

# Once-Monthly Subcutaneous C.E.R.A. Maintains Stable Hemoglobin Control in Patients with Chronic Kidney Disease on Dialysis and Converted Directly from Epoetin One to Three Times Weekly

Wladyslaw Sulowicz,\* Francesco Locatelli,<sup>†</sup> Jean-Philippe Ryckelynck,<sup>‡</sup> Jozsef Balla,<sup>§</sup> Botond Csiky,<sup>||</sup> Kevin Harris,<sup>¶</sup> Patricia Ehrhard,\*\* and Ulrich Beyer;\*\* on behalf of the PROTOS Study Investigators

\*Clinic of Nephrology Collegium Medicum, Jagiellonian University, Cracow, Poland; <sup>†</sup>Department of Nephrology and Dialysis, "A Manzoni" Hospital, Lecco, Italy; <sup>‡</sup>Service de Néphrologie, CHU Clemenceau Centre, Caen, France; <sup>§</sup>Department of Nephrology, University of Debrecen, Debrecen, and <sup>||</sup>Fresenius Dialysis Center, University of Pecs, Pecs, Hungary; <sup>¶</sup>Renal Services and Urology, Leicester General Hospital, Leicester, United Kingdom; and \*\*Pharma Development, F. Hoffmann-La Roche Ltd., Basel, Switzerland

**Background:** C.E.R.A., a continuous erythropoietin receptor activator, is in development to provide anemia correction and stable maintenance of hemoglobin (Hb) levels at extended administration intervals in patients with chronic kidney disease (CKD). This study examined its efficacy and safety when administered up to once monthly in patients who have CKD and are on dialysis and randomly convert directly from epoetin  $\alpha$  or  $\beta$  one to three times weekly.

**Design, setting, participants, and measurements:** In this three-arm, comparator-controlled, open-label, randomized, parallel-group, Phase III study, 572 dialysis patients ( $\geq 18$  yr) who were receiving stable subcutaneous epoetin one to three times weekly were randomly assigned (1:1:1) to continue epoetin or to receive subcutaneous C.E.R.A. once monthly or twice monthly for 52 wk. Dosage was adjusted to maintain Hb  $\pm 1.0$  g/dl of baseline level. Primary end point was mean change in Hb level between baseline and the evaluation period (weeks 29 to 36). **Results:** Mean Hb levels during the evaluation period were similar between groups (once-monthly C.E.R.A. 11.5 g/dl; twice-monthly C.E.R.A. 11.7 g/dl; epoetin 11.5 g/dl). The difference between C.E.R.A. and epoetin in mean change (97.5% confidence interval) in Hb concentration between baseline and evaluation was  $-0.022$  g/dl ( $-0.262$  to  $0.217$ ) for once monthly and  $0.141$  g/dl ( $-0.098$  to  $0.380$ ) for twice monthly. Analysis demonstrated that C.E.R.A. was as effective as epoetin in maintaining Hb and was well tolerated.

**Conclusions:** Subcutaneous C.E.R.A. once or twice monthly successfully maintained tight and stable Hb levels in patients who were on dialysis and randomly converted directly from epoetin one to three times weekly.

*Clin J Am Soc Nephrol* 2: 637-646, 2007. doi: 10.2215/CJN.03631006

Anemia is commonly associated with chronic kidney disease (CKD) (1-3) and contributes to the morbidity and mortality and reduced quality of life in these patients (4-10). Erythropoiesis-stimulating agents (ESA) and clinical practice guidelines have been beneficial in managing renal anemia (11-15), and anemia correction has been associated with improved patient outcomes (16,17). Current guidelines recommend maintenance of hemoglobin (Hb) levels at  $\geq 11$  g/dl (13,14,18). In addition, European and Australian

guidelines specify an upper limit of 12.0 g/dl for patients with cardiovascular disease or diabetes (13,14), whereas US guidelines do not support routine maintenance of Hb  $> 13$  g/dl (18).

Despite these guidelines, many patients still fail to achieve minimum Hb targets (17,19,20). For example, the Dialysis Outcomes and Practice Patterns Study demonstrated that more than one quarter of US patients on dialysis had an Hb level  $< 11$  g/dl, and the incidence was often higher (up to 77%) in other countries (17,20). Moreover, Hb levels fluctuate over short periods of time, such that many patients who have CKD and achieve Hb targets do not maintain their Hb level within target range for extended periods of time (21-24). It has been estimated that only 5% of patients who are on hemodialysis and have an Hb between 11 and 12 g/dl persistently remain within that range for 6 mo (22).

Maintaining Hb levels within target ranges requires close monitoring of Hb and, with current agents, often requires frequent dosage adjustments (23). Hence, maintenance of stable

Received October 31, 2006. Accepted April 16, 2007.

Published online ahead of print. Publication date available at [www.cjasn.org](http://www.cjasn.org).

Responsibility for opinions, conclusions, and interpretation of data lies with the authors.

**Address correspondence to:** Prof. Wladyslaw Sulowicz, Collegium Medicum, Jagiellonian University Department of Nephrology, 15c Kopernika, 31-501, Cracow, Poland. Phone: +48-12-4247892; Fax: +48-12-4247149; E-mail: [wladsul@mp.pl](mailto:wladsul@mp.pl)

Hb levels can be time-consuming and may burden renal units, which already have to cope with the growing incidence and prevalence of CKD (15,25,26). Consequently, we need agents that will provide predictable and stable Hb responses with minimal intervention from health care professionals.

The use of current ESAs at extended administration intervals has been examined in several studies in patients who already had stable Hb levels at administration intervals of at least once weekly (27–31). However, only one study involved patients who were on dialysis (29), in which a stepwise introduction of longer intervals was required. Even so, a proportion of the enrolled patients did not maintain Hb levels. As a result, these studies do not provide strong evidence that such regimens can be applied to the spectrum of patients with CKD encountered in day-to-day clinical practice.

C.E.R.A., a continuous erythropoietin receptor activator, is a novel agent that provides correction of anemia and stable control of Hb levels at extended administration intervals (32). Preclinical and Phase I and II studies demonstrate that C.E.R.A. has unique pharmacologic properties, acting differently than epoetin at the erythropoietin receptor level (33), with a long serum half-life (mean 134 h after intravenous and 139 h after subcutaneous administration in patients who are on peritoneal dialysis) and low clearance (32,34,35). These half-life values are considerably longer than those reported in healthy volunteers for epoetin  $\alpha$  (6.8 h [intravenous] and 19.4 h [subcutaneous]) and epoetin  $\beta$  (8.8 h [intravenous] and 24.2 h [subcutaneous]) (36) and up to five times longer than those reported for darbepoetin  $\alpha$  in patients who are on peritoneal dialysis (25.3 h [intravenous] and 48.8 h [subcutaneous]) (37).

