SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho Biotech Clinical Affairs, LLC NAME OF FINISHED PRODUCT: PROCRIT® NAME OF ACTIVE INGREDIENT(S): Epoetin alfa	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Protocol No.: PR01-06-021 **Title of Study:** A Randomized, Open-Label Clinical Evaluation of PROCRIT™ (Epoetin alfa) for Maintenance Phase Treatment of Patients with Anemia due to Chronic Kidney Disease. (PROMPT study.)		
Principal Investigator: Robert Provenzano, M.D. – St. Clair Specialty Physician, Detroit, MI, USA		
Study Initiation/Completion Dates: 15 March, 2002-23 January, 2004		**Phase of development:** IIIb
Objectives: To evaluate the safety and efficacy of PROCRIT dosing up to every four weeks in subjects with anemia due to Chronic Kidney Disease (CKD) as assessed by hemoglobin (Hb) maintenance, health-related quality of life (QOL) and adverse events (AE).		
Methodology: An open-label, randomized, multi-center study of subjects with CKD. A total of 519 anemic CKD subjects receiving PROCRIT therapy for two or more months and who demonstrated a stable baseline Hb (∅1.0 g/dL) were randomized to one of four treatment groups. PROCRIT was administered at the following doses and dosing frequencies: 10,000 units (U) subcutaneous (sc) every week (QW/Group 1), 20,000 U sc every two weeks (Q2W/Group 2); 30,000 U sc every three weeks (Q3W/Group 3), and 40,000 U sc every four weeks (Q4W/Group 4). Hemoglobin was evaluated at least every two weeks during the 16-week study duration. Hemoglobin assessment and dose adjustments were evaluated and modified as follows. If the Hb was >13.0 g/dL on two consecutive evaluations, PROCRIT therapy was held until dosing week at which the Hb level decreased to 12.0 g/dL or less. PROCRIT therapy was then resumed with a reduction in dose to 50% of the most current dose for the remainder of the study. The dose of PROCRIT was also reduced by 50% of the most current dose for the remainder of the study if there was an increase in Hb of >1.3 g/dL in a two-week period. Dose escalations were not permitted at any time. If at any time during the study period the Hb decreased 20% or more from the baseline Hb value, the subject was to be considered a treatment failure and withdrawn from the study. However, subjects in Q3W or Q4W with treatment failure were assessed for eligibility into a stabilization treatment group using 20,000 U of PROCRIT at a dosage interval of every two weeks for an additional 12 weeks of study treatment.		
Number of Subjects (planned and analyzed): Approximately 800 subjects were to be enrolled. Protocol Amendment I modified the sample size requirements to include 436 subjects. The final number of randomized subjects was 519 (ITT population). The primary efficacy analyses were performed on a Modified Intent to Treat population and included 445 subjects who were randomized, received at least one dose of study drug and satisfied all the Inclusion and Exclusion criteria. The safety analyses were performed on 513 subjects who received at least one dose of the study drug.		
Diagnosis and Main Criteria for Inclusion: Chronic Kidney Disease subjects are defined as subjects with a serum creatinine from 1.5 to 6.0 mg/dL for women and 2.0 to 6.0 mg/dL for men. Subjects receiving PROCRIT therapy for two or more months with stable baseline Hb (∅1.0 g/dL) were eligible for randomization to one of the four treatment groups.		
Test Product, Dose and Mode of Administration: PROCRIT (Epoetin alfa); QW: 10,000 U sc every week, Q2W: 20,000 U sc every two weeks, Q3W: 30,000 U sc every three weeks, Q4W: 40,000 U sc every four weeks; Multidose, Preserved Vial: 1 mL (20,000 U/mL) and Single-Dose, Preservative-Free Vial: 1 mL (40,000 U/mL) were utilized.		
Duration of Treatment: 16 weeks		

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Criteria for Evaluation:

Efficacy: The primary efficacy variable was the final Hb. The secondary efficacy variable was the final assessment of QOL. Quality of life was measured using the Linear Analog Scale Assessment (LASA) and the Kidney Disease Questionnaire (KDQ).

Safety: Subjects were assessed for the incidence and severity of AEs. In addition, vital signs (blood pressure) were assessed during the study period. Clinical laboratory parameters were assessed throughout the study and included every other week Hb assessments, monthly chemistries, baseline and study completion iron studies.

Statistical Methods: The following study populations were defined for the purpose of statistical analyses:

Intent to treat (ITT): Included all subjects randomized (N = 519).

