SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho Biotech Products, L.P. NAME OF FINISHED PRODUCT: PROCRIT® epoetin alfa NAME OF ACTIVE INGREDIENT: Recombinant Human Erythropoietin	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: CR005098

Title of Study: An Open-Label Pilot Study to Evaluate the Effects of Alternate Dosing Of PROCRIT® (epoetin alfa) in the Treatment of Patients with Cancer and Chemotherapy Induced Anemia (60,000 Units Weekly for Four Weeks followed by 60,000 Units Every Two Weeks)

Investigator: N/A

Study Initiation/Completion Dates: 04 September 2003/05 April 2004 | **Phase of development: IIIb**

Objectives: The primary objective of this pilot study was to estimate the hematologic responses for the dosing regimen of PROCRIT (epoetin alfa), starting at a dose of 60,000 units (U) administered subcutaneously (sc) once per week (qw) for four weeks ("Phase A"), followed by a dose of 60,000 U every two weeks (q2w) ("Phase B") in patients with cancer and chemotherapy induced anemia. 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 had received a minimum of one or more doses of PROCRIT. Safety and tolerance of the dosing regimen were also to be assessed throughout the study.

Methodology: This was an open-label, non-randomized, multicenter pilot study. Patients received chemotherapy for a non-myeloid malignancy with baseline hemoglobin (Hb) ≤11 g/dL and who met all inclusion/exclusion criteria were enrolled. The treatment period in this study was divided into two phases. During Phase A, patients received PROCRIT at a starting dose of 60,000 U administered sc qw for a total of four weeks during chemotherapy administration. Patients proceeding to Phase B (i.e. had ≥1 g d/L rise in Hb) received PROCRIT at a dose of 60,000 U sc q2w for up to 12 weeks during chemotherapy administration. The maximum treatment period was 16 weeks for Phases A and B. Patients were to have been followed weekly for two weeks after the last dose of PROCRIT or up to a maximum of 17 weeks on study whichever came first.

Number of Patients (planned and analyzed): 50 patients were planned; 51 were analyzed.

Diagnosis and Main Criteria for Inclusion: Patients with a histologically confirmed non-myeloid malignancy, a baseline Hb ≤11 g/dL and who received chemotherapy were enrolled into the study.

Test Product, Dose and Mode of Administration, Batch No.: The starting dose of PROCRIT was 60,000 U sc qw (Phase A). At Week 5 (i.e., after four weeks of weekly PROCRIT dosing), if the patient's Hb had increased by ≥1 g/dL above Week 1 baseline, the patient began Phase B and receive PROCRIT at a dose of 60,000 U sc q2w for up to 12 weeks. One additional (final) dose was administered at the end of the final cycle of chemotherapy if chemotherapy was completed prior to Week 16. If chemotherapy given on Week 16 no additional PROCRIT dose was administered. Patients were then followed weekly for two weeks after the last dose of PROCRIT or up to a maximum of 17 weeks on study whichever came first. **Non-responders:** If the Hb level had not increased by ≥1 g/dL above Week 1 baseline after four weeks of weekly PROCRIT dosing in Phase A, the patient was withdrawn from the study. Patients who had a Hb decrease by ≥2 g/dL after entering Phase B were withdrawn from the study. **Dose Adjustments:** If, at any time during the study, the Hb level rose to >13 g/dL, PROCRIT therapy was held until Hb reached ≤12 g/dL, then resumed at a reduced dose. The dose was also reduced (from 60,000 U to 40,000 U) if a very rapid Hb response occurred (an increase of more than 1.3 g/dL in a two-week period). A confirmatory Hb level was to have been obtained within 24 hours prior to withholding/reducing any dose. All patients were to receive concomitant ferrous sulfate 325 mg by mouth daily or an equivalent formulation, as tolerated (unless there was a reason the patient should not receive this medication). Batch No.: PROCRIT® 40,000 units/mL for injection, 1 mL vials, NDC 59676-340-01; Bulk D03LE1064, Mfg. lot: Amgen P007983.

