1. SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho Biotech Clinical Affairs, L.L.C.	**INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER**	**(FOR NATIONAL AUTHORITY USE ONLY)**
NAME OF FINISHED PRODUCT: PROCRIT®	**Volume:**	
NAME OF ACTIVE INGREDIENT(S): Epoetin alfa; recombinant human erythropoietin	**Page:**	

Protocol No.: CR005131

Title of Study: An Open-Labeled Study to Evaluate the Effect of Every Other Week PROCRIT® (Epoetin alfa) Dosing on Maintaining Quality of Life and Target Hemoglobin Levels in Anemic HIV-Infected Patients

Principal Investigator: Alexandra M. Levine, MD; USC/Norris Comprehensive Cancer Center and Hospital; 1441 Eastlake Avenue, MS 34; Los Angeles, CA 90033-0804

Publication (Reference): Saag MS, Bowers P, Leitz GJ, Levine AM; Community HIV Anemia Management Protocol Sites (CHAMPS) Study Group. Once-weekly epoetin alfa improves quality of life and increases hemoglobin in anemic HIV+ patients. AIDS Res Hum Retroviruses 2004;20:1037-45.

Study Initiation/Completion Dates: October 15, 2002/ May 28, 2004 | **Phase of development:** 4

Objectives: The objective of this study was to treat anemic (hemoglobin [Hb] ≤12 g/dL), human immunodeficiency virus (HIV)-infected patients with weekly (QW) PROCRIT® to a target Hb of ≥13 g/dL and then to assess if the target Hb level and improvements in Quality of Life (QOL) could be maintained with every other week (Q2W) PROCRIT® dosing. Safety of the above dosing regimen was assessed.

Methodology:

This was an open-label, non-randomized, multi-center study of 24 weeks duration. A total of 292 anemic (Hb ≤12 g/dL) HIV-infected patients who must have been on stable (at least 4 weeks prior to study enrollment) antiretroviral therapy (ART) were enrolled in 70 community-based centers. Quality of life assessments, laboratory results, and transfusion information were obtained during the study. To minimize bias in QOL measurements, patients were kept blinded to Hb, hematocrit (Hct) and laboratory values until all study procedures were completed for the visit.

The study had two phases: an initiation phase and a maintenance phase. During the initiation phase, patients received PROCRIT® administered subcutaneously (sc) QW until a target Hb of ≥13 g/dL was achieved. After patients achieved the target of Hb ≥13 g/dL, they entered the maintenance phase and were converted to a Q2W maintenance dosing regimen.

Number of Subjects (planned and analyzed): A total of 292 patients were enrolled and evaluable for safety; 237 patients were evaluable for efficacy.

Diagnosis and Main Criteria for Inclusion: This study included anemic (Hb ≤12 g/dL), HIV-infected patients and HIV/Hepatitis C (HCV) co-infected patients not receiving HCV treatment. Patients were on a stable ART regimen for at least 4 weeks.

Test Product, Dose and Mode of Administration, Batch No.: PROCRIT® was administered by sc injection. The starting dose of PROCRIT® for all eligible patients was 40,000 units sc QW.

Reference Therapy, Dose and Mode of Administration, Batch No.: This was an open-label study.

Duration of Treatment: 24 weeks

Criteria for Evaluation:

Efficacy

- Change in QOL as measured by Medical Outcomes Study HIV (MOS-HIV) and Linear Outcomes Scale Assessment (LASA)
- Change in Hb level
- Transfusion utilization

Safety

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- Incidence and severity of adverse events (AEs)
- Laboratory tests, including complete blood count (CBC), hematocrit, CD4 lymphocyte count, anti-erythropoietin antibodies (anti-EPO Ab), serum ferritin and folate levels, and plasma HIV RNA levels.
- Blood pressure (complete vital signs and body weight at screening and end of study)

Statistical Methods:

Primary Analyses

The primary endpoint for this study was the effect of PROCRIT® on maintaining QOL improvements (measured primarily by MOS-HIV overall QOL using the general health perceptions scale) during Q2W dosing. The 1-sided 95% confidence interval ([CI]; 100 * (1-α)% CI) of the mean difference for MOS-HIV overall QOL between Week 24 or the last measurement and the beginning of the maintenance phase was obtained. The overall QOL was considered to be maintained if the lower limit of this 95% CI was less than 7 points lower at Week 24 compared with that at the beginning of the maintenance phase.

Secondary Analyses

The paired t-test was used to analyze the change in Hb levels from the beginning of the maintenance phase to Week 24 or last visit and Hb change over time (during the study and during the maintenance phase). The 2-sided 95% CI and *P*-value of the average change from baseline to each time point was reported.

The paired t-test was also used to analyze QOL change over time (during the study and during the maintenance phase) for each MOS-HIV domain (including the physical and mental health summary scores) and LASA scores.

The percentage of patients who received transfusions was summarized.

Analyses of safety included all patients in the safety population. All AEs were classified by body system and preferred term using the Medical Dictionary for Drug Regulatory Affairs (MedDRA; Version 5.1:2002). The number of patients having treatment-emergent AEs was summarized. Counts of patients with events by severity and relationship to study drug were also presented. Any treatment-emergent serious adverse events (SAEs) and discontinuations due to AEs were summarized and listed.

Serum EPO antibodies at baseline, and at Week 24 or early withdrawal were summarized.

The rest of the safety evaluations (i.e., vital signs and clinical laboratory results) were listed, but not summarized.

SUMMARY – CONCLUSIONS

Of 292 enrolled patients, 267 (91.4%) patients responded to PROCRIT® therapy (i.e., responders had a $\geq$1 g/dL increase in Hb level after 8 weeks of study drug) and 237 (81.2%) patients were included in the efficacy population.