Modified Intent to Treat (MITT): Included subjects who were randomized, received at least one dose of study medication, and satisfied all inclusion/exclusion criteria (or, if not satisfied all criteria, had an exemption) (N = 445).

Per Protocol: Included subjects who met MITT criteria and completed all 16 weeks of the study (N = 356).

Safety: Included subjects who received at least one dose of study drug (N = 513).

The primary endpoint for the trial was the final Hb measurement. The secondary endpoints were the final score for each QOL assessment as measured by both the LASA and the KDQ.

All efficacy analyses were performed using the MITT population. In addition, the primary endpoint was evaluated using both the ITT and Per Protocol populations.

The last post-treatment value carried forward method was used to adjust for missing values.

Summary statistics were used to present the baseline characteristics of the study population. Continuous variables were summarized by descriptive statistics (sample size [N], mean, standard deviation, median, minimum, maximum and interquartiles). Categorical variables were summarized by frequency statistics (frequencies and percentages).

Primary Endpoint Analyses: The primary efficacy analyses were non-inferiority assessments between Groups *i* (*i* = 2, 3, and 4) and Group 1 by comparison of the mean final Hb levels. These analyses were performed for the MITT population. Additional analyses were also performed for the Per Protocol and the ITT populations to assess consistency with the results of the MITT analyses.

The Q2W, Q3W, and Q4W groups were considered non-inferior to the QW group if the true differences (in population means, not sample means) (Q2W-QW, Q3W-QW, and Q4W-QW) in mean final Hb levels are greater than -10% of the QW mean final Hb level. The non-inferiority criterion was evaluated at a 1-sided statistical significance level of 0.025. This non-inferiority criterion can be formulated by the following 1-sided hypotheses:

$$\text{Ho: } \sigma_i - \sigma_1 \; \Omega\text{-}0.1\sigma_1$$

vs.

$$\text{Ha: } \sigma_i - \sigma_1 > -0.1\sigma_1,$$

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where i = 2, 3, 4, and σ denotes the underlying mean final Hb level for the group.

These hypotheses can be further simplified as:

$$\text{Ho: } \sigma_i - 0.9\sigma_1 \ \Omega 0$$

vs.

$$\text{Ha: } \sigma_i - 0.9\sigma_1 > 0,$$

which is to test whether each Group i can retain more than 90% of the effect size of Group 1 in terms of mean final Hb level.

Each test was performed at a 0.025 significance level (1-sided) using test statistic Z_i that approximately has a standard normal distribution:

$$Z_i \mid (\overline{X}_i \ 4 \ 0.9\overline{X}_1) / \sqrt{s.e._i^2 \ 2 \ 0.9^2 s.e._1^2},$$

i = 2, 3, 4, where each $\overline{X}$ and *s.e.* denote the mean final Hb and its standard error for the group. Nominal statistical inferences were reported without adjustment for multiplicity. P-values testing non-inferiority from Group 1 are presented for Groups 2, 3 and 4, separately.

Effect of Study Site on Hemoglobin: A two-way analysis of variance was used to evaluate the effect of study site on the final Hb measurements of the four dosing (treatment) groups. The model included terms for treatment, site, and the treatment by site interaction. Due to the small sample size per study site, pooling methodologies were employed to the data prior to analyses involving study site as an independent variable.

Quality of Life: Descriptive statistics were obtained for the QOL (LASA and KDQ) parameters at baseline and final measurement. 90% confidence intervals (CI) of the differences in means on final QOL between the Q2W, Q3W, and Q4W groups versus the QW group were obtained where appropriate. T-tests of the differences in the means between each group and QW were performed for each of the three LASA measures, the total KDQ score and each of the KDQ dimensions. The mean final score for each QOL measurement was compared to the baseline value utilizing a paired t-test.

Hemoglobin Change Over Time: A longitudinal model was applied to the Hb data to assess the association between Hb and treatment group over time. The longitudinal analysis included Hb change from randomization at each scheduled visit (Weeks 3, 5, 7, 9, 11, 13, 15 and 16). The longitudinal model included treatment, time, and the treatment by time interaction. The 90% CI for the mean change for each treatment group was calculated based on the longitudinal model standard errors. The change in Hb from randomization and the absolute Hb over time by study group are also provided in detail separately for the subgroups of subjects whose Hb at randomization were Ω12.0 g/dL and >12.0 g/dL.