Duration of Treatment: The maximum treatment duration was 16 weeks

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Ortho Biotech Products, L.P.	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: PROCRIT® epoetin alfa NAME OF ACTIVE INGREDIENT: Recombinant Human Erythropoietin	Volume: Page:	

Criteria for Evaluation: **Efficacy**: The primary efficacy outcome was a rise in Hb of at least 1 g/dL at any time during Phase A (with Hb values obtained in the 28 days following a transfusion excluded from the analysis). Secondary efficacy outcomes included hematologic responses during Phase B. **Safety**: The following safety evaluations were performed during the study to measure the safety and tolerability of PROCRIT: Adverse events (AE), clinical laboratory tests, vital signs (blood pressure), physical examinations and all occurrences of pure red cell aplasia, loss of effect of PROCRIT in the treatment of anemia and/or a report of the presence of antibody to EPO as defined as a serious adverse event (SAE).

Statistical Methods: This Protocol was designed as a pilot study to evaluate the estimated hematologic responses for the dosing regimen of PROCRIT starting at a dose of 60,000 U administered qw for four weeks ("Phase A"), followed by a dose of 60,000 U q2w ("Phase B") in patients with cancer and chemotherapy induced anemia. The study endpoints were hematologic response in each phase as measured by Hb change and transfusion requirements from baseline to end of study. All response criteria were to be independent of transfusion within four weeks. **Definition of Analysis Populations:** Modified Intent to Treat Population (MITT): MITT was defined as all patients enrolled and treated with at least one dose of study medication. All analyses will be performed using the MITT population. Safety Population: The Safety population was the same population as the MITT population. **Subgroup Populations:** Transfusion-Free MITT Population: Patients in MITT that had no transfusions at any time during the study were included in the Transfusion-Free MITT population. Phase A Only Population: Patients that received at least one dose during Phase A and who did not proceed to Phase B were included in the Phase A Only Subgroup. These were the patients that did not have a Hb value increase from Study Baseline by ≥ 1 g/dL after four weeks of weekly PROCRIT dosing. Phase B Population: Patients who met the Hb response criteria for Phase B and who received at least one dose during Phase B were included in the Phase B Subgroup. Non-MITT Population: Patients that were enrolled in study, but who were never given a study dose of PROCRIT, i.e., patients with only screening data and no dosing data were included in the Non-MITT population.

Primary Efficacy Endpoint: The primary efficacy endpoint was the proportion of patients with a ≥ 1g/dL increase in Hb in Phase A (four weeks).

- Primary Response: ≥1 g/dL Hb increase above baseline (Week 1) at any visit in Phase A (Week 2 to Week 5).

$$P = \frac{Number\ of\ Patients\ with\ (Any\ Week\ Hb\ in\ Phase\ A - Week\ 1\ Hb) \geq 1}{All\ Patients}$$

Secondary Efficacy Variables: The secondary efficacy endpoints were the proportions of patients with hematologic responses (either Major response or Minor response) during Phase B, as defined below.

- Hematologic Major Response: ≥1 g/dL increase above the level achieved in Phase A. This was defined as the average Hb value has ≥1 g/dL increase above the Week 5 Hb value
- Hematologic Minor Response: Maintenance of ≥ the absolute Hb level achieved in Phase A (up to 0.9 g/dL higher)

The "absolute Hb level achieved in Phase A" and the "level achieved in Phase A" were both defined as the Week 5 Hb value.

$$P = \frac{Number\ of\ Patients\ with\ [0 < (Phase\ B\ Average\ Hb - Week\ 5\ Hb) \leq 0.9\,\text{g/dL}]\ or\ [(Phase\ B\ Average\ Hb - Week\ 5\ Hb) \geq 1\,\text{g/dL}]}{Phase\ B\ Population}$$

SYNOPSIS (CONTINUED

NAME OF SPONSOR/COMPANY: Ortho Biotech Products, L.P. NAME OF FINISHED PRODUCT: PROCRIT® epoetin alfa NAME OF ACTIVE INGREDIENT: Recombinant Human Erythropoietin	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Other secondary efficacy variables will include the following:

- The proportion of patients who achieved a Hb increase of ≥1 g/dL from baseline to Week 5 (Phase A) and baseline to Final.

$$P = \frac{Number\ of\ Patients\ with\ [(Week\ 5\ Hb - Week\ 1\ Hb) \geq 1\ g/dL]\ And\ [(Final\ Hb - Week\ 1\ Hb) \geq 1\ g/dL]}{All\ Patients}$$

Note: Final was the last Hb recorded for each patient, i.e. last value carried forward for each patient.