Phase II studies in patients who have CKD indicate that C.E.R.A. corrects anemia and maintains Hb levels within guideline targets when administered up to once monthly in patients who are on dialysis and in those not yet dialyzed (38–40). We report the results of PROTOS (Patients Receiving C.E.R.A. Once a month for the mainTenance Of Stable hemoglobin), a Phase III study of C.E.R.A. that was given subcutaneously at administration intervals of once monthly or twice monthly for the maintenance of Hb levels in patients who had CKD and were on dialysis and randomly converted directly from epoetin  $\alpha$  or  $\beta$ .

## Materials and Methods

### Patients

Patients were screened at 92 centers in 12 European countries, Brazil, Mexico, New Zealand, Panama, South Africa, Taiwan, Thailand, and the United States. Details of major inclusion and exclusion criteria are provided in Table 1. Patients were  $\geq 18$  yr of age, had chronic renal anemia, and were receiving hemodialysis or peritoneal dialysis for  $\geq 12$  wk before screening. They were required to have received treatment with subcutaneous epoetin one to three times weekly with the same administration interval for  $\geq 8$  wk before screening and to have a stable Hb concentration within the range 10.5 to 13.0 g/dl during the baseline period.

The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and local ethics committees. All study participants provided written informed consent.

### Study Design

PROTOS was a three-arm, controlled, open-label, randomized, multicenter, parallel-group, Phase III study designed to compare the efficacy and tolerability of two dosing intervals of subcutaneous C.E.R.A. with that of continued epoetin therapy for the maintenance treatment of anemia in patients who had CKD and were receiving dialysis and had previously been maintained on subcutaneous epoetin  $\alpha$  and  $\beta$  (one to three times a week). After a 4-wk baseline period, when patients continued to receive epoetin, those who were eligible were randomly assigned (1:1:1) to receive subcutaneous C.E.R.A. once a month, to receive subcutaneous C.E.R.A. twice a month, or to continue receiving subcutaneous epoetin at their current dosage and administration interval (Figure 1). Patients were randomly assigned to study treatment *via* a central randomization center with stratification by geographic region.

Starting dosages of C.E.R.A. were based on the epoetin dosage received during the week preceding randomization (Table 2). The study consisted of a dosage titration period during the first 28 wk after the initial dose of study drug (weeks 1 to 28), followed by an 8-wk efficacy evaluation period (weeks 29 to 36) and a 16-wk long-term safety follow-up (weeks 37 to 52; Figure 1).

In the titration and evaluation periods, the dosage of C.E.R.A. was adjusted to maintain patients' Hb within a range of  $\pm 1.0$  g/dl of their baseline Hb and between 10.0 and 13.5 g/dl. During the long-term safety observation period, the dosage of C.E.R.A. was adjusted to maintain Hb levels within a range of 11 to 13 g/dl. Dosage adjustments were permitted for safety at any point during the study. Unless safety concerns dictated otherwise, dosage adjustments for C.E.R.A. were performed at the next scheduled dosing day so that the administration interval remained unchanged throughout the study; however, dosage adjustments were not to be performed more often than once every 4 wk. Dosage adjustments for C.E.R.A. were performed according to a predefined protocol, with the need for adjustment based on consistency of two consecutive Hb assessments. During titration and evaluation, C.E.R.A. dosages were decreased by 25% for Hb increases  $>1$  g/dl *versus* baseline or for Hb  $>13.5$  and  $\leq 14$  g/dl, and increased by 25% for Hb decreases  $>1$  g/dl *versus* baseline or for Hb  $\geq 9$  and  $<10$  g/dl. C.E.R.A. dosage decreases of 50% were made for Hb increases  $>2$  g/dl *versus* baseline and increases of 50% for Hb decreases  $>2$  g/dl *versus* baseline or Hb  $<9$  g/dl. During the long-term safety period, C.E.R.A. dosage was increased or decreased by 25% for Hb  $\geq 9$  and  $<11$  g/dl and Hb  $>13$  and  $\leq 14$  g/dl, respectively, and increased by 50% for Hb  $<9$  g/dl. Treatment was temporarily interrupted if Hb exceeded 14 g/dl. Dosage adjustments for epoetin  $\alpha$  and  $\beta$  were performed according to their respective labeling. For example, dosage increases for epoetin  $\alpha$  were not performed more frequently than once a month, unless clinically indicated, and dosages for epoetin  $\beta$  could be adjusted at intervals of 1 to 2 wk individually for the patient. For all treatment groups, Hb  $<9$  or  $>14$  g/dl and Hb changes  $>2$  g/dl *versus* baseline were to be avoided for safety reasons. Iron supplementation was performed according to individual center practice and adjusted to maintain adequate iron status: serum ferritin  $\geq 100$  ng/ml and transferrin saturation  $\geq 20\%$  (or hypochromic red blood cells [RBC]  $<10\%$ ).

### Study Drug

C.E.R.A. (F. Hoffmann-La Roche Ltd., Basel, Switzerland) was supplied as a solution in vials that contained 1 ml of 50, 100, 200, 400, or 1000  $\mu\text{g/ml}$ . Epoetin  $\beta$  was supplied in multidose vials by F. Hoffmann-La Roche Ltd. for participating study centers located outside the United States. Epoetin  $\alpha$  was obtained from commercial sources by participating sites located in the United States.

Table 1. Major inclusion and exclusion criteria<sup>a</sup>

Inclusion Criteria	Exclusion Criteria
Adult patients ( $\geq 18$ yr of age) with chronic renal anemia	Overt gastrointestinal bleeding or any other bleeding episode necessitating transfusion within 8 wk before screening or during screening/baseline
Regular long-term HD or PD therapy with the same mode of dialysis for at least 12 wk before screening and during screening/baseline	RBC transfusions within 8 wk before screening or during screening/baseline
Kt/V $\geq 1.2$ or urea reduction ratio $\geq 65\%$ for HD patients or weekly Kt/V $\geq 1.8$ for PD patients	Nonrenal causes of anemia ( <i>e.g.</i> , folic acid or vitamin B <sub>12</sub> deficiency, hemolysis, hemoglobinopathies [ <i>e.g.</i> , homozygous sickle-cell disease, thalassemia of all types])
Baseline Hb concentration between 10.5 and 13.0 g/dl (mean of the weekly Hb values determined in weeks -4 to -1)	Acute infection or chronic, uncontrolled or symptomatic inflammatory disease ( <i>e.g.</i> , rheumatoid arthritis, systemic lupus erythematosus)
Stable baseline Hb concentration (defined as an absolute difference $\leq 1$ g/dl between the mean Hb values determined in weeks -4 and -3 and the mean Hb values determined in weeks -2 and -1)	C-reactive protein $>30$ mg/L
Continuous subcutaneous maintenance epoetin therapy (epoetin $\alpha$ formulated with human albumin or epoetin $\beta$ ) with the same dosing interval for at least 8 wk before screening and during screening/baseline	Poorly controlled hypertension necessitating interruption of epoetin treatment in the 6 mo before screening
Stable subcutaneous maintenance epoetin therapy during screening/baseline (no change of the weekly dosage)	Platelets $>500 \times 10^9/L$
Adequate iron status defined as serum ferritin $\geq 100$ ng/ml or transferrin saturation $\geq 20\%$ (or hypochromic RBCs $<10\%$ ; mean of two values determined in weeks -4 and -3)	Pure red cell aplasia
	Chronic congestive heart failure (New York Heart Association class IV)
	High likelihood of early withdrawal/interruption of the study (myocardial infarction, severe or unstable coronary artery disease, stroke, severe liver disease within the 12 wk before screening or during screening/baseline)
	Life expectancy $<12$ mo

<sup>a</sup>Hb, hemoglobin; HD, hemodialysis; PD, peritoneal dialysis; RBC, red blood cell.