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Hemoglobin Maintenance: Hemoglobin maintenance was defined as a mean Hb post-randomization value of at least 11.0 g/dL. For each subject, the mean of all post randomization Hb values was calculated, and if the mean was greater than or equal to 11.0 g/dL, the subject was categorized as having achieved Hb maintenance. Otherwise, the subject was categorized as NOT having achieved Hb maintenance. Hb maintenance comparability of each of Q2W, Q3W, and Q4W with QW was tested via separate (and independent) Fisher's Exact tests.

The percent of subjects categorized as having Hb of at least 11.0 g/dL and the categorizations of percent changes from baseline (>20%, 10 to 20%, >0 to 10%, etc.) were presented by week and at final. Further, the maximum and minimum percent change within each subject were derived and tabulated similarly.

Exploratory analyses using logistic regression were performed to further evaluate Hb maintenance and factors that might have a significant impact on Hb maintenance. These factors included treatment, along with gender, race, diabetes as the primary etiology of renal disease, hypertension as the primary etiology of renal disease, BMI, Hb at randomization, pre-study PROCRIT dose (in 1,000 U), age, transferrin saturation (TSAT), ferritin, albumin, systolic blood pressure and creatinine. The multicollinearity among the factors was assessed.

Treatment Failure and Time to Treatment Failure: Treatment failure was defined as a decrease in Hb of at least 20% from baseline. Treatment failure resulted in discontinuation from the study. The proportions of subjects categorized on the Study Completion Case Report Form page as Treatment Failure=YES and Treatment Failure=NO were presented for each treatment group. Treatment Failure comparability of each of Q2W, Q3W, and Q4W with QW was tested via separate (and independent) Fisher's Exact tests.

The time from Randomization to the Hb value corresponding to the failure of the subject in the study was determined. The Study Day of the first Hb value that corresponds to at least a 20% decrease from baseline was used as the Study Day of Failure. The mean time from Randomization to the Hb value corresponding to the failure of the subject in the study is presented. For each treatment group, the Kaplan-Meier curve corresponding to the data was created. In addition, pair-wise tests (by log-rank) of Q2W, Q3W, and Q4W to QW were performed.

An exploratory logistic regression analysis of the variables associated with Treatment Failure was performed. The following covariates were eligible for inclusion in the exploratory analysis: age, gender, race (White, Black, and Hispanic/other), history of prior dialysis (Yes or No), history of diabetes as primary cause of renal disease (Yes or No), BMI, most recent PROCRIT dose prior to study, baseline laboratories including Hb, creatinine, TSAT, ALB, BUN, triglycerides, ferritin category (quartiles), red blood cell count, as well as treatment group.

Sample Size Determination: A sample size of 200 subjects per arm, for a total of 800 subjects, was initially planned. This sample size calculation assumed a Type I error rate of 2% (2-sided) and 90% power to compare the mean final Hb for each of the Q2W, Q3W, and Q4W groups with the mean for the QW group. The equivalence margin was defined as 10% of the QW mean final Hb. The dropout rate was assumed to be 30%. Based on an interim review of the sample size calculation assumptions when 200 subjects had been enrolled, a revised sample size of 109 evaluable subjects per group (or 436 total) was determined to be adequate for this trial. The revised sample size assumed 90% power and a Type I error rate of 5% (2-sided), or 2.5% (1-sided). The dropout rate was assumed to be 10% based on the interim results.

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS: The primary efficacy analyses were non-inferiority assessments of the mean final Hb measurements of the Q2W, Q3W, and Q4W groups, compared with the QW group (reference group). A non-inferiority assessment, tests the hypothesis that an extended dosing regimen would not be inferior to QW dosing by a prespecified amount or percentage. The Q2W, Q3W, and Q4W groups were considered non-inferior to the QW group if the true differences (in population means, not sample means) (Q2W-QW, Q3W-QW, and Q4W-QW) in mean final Hb levels are greater than -10% of the QW mean final Hb level. The non-inferiority criterion was evaluated at a 1-sided statistical significance level of 0.025, utilizing a z-statistic.

The mean final Hb values were 12.2 g/dL, 11.9 g/dL, 11.2 g/dL, and 11.4 g/dL for QW, Q2W, Q3W, and Q4W, respectively. The difference in mean final Hb between Q2W and QW was -0.3 g/dL; the difference was -1.0 g/dL between Q3W and QW, and the difference was -0.8 g/dL between Q4W and QW. Based on the z-statistic, the Q2W and Q4W groups met the criteria to be considered non-inferior to the QW group ($P \leq 0.008$, 1-sided), while the Q3W group did not ($P = 0.047$, 1-sided). The mean final Hb and the corresponding lower limit of the 95% CI were ≥11.0 g/dL for each group.