- The proportion of patients who entered Phase B and had a Hematologic Minor Response

$$P = \frac{Number\ of\ Patients\ with\ 0 < (Phase\ B\ Average\ Hb - Week\ 5\ Hb) \leq 0.9\ g/dL}{Phase\ B\ Population}$$

- The proportion of patients who entered Phase B and had a Hematologic Major Response

$$P = \frac{Number\ of\ Patients\ with\ (Phase\ B\ Average\ Hb - Week\ 5\ Hb) \geq 1\ g/dL}{Phase\ B\ Population}$$

- The proportion of patients who achieved a Hb increase of ≥2 g/dL from baseline to each Protocol-scheduled study visit and final

$$P = \frac{Number\ of\ Patients\ with\ (Any\ Week\ Hb\ in\ Study - Week\ 1\ Hb) \geq 2}{All\ Patients}$$

- The proportion of patients who achieved a Hb increase of ≥2 g/dL from baseline to Week 9 and baseline to Final

$$P = \frac{Number\ of\ Patients\ with\ [(Week\ 9\ Hb - Week\ 1\ Hb) \geq 2\ g/dL]\ And\ [(Final\ Hb - Week\ 1\ Hb) \geq 2\ g/dL]}{All\ Patients}$$

Note: Final was the last Hb recorded for each patient, i.e. last value carried forward for each patient.

- Mean Proportion of weeks during which a patient's Hb met the definition of Hematologic Minor Response. The proportion for each patient was calculated first as below and then average across all patients.

$$P = \frac{Number\ of\ Weeks\ in\ Phase\ B\ that\ 0 < (Week\ Hb - Week\ 5\ Hb) \leq 0.9\ g/dL}{All\ Number\ of\ Weeks\ in\ Phase\ B\ up\ to\ 12\ weeks}$$

- Mean Proportion of weeks during which a patient's Hb met the definition of Hematologic Major Response. The proportion for each patient was calculated first as below and then average across all patients.

$$P = \frac{Number\ of\ Weeks\ in\ Phase\ B\ that\ (Week\ Hb - Week\ 5\ Hb) \geq 1\ g/dL}{All\ Number\ of\ Weeks\ in\ Phase\ B\ up\ to\ 12\ weeks}$$

Mean number of Study Days to 1st Response in Each Phase for MITT Population.