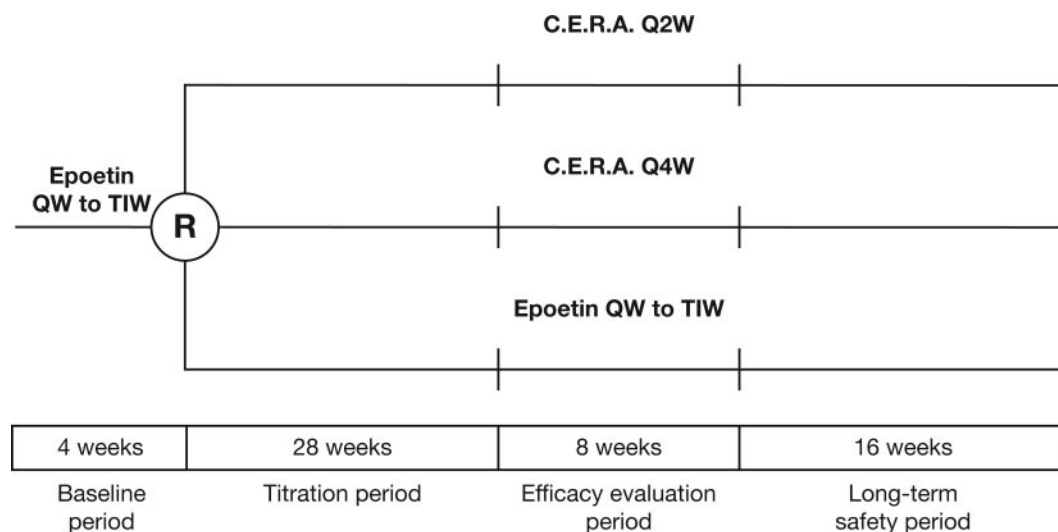


Figure 1. Study design. C.E.R.A. Q2W, twice-monthly continuous erythropoietin receptor activator; C.E.R.A. Q4W, once-monthly continuous erythropoietin receptor activator; epoetin QW to TIW, epoetin one to three times weekly; R, randomization.

Table 2. Starting doses of C.E.R.A.<sup>a</sup>

Previous Epoetin Dosage (IU/wk)	C.E.R.A. Starting Dosage ( $\mu\text{g}/2\text{ wk}$ )	C.E.R.A. Starting Dosage ( $\mu\text{g}/4\text{ wk}$ )
<8000	60	120
8000 to 16,000	100	200
>16,000	180	360

<sup>a</sup>C.E.R.A., continuous erythropoietin receptor activator.

### Assessments

Patients were assessed weekly during the screening/baseline, titration, and evaluation periods and once every 2 wk during the long-term safety observation period. Hb, BP, and heart rate were measured at each visit. Iron and other laboratory parameters were measured at screening/baseline, then every 8 wk from week 5 (iron parameters were assessed every 4 wk during the evaluation period), and at the final visit. Physical examination and electrocardiograms were performed at screening/baseline, at weeks 29 and 37 (electrocardiogram only), and at the final visit. Immunogenicity testing to the study medications was carried out at weeks 1, 13, 29, and 41 and at the final visit using ELISA performed by a central laboratory.

### Statistical Analyses

The primary efficacy analysis compared, separately, the mean change in Hb level between the baseline and evaluation period for patients who received C.E.R.A. once monthly or twice monthly with that for epoetin. For demonstration of noninferiority, the lower limit of the two-sided 97.5% adjusted confidence interval (CI) for the difference between epoetin and C.E.R.A. in mean change in Hb level had to be above  $-0.75\text{ g/dl}$ . The 97.5% CI was calculated with adjustment for covariates that might influence Hb response (baseline Hb and geographic region). A sample size of 465 patients (155 patients per treatment arm) was determined to provide 90% power to show that C.E.R.A. administered at a lower frequency is as effective as epoetin.

The primary end point analysis was conducted in the per-protocol (PP) population because this approach to noninferiority analysis is more stringent than using the intent-to-treat (ITT) population. Patients were excluded from the PP population on the basis of the following criteria: fewer than five Hb measurements during evaluation, missing doses of study medication in weeks 26 to 35, nonstable baseline Hb, inadequate iron status at baseline or evaluation, RBC transfusion at baseline or blood loss within weeks 21 to 33, hemoglobinopathies, or hemolysis. Secondary end points consisted of the number of patients who maintained average Hb concentration within  $\pm 1.0\text{ g/dl}$  of their average baseline Hb concentration during the evaluation period and the incidence of RBC transfusions during the titration and evaluation periods. Confirmatory analysis of the primary end point was performed on the ITT population (all patients who were randomly assigned to treatment). Secondary end points were compared among treatment groups in the ITT population using descriptive methods.

## Results

### Patients

The ITT population comprised 572 patients from 89 centers in 20 countries; 70% from Europe (*e.g.*, France 14.0%, Hungary 13.6%, and Poland 9.3%) and 11.9% from the United States. The study began in March 2004 and was completed in September 2005.

Patient disposition is shown in Figure 2. In total, 499 patients completed the evaluation phase and 461 patients completed the safety follow-up phase of the study. Reasons for premature withdrawal of 111 patients were death ( $n = 41$ ), kidney transplantation ( $n = 39$ ), refusal of treatment ( $n = 13$ ), adverse events (AE;  $n = 2$ ), insufficient therapeutic response ( $n = 2$ ), failure to return ( $n = 1$ ), and other ( $n = 13$ ). One patient in the once-monthly C.E.R.A. group did not receive study medication and was excluded from the safety population ( $n = 571$ ).