The mean duration of study drug treatment for the efficacy population was 22.8 weeks overall. The mean time to reach maintenance phase was 4.5 weeks. During the maintenance phase, 94% of patients in the efficacy population received doses of 40,000 U only, and 6% received at least one dose of 60,000 U. On average, patients required 4 QW doses to reach the maintenance phase. During the maintenance phase, the majority of patients had dosing intervals ranging from every 2 weeks (46.4%) to every 3 weeks (29.3%).

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EFFICACY RESULTS:

Primary Results

Quality Of Life

In the efficacy population, the mean change of the MOS-HIV overall QOL using the general health perceptions scale from Day 1 of the maintenance phase to Week 24 or last visit was –0.8 ± 18.6 (the lower limit of the 1-sided 95% CI: -3.0), which met the criteria for maintaining QOL.

Statistically significant improvements were observed in all 10 domains of the MOS-HIV QOL Assessment, the health transition item, and the physical and mental health summaries of the MOS-HIV from Baseline to Day 1 of the maintenance phase ($P \leq 0.001$ except for role function $P=0.048$) and from Baseline to Week 24 or last visit ($P<0.001$ except for role function $P=0.019$). The largest improvements from Baseline to Day 1 of maintenance phase were observed within the energy/fatigue and health transition domains (17.0 and 17.3 points, respectively). Improvements in all MOS-HIV domains were maintained from Day 1 of maintenance phase to Week 24 or last visit. MOS-HIV results were similar in the modified efficacy (excluding patients with transfusions) and ad hoc analysis populations (excluding patients with baseline Hb >12 g/dL). Improvements in MOS-HIV scores were also associated with increases in Hb. The non-efficacy population (patients who either did not have an Hb increase of ≥1 g/dL from baseline or did not reach the target Hb level of ≥ 13g/dL by Week 8) did not have a substantial improvement in most of the MOS-HIV domain scores.

PROCRIT® therapy also resulted in statistically significant improvements in all 3 LASA domains, and improvements in all LASA domains were maintained from Day 1 of maintenance phase to Week 24 or last visit, supporting the results above.

Secondary Results

Hemoglobin

Hemoglobin levels for the efficacy population showed a statistically significant increase from Baseline to Day 1 of the maintenance phase and to Week 24/last visit (increase of 2.5 g/dL to 13.4 g/dL at Day 1 of maintenance phase and increase of 1.9 g/dL to 12.8 g/dL at Week 24, $P<0.001$ for both). Results were similar for the modified efficacy population (excluding patients who received transfusions).

The median Hb at Day 1 of the maintenance phase was 13.3 g/dL (range 13.0 – 15.4 g/dL) and the median time to achieve the target Hb level was 3.4 weeks (range 1.0 – 20.9 weeks). .

Changes in Hb levels were not affected by race, gender, baseline CD4 counts, or viral load changes during study participation. In addition, neither previous use of AZT nor concurrent AZT usage has an effect on changes in Hb levels.

Transfusions

In the efficacy population 4% (8/237) patients received a transfusion during the study, and 2.1% (5/237) patients received a transfusion during the maintenance phase.

SAFETY RESULTS:

Adverse Events

Treatment-emergent AEs were reported for a total of 72.9% (213/292) of patients.

The most common treatment-emergent AEs were diarrhea NOS (8.9%), nausea (8.2%), fatigue (7.5%), headache (6.8%), and upper respiratory tract infections NOS (6.5%).

The majority of the patients experienced AEs that were mild (22.9%) or moderate (34.2%) in severity. Overall, 15.8% of patients had treatment-emergent AEs that were considered severe by the investigator.

The majority of patients (196/213) had AEs that were considered unrelated to study drug. The overall incidence of

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patients who experienced study drug-related AEs was 5.8% (17/292).

A total of 20 (6.8%) patients discontinued study drug due to an AE. The majority of AEs leading to study discontinuation were moderate to severe in intensity. Most (17/20) events were considered unrelated to study drug.

Serious Adverse Events

A total of 52 (17.8%) patients experienced SAEs during study drug treatment. All of the SAEs were considered unrelated to study drug, and the majority of SAEs were considered moderate or severe in intensity.

Deaths

Overall, 7 (2.4%) patients had treatment-emergent SAEs resulting in death, and 2 patients had AEs that were not treatment-emergent but resulted in death. Eight of these deaths were considered unrelated to study drug, and one death due to hepatic encephalopathy was considered to have a doubtful relationship to study drug.

Thrombotic Vascular Events (TVEs)

The incidence of patients who experienced treatment-emergent TVEs was 5.8% (17/292). In the opinions of the investigators, none of the reported TVEs were related to PROCRIT®. There were 2 deaths due to treatment-emergent TVEs (gastrointestinal hemorrhage NOS and congestive cardiac failure); both events were considered unrelated to study drug.

No clinically important changes in laboratory values, vital signs, or physical examination findings were found during this study.

EPO Antibodies

All of the patients treated with PROCRIT® during this study remained negative for anti-EPO antibodies from Baseline through Week 24 or last visit.

CONCLUSION:

Anemic, HIV-infected patients maintained improvements in QOL once reaching a target Hb level of 13 g/dL with Q2W or Q3W dosing of PROCRIT®. The majority of patients were able to maintain a target Hb level of approximately 13 g/dL with Q2W or Q3W dosing regimens of 40,000 units of PROCRIT®. The longer dosing intervals of PROCRIT® during a maintenance phase may potentially provide greater patient and provider convenience.

Date of the report: 12 March 2007

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