SYNOPSIS, CR010414

Issue Date: 15 September 2009
Document No.: EDMS-USRA-11205999:2.0

Name of Sponsor/Company	Ortho Biotech Oncology Research & Development, a unit of Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Name of Finished Product	PROCRIT® (epoetin alfa)
Name of Active Ingredient(s)	Recombinant human erythropoietin (r-HuEPO)

Protocol No.: CR010414

Title of Study: A Randomized, Open-Label, Multicenter Study of Epoetin Alfa Comparing Two Dosing Regimens, Once-every-two-weeks and Once-every-four-weeks, with Once-weekly Dosing Regimen for Maintenance Treatment in Anemic Subjects With Chronic Kidney Disease

Coordinating Investigator: N/A

Publication (Reference): Pergola PE, Gartenberg G, Fu M, Bowers P, Sun S. Every 2 and 4 Week Dosing with Epoetin Alfa is Noninferior to Once Weekly Dosing in Pre-Dialysis Subjects With Anemia of Chronic Kidney Disease: An Open-Label Randomized Study. Abstract accepted for poster presentation at ASN Renal Week 2009.

Study Period: 21 June 2007/26 March 2009

Phase of Development: 3

Objectives: The primary objective of the study was to demonstrate that every-2-weeks and every-4-weeks treatment with epoetin alfa in subjects with anemia associated with chronic kidney disease (CKD) was not inferior to once-weekly treatment with respect to the mean change in hemoglobin from baseline to the average of the last 12 weeks of treatment.

The secondary objectives of the study were to assess the maintenance of hemoglobin concentrations, 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, parallel-group study. Subjects not on dialysis with anemia associated with CKD who were already maintained on a stable dose of epoetin alfa administered once weekly, and who met all study inclusion criteria and none of the exclusion criteria, were randomly assigned in a 1:1:2 ratio to receive subcutaneous (s.c.) epoetin alfa once weekly (Group 1), every 2 weeks (Group 2), or every 4 weeks (Group 3). Open-label treatment continued for a total of 36 weeks. Iron therapy was strongly recommended during the study to maintain a subject's transferrin saturation (TSAT) 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 dose was held for hemoglobin concentration >11.9 g/dL or hemoglobin rate of rise ≥1.5 g/dL in the prior 2 weeks. Epoetin alfa dose was reduced for hemoglobin rate of rise ≥1.0 but <1.5 g/dL in the prior 2 weeks. Epoetin alfa dose was increased for hemoglobin concentration ≤10.5 g/dL with rate 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 post-treatment 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): 400 subjects were planned (100 subjects each in the once-weekly and every-2-weeks groups, 200 subjects in the every-4-weeks group); 430 were randomized (108, 107, and 215 subjects, respectively). Efficacy analyses were performed on the modified intent-to-treat population (N=428), 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=430), 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 and <60 mL/min/1.73 m^2). Subjects had hemoglobin concentration between 10.0 and 11.9 g/dL, inclusive, on at least 2 measurements taken at least 1 week apart during the 4 weeks before randomization, and confirmed at the Week 1 visit, while on a stable weekly dose of epoetin alfa (≤20,000 IU once weekly).

Subjects were excluded from the study for reasons which included, but were not limited to the following: serum ferritin concentration <50 ng/mL and TSAT <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 1 mL vial 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 once weekly, every 2 weeks, or every 4 weeks. Self-administration of study drug was prohibited. The batch numbers for epoetin alfa were P102183, P089501, P089396, P084064, and P067994. Niferex®-150 mg Forte Capsules (batch numbers 75821 and 75819) for iron supplementation were supplied to sites to give to subjects as required.

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

Duration of Treatment: 36-week, open-label treatment phase (which consisted of conversion and maintenance treatment), followed by a 4-week post-treatment 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 12 weeks of treatment. The secondary efficacy endpoint was the proportion of weeks per subject in which the hemoglobin concentration was between 10.0 and 11.9 g/dL, inclusive, during Weeks 13 to 37.

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

Statistical Methods: For comparisons of the mean change in hemoglobin from baseline to the average of the last 12 weeks of treatment 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 model, with baseline hemoglobin as a covariate.

Summary statistics for the proportion of weeks per subject in which the hemoglobin concentration was between 10.0 and 11.9 g/dL, inclusive, during Weeks 13 to 37 were prepared for each treatment group.

