PEGINESATIDE TO MANAGE ANEMIA IN CHRONIC KIDNEY DISEASE PATIENTS ON PERITONEAL DIALYSIS

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◆ **Background:** Peginesatide is a novel, synthetic, peptide-based pegylated erythropoiesis-stimulating agent that is designed specifically to stimulate the erythropoietin receptor. The purpose of the present study was to assess, for the first time, the efficacy and safety of peginesatide in chronic kidney disease (CKD) patients receiving peritoneal dialysis (PD) and previously on epoetin treatment.

◆ **Methods:** In this open-label multicenter study, 59 PD patients with CKD were converted from epoetin (alfa or beta) to once-monthly peginesatide. Doses were titrated to maintain hemoglobin levels between 10 g/dL and 12 g/dL during the 25 weeks of the study. The primary endpoint was change from baseline in mean hemoglobin values during the evaluation period (weeks 20–25).

◆ **Results:** The mean hemoglobin value during the evaluation period was 11.3 ± 1.07 g/dL, and the mean change from baseline was 0.10 ± 1.15 g/dL (95% confidence limits: $-0.24, 0.44$ g/dL). During the evaluation period, most patients maintained hemoglobin levels between 10 g/dL and 12 g/dL (63.0%) and within ± 1.0 g/dL of baseline (60.9%). The median weekly epoetin dose at baseline was 96.0 U/kg, and the median starting peginesatide dose was 0.047 mg/kg. Forty-three patients (72.9%) completed the study. Six patients (10.2%) received red blood cell transfusions. The observed adverse event profile was consistent with underlying conditions in the PD patient population. The most common adverse event was peritonitis (20.3%), a complication commonly associated with PD. Four deaths occurred during the study (2 related to septic shock, and 1 each to myocardial ischemia and myasthenia gravis).

◆ **Conclusions:** In this study, once-monthly peginesatide maintained hemoglobin levels in PD patients after conversion from epoetin.

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Chronic kidney disease (CKD) is a global problem that is affecting increasing numbers of people (1), including hemodialysis (HD), peritoneal dialysis (PD), and non-dialysis patients. Anemia associated with CKD is primarily a result of the inability of diseased kidneys to produce adequate amounts of endogenous erythropoietin. Anemia increases in prevalence with progressive deterioration in renal function and affects almost all patients with moderate-to-severe CKD (2). In addition to intravenous iron, the standard treatment for CKD-associated anemia is administration of erythropoiesis-stimulating agents (ESAs). Use of such agents has been associated with transfusion avoidance (3).

Peginesatide (Omontys; Affymax Inc., Palo Alto, CA, U.S.A.) is a novel, synthetic, peptide-based pegylated ESA that is designed specifically to stimulate the erythropoietin receptor. Peginesatide has been studied in both non-dialysis (4) and dialysis patients (5,6). In March 2012, it was approved in the United States for once-monthly (Q4W) subcutaneous or intravenous administration for the treatment of anemia in CKD patients on dialysis. Subsequently, in February 2013, it was voluntarily recalled because of new post-marketing reports of serious hypersensitivity reactions (7).

As CKD progresses, patients often require dialysis. Compared with in-center HD, PD requires fewer visits to dialysis centers and is therefore more easily incorporated into daily life (8). In the United States, about 7% of patients who require dialysis receive PD (9).

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Although PD patients do not normally require frequent visits to dialysis centers, if therapy with an ESA is required, more frequent trips may be necessary to receive that therapy. An ESA with an extended dosing interval, such as peginesatide, would allow PD patients to receive fewer injections (10), which could potentially reduce the burden related to administration of ESAs for patients, caregivers, and physicians. An extended dosing interval might also be of value to patients who are able to self-administer ESA therapy at home; reducing the required number of injections might possibly improve treatment compliance. The effect of injection frequency on treatment compliance with ESAs has not yet been established, but results from a community-based study that evaluated compliance in PD patients who were self-administering epoetin showed that common reasons for missed doses were forgetfulness and injection pain (11).