A total of 98 patients in the ITT population did not fulfill the criteria for inclusion in the PP population (38, 36, and 24 for the once-monthly C.E.R.A., twice-monthly C.E.R.A., and epoetin

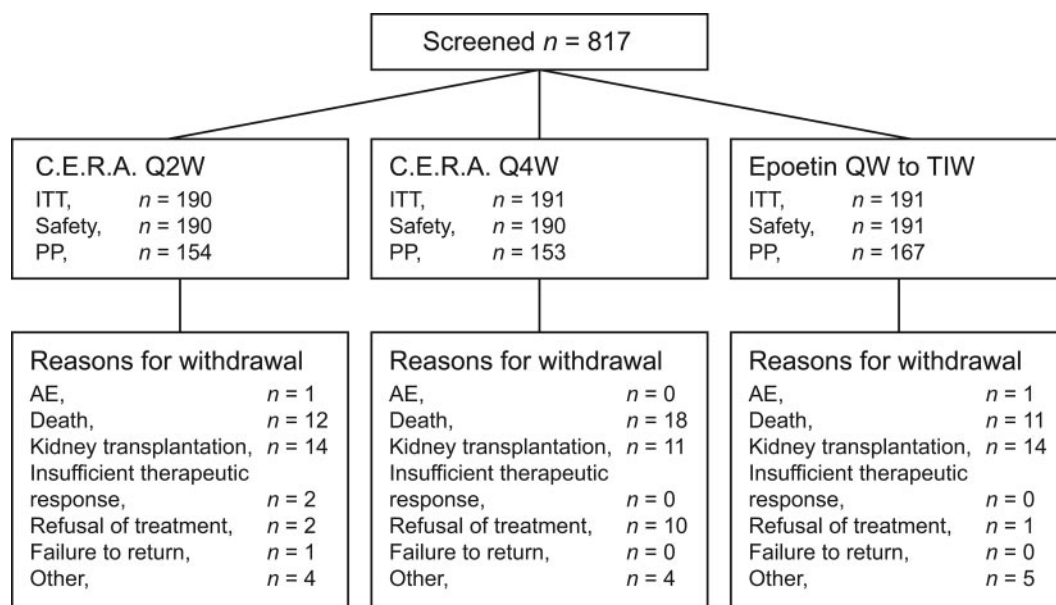


Figure 2. Summary of study populations and patient disposition. AE, adverse event; ITT, intent-to-treat; PP, per-protocol.

groups, respectively). The most common reasons for exclusion were fewer than five Hb values or no valid Hb value during the evaluation period (25, 27, and 16 patients, respectively) and/or inadequate iron status during the evaluation period or no valid value (22, 29, and 15 patients, respectively). Demographic and baseline characteristics were similar between treatment groups for the ITT population (Table 3) and for the PP population and were generally representative of the population from which they were derived.

The primary causes of CKD across all treatment groups were hypertension/large vessel disease (28%), diabetes (25%), and glomerulonephritis (21%). Comorbidities were common in the patients who participated in the study (Table 4). Diabetes and history of ischemic heart disease were each present in approximately one third of patients. A total of 89% of patients in both C.E.R.A. groups and 87% in the epoetin group reported at least one other pre-existing condition in addition to the predefined risk factors.

Before randomization, >50% of patients in each group received epoetin at intervals of two or three times per week; approximately 95% received  $\leq 16,000$  IU/wk epoetin. Mean Hb levels at baseline were similar between treatment groups (Table 3). A similar percentage of patients were receiving supplementary iron at baseline in each treatment group (once-monthly C.E.R.A. 84%; twice-monthly C.E.R.A. 82%; epoetin 81%).

#### Efficacy Evaluation

Mean Hb levels during the baseline, evaluation, and follow-up periods were similar in the three study groups (Table 5,

Figure 3). For the primary efficacy analysis (PP population), after adjustment for covariates, the mean change in Hb from baseline to the evaluation period was  $-0.131$  g/dl for once-monthly C.E.R.A.,  $0.032$  g/dl for twice-monthly C.E.R.A., and  $-0.109$  g/dl for epoetin. The difference in the mean change (97.5% CI) in Hb between the C.E.R.A. groups and the epoetin group was  $-0.022$  g/dl ( $-0.262$  to  $0.217$ ) for once-monthly C.E.R.A. and  $0.141$  g/dl ( $-0.098$  to  $0.380$ ) for twice-monthly C.E.R.A. The lower limit of the 97.5% CI was therefore well above the prespecified margin of  $-0.75$  g/dl in both groups, demonstrating that once-monthly or twice-monthly C.E.R.A. (both  $P < 0.0001$ ; Figure 4) is as effective as epoetin in maintaining anemia control among these patients who randomly converted directly from epoetin (one to three times a week). Similar data were obtained for the ITT population (Figure 4).

For the secondary analyses, the proportions of patients with mean Hb within  $\pm 1.0$  g/dl of baseline values during the evaluation period were 66.1, 75.6, and 72.2% in the once-monthly C.E.R.A., twice-monthly C.E.R.A., and epoetin groups, respectively (ITT population). The proportion of patients who maintained stable Hb within the range 10.0 to 13.5 g/dl during the evaluation period was similarly high in all groups (88.1% for once-monthly C.E.R.A., 91.5% for twice-monthly C.E.R.A., and 88.1% for epoetin), with only a very small proportion with Hb  $> 13.5$  g/dl (1.8% for once-monthly C.E.R.A., 1.2% for twice-monthly C.E.R.A., and 2.8% for epoetin).

In a *post hoc* analysis of inpatient Hb variability, the mean within-patient SD for Hb during the titration period (ITT pop-

Table 3. Baseline characteristics and demographics (ITT population)<sup>a</sup>

Characteristic	Twice-Monthly C.E.R.A. (n = 190)	Once-Monthly C.E.R.A. (n = 191)	Epoetin One to Three Times a Week (n = 191)
Male, n (%)	108 (57)	117 (61)	110 (58)
Mean (SD) age, yr	60.5 (15.4)	62.3 (15.4)	60.4 (14.7)
Mean (SD) weight, kg	70.8 (15.7)	69.0 (14.9)	69.3 (15.7)
Mean (SD) Hb, g/dl	11.70 (0.72)	11.66 (0.71)	11.65 (0.70)
Dialysis type, HD/PD, n	176/14	177/14	171/20
Mean (SD) Kt/V	1.53 (0.27)	1.57 (0.34)	1.54 (0.29)
Median TSAT, % (IQR)	30.45 (23.00 to 39.00)	27.55 (22.50 to 36.50) <sup>b</sup>	30.50 (22.79 to 40.00) <sup>c</sup>
Median ferritin, ng/ml (IQR)	417.75 (240.05 to 659.00)	426.50 (253.25 to 660.50)	435.00 (275.50 to 651.65) <sup>c</sup>
Previous weekly epoetin dose, n (%)			
<8000 IU	126 (66.3)	127 (66.5)	124 (64.9)
8000 to 16,000 IU	55 (28.9)	52 (27.2)	60 (31.4)
>16,000 IU	9 (4.7)	12 (6.3)	7 (3.7)
Previous epoetin schedule, n (%)			
once weekly	81 (42.6)	83 (43.5)	89 (46.6)
twice weekly	55 (28.9)	56 (29.3)	55 (28.8)
three times weekly	54 (28.4)	52 (27.2)	47 (24.6)
Cause of CKD, n (%)			
hypertension/large vessel disease	53 (28)	52 (27)	54 (28)
diabetes	48 (25)	44 (23)	50 (26)
glomerulonephritis	43 (23)	42 (22)	35 (18)
interstitial nephritis/pyelonephritis	23 (12)	29 (15)	30 (16)
undefined	24 (13)	20 (10)	18 (9)
polycystic kidney disease	11 (6)	8 (4)	16 (8)

<sup>a</sup>CKD, chronic kidney disease; IQR, interquartile range; ITT, intent-to-treat; TSAT, transferrin saturation.