Missing Data: For efficacy endpoints, the Last Value Carried Forward method was used to impute the data. Missing data points were queried for correctness and appropriateness and the reasons were examined in relationship to study withdrawal/termination. **Sample Size Determination:** A total of 51 patients were enrolled for this pilot study to estimate the hematologic responses for this dosing regimen and the overall transfusion requirements (i.e. percent of patients transfused, number of transfusion units per patient). The information from this pilot study may be used to design a larger efficacy study.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Ortho Biotech Products, L.P. NAME OF FINISHED PRODUCT: PROCRIT® epoetin alfa NAME OF ACTIVE INGREDIENT: Recombinant Human Erythropoietin	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Baseline Assessment: Continuous variables were summarized by descriptive statistics (sample size, mean, standard deviation, median, minimum, maximum, range and interquartiles). Categorical variables were summarized by frequency statistics (frequencies, percentages and cumulative percentages). **Analyses Performed:** All planned analyses were performed as described above with the exception that in the analyses that assessed change in Hb, Hb values that were collected within 28 days following a red blood count (RBC) transfusion were not included. **Additional analysis performed after the study completion**: After database lock, a review of the dosing and efficacy analysis resulted in a decision to provide additional information for these variables. **Dosing Information**: In addition to the statistical analysis plan which described dosing for the study population as a whole, detailed assessments of dosing by study period and population were added. Total cumulative units, duration of exposure, total number of doses, average days between doses, and average units per dose was provide for Study Week 1 through Study Week 4 for the MITT population and for Study Week 5 to the End of Study for the Phase B population only. **Response Information**: Response was further examined by identifying patients who had Hb levels greater than, or equal to 13 g/dL during the study and/or Hb increases greater than, or equal to 1.3 g/dL within any two-week period during the study. This assessment was performed for the MITT and the Phase B only population for Study Weeks 1 to 5, 6 to 16, and anytime during the study. In addition, the Phase A only population was assessed in this manner for Study Weeks 1 to 5. **Safety Analyses Planned:** The safety parameters to be evaluated were the incidence and severity of AEs, laboratory tests (hematology and serum chemistry), and vital signs measurement (blood pressure). All individual values were to be listed. In addition, incidence of anti-EPO Abs at baseline and study completion/early withdrawal were to have been evaluated in patients who had received a minimum of one dose of PROCRIT. **Adverse Events:** The product specific WHO-ART (World Health Organization Drug Dictionary – Adverse Reaction Terminology) was to be used for the coding of all AEs reported. Adverse Events were to be tabulated according to severity and drug relationship and would be categorized by system organ class and preferred term. In addition, summaries were to be prepared of 1) AEs reported in at least 5% of patients, 2) AEs that were considered Thrombotic Vascular Events (TVE) and selected AEs, 3) deaths, 4) SAEs occurring from the first study-related procedure and 90 days after the last study-related procedure, as well as 5) AEs leading to withdrawal from treatment. All summaries were generated without specific hypothesis and were based on the safety population, i.e., all randomized patients for whom assessments of safety parameters were available. **Clinical Laboratory Tests:** Laboratory values were to be compared to their generic reference ranges. The data were transformed to units of the international system (SI-units) as a basis for the evaluation. **Vital Signs and Physical Examination:** Vital signs (blood pressure) parameters were to be analyzed descriptively. **Serum Erythropoietin Antibodies:** Descriptive statistics were to be used to summarize the serum erythropoietin antibodies. **Analyses Performed:** All analyses were performed as planned except that the MedDRA Version 6.0 (Medical Dictionary for Regulatory Activities) was used for coding of all AEs reported instead of WHO-ART.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: **Data Sets Analyzed***:* Analysis of the primary efficacy outcome was performed on the MITT population. Analyses of the secondary efficacy outcomes were performed either on the MITT population or the Phase B population, as appropriate. In addition, data were also presented for the Phase A only population and the transfusion-free MITT population. **Primary Efficacy Analysis:** The primary efficacy outcome was a rise in Hb of at least 1 g/dL at any time during Phase A (with Hb values obtained in the 28 days following a transfusion excluded from the analysis). The primary outcome was achieved by 33 (64.7%) patients. Four of the 33 patients who had a Hb rise of at least 1 g/dL were withdrawn from the study prior to Week 5, leaving 29 patients who entered Phase B. The mean number of days to a response during Phase A was 15.5 days. **Secondary Efficacy Analysis:** Secondary efficacy outcomes included hematologic responses during Phase B. There were 29 patients who qualified for Phase B and were assessed for the secondary outcome. The mean Hb at Week 5 for the 29 patients who qualified for Phase B was 12.4 mg/dL. Twelve of the 29 patients (41.4%) had a hematologic response in Phase B (i.e. Phase B average Hb ≥ Week 5 Hb value). A major hematologic response (defined as an increase in Hb ≥1 g/dL compared to the Phase B baseline obtained at Week 5) was observed in two (6.9%) of the 29 patients who qualified for Phase B; and ten (34.5%) had a minor hematologic response (defined as the average Hb during Phase B being between 0 and 0.9 g/dL above the Phase B baseline from Week 5). Between the two patients who

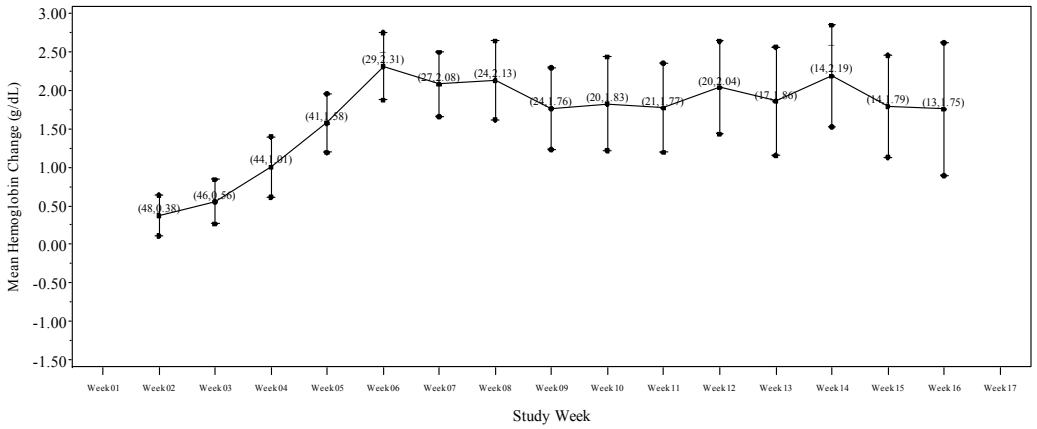
SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Ortho Biotech Products, L.P. NAME OF FINISHED PRODUCT: PROCRIT® epoetin alfa NAME OF ACTIVE INGREDIENT: Recombinant Human Erythropoietin	Volume: Page:	