The results of two phase III studies in HD patients who were converted from epoetin treatment demonstrated that Q4W peginesatide was similar in efficacy to epoetin and maintained hemoglobin levels (6). The purpose of the present study was to evaluate the ability of Q4W peginesatide to maintain hemoglobin levels in PD patients after conversion from epoetin (alfa or beta). The safety of peginesatide was also assessed.

METHODS

STUDY POPULATION

The study included adult patients with CKD who had been receiving PD for 3 months or more before enrollment. Patients were required to have been receiving stable treatment with epoetin (alfa or beta) for 8 weeks or more, and to have a mean of 4 consecutive hemoglobin values in the 10.0 – 12.0 g/dL range during screening, and a ferritin level of 100 ng/mL or more (see Table 1 for key eligibility criteria). Patients provided written informed consent before participating in any study-specific procedures. The protocol was approved by the Independent Ethics Committee or Institutional Review Board of the participating centers (see NCT00752791 at <http://clinicaltrials.gov>). The study was conducted in accordance with the Declaration of Helsinki (2002 version), the International Conference on Harmonization Good Clinical Practice Guidelines, and all applicable regulatory requirements.

STUDY DESIGN

This phase II multicenter open-label study comprised these phases:

- A screening period (weeks –6 to –1)

TABLE 1
Key Inclusion and Exclusion Criteria

Inclusion criteria

1. The patient is a man or woman and 18 – 90 years of age, inclusive.
2. The patient has chronic kidney disease and has been on peritoneal dialysis for 3 months or more before enrollment.
3. The patient is on stable subcutaneous epoetin (alfa or beta) maintenance therapy continuously prescribed for a minimum of 8 weeks before enrollment.
4. The patient has 4 consecutive hemoglobin measurements (mean ≥ 10.0 g/dL and ≤ 12.0 g/dL) during the screening period, with the difference between the mean of the first confirmed measurements (2 consecutive) and the mean of the last confirmed measurements (2 consecutive) being 1.0 g/dL or less.
5. The patient has 1 ferritin measurement of 100 ng/mL or more within 4 weeks before enrollment.

Exclusion criteria

1. The patient has a known bleeding or coagulation disorder.
2. The patient has a known hematologic disease or cause of anemia other than renal disease (for example, pure red cell aplasia, homozygous sickle-cell disease, thalassemia, multiple myeloma, hemolytic anemia, myelodysplastic syndrome).
3. The patient has received a recent course of intensive iron replacement (that is, more than 500 mg administered intravenously in the 28 days before enrollment).
4. The patient has advanced chronic congestive heart failure defined by a New York Heart Association class of III or IV.
5. The patient has a known history of seizure disorder or has received antiepileptic medication for a seizure disorder within 6 months before enrollment.
6. The patient is scheduled for kidney transplantation. (Patients currently on a transplant waiting list were not excluded unless a donor had been identified.)

- Enrollment (week 0)
- An interval free of ESAs (during which patients who were receiving treatment with an ESA every other week stopped that agent for 2 weeks, and all other patients stopped their agent for 1 week)
- A titration period (weeks 1 – 19)
- An evaluation period (weeks 20 – 25).

The starting dose of peginesatide was determined based on each patient's total weekly dose of epoetin alfa or beta (Table 2). After the first peginesatide dose, patients received peginesatide Q4W. Doses were adjusted (Table 3) to maintain hemoglobin levels in the range

TABLE 2
Peginesatide Starting Doses

Epoetin alfa or beta (U/kg) Weekly dose during screening	Peginesatide (mg/kg) Starting dose (repeated every 4 weeks)
<100	0.04
100 to <200	0.08
200 to <300	0.12
≥300	0.16

TABLE 3
Guidelines for Dose Adjustments

Hemoglobin	Adjustment action
<9.5 g/dL or decline of 1.0–1.5 g/dL from baseline ^a	25% dose increase
Decline of >1.5 g/dL from baseline ^a	50% dose increase
≥12.0 g/dL	25% dose decrease
≥12.5 g/dL	Dose delay until hemoglobin reaches <12.5 g/dL; 25% dose decrease on recommencement
Increase of >1.0 g/dL over the level recorded 2 weeks earlier	25% dose decrease

^a Mean of the 4 measurements taken most recently before enrollment and of the measurement taken on the day of enrollment.