<sup>b</sup>n = 189.

<sup>c</sup>n = 190.

Table 4. Summary of pre-existing risk factors for vascular events and hemorrhages at baseline (ITT population)

Risk Factor, n (%)	Twice-Monthly C.E.R.A. (n = 190)	Once-Monthly C.E.R.A. (n = 191)	Epoetin One to Three Times a Week (n = 191)
All body systems	184 (97)	187 (98)	184 (96)
Arterial hypertension	153 (81)	168 (88)	171 (90)
Hyperlipidemia	93 (49)	87 (46)	96 (50)
Ischemic heart disease	59 (31)	68 (36)	67 (35)
Diabetes	62 (33)	52 (27)	63 (33)
Peripheral vascular disease	37 (19)	34 (18)	28 (15)
Venous thrombosis	25 (13)	44 (23)	30 (16)
Congestive heart failure	26 (14)	39 (20)	30 (16)
Cerebral vascular disease	18 (9)	15 (8)	18 (9)
Hemorrhage	17 (9)	18 (9)	12 (6)

Table 5. Summary of average Hb by study period (PP population)<sup>a</sup>

Study Period	n	Mean Hb (SD), g/dl
Baseline (weeks -4 to -1)		
twice-monthly C.E.R.A.	154	11.70 (0.72)
once-monthly C.E.R.A.	153	11.58 (0.72)
epoetin	167	11.64 (0.70)
Evaluation period (weeks 29 to 36)		
twice-monthly C.E.R.A.	154	11.70 (1.04)
once-monthly C.E.R.A.	153	11.46 (0.99)
epoetin	167	11.52 (1.07)
Long-term safety period (weeks 37 to 52)		
twice-monthly C.E.R.A.	152	11.61 (0.98)
once-monthly C.E.R.A.	149	11.51 (0.99)
epoetin	164	11.55 (1.07)

<sup>a</sup>PP, per-protocol.

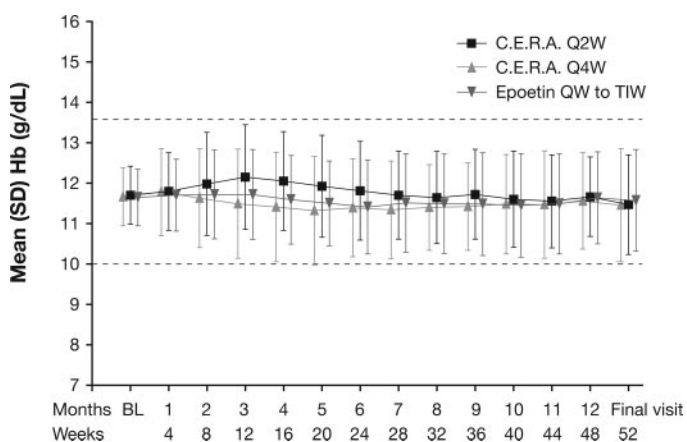


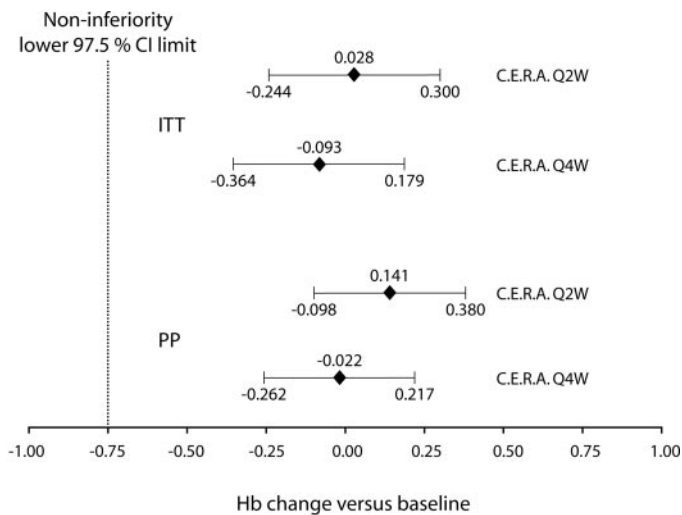
Figure 3. Mean monthly hemoglobin (Hb) values (ITT population).

ulation) in the once-monthly C.E.R.A., twice-monthly C.E.R.A., and epoetin groups was 0.85, 0.84, and 0.78 g/dl, respectively (NS for each C.E.R.A. group *versus* the epoetin group). Within-patient SD for Hb during the evaluation period were also

similar across treatment groups (ITT population): 0.57, 0.52, and 0.57 g/dl for once-monthly C.E.R.A., twice-monthly C.E.R.A., and epoetin, respectively (NS for each C.E.R.A. group *versus* the epoetin group).

The percentage of patients who required RBC transfusion was low in the once-monthly C.E.R.A. and twice-monthly C.E.R.A. groups (10.5 and 6.3%, respectively) and the epoetin group (9.9%; safety population), confirming the safety of direct conversion of patients who were stable on epoetin.

An exploration of dosages of trial medication in the safety population revealed that baseline median dosages were 120  $\mu\text{g}/4$  wk (interquartile range [IQR] 120 to 200) and 60  $\mu\text{g}/2$  wk (IQR 60 to 100) for C.E.R.A. and 6000 IU/wk (IQR 4000 to 10,000) for epoetin. During the evaluation period, the median dosages of C.E.R.A. were 150  $\mu\text{g}/4$  wk (IQR 91 to 250) and 56  $\mu\text{g}/2$  wk (IQR 27 to 84), and these remained the same during the rest of the study. The median dosage of epoetin was 5500 IU/wk (IQR 3000 to 9000) during the evaluation period and 6000 IU/wk (IQR 3000 to 10,000) during the remainder of the study. The median (IQR) number of dosage changes per patient throughout the entire study period was 6 (3 to 9) for twice-



P < 0.0001 for all comparisons

Figure 4. Noninferiority test for difference in mean change in Hb level from baseline for C.E.R.A. versus epoetin. CI, confidence interval.

monthly C.E.R.A., 4 (2 to 7) for once-monthly C.E.R.A., and 5 (3 to 8) for epoetin; these occurred most frequently during the titration and long-term follow-up periods. For the epoetin group, this did not include dosage changes that were the result of differences in the split of doses from 1 wk to another, provided that the total weekly dosage remained the same.

