (41.1%) patients had a dose withheld

<u>NAME OF SPONSOR/COMPANY:</u> Ortho Biotech Clinical Affairs, L.L.C.	<u>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</u>	<u>(FOR NATIONAL AUTHORITY USE ONLY)</u>
<u>NAME OF FINISHED PRODUCT:</u> epoetin alfa	Volume:	
<u>NAME OF ACTIVE INGREDIENT(S):</u> epoetin alfa	Page:	

SUMMARY – CONCLUSIONS (continued)

EFFICACY RESULTS: The primary population for all analyses was the ITT population. All efficacy analyses were independent of RBC/Whole Blood transfusions within 4 weeks (i.e., Hb values occurring within 28 days after a transfusion were not eligible to be considered in calculating changes from baseline in Hb values or in the determination of response). The Last Value Carried Forward (LVCF) method was used to impute missing data for efficacy analysis of Hb values at the end of the study.

Primary endpoint: Eighty-four patients (67.7%; 95% CI: 59.5, 76.0) had a major response during the IP.

Secondary endpoints: Fourteen patients (11.3%; 95% CI: 5.7, 16.9) had a minor response during the IP. During the MP (n=84), using the “average within phase” method, 47 patients (56.0%; 95% CI: 45.3, 66.6) had a major response and 4 patients (4.8%; 95% CI: 0.2, 9.3) had a minor response. During the MP (n=84), using the “data at all weeks within phase” method, 5 patients (6.0%; 95% CI: 0.9, 11.0) had a major response and 5 patients (6.0%; 95% CI: 0.9, 11.0) had a minor response.

Eighteen patients of the 129 enrolled (14.0%) received 1 or more PRBC transfusions during the IP, and none of the 84 patients who proceeded to the MP received a PRBC transfusion during the MP.

SAFETY RESULTS: PROCRT was generally safe and well tolerated. Clinical laboratory tests, blood pressure readings taken throughout the study, or other safety assessments suggested no clinically relevant mean changes from baseline. Anti-EPO Ab results (n=48) were negative for all assessments. No cases of suspected loss of effect were reported by the investigators.

The incidence of AEs is shown below. Thrombotic vascular events were reported in 28 (21.7%) patients during the study. The incidence and types of TVEs and CRTVEs are shown below. These data reflect TVEs occurring during treatment or within 90 days after study completion or withdrawal.

Incidence of Adverse Events during Study Treatment
(Study PR02-27-015: Safety Population, N=129)

Patients with any AE, n (%)	123 (95.3)
Patients with any drug-related AE	5 (3.9)
Deaths	29 (22.5)
Patients with any SAE	65 (50.4)
Patients with any AE leading to permanent discontinuation from study	8 (6.2)
Patients with any thrombotic vascular event (TVE)	28 (21.7)

Note: Unique events for a patient are counted once within each MedDRA System Organ Class and Preferred Term.

<u>NAME OF SPONSOR/COMPANY:</u> Ortho Biotech Clinical Affairs, L.L.C. <u>NAME OF FINISHED PRODUCT:</u> epoetin alfa <u>NAME OF ACTIVE INGREDIENT(S):</u> epoetin alfa	<u>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER</u> Volume: Page:	<u>(FOR NATIONAL AUTHORITY USE ONLY)</u>
<u>SAFETY RESULTS (continued):</u>		
<p style="text-align: center;">Incidence of TVEs and CRTVEs Occurring With Hb change* (Study PR02-27-015: Safety Population, N=129)</p>		
Patients with at least one TVE	n 28	
Patients with at least one CRTVE	15	
Types of CRTVEs (preferred term)		
Myocardial Infarction	2	
Myocardial Ischemia	1	
Portal Vein Thrombosis	1	
Hemiparesis	2	
Transient Ischemic Attack	1	
Pulmonary Embolism ^a	1	
Deep Vein Thrombosis	7	
Subclavian Vein Thrombosis	1	
Venous Thrombosis NOS Limb	1	
Incidence of Hb rate of rise (RoR) >1 g/dL in a 2-week period	Hb RoR	No Hb RoR
Patients with TVEs	23/97 (23.7)	4/31 (12.9)
Patients with CRTVEs	12/97 (12.4)	2/31 (6.5)
Incidence of Hb >13 g/dL	At least one Hb > 13 g/dL	All Hb values ≤ 13 g/dL
Patients with TVEs	13/47 (27.7)	14/81 (17.3)
Patients with CRTVEs	7/47 (14.9)	7/81 (8.6)
* Note: Hb changes may have occurred either before or after the TVE/CRTVE.		
^a Patient did not have a post-dose Hb and is not included in the TVE post hoc analysis. Grouped terms defined as a TVE and clinically relevant TVE were defined by the sponsor. TVEs that were not considered clinically relevant were chest pain and chest discomfort.		
The incidence of a TVE or a CRTVE occurring during the treatment period or within 90 days of study completion or withdrawal was somewhat higher among subjects exhibiting a >1 g/dL rise in Hb over a 2-week period or a Hb rise to >13 g/dL at any time versus those who did not exhibit either Hb response.		
CONCLUSION: PROCRIT (epoetin alfa) at a starting dose of 60,000 U administered sc qw to achieve a target Hb of ≥12 g/dL in the IP, followed by a maintenance dose of 60,000 U q2w in the MP (to maintain Hb range 11.5 to 12.5 g/dL), was safe and well tolerated in anemic cancer patients receiving chemotherapy. Efficacy data from this open-label, pilot study suggest that maintenance therapy can be administered less frequently than weekly and still maintain average Hb levels within the target range.		

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.