10 – 12 g/dL and within ±1.5 g/dL of baseline (defined as the mean of the 4 hemoglobin values obtained most recently before enrollment and the hemoglobin value taken at enrollment). Iron levels were recommended to be maintained according to the Kidney Disease Outcomes Quality Initiative treatment guidelines (12). Patient visits occurred every other week during the titration period and every week during the evaluation period.

STUDY DRUG

Peginesatide (Affymax Inc.) was supplied as an aqueous phosphate-buffered isotonic sorbitol solution (pH approximately 6.0). Each single-use glass vial contained 1 mL solution at a concentration of 10 mg/mL peginesatide. The formulation included polysorbate 20 as a surfactant. Vials were stored at 2°C – 8°C.

ASSESSMENTS

At each study visit, hemoglobin, concomitant medications, information about transfusions and phlebotomies, and adverse events were assessed. At screening, at enrollment, and monthly thereafter, blood chemistry and hematology, serum pregnancy test (for women of childbearing potential), vital signs, and samples for assessment of peginesatide-specific antibodies were obtained. Iron status evaluation, physical examination, and electrocardiography were performed periodically. Hemoglobin and all laboratory tests were performed by a central laboratory.

STATISTICAL ANALYSES

Patients who received at least 1 dose of the study drug were included in all analyses. Baseline and demographic characteristics are summarized descriptively.

The primary efficacy endpoint was the mean change in hemoglobin from baseline to the evaluation period (that is, the mean hemoglobin value from weeks 20 – 25). A 2-sided 95% confidence interval (CI) of the estimated mean change from baseline was derived from the t distribution. Secondary endpoints included the percentage of patients with mean hemoglobin values in the range 10 – 12 g/dL, the percentage of patients with a change in hemoglobin value within ±1.0 g/dL from baseline to evaluation, and the percentage of patients who received red blood cell transfusions during the titration and evaluation periods. For all secondary endpoints, a two-sided 95% CI of the estimated percentage was calculated using normal approximation with continuity correction. Primary and secondary endpoints are summarized descriptively. First and last doses of peginesatide during the titration and evaluation periods are also summarized descriptively.

All reported adverse events were graded (that is, grades 1 – 5) using the National Cancer Institute's *Common Terminology Criteria for Adverse Events* (13); events graded as 1 or 2 were considered mild and moderate respectively. Safety evaluations included the incidences of adverse events, adverse events leading to withdrawal, serious adverse events and deaths; the proportions of patients who received phlebotomies and had hemoglobin excursions (that is, 2 consecutive hemoglobin values exceeding 12 g/dL, 13 g/dL, or 14 g/dL); clinical laboratory results, iron levels, vital signs, and peginesatide-specific antibodies. All safety results are summarized descriptively.

This study was sponsored by Takeda Development Center Americas, Inc. (Deerfield, IL, USA), with collaboration from Affymax Inc. (Palo Alto, CA, USA). Takeda

Development Center Americas was responsible for collection and analysis of the data. All authors, including those employed by Takeda Development Center Americas, had access to the study data and approved the final version of the manuscript.

DETERMINATION OF SAMPLE SIZE

The study had a target enrollment of 60 patients. Given the sample size, a 2-sided 95% CI based on the *t* distribution for the mean change in hemoglobin from baseline to the evaluation period would have an interval that extended no more than 0.26 g/dL from the observed mean change in hemoglobin, with 90% coverage probability. It was assumed that a standard deviation of change in hemoglobin from baseline is 0.9 g/dL, based on results from a study of epoetin beta in PD patients with chronic anemia (14).

RESULTS

PATIENT DISPOSITION AND BASELINE AND DEMOGRAPHIC CHARACTERISTICS

The study was conducted from October 2008 to May 2010. Figure 1 shows patient disposition. Of the 153 patients who were screened, 59 patients were enrolled

Figure 1 — Patient disposition. ^aThree additional deaths were reported during the study.

