

# Subcutaneous C.E.R.A. for the Treatment of Chronic Renal Anemia in Predialysis Patients

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**Background:** We investigated the efficacy, safety and tolerability of once-monthly administration of C.E.R.A. in erythropoiesis stimulating agents (ESAs) naive predialysis patients with CKD for anemia treatment

**Study Design:** Single arm, open label study.

**Methods:** A total of 75 patients (mean (SD) age was 52.8 (16.4) years, 76.0% were female) were included in this study conducted between 12 August 2008 and 30 October 2009 in 9 centers across Turkey. The mean change in Hb concentration (g/dL) between baseline (week 0) and the efficacy evaluation period (EEP) was the primary efficacy parameter evaluated in three consecutive periods including a dose titration period (DTP; with initial 1.2 µg/kg dose of C.E.R.A., subcutaneously, 28 weeks), EEP (8 weeks) and a long-term safety period (16 weeks).

**Results:** Our analysis revealed an improvement in Hb levels from baseline value of 9.4 (0.4) g/dL to time adjusted average level of 11.4 (0.7) g/dL in EEP in the

per protocol (PP) population and from 9.3 (0.5) g/dL to 11.1 (1.0) g/dL in intent-to-treat (ITT) population. Mean (SD) change in Hb levels from baseline to EEP was 2.0 (0.7) g/dL in the PP population (primary endpoint) and 1.7 (1.1) g/dL in the ITT population. The percentage of patients whose Hb concentrations remained within the target range of 10.0-12.0 g/dL throughout the EEP was 43.9% (95% CI: 28.5-60.3%) in the PP population and 38.7% (95% CI: 27.6% to 50.6%) in the ITT population. A total of 206 adverse events (AE) were reported in 77.0% of patients with hypertension (20%) as the most frequent AE.

**Conclusion:** Once-monthly subcutaneous C.E.R.A. administration is effective and safe in the treatment of anemia in pre-dialysis patients with CKD, who are not currently treated with ESAs.

**Keywords:** C.E.R.A., chronic kidney disease, efficacy, hemoglobin levels, safety, tolerability

The likelihood of overt anemia increases as the glomerular filtration rate (GFR) declines below 60 mL/min in patients with chronic kidney disease (CKD) (1). Exogenous replacement of erythropoietin is now a well-accepted therapy in CKD (2,3) along with growing interest in the use of erythropoiesis

stimulating agents (ESAs) (4). Continuous erythropoietin receptor activator (C.E.R.A.; F. Hoffmann-La Roche AG, Turkey) is an ESA developed by attaching a pegylation chain on to epoetin beta, which markedly prolonged the circulating half-life of the molecule to around 130 hours, allowing ad-

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ministration of the drug at extended intervals in the correction as well as maintenance periods (5,6).

Our study was designed to investigate the efficacy, safety and tolerability of monthly administration of C.E.R.A. in predialysis patients with chronic renal anemia (CRA) who are not currently treated with ESAs for the correction and subsequent maintenance of hemoglobin (Hb) concentrations.

## MATERIALS AND METHODS

Seventy-five patients (mean(SD) age: 52.8(16.4) years, 76.0% females) were included in this single arm, open label study conducted between 12 August 2008 and 30 October 2009 in nine tertiary nephrology centers across Marmara (Edirne, Istanbul), Central Anatolia (Ankara, Konya), South-eastern Anatolia (Diyarbakir) and Aegean (Denizli) Regions of Turkey. Patients aged ≥18 years, diagnosed with CRA, Hb levels of 8.5-10.0 g/dL, adequate iron status (serum ferritin and transferrin saturation >100 ng/mL and >20%, respectively), no prior ESA therapy for three months prior to enrollment, followed as an outpatient (non-hospitalized) and at pre-dialysis stage (GFR <30mL/min) were included. Exclusion criteria are shown in Table 1.