EFFICACY RESULTS (continued): met the major hematologic response criteria, the mean percent of weeks they met the major response criteria was 62%, whereas they met the minor response criteria for a mean of 23% of weeks. Among the ten patients who met the minor response criterion, the mean percent of weeks they met the major response criteria was 23%, whereas they met the minor response criteria for a mean of 39% of weeks. Among the 17 patients who did not have a hematologic response, the mean percent of weeks they met the major response criteria was 1%, whereas they met the minor response criteria for a mean of 11% of weeks. **Other Efficacy Analyses:** An analysis was performed that assessed the number of patients whose Week 5 Hb achieved a ≥1 g/dL increase above the Week 1 baseline value and whose final Hb also was ≥1 g/dL higher than the Week 1 baseline. There were 20 of the 51 patients (39.2%) in the MITT population who achieved their endpoint. Therefore 20 (69%) of the 29 patients whose Week 5 Hb was ≥1 g/dL greater than the Week 1 baseline maintained this increase through to study end. There were 10 patients (19.6%) whose Week 9 Hb was at least 2 g/dL greater than their Week 1 baseline Hb and 12 patients (23.5%) whose final Hb was at least 2 g/dL greater than their Week 1 baseline Hb. There were only five patients (5.8%) whose Hb was at least 2 g/dL above Week 1 baseline both at Week 9 and for their final Hb. Efficacy analyses were also performed on the transfusion-free MITT population. These results were not substantially different than those described above. **Change in Hemoglobin over Time:** Figure 1 illustrates that in the MITT population the mean Hb change was a mean increase of more than 2 g/dL by Week 6 and that the Hb remained relatively stable from that time forward. Figure 2 displays the Hb change during Phase B for the Phase B population and shows that the Hb tends to decline over time. Overall there was a decline of 0.7 g/dL (from 12.4 to 11.7 mg/dL) from baseline to the final study Hb. Figure 3 illustrates the change in Hb by study week separately for the Phase A only population and the Phase B population. The Phase A only population (i.e. patients who did not achieve ≥1 g/dL rise from the Week 1 baseline and Week 5) shows almost no change in Hb over time, while the Phase B population shows a mean increase of 2.25 g/dL at Week 5, which declines to a mean increase from baseline of approximately 1.7 g/dL at the end of the study (i.e. mean Hb at Week 5 was 12.4 g/dL, mean Hb at Week 16 was 11.8 g/dL). Only two patients had received red cell transfusions within the six months prior to the study (none within one month prior to the start of the study, which was an exclusion criterion) and only four patients received a total of five transfusions during the study, with three of the patients being transfused during the first fours weeks. Note that Hb values collected within 28 days after transfusion are excluded from the efficacy analyses as well as the Hb over time analyses.

Figure 1: Mean Hemoglobin Change from Study Baseline (g/dL) by Study Week

(Study PR03-27-007: Modified Intent to Treat Population)



SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Ortho Biotech Products, L.P. NAME OF FINISHED PRODUCT: PROCRIT® epoetin alfa NAME OF ACTIVE INGREDIENT: Recombinant Human Erythropoietin	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Figure 2: Mean Hemoglobin Change From Phase B Baseline (g/dL) by Study Week

(Study PR03-27-007: Phase B Population)