(at 16 sites in the United States, 4 in the United Kingdom, 3 in Australia, 2 in Italy, and 1 in New Zealand). The most common reason for screen failure was not meeting entrance criteria (88.3%, Figure 1). The study treatment was completed by 43 patients (72.9%), and 7 patients withdrew from the study because of adverse events. Each particular adverse event leading to withdrawal occurred in a single patient; most of the effects were gastrointestinal in nature (abdominal hernia, abdominal abscess and cellulitis, peritonitis because of an infected catheter or perforated diverticula). One patient discontinued because of a protocol deviation (the patient received epoetin during the study). Other common reasons for withdrawal were renal transplantation ($n = 3$) and a switch from PD to HD ($n = 2$).

Table 4 summarizes baseline and demographic characteristics. A slight majority of patients were women (54.2%) and white (79.7%); mean age was 54.0 years. The mean hemoglobin level was 11.2 ± 0.50 g/dL at baseline. All patients were receiving subcutaneous epoetin, and the median weekly dose of epoetin at baseline was 96.0 U/kg. Most patients had a history of hypertension (98.3%) and hyperlipidemia (71.2%). A few patients (6.8%) had mild congestive heart failure (New York Heart Association class I or II), and no patients had moderate or severe congestive heart failure (class III or IV). Nineteen patients (32.2%) received iron supplementation during the study (8 received intravenous iron, 10 received oral iron, and 1 received both intravenous and oral iron).

EFFICACY ENDPOINTS

The mean hemoglobin value during the evaluation period (weeks 20 – 25) was 11.3 ± 1.07 g/dL, and the mean change from baseline was 0.10 ± 1.15 g/dL (95% CI: -0.24 g/dL to 0.44 g/dL; Table 5; Figure 2). Most patients (63.0%) maintained hemoglobin levels within the range 10 – 12 g/dL during the evaluation period (Table 5, Figure 3), most (60.9%) maintained hemoglobin levels within ± 1.0 g/dL from baseline (Table 5), and 6 (10.2%) received red blood cell transfusions during the study (Table 5). Mean hemoglobin levels were maintained within the 10 – 12 g/dL range at all time points after conversion from epoetin (range: 11.2 – 11.7 g/dL; Figure 3). The highest mean hemoglobin level was 11.7 g/dL (weeks 5 – 9); thereafter, the mean hemoglobin level declined gradually to 11.3 g/dL at last assessment.

PEGINESATIDE DOSING

In the full analysis population, the median starting dose of peginesatide was 0.046 mg/kg (range:

TABLE 4
Baseline and Demographic Characteristics

Characteristic	Value ^a
Patients (<i>n</i>)	59
Men [<i>n</i> (%)]	27 (45.8)
Mean age (years)	54.0±16.0
Race [<i>n</i> (%)]	
White	47 (79.7)
Black	10 (16.9)
Asian	2 (3.4)
Primary cause of CKD [<i>n</i> (%)]	
Diabetes	11 (18.6)
Hypertension	11 (18.6)
Polycystic kidney disease	5 (8.5)
Unknown	3 (5.1)
Urologic	2 (3.4)
Interstitial nephritis	1 (1.7)
Autoimmune disease	1 (1.7)
Cause not collected	25 (42.4)
NYHA CHF class [<i>n</i> (%)]	
I–II	4 (6.8)
III–IV	0
Cardiovascular risk history [<i>n</i> (%)]	
Hypertension	58 (98.3)
Hyperlipidemia	42 (71.2)
Diabetes	18 (30.5)
Coronary artery disease	9 (15.3)
Duration of PD [<i>n</i> (%)]	
≤1 Year	13 (22.0)
>1 Year	46 (78.0)
Hemoglobin (g/dL)	
Median	11.3
IQR (Q1, Q3)	10.9, 11.6
hs-CRP (mg/L)	
Median	3.8
IQR (Q1, Q3)	1.4, 10.1
Transferrin saturation (%)	
Median	30.0
IQR (Q1, Q3)	26.0, 37.5
Ferritin (ng/mL)	
Median	255.7
IQR (Q1, Q3)	158.2, 361.6
Epoetin	
Median weekly dose (U/kg)	96.0
Dose level [<i>n</i> (%)]	
<100 U/kg	31 (52.5)
100 to <200 U/kg	16 (27.1)
200 to <300 U/kg	5 (8.5)
≥300 U/kg	7 (11.9)

CKD = chronic kidney disease; NYHA = New York Heart Association; CHF = congestive heart failure; PD = peritoneal dialysis; hs-CRP = high-sensitivity C-reactive protein.