Written informed consent was obtained from each subject and the protocol of the study was conducted in accordance with the ethical principles stated in the “Declaration of Helsinki” and approved by the institutional ethics committee of the coordinator center.

### Study visits and data collection

Eligible patients were enrolled at week 0. Patients then entered a 28-week dose titration period (DTP). The DTP was followed by an 8-week efficacy evaluation period (EEP) and then a 16-week long-term safety period (LTSP).

### Primary efficacy parameter

The primary efficacy parameter was the mean change in Hb concentration (g/dL) between baseline (week 0) and EEP. The mean Hb concentration for each individual patient during the EEP was estimated as a time adjusted average ( $H_i$ : Hb value at time-point;  $t_i$ : study day;  $t_0$ =first day of EEP;  $t_n$ =last day of EEP;  $\Sigma$ : Total) by  $\hat{\mu} = \frac{1}{2(t_n - t_0)} \sum_i (H_i + H_{i-1})(t_i - t_{i-1})$ .

The successive changes in Hb during all study period were defined by:  $\hat{\sigma} = \frac{1}{2(t_n - t_0)} \sum_i (H_i - H_{i-1})^2 (t_i - t_{i-1})$ .

### Secondary efficacy parameters

The percentage of patients whose Hb concentration remained within the target range of 10.0-12.0 g/dL, the mean

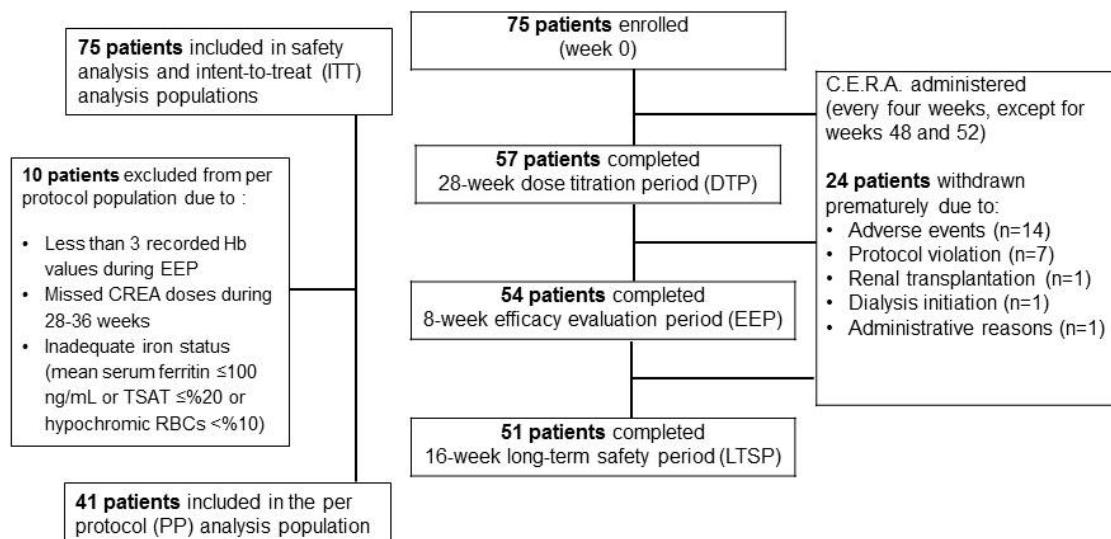
**TABLE 1.** Exclusion criteria of the study