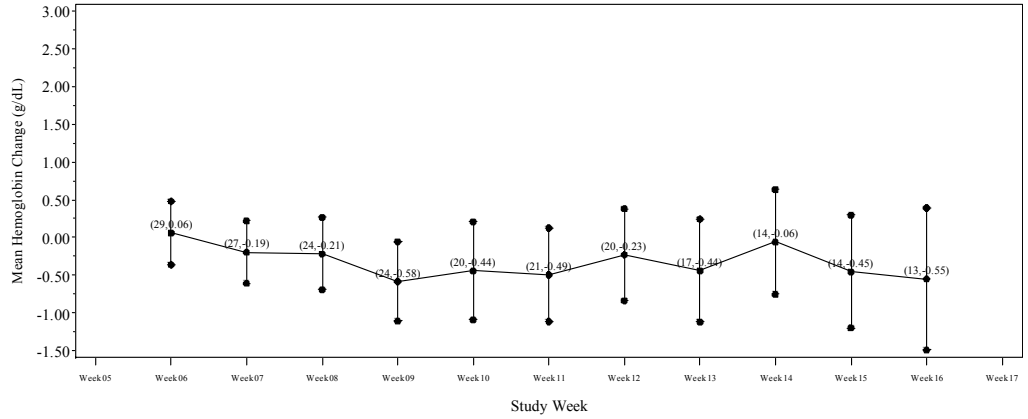
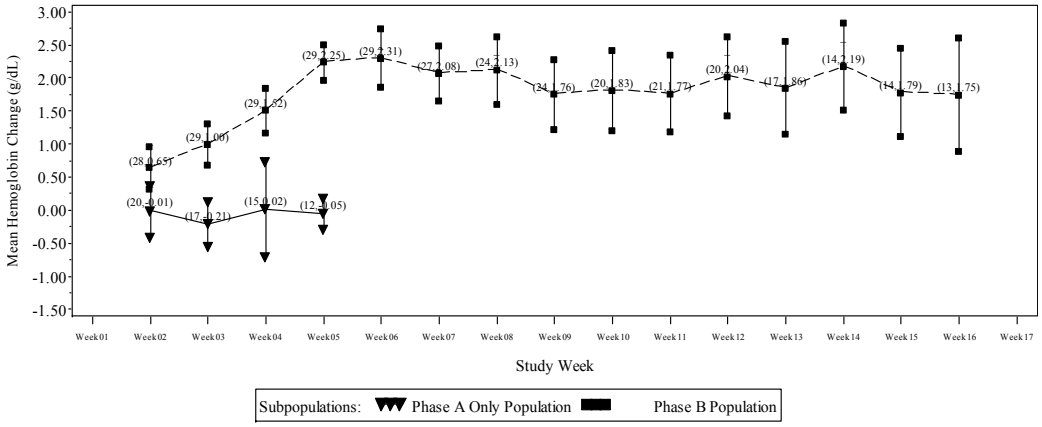


Figure 3: Mean Hemoglobin Change from Study Baseline (g/dL) by Subpopulation

(Study PR03-27-007: Modified Intent to Treat Population)



Efficacy Conclusions: The primary efficacy outcome was a rise in Hb of at least 1 g/dL at any time during Phase A (with Hb values obtained in the 28 days following a transfusion excluded from the analysis). The primary outcome was achieved by 33 (64.7%) patients. Four of the 33 patients who had a Hb rise of at least 1 g/dL were withdrawn from the study prior to Week 5, leaving 29 patients who entered Phase B. The mean number of days to a response during Phase A was 15.5 days. Secondary efficacy outcomes included hematologic responses during Phase B. There were 29 patients who qualified for Phase B and were assessed for the secondary efficacy outcome. The mean Hb at Week 5 for the 29 patients who qualified for Phase B was 12.4 mg/dL. Twelve of the 29 patients (41.4%) had a hematologic response in Phase B (i.e. Phase B average Hb ≥ Week 5 Hb value). A major hematologic response (defined as an increase in Hb ≥1 g/dL compared to the Phase B baseline from Week 5) was observed in two (6.9%) of the 29 patients who qualified for Phase B; and ten (34.5%) had a minor hematologic response (defined as the average Hb during Phase B being between 0 and 0.9 g/dL above the Phase B baseline from Week 5. The mean Hb at the onset of Phase B was 12.4 mg/dL; therefore, the majority of patients with a hematologic response in Phase B had a minor response. An analysis was performed that assessed the number of patients whose