^a Mean ± standard deviation for normally distributed variables, and median with interquartile range (IQR) expressed as quartile 1, quartile 3 (Q1, Q3) for non-normally distributed variables.

0.03 – 0.17 mg/kg). The median dose of peginesatide declined during the course of the study: 0.044 mg/kg (range: 0.01 – 0.37 mg/kg) at the end of the titration period and 0.036 mg/kg (range: 0.01 – 0.34 mg/kg) at the end of the evaluation period (that is, last dose). Median doses of peginesatide were: first dose, 4.50 mg (range: 2.0 – 18.0 mg); end of titration period, 3.80 mg (range: 1.1 – 36.0 mg); end of evaluation period, 2.55 mg (range: 0.8–21.2 mg).

In the population of patients who completed the evaluation period (*n* = 43), the median starting dose of peginesatide was 0.043 mg/kg (range: 0.03 – 0.17). The median dose of peginesatide decreased during the course of the study: 0.038 mg/kg (range: 0.01 – 0.23 mg/kg) at the end of the titration period, and 0.036 mg/kg (range: 0.01 – 0.34 mg/kg) at the end of the evaluation period (that is, last dose). Median doses of peginesatide for this population were as follows: first dose, 4.00 mg (range: 2.0 – 16.0 mg); end of the titration period, 3.00 mg (range: 1.1 – 14.1 mg); end of the evaluation period, 2.55 mg (range: 0.8 – 21.2 mg).

A peginesatide dose was delayed in 26 patients because of high hemoglobin levels. The mean time that the dose was delayed was 44.5 ± 8.7 days, and the mean hemoglobin level when peginesatide dosing was resumed was 11.7 ± 0.7 g/dL.

SAFETY

Total exposure to peginesatide during the study was 24.8 patient-years. Patients were treated for a mean of 21.9 weeks (range: 5 – 30 weeks).

The most commonly reported adverse events (>10% of patients) were peritonitis (20.3%), diarrhea (15.3%), hypertension (13.6%), dyspnea (11.9%), cough (10.2%), and hypotension (10.2%). Of the 12 patients who reported peritonitis events, 9 were reported as serious adverse events. Myocardial ischemia was reported in 2 patients (3.4%), and cerebrovascular accident was reported in 1 patient (1.7%) in this study; hemoglobin levels measured before those events were 12.5 g/dL, 12.9 g/dL, and 12.1 g/dL respectively.

Serious adverse events occurred in 27 patients (45.8%). In addition to peritonitis, other serious adverse events reported by more than 1 patient were dyspnea (*n* = 2, 3.4%) and respiratory failure (*n* = 2, 3.4%).

Four patients died during the study. A 72-year-old woman with a history of diverticulosis and hypertension received all her scheduled doses of peginesatide; about 4 months after the last dose, she died from sepsis secondary to a perforated colon. A 52-year-old woman with a history of peritonitis experienced severe peritonitis 25

TABLE 5
Primary and Secondary Endpoints

Endpoint type	Value [mean (95% CL)]
Primary	
Change in hemoglobin from baseline ^a to evaluation (g/dL)	0.10 (−0.24, 0.44)
Secondary	
Patients with hemoglobin within 10.0–12.0 g/dL during evaluation (%)	63.0 (48.0, 78.1)
Patients with hemoglobin change within ± 1.0 g/dL from baseline during evaluation (%)	60.9 (45.7, 76.1)
Red blood cell transfusions (%)	10.2 (1.6, 18.7)

CL = confidence limits.