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 361 (84%) subjects completed the study (defined as completion of all assessments at Week 37 of the post-treatment phase), while 69 (16%) subjects discontinued prior to study completion. The most common reasons for discontinuation were other (24 [6%] subjects) and adverse event (18 [4%] subjects). The proportion of subjects who discontinued from the study increased slightly as the dosing interval increased: 12%, 14%, and 19%, respectively, in the once-weekly, every-2-weeks, and every-4-weeks groups.

The majority of demographic and baseline characteristics were well balanced among the 3 treatment groups. Median age in the once-weekly group was 71 years, compared with 72 years in both the every-2-weeks and every-4-weeks groups. Median GFR at baseline was somewhat higher in the every-2-weeks group (29.5 mL/min/1.73 m^2) as compared with the once-weekly (24.0 mL/min/1.73 m^2) and every-4-weeks (26.0 mL/min/1.73 m^2) groups. Median baseline hemoglobin concentration was 11.0 g/dL in the once-weekly group, and 11.2 g/dL in both the every-2-weeks and every-4-weeks groups.

EFFICACY RESULTS:

Primary Efficacy Endpoint: Both the every-2-weeks and every-4-weeks regimens were noninferior to the once-weekly regimen with respect to change in hemoglobin from baseline to the average of the last 12 weeks of treatment, with the lower limits of the 95% CIs above the prespecified noninferiority margin of -1 g/dL (Table 1). The estimated difference between the every-2-weeks and once-weekly groups was -0.03 g/dL with a standard error of 0.09 g/dL (95% CI: -0.21, 0.15). The estimated difference between the every-4-weeks and once-weekly groups was -0.09 g/dL with a standard error of 0.08 g/dL (95% CI: -0.25, 0.06).

Table 1: Change in Hemoglobin Concentration (g/dL) From Baseline to the Average of the Last 12 Weeks of Treatment: Excluding Data Collected Postdialysis
(Study EPO-AKD-3002: Modified Intent-to-Treat Analysis Set)

	QW (N=107)	Q2W (N=106)	Q4W (N=215)
N	107	105	215
Mean baseline	11.03	11.13	11.17
Mean change (SD)	-0.02 (0.728)	-0.10 (0.774)	-0.19 (0.738)
(minus QW)			
Diff. of LS means (SE)		-0.03 (0.092)	-0.09 (0.079)
95% CI		(-0.208; 0.153)	(-0.249; 0.063)

CI=confidence interval; diff=difference; LS=least squares; Q2W=every 2 weeks; Q4W=every 4 weeks; QW=once weekly; SD=standard deviation; SE=standard error
Note: ANCOVA model with baseline hemoglobin alone as a covariate.
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Secondary Efficacy Endpoint: The median of the proportion of weeks per subject in which the hemoglobin concentration was between 10.0 and 11.9 g/dL, inclusive, during Weeks 13 to 37 was 0.87 (87% of weeks) in the once-weekly group, 0.88 (88% of weeks) in the every-2-weeks group, and 0.83 (83% of weeks) in the every-4-weeks group.

SAFETY RESULTS:

Hemoglobin-Related Safety Endpoints:

The proportion of subjects who exceeded the hemoglobin ceiling of 11.9 g/dL (the threshold for withholding study drug) at least once during Weeks 1 to 37 was highest in the every-2-weeks group (84.8%, versus 73.8% and 74.9%, respectively, for the once-weekly and every-4-weeks groups). The median per-subject frequency of having exceeded a hemoglobin concentration of 11.9 g/dL during Weeks 1 to 37 was lower for the once-weekly group (2 times) versus the every-2-weeks and every-4-weeks groups (3 times).

The mean maximum hemoglobin concentration during Weeks 1 to 37 was comparable across the 3 treatment groups: 12.4 g/dL, 12.5 g/dL, and 12.5 g/dL, respectively, in the once-weekly, every-2-weeks, and every 4 weeks groups.

