SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	PROCRIT® (epoetin alfa)
Name of Active Ingredient(s)	Recombinant human erythropoietin (rHuEPO)

Protocol No.: EPO-AKD-3001, CR010411

Title of Study: A Randomized, Open-Label, Multicenter Study of Epoetin Alfa Comparing Two Extended-Dosing Regimens, Once-Weekly and Every-Two-Weeks, With the Three-Times-Weekly Dosing Regimen for Initiation and Maintenance Treatment in Anemic Subjects With Chronic Kidney Disease

Coordinating Investigator: NA

Publication (Reference): Pergola PE, Gartenberg G, Fu M, Bowers P. Extended Dosing Regimens of Epoetin Alfa (EPO) in EPO−Naïve, Predialysis Subjects with Anemia of Chronic Kidney Disease (CKD): An Open−Label Randomized Study (abstract). J Amer Soc Nephrol 2008;19:523A.

Study Period: 29 August 2006/21 February 2008

Phase of Development: 3

Objectives: The primary objective of the study was to demonstrate that once-weekly and every-2-weeks treatment with epoetin alfa in subjects with anemia associated with chronic kidney disease (CDK) was noninferior to 3-times-weekly treatment with respect to the mean change in hemoglobin from baseline to the average of the last 8 weeks of treatment through Week 22.

The secondary objectives of the study were to assess the increase in hemoglobin from baseline, the proportion of subjects who exceeded the hemoglobin ceiling, the maximum hemoglobin concentration, the rate of rise of hemoglobin, the maximum rate of rise of hemoglobin, and overall safety.

Methods: This was a randomized, open-label, multicenter study. Subjects not on dialysis with anemia associated with CKD who met all study inclusion criteria and none of the exclusion criteria were randomly assigned in a 1:1:1 ratio to receive subcutaneous (s.c.) epoetin alfa 3 times weekly (initial dose 50 international units [IU]/kg) (Group 1), once weekly (initial dose 10,000 IU) (Group 2), or every 2 weeks (initial dose 20,000 IU) (Group 3). Open-label treatment continued for a total of 44 weeks; subjects in Group 1 were switched to once weekly treatment at Week 23 (initial dose 10,000 IU), while subjects in Groups 2 and 3 continued their current treatment. Iron therapy was strongly recommended during the study to maintain a subject's transferrin saturation at a level >20%. Oral iron supplement (Niferex®) was provided to the sites for use by subjects at the discretion of the investigator. Subjects in all groups were scheduled to have weekly visits, and hemoglobin concentration was measured locally on a weekly basis. Epoetin alfa doses were held for hemoglobin concentrations >11.9 g/dL or hemoglobin rates of rise ≥1.5 g/dL in the prior 2 weeks. A dose was reduced for hemoglobin rates of rise ≥1.0 g/dL but <1.5 g/dL in the prior 2 weeks. A dose was increased for hemoglobin concentrations ≤10.5 g/dL with rates of rise <0.5 g/dL in the prior 2 weeks.

Any subject who started renal replacement therapy during the study returned for a predialysis visit and began treatment with the appropriate erythropoiesis-stimulating agent (ESA) according to the dosing schedule and the route of administration that were standard practice for the dialysis unit. Administration of study drug was discontinued. Weekly evaluations continued for these subjects until they completed the posttreatment phase, but the data collected after the start of renal replacement therapy were not included in the primary statistical analyses.

Number of Subjects (planned and analyzed): 375 subjects were planned (125 per group); 375 were randomized. Efficacy analyses were performed on the modified intent-to-treat population (N=369), which was defined as all subjects who were randomized and had at least 1 postrandomization hemoglobin assessment. Safety analyses were performed on the safety population (N=373), which was defined as all subjects who received at least 1 injection of study drug.

Diagnosis and Main Criteria for Inclusion: Subjects were aged 18 years or older with CKD (defined as glomerular filtration rate [GFR] ≥15 mL/min per 1.73 m^2 and <60 mL/min per 1.73 m^2). Subjects required support of an ESA due to anemia associated with their CKD for 1 of the following reasons: 1) subject had never received ESA therapy and hemoglobin was <10.5 g/dL; 2) subject had never received ESA therapy and hemoglobin was <11.0 g/dL with a documented hemoglobin decrease of ≥1 g/dL within the prior 12 months; or 3) subject had not received ESA therapy within the 2 months before screening, resulting in a documented ≥1 g/dL hemoglobin decrease since stopping ESA therapy and hemoglobin was <11.0 g/dL.

Subjects were excluded from the study for any of the following reasons: serum ferritin concentration <50 ng/mL and transferrin saturation <20%; serum iron overload; poorly controlled hypertension; a history of deep venous thrombosis or pulmonary embolus within 12 months before screening; or a history of stroke, transient ischemic attack, acute coronary syndrome, or other arterial thrombosis within 6 months before screening.