Safety and Tolerability

The incidences of AEs and serious AEs are given in Table 6. In total, 90% of patients across all treatment groups experienced

at least one AE. The most commonly reported AEs were hypertension, procedural hypotension (induced by dialysis), nasopharyngitis, headache, and diarrhea (Table 6). Most events were mild or moderate in intensity and distributed evenly across the three treatment groups.

The incidence of treatment-related AEs was low in all groups (once-monthly C.E.R.A. 6%; twice-monthly C.E.R.A. 4%; epoetin 2%). Four patients experienced serious treatment-related AEs. Three patients in the once-monthly C.E.R.A. group experienced convulsion, arteriovenous fistula thrombosis, and gastrointestinal necrosis and sepsis (fatal outcome), and one patient in the epoetin group received a diagnosis of pure red cell aplasia and was withdrawn from treatment. Anti-erythropoietin or anti-C.E.R.A. antibodies were not detected in any patient in the C.E.R.A. groups. Two patients discontinued prematurely as a result of serious AE not related to study treatment: hypertension in the twice-monthly C.E.R.A. group and hemorrhagic gastritis in the epoetin group. The most common causes of the 43 deaths during the study were cardiac disorders (n = 23), followed by infections and infestations (septic shock n = 3; various forms of sepsis n = 3; bronchopneumonia n = 1). Only one death was considered related to study treatment (once-monthly C.E.R.A.: gastrointestinal necrosis followed by sepsis). There were no clinically relevant changes in vital signs or iron or laboratory parameters during the study. Dialysis adequacy was similar across the three groups and was maintained during the study.

Discussion

PROTOS is the first large-scale study to demonstrate direct random conversion of patients who have CKD and are on dialysis to subcutaneous once- or twice-monthly C.E.R.A. Mean Hb levels during the evaluation period for patients who re-

Table 6. Overall and most frequent AE (≥8% patients in at least one group; safety population)<sup>a</sup>

AE, n (%)	Twice-Monthly C.E.R.A. (n = 190)	Once-Monthly C.E.R.A. (n = 191)	Epoetin One to Three Times a Week (n = 191)
Hypertension	27 (14)	30 (16)	25 (13)
Procedural hypotension <sup>b</sup>	17 (9)	29 (15)	20 (10)
Nasopharyngitis	18 (9)	19 (10)	18 (9)
Headache	15 (8)	20 (11)	19 (10)
Diarrhea	20 (11)	15 (8)	14 (7)
Muscle spasms	16 (8)	14 (7)	17 (9)
Fluid overload	9 (5)	15 (8)	18 (9)
Arteriovenous fistula site hemorrhage	18 (9)	15 (8)	5 (3)
Arteriovenous fistula thrombosis	13 (7)	15 (8)	8 (4)
Angina pectoris	2 (1)	15 (8)	4 (2)
Any AE	171 (90.0)	177 (93.2)	167 (87.4)
Serious AE	70 (36.8)	73 (38.4)	85 (44.5)
AE leading to withdrawal	1 (0.5)	0 (0.0)	2 (1.0)
Deaths <sup>c</sup>	13 (6.8)	18 (9.5)	12 (6.3)

<sup>a</sup>AE, adverse event.

<sup>b</sup>Hypotension during dialysis.

<sup>c</sup>Two deaths occurred within 30 d of the last dose of study drug; therefore, only 41 deaths were recorded as reasons for premature withdrawal.

ceived C.E.R.A. were within current guideline ranges (11.46 and 11.70 g/dl, respectively), and the difference in Hb level between baseline and evaluation was within  $\pm 0.15$  (0.032 and  $-0.131$ ) in both C.E.R.A. groups. Hence, the results of this study show that switching directly from administration of epoetin  $\alpha$  or  $\beta$  one to three times weekly to C.E.R.A. at extended dosing intervals is effective for maintaining tight, sustained, and predictable control of Hb levels within target range in this patient population. Moreover, mean Hb values remained stable during the evaluation and long-term safety periods, demonstrating maintenance of Hb control over time. In addition, C.E.R.A. was generally well tolerated. Most AEs that were reported during the study were consistent with the morbidity that is associated with advanced CKD and not considered related to study medication.

PROTOS thus confirms findings from Phase II studies that the unique pharmacologic properties of C.E.R.A. enable it to provide sustained maintenance of target Hb levels when administered up to once monthly (38–40). Furthermore, data from this study are consistent with the results of a similarly designed Phase III study in which intravenous C.E.R.A. effectively maintained Hb levels in patients who had CKD and were on dialysis and converted directly from epoetin one to three times weekly to once- or twice-monthly C.E.R.A. (41). One previous, single-arm study examined the efficacy of once-monthly ESA administration in patients who had CKD and were on dialysis (29); the administration interval was sequentially extended contingent on patient response. In contrast, our study required patients to convert directly to receive C.E.R.A. only at the administration interval to which they were randomly assigned.

The demographic and baseline characteristics of patients were consistent with the general dialysis population and demonstrated a high prevalence of comorbid diseases. Hence, the study population was largely representative of patients who are on dialysis and treated for renal anemia in clinical practice.

The growing number of patients with CKD and the burden of managing this disease and its complications (15,42,43) highlight the expected benefits of C.E.R.A. We propose that the ability of C.E.R.A. to maintain tight Hb levels with once-monthly administration should improve anemia management in CKD by alleviating the increasing workload of health care professionals. Once-monthly administration will save up to 144 injections per patient per year compared with three times weekly dosing.

## Conclusion

PROTOS is the first randomized, controlled study of direct conversion of patients who have CKD and are on dialysis from a stable regimen of epoetin up to three times weekly to once-monthly subcutaneous C.E.R.A. This study confirms the efficacy and the safety of once-monthly subcutaneous C.E.R.A. for maintaining tight control of Hb levels within recommended ranges in patients who are converted directly from epoetin administered one to three times weekly. The use of subcutaneous C.E.R.A. once monthly to achieve tight, sustained control of Hb may provide an opportunity to improve overall disease

management for all patients with CKD without adding to the work burden of CKD on health care resources.

## Acknowledgments

The PROTOS study was sponsored by F. Hoffmann-La Roche Ltd. (Basel, Switzerland).

Data from this study were previously published in abstract form ([Abstract SP424]. *Nephrol Dial Transplant* 21[Suppl 4]: iv156–iv157, 2006).