The above analyses were also performed on the Per Protocol and ITT populations. The results of the Per Protocol analyses were consistent with the primary analyses. The Q2W and Q4W groups were non-inferior to the QW group while the Q3W group was not (p-values <0.001, 0.083, and 0.024 for Q2W, Q3W, and Q4W compared to QW, respectively). The results of the ITT analyses showed that all three groups were non-inferior to the QW group (p-values <0.001, 0.013, and 0.004 for Q2W, Q3W, and Q4W compared to QW, respectively).

An analysis of variance model, with terms for treatment group, pooled site, and their interaction, was used to evaluate the effect of site on the outcome of final Hb values. Although statistically significant site differences in Hb were observed, they were not considered meaningful since they were small in magnitude and the treatment by site interaction term was not statistically significant.

Hemoglobin Change From Randomization Value: An ANCOVA was performed assessing treatment group and baseline Hb in relation to final Hb. Pair-wise comparisons yielded several statistically significant differences in final Hb between study groups. Specifically, Q3W and Q4W had lower final Hb values than QW and Q2W.

The change in Hb from randomization and the absolute Hb are illustrated in the figures below. Based on the longitudinal model, only QW and Q3W showed statistically significant changes from the randomization value. QW showed an increase in Hb of 0.37 (90% CI 0.23, 0.50), while Q3W showed a decline of 0.32 (90% CI –0.45, -0.19). The changes in Hb from randomization were not statistically significant for the Q2W and Q4W groups. Compared to QW, the change in Hb over time was not significantly different for Q2W (p=0.28), but was significantly lower for Q3W and Q4W (p<0.001).

The change in Hb from randomization and the absolute Hb over time by study group are also provided in detail separately for the subgroups of subjects whose Hb at randomization were ≤12.0 g/dL and >12.0 g/dL. For the subgroup with Hb ≤12.0 g/dL at randomization, mean Hb values were more likely to rise or stay stable over time, whereas for the subgroup with Hb >12.0 g/dL at randomization mean Hb values declined over time in each of the study groups.

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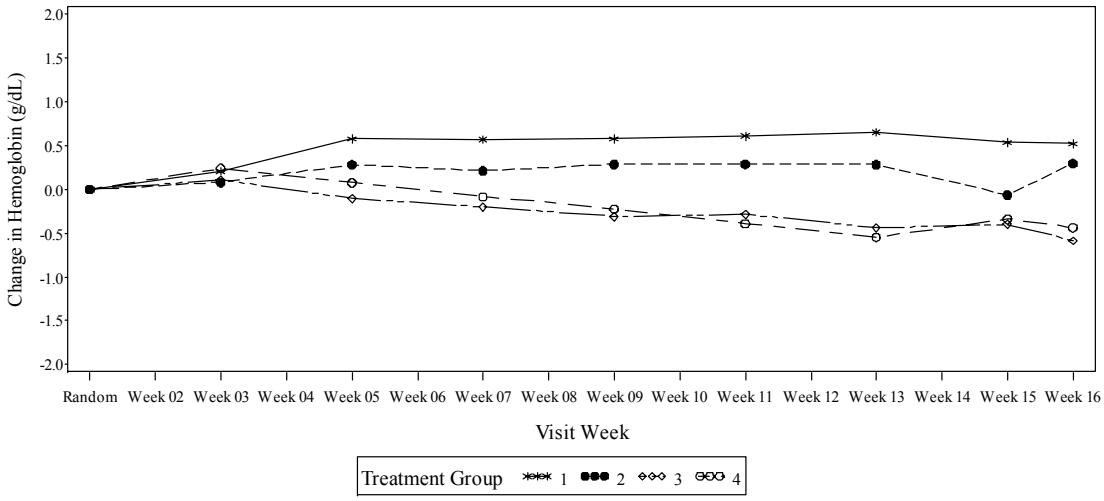
Mean Hemoglobin Change from Randomization by Study Week and Treatment Group

(Study PR01-06-021 Modified Intent to Treat Subjects)