Test Product, Dose and Mode of Administration, Batch No.: Each vial of PROCRIT contained approximately 1 mL of drug and contained 4,000, 10,000, 20,000, or 40,000 IU/mL epoetin alfa. The 4,000, 10,000, and 40,000 IU/mL strengths were single-dose preservative-free vials; the 20,000 IU/mL strength was a multidose vial with 1% benzyl alcohol as preservative. Epoetin alfa was administered s.c. 3 times weekly, once weekly, or every 2 weeks. Self-administration of study drug was prohibited. The services of a home health care agency were available to provide injections to subjects in the 3-times-weekly group. The batch numbers for epoetin alfa were P041161, P057913, P039088, P057038, P058178, P047017, and P067994. Niferex® 150 mg capsules (batch number 71749) for iron supplementation were supplied to sites to give to patients as required.

Reference Therapy, Dose and Mode of Administration, Batch No.: No reference therapy was administered.

Duration of Treatment: 44-week, open-label treatment phase (which consisted of a 22-week initiation and maintenance period followed by a 22-week safety period), followed by a 4-week posttreatment phase (which consisted of a completion [or early withdrawal] visit and a follow-up contact).

Criteria for Evaluation:

Efficacy: The primary efficacy endpoint was the change in hemoglobin from baseline to the average of the last 8 weeks of treatment through Week 22. The secondary efficacy endpoint was the proportion of subjects with an increase of ≥1 g/dL in hemoglobin concentration from baseline by Week 9.

Safety: Safety evaluations included assessment of the incidence and severity of adverse events (including thromboembolic vascular events and hypertension), clinical laboratory tests (including specific hemoglobin assessments as secondary safety endpoints), vital sign measurements, physical examination findings, and measurement of serum erythropoietin antibodies.

In addition, efficacy (mean weekly hemoglobin concentrations) and safety (incidence of treatment-emergent adverse events) were separately evaluated in the 3-times-weekly group during the periods immediately preceding (Weeks 14 to 22) and following (Weeks 23 to 31) the transition from 3-times-weekly to once-weekly dosing.

Statistical Methods: For comparisons of the mean change in hemoglobin from baseline to the average of the last 8 weeks of treatment through Week 22 between Groups 1 and 2 and between Groups 1 and 3, an estimate of the difference in means (Group 2 minus Group 1 and Group 3 minus Group 1)

was computed along with the 2-sided 95% confidence interval (CI) for the difference. The estimate of the difference and the CI were calculated using an analysis of covariance, including baseline hemoglobin and study center as covariates.

Proportions of subjects with an increase of ≥1 g/dL in hemoglobin concentration from baseline by Week 9 were presented for each treatment group. Comparisons between Group 1 and Group 2 and between Group 1 and Group 3 were performed by computing an estimate of the difference in proportions (Group 2 minus Group 1 and Group 3 minus Group 1) along with the 2-sided 95% CI for the difference.

Safety data, including adverse events, clinical laboratory test results, vital sign measurements, and results of serum erythropoietin antibody testing, were summarized.

RESULTS:

A total of 284 (76%) subjects completed the study (defined as completion of all assessments at Week 45 of the posttreatment phase), while 89 (24%) subjects discontinued prior to study completion. The most common reasons for discontinuation were subject choice/withdrawal of consent (26 [7%] subjects) and other (23 [6%] subjects). Reasons for discontinuation were similar across the 3 treatment groups.

The majority of demographic and baseline characteristics were well balanced among the 3 treatment groups. Median age in the 3-times-weekly group was 73 years, compared with 70 years in the once-weekly and every-2-weeks groups. The overall mean estimated GFR was 30 mL/min (30.7 mL/min for the 3-times-weekly group, 29.8 mL/min for the once-weekly group, and 29.5 mL/min for the every-2-weeks group). Median baseline hemoglobin concentration was 9.7 g/dL for the 3-times-weekly group, 9.8 g/dL for the once-weekly group, and 10.0 g/dL for the every-2-weeks group. The median weight-adjusted initiation dose (Week 1 dose) was higher in the 3-times-weekly group (139.7 IU/kg/week) compared with the once-weekly and every-2-weeks groups (116.9 IU/kg/week and 125.0 IU/kg/week, respectively). This is due to the fact that the initial doses in the latter 2 extended dosing regimen groups were fixed at 10,000 IU and 20,000 IU, respectively, while the initial dose in the 3-times-weekly group was based on each subject's individual weight. Since the median weight was 81.0 kg, the median weight-adjusted dose was lower in the extended dosing groups compared with the 3-times-weekly group.