- Transfusion of red blood cells during the two months prior to enrollment
- Poorly controlled hypertension (systolic/diastolic BP of 170/100 mmHg in the sitting position despite antihypertensive medications and requirement for hospitalization in the last 6-months)
- Significant acute or chronic bleeding (e.g. Overt gastrointestinal bleeding)
- Active malignant disease (except non-melanoma skin cancer)
- Hemolysis (based on identification of haptoglobin levels <30 mg/dL (3.54 μmol/L) or results of any reliable hemolysis test)
- Hemoglobinopathies (e.g. Homozygous Sickle cell anemia, all types of thalassemia)
- Folic acid deficiency (not corrected within the last 2-month period and based on local laboratory findings such as erythrocyte MCV 105 fl)
- Vitamin B12 deficiency (not corrected within the last 2-month period and based on local laboratory findings such as erythrocyte MCV 105 fl)
- Thrombocyte count > 500x10<sup>9</sup>/L or <100x10<sup>9</sup>/L
- Pure red blood cell aplasia
- Epileptic seizure during previous six months
- Congestive heart failure (NYHA Class IV)
- Myocardial infarction or stroke, severe or unstable coronary artery disease, severe liver disease at investigator’s discretion, during the previous three months
- Uncontrolled or symptomatic secondary hyperparathyroidism at investigator’s discretion
- Pregnancy or lactation period
- Women of child bearing potential with no effective contraceptive method
- Participation in another clinical trial or receiving any study product or treatment in the previous 3 months
- Known hypersensitivity to recombinant human erythropoietin, polyethylene glycol or to any constituent of the study medication,
- Planned (date) elective surgery during the study period except for cataract surgery or vascular access surgery.

time (days) spent in the target range and the time (days) to achievement of response during EEP were amongst the secondary efficacy parameters. Others included the proportion of patients requiring dose adjustments during dose titration and evaluation periods as well as the documentation of RBC transfusions administered during the study in cases of medical need with respect to indications, specified by type, number of units transfused, total volume transfused and pre-transfusion Hb level.

### C.E.R.A. treatment

C.E.R.A. was administered subcutaneously every four weeks, i.e. weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44



**FIG. 1.** Patient disposition

but not in weeks 48 and 52, after all visit specific assessments were done.

The initial dose was selected as 1.2 µg/kg subcutaneously every four weeks. Initial dosing and all subsequent adjustments were made using the nearest available Pre-filled Syringe (PFS) or combination of PFSs. Dose adjustment was not performed more frequently than once every four weeks while Hb >12 g/dL, <10 g/dL or Hb changes of more than 2 g/dL per month were avoided.

Once the patient achieved Hb concentration within the target range, dose adjustments after achievement of response were made to maintain the individual patients' Hb between 10.0 and 12.0 g/dL.

### Statistical analysis

All screened patients (n=75) received at least one C.E.R.A. dose, and were included in safety analysis and intent-to-treat (ITT) analysis populations, while only 41 patients were included in per protocol (PP) analysis population. Data were expressed as "mean ± standard deviation (SD)", percent (%) and median (min-max) where appropriate.

Statistical analysis was performed using SPSS computer software (version 13.0, SPSS Inc. Chicago, IL, USA).

## RESULTS

### Study population

Fifty-one patients (68%) completed the prescribed course of C.E.R.A. medication. Premature withdrawal (n=24) was

due to adverse events in 14 patients, protocol violation in 7 patients, other reasons including renal transplantation (n=1) and dialysis initiation (n=1) in two patients and administrative reasons in one patient (Fig 1).

Of the 75 patients who completed a baseline visit, 57 completed the titration period. Fifty-four out of 57 patients completed the evaluation period, and 51 completed the LTSP. While 51 patients completed the LTSP, only 41 were included in the PP analysis population, since 10 patients could not be included in the PP population due to presence of less than 3 recorded Hb values during the efficacy evaluation period, missed CREA administration during weeks 28-36 or inadequate iron status (mean serum ferritin ≤100 ng/mL or TSAT ≤20% or hypochromic RBCs <10%) (Figure 1).

Demographic data and baseline characteristics related to hemogram and iron parameters are summarized in Table 2.

### Primary efficacy parameter

In the PP population, the mean (SD) Hb level at baseline was 9.4 (0.4) g/dL. The time adjusted average of Hb during the EEP was 11.4 (0.7) g/dL. The mean (SD) change in Hb concentration between baseline and EEP was 2.0 (0.7) g/dL (Table 3).