PROTOS Study Investigators: H.J. Adrogue, F.W. Albert, A. Albertazzi, J.-C. Aldigier, M. Amato, H.-G. Asmus, A. Bajo Rubio, J. Balla, P. Barany, E. Barranco, G. Barril, P. Bataille, F. Berthou, K. Bidas, T. Boichchio, C. Breen, W. Buranachokpaisan, J. Burkart, P.-L. Caraman, N. Coplon, R. Correa-Rotter, M. Couttenye, B. Csiky, S. Dawood, A. Debure, H. Deodhar, H. Dieperink, S.A. Draibe, R. D'Souza, M. Feriani, J. Fort, L.E. Garrett, Jr., J. Gasco Company, M. Germain, C. Granolleras, K. Harris, I. Henderson, J.C. Kallmeyer, J. Kaufman, H. Keuleers, M. Klinger, P. Koskinen, E. Ladányi, N. Lameire, E. Le Guen, K. Lempert, F. Locatelli, K. Lynn, I.C. Macdougall, I. MacPhee, F. Malberti, P. Marchini, A.P. Maxwell, R. McCrary, F. Metivier, K. Metsarinne, I.P. Naicker, E.D. Neto, P. Nolen, S. Opatrna, J.-P. Ortiz, P. Peeters, J. Penfield, J. Pengloan, R. Perez, W. Phumratanaprapin, G. Pidgeon, L. Piera, J. Portoles, W.Y. Qunibi, M.C. Riella, C. Rikker, B. Rutkowski, J.-P. Ryckelynck, H. Saha, D. Sanchez-Guisande, R. Schmidt, R. Selgas, K.-H. Shu, D. Sobotova, T. Stompor, W. Sulowicz, V. Sumethkul, C. Sun, P. Thanakitcharu, P. Thon, K. Tungsanga, I. Valkovsky, D. Verbeelen, Z. Vezekenyi, L.G. Weiss, P. Williams, K.-D. Wu.

Medical writing support was provided by Margaret Duggan-Keen, Melanie Jones, and Christine Gardner at Prime Medica Ltd. during the preparation of this article, supported by F. Hoffmann-La Roche Ltd.

## Disclosures

Professor Locatelli has received honoraria from and has acted as a scientific advisor for F. Hoffmann-La Roche, Dompé, Shire, and Amgen. Professor Ryckelynck and Dr Harris have received honoraria from and have acted as scientific advisors for F. Hoffmann-La Roche. No financial conflict of interest exists for Professor Sulowicz, Professor Balla, or Dr Csiky. Drs Ehrhard and Beyer are full-time employees of F. Hoffmann-La Roche, as indicated on the title page with the authors' affiliations.

## References

1. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J: Association of kidney function with anemia: The Third National Health and Nutrition Examination Survey (1988–1992). *Arch Intern Med* 162: 1401–1408, 2002
2. Hsu CY: Epidemiology of anemia associated with chronic renal insufficiency. *Curr Opin Nephrol Hypertens* 11: 337–341, 2002
3. McClellan W, Aronoff SL, Bolton WK: The prevalence of anemia in patients with chronic kidney disease. *Curr Med Res Opin* 20: 1501–1510, 2004
4. Evans RW, Rader B, Manninen DL: The quality of life of hemodialysis recipients treated with recombinant human erythropoietin. *JAMA* 263: 825–830, 1990
5. Barany P, Petterson E, Konarski-Svensson JK: Long-term effects on quality of life in haemodialysis patients of correction of anaemia with erythropoietin. *Nephrol Dial Transplant* 8: 426–432, 1993
6. Madore F, Lowrie EG, Brugnara C, Lew NL, Lazarus JM,