EFFICACY RESULTS:

Primary Efficacy Endpoint: Both the once-weekly and every-2-weeks regimens were found to be noninferior to the 3-times-weekly regimen in terms of change in hemoglobin from baseline to the average of the last 8 weeks of treatment through Week 22, with the lower limits of the 95% CIs above the prespecified noninferiority margin of –1 g/dL. The estimated difference between the once-weekly and 3-times-weekly groups was –0.17 g/dL (95% CI, –0.38 to 0.04), and –0.43 g/dL (95% CI, –0.64 to -0.22) between the every-2-weeks and 3-times-weekly groups (Table 1).

Table 1: Change in Hemoglobin (g/dL) from Baseline to the Average of the Last 8 Weeks of Treatment Through Week 22: Excluding Data Collected Postdialysis
(Study EPO-AKD-3001: Modified Intent-to-Treat Analysis Set)

	TIW	QW	Q2W
	(N=121)	(N=124)	(N=124)
N	121	124	123
Mean baseline	9.63	9.71	9.82
Mean change (SD) (minus TIW)	1.81 (0.910)	1.59 (0.997)	1.27 (0.906)
Diff. of LS Means (SE)		-0.17 (0.106)	-0.43 (0.107)
95% CI		(-0.380; 0.037)	(-0.641; -0.221)

CI=confidence interval; Diff=difference; LS=least squares; Q2W=every 2 weeks; QW=once weekly; SD=standard deviation; SE=standard error; TIW=3 times weekly
Note: ANCOVA model with baseline hemoglobin concentration alone as covariate.
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Secondary Efficacy Endpoint: The proportion of subjects with an increase of ≥1 g/dL in hemoglobin concentration from baseline by Week 9 was higher in the 3-times-weekly group (95.9%) compared with the once-weekly (87.1%) and every-2-weeks (85.5%) groups.

In addition, subjects in the 3-times-weekly group maintained adequate hemoglobin concentrations once they were switched to once-weekly dosing. The weekly mean (SD) hemoglobin concentrations during the 8 weeks prior to (Weeks 14 to 22) and after (Weeks 23 to 31) the switch from 3-times-weekly to once-weekly dosing were 11.51 (0.82) g/dL and 11.44 (0.79) g/dL, respectively.

SAFETY RESULTS:

Secondary Safety Endpoints:

The proportion of subjects who exceeded a hemoglobin concentration of 11.9 g/dL (the threshold for withholding a dose of epoetin alfa) during the first 22 weeks of treatment was higher in the 3-times-weekly group (86.2%) compared with the once-weekly group (78.4%) and the every-2-weeks group (71.2%).

The median per-subject frequency of exceeding the Hb threshold of 11.9 g/dL during the first 22 weeks of treatment was higher in the 3-times-weekly group (6 times), compared with the once weekly group (4 times) and the every2-weeks group (3 times).

The mean [SD] maximum hemoglobin concentration during the first 22 weeks of treatment was slightly higher in the 3-times-weekly group (12.9 [1.2] g/dL) compared with the once-weekly (12.6 [1.2] g/dL) and every-2-weeks (12.4 [1.3] g/dL) groups.

The proportion of subjects who experienced a hemoglobin rate of rise ≥1 g/dL in any 2-week period during the first 22 weeks of treatment was 96.7% in the 3-times-weekly group, 92.8% in the once weekly group, and 91.2% in the every-2-weeks group.

The mean (SD) maximum hemoglobin rate of rise during the first 22 weeks of treatment was 2.0 (0.8) g/dL , 2.0 (1.0) g/dL, and 1.9 (1.0) g/dL in the 3-times-weekly, once-weekly, and every-2-weeks groups, respectively.

Adverse Events:

The proportions of subjects experiencing at least 1 treatment-emergent adverse event or at least 1 drug-related, treatment-emergent adverse event during the first 22 weeks of treatment were comparable among the groups (Table 2).

Table 2: Overall Summary of Adverse Events During First 22 Weeks of Treatment: Excluding Data Collected Postdialysis
(Study EPO-AKD-3001: Analysis Set: Safety Population Analysis Set)

Events	TIW (N=123) n (%)	QW (N=125) n (%)	Q2W (N=125) n (%)	Total (N=373) n (%)
Subjects with any adverse events	86 (70)	84 (67)	95 (76)	265 (71)
Subjects with treatment-emergent adverse events	83 (68)	83 (66)	95 (76)	261 (70)
Subjects with drug-related treatment-emergent adverse events[a]	10 (8)	8 (6)	6 (5)	24 (6)
Subjects with treatment-emergent serious adverse events	19 (15)	27 (22)	28 (22)	74 (20)
Subjects with treatment-emergent investigator-confirmed thromboembolic vascular events	2 (2)	2 (2)	3 (2)	7 (2)
Subjects with treatment-emergent hypertension	14 (11)	11 (9)	6 (5)	31 (8)
Subjects with treatment-emergent adverse events leading to study discontinuation	1 (1)	1 (1)	2 (2)	4 (1)
Number of subjects who died due to an adverse event	0 (0)	6 (5)	3 (2)	9 (2)

Q2W=every 2 weeks; QW=once weekly; TIW=3 times weekly

[a] Drug-related treatment-emergent adverse events were defined as possible, probable, or very likely.