^a Mean of the 4 measurements taken most recently before enrollment and of the measurement taken on the day of enrollment.

Figure 2 — Mean change in hemoglobin concentrations over time. SD = standard deviation.

days after her first and only dose of peginesatide; this patient died about 4 weeks after the dose of peginesatide from sepsis, sclerosing peritonitis, and respiratory failure. A 72-year-old man with long-standing cardiovascular morbidity (ischemic heart disease, atrial fibrillation, cerebrovascular insult, and hypertension) died from myocardial ischemia 35 days after receiving his first and only dose of the study drug. A 57-year-old man with a history of hypertension, diabetes, and peripheral vascular disease was hospitalized 44 days after his fourth and last dose of the study drug. His condition deteriorated, and the patient died on study day 216 from complications of myasthenia gravis.

No therapeutic phlebotomies were performed during the course of the study.

Overall, more patients experienced hemoglobin excursion during the titration period than during the evaluation period; no hemoglobin excursions exceeded 14 g/dL (Table 6). Patients spent a mean of 62.7 ± 43.8 days and 32.7 ± 30.3 days above the 12.0 g/dL and 13.0 g/dL hemoglobin levels respectively. A review of

Figure 3 — Mean hemoglobin concentrations over time. SD = standard deviation.

TABLE 6
Hemoglobin Excursions, by Study Period

Hemoglobin excursion ^a	Patients [<i>n</i> (%)] experiencing excursions during	
	Titration period (<i>n</i> =59)	Evaluation period (<i>n</i> =46)
To >12 g/dL	30 (50.8)	11 (23.9)
To >13 g/dL	6 (10.2)	1 (2.2)
To >14 g/dL	0	0

^a Two consecutive hemoglobin values.

adverse events was conducted for patients with 2 or more hemoglobin excursions above 12 g/dL. In general, no temporal association was noted between hemoglobin excursions and cardiovascular or thrombotic events.

No patients experienced elevated aspartate aminotransferase (>3 times the upper limit of normal), and no patients experienced elevated bilirubin (>2 times the upper limit of normal). One patient had a markedly,

but transiently, elevated abnormal level of alanine aminotransferase, with no associated adverse events; and 1 patient had transiently elevated alkaline phosphatase that was resolved during continued treatment with the study drug.

Mean serum albumin was maintained from baseline (34.0 ± 4.2 g/L) to week 25 (34.7 ± 4.9 g/L). Mean ferritin was maintained from baseline (281.0 ± 143.7 ng/mL) to week 25 (287.2 ± 194.6 ng/mL). Mean transferrin saturation was also maintained from baseline ($33.6\% \pm 12.1\%$) to week 25 ($33.4\% \pm 11.9\%$).

No patient developed peginesatide-specific antibodies during the study.

DISCUSSION

This study was the first to evaluate the ability of Q4W peginesatide to maintain hemoglobin levels after conversion from epoetin (alfa or beta) taken 3 times per week in PD patients. Doses of peginesatide were titrated on an individual basis to maintain hemoglobin levels within the study target range (10 – 12 g/dL).

Overall, peginesatide maintained hemoglobin levels after conversion from epoetin. Maintenance of hemoglobin levels was evident for 25 weeks of treatment, with similar mean values observed at baseline and during the evaluation period (11.2 g/dL and 11.3 g/dL respectively). During the evaluation period, most patients maintained hemoglobin levels within the range 10 – 12 g/dL and within ± 1.0 g/dL from baseline. The percentage of patients who received red blood cell transfusions during the study was 10.2%. These results are consistent with the published literature for the current clinical use of ESAs in PD patients. For example, in a retrospective cohort study involving almost 14 000 Medicare PD patients treated with epoetin, 68% of patients had mean hemoglobin values between 10 g/L and 11.9 g/L over a 6-month period, and 61% of patients had post-baseline hemoglobin levels within 1.0 g/dL of baseline (15).