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Ortho Biotech Products, L.P. NAME OF FINISHED PRODUCT: PROCRIT® epoetin alfa NAME OF ACTIVE INGREDIENT: Recombinant Human Erythropoietin	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Efficacy Conclusions (continued): Week 5 Hb achieved a ≥1 g/dL increase above the Week 1 baseline value and whose final Hb also was ≥1 g/dL higher than the Week 1 baseline. There were 20 of the 51 patients (39.2%) in the MITT population who achieved their endpoint. Therefore 20 (69%) of the 29 patients whose Week 5 Hb was ≥1 g/dL greater than the Week 1 baseline maintained this increase through to study end. There were 10 patients (19.6%) whose Week 9 Hb was at least 2 g/dL greater than their Week 1 baseline Hb and 12 patients (23.5%) whose final Hb was at least 2 g/dL greater than their Week 1 baseline Hb. There were only five patients (5.8%) whose Hb was at least 2 grams above Week 1 baseline both at Week 9 and for their final Hb. In the MITT population the mean Hb change was an increase of approximately 2 g/dL by Week 6 from Week 1 baseline with the Hb remaining relatively stable from that time forward. During Phase B, Hb tended to decline over time with a mean decrease of 0.7 g/dL by the end of the study. The Phase A only population (i.e. patients who did not achieve ≥1 g/dL rise from the Week 1 baseline and Week 5) showed almost no change in Hb over time, while the Phase B population showed a mean increase from Week 1 baseline of 2.25 g/dL at Week 5, which declined to a mean increase from Week 1 baseline of approximately 1.7 g/dL at the end of the study (i.e. mean Hb at Week 5 was 12.4 g/dL, mean Hb at Week 16 was 11.8 g/dL).

SAFETY RESULTS: Data Sets Analyzed: Safety analyses were performed on the Safety population, which included all patients who received at least one dose of study drug. **Summary of All Adverse Events**: As expected in a cancer population AEs were common with 94.1% (N=48) of patients experiencing at least one AE. All analyses were performed as planned except that the MedDRA Version 6.0 (Medical Dictionary for Regulatory Activities) was used for coding of all AEs reported instead of WHO-ART. The most commonly reported AEs were Nausea (23.5%), Asthenia (21.6%), and Fatigue (21.6%). Most events were CTC grades 1-3, with only nine that were CTC grade 4 (febrile neutropenia, leucopenia, neutropenia, thrombocytopenia, cardiac failure, asthenia, disease progression, dehydration, and respiratory distress) and only one event (sepsis) that was CTC grade 5. Most AEs were considered not related or doubtful as the relationship to study drug. Three events (bone pain [CTC grade 1], bone pain [CTC grade 2] and one headache [CTC grade 2]) were reported as possibly related, and two events (constipation [CTC grade 2] and nausea [CTC grade 2]) were reported as probably related to study drug. **Thrombotic Vascular Events:** A list of TVEs based on MedDRA Version 6.0 was used to generate summaries and individual listings for the TVEs. TVEs were reported in a total of two (3.9%) of the 51 patients. Patient 023-039 was reported as having a deep venous thrombosis on Study Day 1, which the Investigator reported as not related to study drug. Patient 009-035 had chest pain reported on study Day 25. The chest pain was reported by the Investigator as not related to study drug. The chest pain was reported as related to a fall. **Deaths**: There were three (5.9%) patients who died during the study. Two died from disease progression and one from sepsis. None of the deaths were judged by the Investigator to be related to treatment with study drug. **Serious Adverse Events**: At least one SAE was reported in 13 (25.5%) patients. There was no specific SAE that was reported in more than two patients. **Other Significant Adverse Events**: Approximately two-thirds of the patients (64.7%) had at least one of these selected AEs reported. As expected among cancer patients the most commonly reported of these events were Fatigue (21.6%) and Neutropenia (17.6%). **Discontinuation Due to an Adverse Event**: There were three patients in whom AEs were reported as resulting in permanent discontinuation of study drug. Two of these patients died following the AE resulting in discontinuation (one from disease progression; one from sepsis; and the third patient had pyrexia and congestive heart failure, both of which resolved without sequelae). The Investigators considered these AEs to be not related to study drug. **Clinical Laboratory Evaluation**: **Laboratory Values Over Time**: There were no clinically meaningful changes in the other CBC parameters over time. The change in Hct over time was consistent with that observed for Hb. The final RBC count was significantly higher than that obtained as the Week 1 baseline (3.5 vs. 3.7 cells x 10^{12}/L, p = 0.001). The mean final WBC and platelet counts were not significantly different from the counts obtained at Week 1 baseline. **Individual Clinically Significant Abnormalities**: Individual changes in laboratory parameters were as expected for this patient population. Fluctuations associated with chemotherapy often occurred and were assessed at the sites. When appropriate were reported as AEs. Assay results for erythropoietin antibody production were negative for all patients.