Note: Treatment-emergent adverse events, defined as all adverse events that occurred or stopped after the first dose of study drug, were included in the table.

Note: Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events

Note: Adverse events that occurred on the same day as dialysis were determined to have occurred prior to dialysis.

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Approximately 80% of all subjects had a treatment-emergent adverse event, and 10% had a drug-related, treatment emergent adverse event, during the study period (Weeks 1 to 44). The percentages were comparable among treatment groups.

During the first 22 weeks of treatment, the number of deaths was low (9 [2%] total subjects across the 3 treatment groups: no subjects in the 3-times-weekly group, 6 [5%] subjects in the once-weekly group, and 3 [2%] subjects in the every-2-weeks group). The number of deaths over the entire treatment period was also low (14 [4%] total subjects across the 3 treatment groups: 4 [3%] subjects in the 3-times-weekly group, 6 [5%] subjects in the once-weekly group, and 4 [3%] subjects in the every-2-weeks group).

The most commonly reported treatment-emergent adverse events during the first 22 weeks of treatment were hypertension and urinary tract infection (each occurring in 29 [8%] subjects) and diarrhea (25 [7%] subjects). Rates of individual treatment-emergent adverse events during the first 22 weeks of treatment were comparable across the 3 treatment groups.

The proportion of subjects with thromboembolic vascular events was low and identical (2%) across the treatment groups during Weeks 1 to 22. Whereas, during Weeks 23 to 44, after the 3-times-weekly group switched to once-weekly dosing, the proportion of subjects with investigator-confirmed thromboembolic vascular events in the 3-times-weekly, once-weekly, and every-2-weeks groups was 0, 3%, and 4%, respectively.

During the first 22 weeks of treatment, the incidence of treatment-emergent hypertension was 8% overall and was higher in the 3-times-weekly group (14 [11%] subjects), compared with the

once-weekly group (11 [9%] subjects), and the every-2-weeks group (6 [5%] subjects). The overall incidence over the entire 44-week treatment period was 12% (13%, 14%, and 10% in the 3-times-weekly, once-weekly, and every-2-weeks groups, respectively).

No apparent differences were observed in the incidence or type of treatment-emergent adverse events, or in the incidence of thromboembolic vascular events, or adverse events of hypertension before and after the switch from 3-times-weekly to once-weekly dosing. A higher incidence of treatment-emergent serious adverse events was observed in the 9 weeks (Weeks 23 to 31) after the transition to once-weekly dosing (9 [8%] subjects), compared with the 9 weeks (Weeks 14 to 22) before the switch (4 [4%] subjects), although the number of subjects with serious adverse events was low in both periods.

STUDY LIMITATIONS: This is the first of 2 studies of extended dosing of epoetin alfa in predialysis CKD subjects with anemia. Both studies were designed with input from the FDA and approved under a Special Protocol Assessment. The studies are powered to show non-inferiority in efficacy. There has been concern with regard to dosing of ESAs and the development of thromboembolic events. It was further thought that the occurrence of thromboembolic vascular events was related to exceeding a hemoglobin concentration ceiling and a rapid rate of rise of hemoglobin concentration. Given the low rates of thromboembolic vascular events in this patient population, the study was not designed to detect a difference in the occurrence of these types of events. Instead, excursions above the hemoglobin concentration ceiling and incidence of rapid hemoglobin rates of rise were chosen as surrogate endpoints for thromboembolic events.

CONCLUSIONS:

Both the once-weekly and every-2-weeks extended dosing regimens of epoetin alfa were effective in maintaining hemoglobin concentrations within an acceptable therapeutic range and were comparable to the approved 3-times-weekly dosing regimen.

All 3 dosing regimens, once weekly, every 2 weeks, and 3 times weekly, were safe and generally well tolerated. No new safety signals were identified.

Extended dosing provides a potential treatment option that represents a significant clinical benefit to patients. Less frequent administration of drug reduces the number of injections, is more convenient, may increase patient compliance, and will reduce the health care burden on pharmacies, clinics, and caregivers.

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