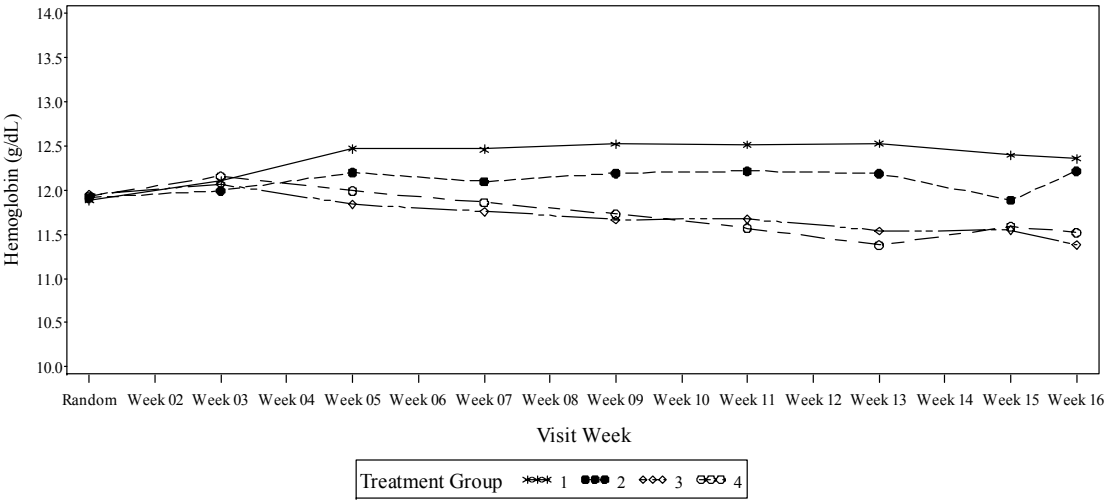
j



Mean Hemoglobin by Study Week and Treatment Group

(Study PR01-06-021 Modified Intent to Treat Subjects)

j



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Hemoglobin Maintenance: Hemoglobin maintenance was achieved (i.e. the mean of all post-randomization Hb values was ∅1.0 g/dL) in at least 75% of subjects in each of the four dosing groups. Hemoglobin maintenance was similar for QW and Q2W (93.5% and 89.5%, respectively). Although the percentages of subjects who maintained Hb ∅1.0 g/dL in the Q3W and Q4W groups were statistically significantly lower than in the QW group, more than 75% of subjects in the Q3W and Q4W groups maintained Hb at or above 11.0 g/dL in these more extended dosing regimens (77.2% and 76.0%, respectively).

Logistic regression analyses were also performed to assess the factors associated with Hb maintenance. Besides treatment, variables significantly associated with Hb maintenance included baseline Hb (odds ratio for non-maintenance 0.28 per g/dL Hb increase) and pre-study epoetin alfa dose (odds ratio for non-maintenance 1.06 per 1,000 U increases in pre-study epoetin alfa dose). Subjects with a higher BMI were also less likely to maintain Hb ∅1.0 g/dL (odds ratio for non-maintenance 1.06 per kg/m^2 BMI increase). A subgroup analysis on Q3W and Q4W subjects identified the same three factors (baseline Hb, pre-study dose, and BMI) that were significantly associated with Hb maintenance.

Hemoglobin Maintenance and Treatment Failure by PROCRIT Dosing

(Study PR01-06-021: Modified Intent to Treat Population)

	QW (N=109)	Q2W (N=115)	Q3W (N=116)	Q4W (N=105)
% Subjects with Hb maintenance (mean of Week 2 and later Hb values ∅1.0 g/dL)*	93.5	89.5	77.2**	76.0**
% Subjects with treatment failure (20% decline in Hb)	5.5	6.1	7.8	10.5

* Note for Hb maintenance: There were five subjects lost to follow-up for whom data were not included in the analyses. P-value for treatment comparability of each group to QW from Fisher's Exact Test.

** $p<0.001$

Treatment Failure and Time to Treatment Failure: The percentage of subjects with treatment failure (defined as a decline in Hb of at least 20%) was low for all groups. Based on the log-rank analysis, time to treatment failure did not differ significantly among treatment groups. Few treatment failures were observed in the study, 6 (5.5%), 7 (6.1%), 9 (7.8%), and 11 (10.5%) for the QW, Q2W, Q3W, and Q4W groups, respectively.

Logistic regression analysis was also performed to assess the factors associated with treatment failure. In this analysis, the study group was not statistically significantly associated with treatment failures. Baseline Hb and pre-study PROCRIT dose were statistically significant predictors of the likelihood of treatment failure ($p<0.001$ for baseline Hb and $p<0.0277$ for pre-study PROCRIT dose), with higher levels of each factor predicting a greater likelihood of failure.