- Bridges K, Owen WF: Anemia in hemodialysis patients: Variables affecting this outcome predictor. *J Am Soc Nephrol* 8: 1921-1929, 1997
7. Ma JZ, Ebben J, Xia H, Collins AJ: Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol* 10: 610-619, 1999
  8. Gerson A, Hwang W, Fiorenza J, Barth K, Kaskel F, Weiss L, Zelikovsky N, Fivush B, Furth S: Anemia and health-related quality of life in adolescents with chronic kidney disease. *Am J Kidney Dis* 44: 1017-1023, 2004
  9. Li S, Foley RN, Collins AJ: Anemia, hospitalization, and mortality in patients receiving peritoneal dialysis in the United States. *Kidney Int* 65: 1864-1869, 2004
  10. Perlman RL, Finkelstein FO, Liu L, Roys E, Kiser M, Eisele G, Burrows-Hudson S, Messana JM, Levin N, Rajagopalan S, Port FK, Wolfe RA, Saran R: Quality of life in chronic kidney disease (CKD): A cross-sectional analysis in the renal research institute-CKD study. *Am J Kidney Dis* 45: 658-666, 2005
  11. Barrett BJ, Fenton SS, Ferguson B, Halligan P, Langlois S, Mccready WG, Muirhead N, Weir RV: Clinical practice guidelines for the management of anemia coexistent with chronic renal failure. Canadian Society of Nephrology. *J Am Soc Nephrol* 10[Suppl 13]: S292-S296, 1999
  12. National Kidney Foundation: K/DOQI clinical practice guidelines for anemia of chronic kidney disease, 2000. *Am J Kidney Dis* 27[Suppl 1]: S182-S238, 2001
  13. Locatelli F, Aljama P, Barany P, Canaud B, Carrera F, Eckardt KU, Horl WH, Macdougall IC, Macleod A, Wiecek A, Cameron S, European Best Practice Guidelines Working Group: Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure. *Nephrol Dial Transplant* 19[Suppl 2]: ii1-ii47, 2004
  14. Pollock C, McMahon L: Haemoglobin. *Nephrology* 10[Suppl 4]: S108-S115, 2005
  15. US Renal Data System: *USRDS 2005 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2005
  16. Locatelli F, Pisoni RL, Combe C, Bommer J, Andreucci VE, Piera L, Greenwood R, Feldman HI, Port FK, Held PJ: Anaemia in haemodialysis patients of five European countries: Association with morbidity and mortality in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 19: 121-132, 2004
  17. Pisoni RL, Bragg-Gresham JL, Young EW, Akizawa T, Asano Y, Locatelli F, Bommer J, Cruz JM, Kerr PG, Mendelssohn DC, Held PJ, Port FK: Anemia management and outcomes from 12 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 44: 94-111, 2004
  18. National Kidney Foundation: K/DOQI clinical practice guidelines: 2006 update. *Am J Kidney Dis* 47[Suppl 3]: S11-S145, 2006
  19. Centers for Medicare & Medicaid Services. 2004 Annual Report, End Stage Renal Disease Clinical Performance Measures Project. Department of Health and Human Services, Centers for Medicare & Medicaid Services, Office of Clinical Standards & Quality, Baltimore, December 2004
  20. Locatelli F, Pisoni RL, Akizawa T, Cruz JM, DeOreo PB, Lanmeire NH, Held PJ: Anemia management for hemodialysis patients: Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines and Dialysis Outcomes and Practice Patterns Study (DOPPS) findings. *Am J Kidney Dis* 44[Suppl 2]: 27-33, 2004
  21. Lacson E Jr, Ofsthun N, Lazarus M: Effect of variability in anemia management on hemoglobin outcomes in ESRD. *Am J Kidney Dis* 41: 111-124, 2003
  22. Collins AJ, Brenner RM, Ofman JJ, Chi EM, Stuccio-White N, Krishnan M, Solid C, Ofsthun NJ, Lazarus JM: Epoetin alfa use in patients with ESRD: An analysis of recent US prescribing patterns and hemoglobin outcomes. *Am J Kidney Dis* 46: 481-488, 2005
  23. Fishbane S, Berns JS: Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. *Kidney Int* 68: 1337-1343, 2005
  24. Regidor DL, Kopple JD, Kovesdy CP, Kilpatrick RD, McAllister CJ, Aronovitz J, Greenland S, Kalantar-Zadeh K: Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. *J Am Soc Nephrol* 17: 1181-1191, 2006
  25. Collins AJ, Li S, Gilbertson DT, Liu J, Chen SC, Herzog CA: Chronic kidney disease and cardiovascular disease in the Medicare population. *Kidney Int* 87: S24-S31, 2003
  26. El Nahas AM, Bello AK: Chronic kidney disease: The global challenge. *Lancet* 365: 331-340, 2005
  27. Jadoul M, Vanrenterghem Y, Foret M, Walker R, Gray SJ: Darbepoetin alfa administered once monthly maintains haemoglobin levels in stable dialysis patients. *Nephrol Dial Transplant* 19: 898-903, 2004
  28. Disney A, de Jersey P, Kirkland G, Mantha M, Charlesworth J, Gallagher M, Harris D, Gock H, Mangos S, MacMillan J, Viswalingam A: Aranesp<sup>®</sup> (darbepoetin alfa) administered once monthly (QM) maintains hemoglobin (Hb) levels in chronic kidney disease (CKD) patients [Abstract]. *Nephrol Dial Transplant* 20[Suppl 5]: v254, 2005
  29. Ling B, Walczyk M, Agarwal A, Carrol W, Lui W, Brenner R: Darbepoetin alfa administered once monthly maintains hemoglobin concentrations in patients with chronic kidney disease. *Clin Nephrol* 63: 327-334, 2005
  30. Provenzano R, Bhaduri S, Singh AK; for the PROMPT Study Group: Extended epoetin alfa dosing as maintenance treatment for the anemia of chronic kidney disease: The PROMPT study. *Clin Nephrol* 2: 113-123, 2005
  31. Agarwal AK, Silver MR, Reed JE, Dhingra RK, Liu W, Varma N, Stehman-Breen C: An open-label study of darbepoetin alfa administered once monthly for the maintenance of haemoglobin concentrations in patients with chronic kidney disease not receiving dialysis. *J Intern Med* 260: 577-585, 2006
  32. Macdougall IC: C.E.R.A. (continuous erythropoietin receptor activator): A new erythropoiesis-stimulating agent for the treatment of anemia. *Curr Hematol Rep* 4: 436-440, 2005
  33. Brandt M, Lanzendorfer M, Frische J, Haselbeck A, Jarsch M: Different receptor binding activity of C.E.R.A. (continuous erythropoietin receptor activator) compared with epoetin beta determined by surface plasmon resonance and competition assay on UT-7 cells [Abstract]. *Nephrol Dial Transplant* 21[Suppl 4]: iv9, 2006
  34. Dougherty FC, Reigner B, Jordan P, Pannier A: C.E.R.A. (continuous erythropoiesis receptor activator): Dose-response, pharmacokinetics and tolerability in Phase I multiple ascending dose studies [Abstract]. *Proc Am Soc Clin Oncol* 23: 603, 2004

35. Macdougall IC, Robson R, Opatrna S, Liogier X, Pannier A, Jordan P, Dougherty FC, Regnier B: Pharmacokinetics and pharmacodynamics of intravenous and subcutaneous continuous erythropoietin receptor activator in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 1: 1211-1215, 2006
36. Halstenson CE, Macres M, Katz SA, Schnieders JR, Watanabe M, Sobota JT, Abraham PA: Comparative pharmacokinetics and pharmacodynamics of epoetin alfa and epoetin beta. *Clin Pharmacol Ther* 50: 702-712, 1991
37. Macdougall IC, Gray SJ, Elston O, Breen C, Jenkins B, Browne J, Egrie J: Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients. *J Am Soc Nephrol* 10: 2392-2395, 1999
38. Locatelli F, Villa G, de Francisco ALM, Albertazzi A, Adrogue HJ, Dougherty FC, Beyer U; on behalf of the BA16286 Study Investigators: Effect of a continuous erythropoietin receptor activator (C.E.R.A.) on stable haemoglobin in patients with CKD on dialysis. *Curr Med Res Opin* 23: 969-979, 2007
39. Besarab A, Moro O, Salifu MO, Lunde NM, Bansal V, Fishbane S, Dougherty FC, Beyer U: Efficacy and tolerability of intravenous C.E.R.A. in patients with CKD on dialysis previously treated with epoetin alfa: A randomized, open-label, 19-week, dose-finding study, with a 12-month extension phase. *Clin Ther* 26: 626-639, 2007
40. Provenzano R, Besarab A, Macdougall IC, Ellison DH, Maxwell AP, Sulowicz W, Klinger M, Rutkowski B, Correa-Rotter R, Dougherty FC; on behalf of the BA16528 Study Investigators: The continuous erythropoietin receptor activator (C.E.R.A.) corrects anemia at extended administration intervals in patients with chronic kidney disease not on dialysis: Results of a phase II study. *Clin Nephrol* 67: 306-317, 2007
41. Levin NW, Fishbane S, Zeig S, Nassar G, Moran J, Villa G, Dougherty FC: Intravenous (IV) C.E.R.A. (continuous erythropoietin receptor activator) administered once every 2 weeks or once monthly maintains haemoglobin (Hb) levels in patients with chronic kidney disease (CKD) on dialysis [Abstract]. *Nephrol Dial Transplant* 21[Suppl 4]: iv117, 2006
42. Xue JL, Ma JZ, Louis TA, Collins AJ: Forecast of the number of patients with end-stage renal disease in the United States to the year 2010. *J Am Soc Nephrol* 12: 2753-2758, 2001
43. Roderick P, Davies R, Jones C, Feest T, Smith S, Farrington K: Simulation model of renal replacement therapy: Predicting future demand in England. *Nephrol Dial Transplant* 19: 692-701, 2004