Confirming the results in the PP population, in the ITT population, the mean change in Hb concentration between baseline and EEP was 1.7 (1.1) g/dL with Hb at baseline of 9.3 (0.5) g/dL and the time adjusted average of Hb during the EEP of 11.1 (1.0) g/dL (Table 3).

Mean Hb levels in safety population throughout the study are presented in Figure 2.

**TABLE 2.** Patient demographics, baseline etiological and clinical characteristics in the safety population (n=75)

	Mean (SD)
Age (years)	52.8 (16.4)
Gender	n (%)
Female	57 (76.0)
Male	18 (24.0)
Baseline hematologic findings	Mean (SD)
Hb (g/dL)	9.3 (0.5)
Erythrocyte MCV (fL)	88.0 (7.6)
Hct (fraction)	0.28 (0.0)
Ferritin concentration ( $\mu$ g/L)	281.6 (163.1)
Transferrin saturation (%)	37.2 (42.2)
Iron concentration ( $\mu$ mol/L)	14.4 (10.3)
Total iron-binding capacity ( $\mu$ mol/L)	44.1 (12.6)
CRP concentration (mg/L)	8.8 (12.8)
White blood cell count (10 <sup>9</sup> /L)	7.3 (2.1)
Thrombocyte count (10 <sup>9</sup> /L)	252.1 (82.6)
Etiology of CKD*	n (%)
Diabetes mellitus	27 (36.3)
Hypertension/large vessel disease	25 (33.3)
Interstitial nephritis/pyelonephritis	10 (13.3)
Glomerulonephritis	5 (6.7)
Polycystic kidney disease	5 (6.7)
Risk factors*	n (%)
Arterial Hypertension	61 (81.3)
IDDM	15 (20.0)
NIDDM	15 (20.0)
Hyperlipidemia	15 (20.0)
PTCA	7 (9.3)
Myocardial infarction	5 (6.7)

\*observed in  $\geq 5\%$  of the patients.

CKD: chronic kidney disease; Hb: hemoglobin; Hct: hematocrit; CRP-C-reactive protein; IDDM: insulin-dependent diabetes mellitus; NIDDM: non-insulin-dependent diabetes mellitus; MCV: mean corpuscular volume; PTCA: percutaneous transluminal coronary angiography

### Secondary efficacy parameters

The percentage of patients whose Hb concentrations remained within the target range of 10.0-12.0 g/dL throughout the EEP was 43.9 (18 out of 41 patients) with a 95% Clopper-Pearson confidence interval from 28.5% to 60.3%. In the ITT population, the result was 38.7% (29 out of 75 patients) with a 95% Clopper-Pearson confidence interval from 27.6% to 50.6% (Table 3).

The percentage of patients whose time adjusted average Hb remains within the target range of 10.0-12.0 g/dL throughout the EEP was 73.2% (30 out of 41 patients) with a 95% Clopper-Pearson confidence interval from 57.1% to 85.8%. In the ITT population, the result was 54.7% (41 out of 75 patients) with a 95% Clopper-Pearson confidence interval from 42.8% to 66.2% (Table 3).