Median doses of peginesatide declined over the course of the study in the full-analysis population (median starting peginesatide dose: 0.046 mg/kg; median ending peginesatide dose: 0.036 mg/kg). The same decline was also observed in the completer population (median starting peginesatide dose: 0.043 mg/kg; median ending peginesatide dose: 0.036 mg/kg), indicating that the decline in peginesatide dose observed in the full-analysis population was not a result of discontinuation by patients with high peginesatide starting doses. Iron parameters (serum ferritin and transferrin saturation) were maintained. Those observations indicate that hemoglobin levels could be maintained by dose titration.

The adverse event profile observed in this study was consistent with the underlying condition of the studied population of PD patients with CKD. The most frequently reported adverse event was peritonitis (20.3%). Peritonitis is a complication commonly associated with PD (16,17), and it is often the reason that patients switch from PD to HD (18). Studies of treatment with ESAs in patients on PD have reported peritonitis rates ranging from 9.3% to 29.4% (10,14,19).

Transient hemoglobin excursion to more than 12 g/dL occurred in 51% of the patients during the 18-week titration period and in 24% of the patients during the 6-week evaluation period. The protocol dose titration guideline specified that a dose reduction should occur when hemoglobin reached or exceeded 12 g/dL. An earlier dose reduction when hemoglobin values were increasing and approaching 12 g/dL might have avoided some of the recorded excursions. Few patients experienced a hemoglobin excursion above 13 g/dL, and no patient experienced a hemoglobin excursion beyond 14 g/dL. There was no association between the hemoglobin excursions and cardiovascular or thrombotic adverse events. Overall, myocardial ischemia occurred in 2 patients, and cerebrovascular accident, in 1 patient in this study. No trends in abnormal laboratory values were observed.

This study has several limitations. The number of PD patients enrolled was small relative to HD patients in similar studies. However, the number of available PD patients is limited: 27 500 patients were on PD in the United States in 2009, compared with more than 370 000 on HD (20). In addition, this relatively short open-label trial lacked a comparator group. Phase III peginesatide studies have addressed some of those limitations (6). Also, a high rate of screen failure occurred in our study. Those failures occurred largely because the entrance criteria were rigorous, trying to ensure that entrants were relatively stable, because each patient was acting as his or her own control. Highly stable patients were necessary to assure reliable results.

One of the strengths of this study is that it was the first to assess the use of a once-monthly ESA for the treatment of renal anemia in PD patients. The trial program for methoxy polyethylene glycol-epoetin beta included some PD patients in specific trials, but the patient populations were always heterogeneous—that is, they included both HD and PD patients (21,22).

Hemodialysis patients generally receive ESA treatment during dialysis sessions, and so a separate injection is unnecessary. On the other hand, a separate subcutaneous injection is necessary for administration of ESAs to PD patients. Limiting the number of ESA injections is therefore desirable in this patient population. In dialysis

patients, epoetin alfa and beta are often administered 2 – 3 times each week (23,24); darbepoetin alfa, which has a longer half-life than does epoetin alfa or beta, might allow for less frequent dosing (once weekly) (25). Although a Q4W ESA, methoxy polyethylene glycol-epoetin beta, is available in Europe (26) and other parts of the world, no such ESA is currently available in the United States. Furthermore, all these ESAs are recombinant erythropoietin proteins and have the potential to induce anti-erythropoietin antibodies and pure red cell aplasia (27). Peginesatide is a synthetic peptide-based ESA that has no sequence homology to erythropoietin and thus has the additional advantage of not being immunologically cross-reactive with endogenous or recombinant erythropoietin. Although none of the patients in the current study developed peginesatide-specific antibodies, such antibodies have been detected in patients in other studies conducted during the peginesatide development program (4).

Peginesatide was voluntarily recalled in February 2013 because of new post-marketing reports of serious hypersensitivity reactions (7). Hypersensitivity of that type was not observed with administration of peginesatide during the trial described in this paper.

CONCLUSIONS

The present study was the first to investigate a once-monthly ESA (peginesatide) in an all-PD patient population. Peginesatide maintained hemoglobin within the range of 10 – 12 g/dL after conversion from epoetin alfa or beta.

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DISCLOSURES

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