SYNOPSIS (CONTINUED)

NAME OF SPONSOR/COMPANY: Ortho Biotech Products, L.P. NAME OF FINISHED PRODUCT: PROCRIT® epoetin alfa NAME OF ACTIVE INGREDIENT: Recombinant Human Erythropoietin	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

SAFETY RESULTS (continued): Other Safety Observations: Vital Signs and Physical Findings: The mean changes in systolic and diastolic blood pressure over time were not clinically meaningful. **Final Tumor & Eastern Cooperative Oncology Group (ECOG) Performance Status:** Only three of the 26 patients in whom tumor response is available had progressive disease. The majority of patients (86.6%) were ECOG status 0 (42.2%) or 1 (44.4%) at their final assessment. Of the 45 patients who had final ECOG status assessed, compared to the Week 1 baseline ECOG assessment, 12 improved, 25 remained the same and only eight had a worse performance status. **Unplanned Radiation Therapy:** Only one patient received unplanned radiation therapy during the study. As per the Protocol all patients received concomitant chemotherapy. **Safety Conclusions:** As expected in a cancer population AEs were common with 94.1% of patients experiencing at least one AE. The most commonly reported AEs were Nausea (23.5%), Asthenia (21.6%), and Fatigue (21.6%). Most events were CTC grades 1-3, with a small number that were CTC grade 4 and only one event (sepsis) that was CTC grade 5. Most AEs were considered not related or doubtful as the relationship to study drug. Three events (two bone pain and one headache) were reported as possibly related, and two events (constipation and nausea) were reported as probably related to study drug. Thrombotic vascular events were reported in a total of two (3.9%) of the 51 patients. Patient 023-039 was reported as having a deep venous thrombosis on Study Day 1, which the Investigator reported as not related to study drug. Patient 009-035 had chest pain reported on Study Day 25. The chest pain was reported by the Investigator as not related to study drug. The chest pain was reported as related to a fall. There were three (5.9%) patients who died during the study two died from disease progression and one from sepsis. None of the deaths were judged by the Investigator to be related to treatment with study drug. At least one SAE was reported in 13 (25.5%) patients. There was no specific SAE that was reported in more than two patients. There were three patients in whom AEs were reported as resulting in permanent discontinuation of study drug. Two of these patients died following the AE resulting in discontinuation (one from disease progression; one from sepsis; and the third patient had pyrexia and congestive heart failure, both of which resolved without sequelae). The Investigators considered these AEs to be not related to study drug. Other than the changes in Hb reported in the efficacy section, there were no clinically meaningful changes in the other hematologic parameters over time. There were no patients in the study who had a positive erythropoietin antibody titer. The mean changes in systolic and diastolic blood pressure over time were not clinically meaningful. Only three of the 26 patients in whom tumor response was available had progressive disease. The majority of patients (86.6%) were ECOG status 0 (42.2%) or 1 (44.4%) at their final assessment. Of the 45 patients who had final ECOG status assessed, compared to the Week 1 baseline ECOG assessment, 12 improved, 25 remained the same and only eight had a worse performance status. .Most patients did not have a shift in their ECOG performance status. Only one patient received unplanned radiation therapy during the study. In summary, epoetin alfa was well tolerated at the doses used in this pilot study with the numbers of patients experiencing deaths, or other categories of AEs was consistent with expectations for this population.

CONCLUSION: As a pilot study, conclusions from results must be weighted in the context of small sample sizes. Observations from this study demonstrate that approximately two-thirds of cancer patients receiving chemotherapy can have a hematologic response to weekly doses of 60,000 U of epoetin alfa. The results of the study also suggest that almost half of patients who responded to the weekly dosing regimen can have their hematologic response maintained or extended with a dosing regimen of 60,000 U of epoetin alfa q2w who drop only 0.7 g/dL. In addition, very few patients showed a large decline (i.e. >2 g/dL) in Hb on the alternate weekly regimen. In addition, very few patients showed a large decline (i.e. >2 g/dL) in Hb on the alternate weekly regimen. Therefore a strategy of switching to extended epoetin alfa dosing once an initial Hb response is achieved with weekly dosing is a safe option for a large number of patients for the duration studied provided they are regularly monitored for Hb response Those patients who fail to maintain a Hb level with extended dosing can either be switched back to more conventional dosing schedules or otherwise have their dose titrated. Such an approach individualizes patient treatment for maximum effect and convenience. Epoetin alfa was well tolerated at the doses used in this pilot study with the numbers of patients experiencing deaths, or other categories of AEs being consistent with expectations for this population.

Date of the report: 22 August 2005

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.