A more detailed assessment of the percent change in Hb was performed that summarized categories of percent change from randomization (>20% increase, >10 to 20% increase, >0 to 10% increase, no change, <-10% to <0% decrease, -20% to -10% decrease, and <-20% decrease) for each week as well as the lowest and highest percent Hb change per subject. Consistent with the data described above, decreases in the -20% to -10% range were somewhat higher in Q3W and Q4W than in QW and Q2W. In addition, QW had the highest frequencies of Hb increases in the >10 to 20% and the >20% ranges, suggesting that for some subjects 10,000 U every week represented an increase in dose compared to their pre-study regimen.

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Quality of Life Assessment: Changes in measures of QOL during the study did not differ significantly between the QW and any of the other study groups for any of the LASA assessments or for the KDQ Total score or specific domain assessments. Overall, the QOL scores were maintained during the course of the study.

SAFETY RESULTS: Summaries and analyses of safety variables were performed based on data from all subjects dosed (safety population). All reported AEs were summarized by body system, preferred term, included term, severity and relationship to study drug during the study period.

The incidence and spectrum of AEs were as expected in a CKD population. In no category of AE was there a concern of either an excessive rate of occurrence overall or in relation to treatment group.

Overall, the most frequently reported AEs for all subjects were hypertension (6.8%) and peripheral edema (5.7%). Most AEs were of mild or moderate severity, were unrelated to study drug, and were resolved before study completion.

Thrombotic vascular events (TVEs) were reported in 2.5% of subjects with no clinically meaningful differences among the treatment groups. The most frequently reported TVE was chest pain (1.0%). There were six events that were considered clinically relevant including two subjects with cardiac arrest, one with myocardial infarction, one coronary artery occlusion, one deep venous thrombosis and one peripheral vascular disease; none of the events were reported as being related to study drug. Exploratory analyses that assessed the occurrence of TVEs and serious adverse events (SAEs) in relation to an Hb of ∅13.0 g/dL or a rise in Hb of >1.0 g/dL in any two-week period did not suggest an association between TVEs and either a high Hb or a rapid increase in Hb. However, these preliminary analyses are not definitive.

There were seven deaths (1.4%) during the study, none of which were reported as related to study drug. The incidences of SAEs were comparable across the four study groups. No specific AE type was reported in more than 2% of subjects. Assessment of individual subject plots of Hb over time with respect to the timing of TVEs and SAEs did not suggest a relationship between Hb and these AEs.

In general, there were no noteworthy differences among the treatment groups in the incidence of AEs, TVEs, deaths or SAEs.

There were no clinically unexpected changes in laboratory values over time. Glomerular filtration rate (GFR) was maintained across all study groups with the final GFR of 20.3 ml/min/1.73m^2 being unchanged from baseline.

There were no clinically unexpected changes in blood pressure values over time. Blood pressure changes over time did not show clinically important differences between the treatment groups.

In summary, epoetin alfa treatment was well tolerated and there were no differences between the treatment groups either in mortality, or in the occurrence of AEs.

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CONCLUSIONS: A schedule of 20,000 U Q2W was as effective as a dose of 10,000 U QW in maintaining Hb levels (>89% of subjects), while 30,000 U Q3W and 40,000 U Q4W maintained Hb levels in approximately 75% of subjects. In total, 84% of subjects successfully maintained mean Hb levels ∅11.0 g/dL with extended epoetin alfa dosing schedules of up to Q4W. As the differences in mean final Hb between Q2W and QW, and Q4W and QW were found to be greater than the pre-specified non-inferiority margin (-10% of the QW final Hb level), the Q2W and Q4W groups were considered non-inferior to the QW group. The results of this study suggest that extended epoetin alfa dosing is a treatment alternative to maintain an Hb level ∅11.0 g/dL for the majority of pre-dialysis subjects with anemia of CKD. Approximately 90% of subjects at a Q2W dosing schedule and over 75% of subjects at a Q3W or Q4W dosing schedule will maintain Hb levels consistent with Kidney Disease Outcome Quality Initiative guidelines. Therefore, a strategy of switching to extended epoetin alfa dosing once a stable Hb level is achieved with QW epoetin alfa is a viable option for a vast majority of these subjects. Those subjects who fail to maintain a Hb level with extended dosing can either be switched back to more conventional dosing schedules or be titrated to a higher dose. Such an approach has advantages in both convenience and comfort for subjects (less office visits and injections), and may result in decreased costs. Epoetin alfa treatment was well tolerated, and there were no differences between the treatment groups either in mortality or in the occurrence of AEs.

Date of the report: 25 May 2005

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