The proportion of subjects who experienced a hemoglobin rate of rise ≥2 g/dL in any 2-week period during Weeks 1 to 37 was 34.6%, 31.4%, and 31.6%, respectively, in the once-weekly, every-2-weeks, and every-4-weeks groups. The mean maximum hemoglobin rate of rise during Weeks 1 to 37 was 1.8 g/dL, 1.7 g/dL, and 1.8 g/dL in the once-weekly, every-2-weeks, and every-4-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 were generally similar among the treatment groups, as were proportions of subjects experiencing treatment-emergent investigator-confirmed thromboembolic vascular events, treatment-emergent hypertension, and discontinuation due to treatment-emergent adverse events (Table 2). A slightly lower proportion of subjects in the once-weekly group experienced treatment-emergent serious adverse events, as compared with the every-2-weeks and every-4-weeks groups, however, the proportions of subjects with drug-related treatment-emergent serious adverse events were similar. Proportions of subjects who died were likewise similar across the 3 treatment groups.

Table 2: Overall Summary of Adverse Events During the Study: Excluding Data Collected Postdialysis (Study EPO-AKD-3002: Safety Population Analysis Set)

Events	QW (N=108) n (%)	Q2W (N=107) n (%)	Q4W (N=215) n (%)	Total (N=430) n (%)
Subjects with any adverse events	85 (79)	78 (73)	170 (79)	333 (77)
Subjects with treatment-emergent adverse events	84 (78)	77 (72)	170 (79)	331 (77)
Subjects with drug-related treatment-emergent adverse events[a]	8 (7)	4 (4)	17 (8)	29 (7)
Subjects with treatment-emergent serious adverse events	24 (22)	28 (26)	56 (26)	108 (25)
Subjects with drug-related treatment-emergent serious adverse events	1 (1)	0 (0)	4 (2)	5 (1)
Subjects with treatment-emergent investigator-confirmed thromboembolic vascular events	3 (3)	5 (5)	7 (3)	15 (4)
Subjects with treatment-emergent hypertension	13 (12)	14 (13)	26 (12)	53 (12)
Subjects with treatment-emergent adverse events leading to study discontinuation	3 (3)	4 (4)	11 (5)	18 (4)
Subjects who died due to an adverse event	4 (4)	3 (3)	9 (4)	16 (4)

Q2W=every 2 weeks; Q4W=every 4 weeks; QW=once weekly
Note: Treatment-emergent adverse events, defined as those adverse events with an onset date no earlier than the individual treatment start date and no later than the individual treatment phase end date (prior to dialysis), 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.
[a] Drug-related treatment-emergent adverse events defined as possible, probable, or very likely.
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Sixteen (4%) subjects died during the study: 4 (4%) subjects in the once-weekly group, 3 (3%) subjects in the every-2-weeks group, and 9 (4%) subjects in the every-4-weeks group.

The most commonly reported treatment-emergent adverse events during the study were hypertension (occurring in 49 [11%] subjects), urinary tract infection (35 [8%] subjects), edema (34 [8%] subjects), and hyperkalemia (33 [8%] subjects). The types of adverse events observed in this study are similar to those seen in predialysis patients with CKD not receiving epoetin alfa treatment. Overall, the rates of events by

system organ class were generally comparable across the 3 treatment groups, with no consistent pattern emerging across the various system organ classes between rates of events and dosing interval.

The proportion of subjects with treatment-emergent investigator-confirmed thromboembolic vascular events during Weeks 1 to 37 was low across the 3 treatment groups (3 [3%] subjects in the once-weekly group, 5 [5%] subjects in the every-2-weeks group, and 7 [3%] subjects in the every-4-weeks group).

The incidence of treatment-emergent hypertension was comparable across the 3 treatment groups: 13 (12%) subjects, 14 (13%) subjects, and 26 (12%) subjects in the once-weekly, every-2-weeks, and every-4-weeks groups, respectively.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

In subjects not on dialysis with anemia associated with CKD, both the every 2-weeks and every-4-weeks dosing regimens of epoetin alfa maintained hemoglobin concentrations within an acceptable therapeutic range and had efficacy profiles similar to that of the once-weekly dosing regimen.

All 3 dosing regimens, once weekly, every 2 weeks, and every 4 weeks, were safe and generally well tolerated. No new safety signals were identified.

The results of this study demonstrate that subjects receiving once-weekly maintenance treatment can be converted to more extended dosing regimens (every 2 weeks and every 4 weeks) in an effective and safe manner, and that these more extended dosing regimens are effective and safe over an extended treatment period.

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