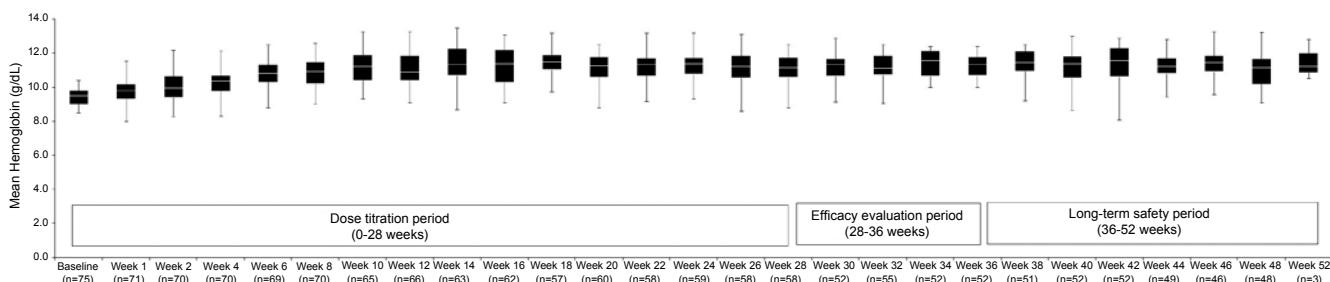
The mean (SD) time spent in the target range of 10.0-12.0 g/dL during the EEP was calculated to be 40.6 (16.3) days in the PP population and 39.8 (18.2) days in the ITT population. During the DTP, the mean time spent in the target ranges in the PP and ITT populations were 131.6 (43.4) and 109.6 (53.2) days, respectively. During the LTSP, the mean time spent in the target range was 61.1 (24.0) days in the PP population and 59.9 (24.4) days in the ITT population (Table 3).

The mean (SD) times for achievement of response in the PP and ITT populations were 24.2 (21.0) and 28.4 (26.0) days, respectively (Table 3).

### Dose adjustments

The initial drug dose was patient weight  $\times 1.2 \mu$ g. During the DTP, dose adjustment was necessary in 35 out of 41 patients (85.4%) in the PP population (Table 2). In the ITT population during the DTP, dose adjustment was necessary in 62 patients (82.7%) (Table 3).

All 41 patients in the PP population entered the EEP. The drug dose needed to be adjusted in 23 patients (56.1%). Fifty-seven patients out of 75 patients included in the ITT population entered the EEP. The drug dose had to be adjusted in 28 patients (49.1%) (Table 3). In the PP population, all 41 patients entered the LTSP. The drug dose needed to be adjusted in 24 patients (59%) (Table 3).

**FIG. 2.** Hemoglobin levels in the safety population (n=75)

**TABLE 3.** Efficacy parameters

	PP population (n=41)	ITT population (n=75)	
Primary efficacy parameters	Mean (SD)	Mean (SD)	
Hb level at baseline (g/dL)	9.4 (0.4)	9.3 (0.52)	
Time adjusted Hb level during EEP (g/dL)	11.4 (0.7)	11.1 (1.0)	
Change in Hb (baseline to EEP) (g/dL)	2.0 (0.7)	1.7 (1.1)	
Secondary efficacy parameters	n (%)	CI (min; max)	n (%)
% with Hb in the target range*	18 (43.9)	28.5; 60.3	29 (38.7)
% with time adjusted Hb in TR*	30 (73.2)	57.1; 85.8	41 (54.7)
Time spent in Hb TR* (days)	Mean (SD)	Mean (SD)	
During DTP	131.6 (43.4)	109.6 (53.5)	
During EEP	40.6 (16.3)	39.8 (18.2)	
During LTSP	61.1 (24.0)	59.9 (24.4)	
Time to response during EEP (days)	24.2 (21.0)	28.4 (26.0)	
Need for dose adjustments	n (%)	n (%)	
During DTP	35 (85.4)	62 (82.7)	
During EEP	23 (56.1)	28 (49.1) (n=57)	
During LTSP	24 (59.0)	29 (54.0) (n=54)	
Change in Hb concentration (g/dL)	Mean (SD)	Mean (SD)	
Between baseline and DTP	1.8 (0.6)	1.6 (0.8)	
Between baseline and LTSP	1.9 (0.8)	1.6 (1.2)	

\* TR: target range = 10.0-12.0 g/dL

CI: Clopper-Pearson confidence interval; Hb: hemoglobin; DTP: dose titration period; EEP: efficacy evaluation period; LTSP: long-term safety period

**TABLE 4.** Extent of exposure to trial medication

Extent of exposure to trial medication	Mean (SD)	
Cumulative dose up to week 44 (μg)	1016 (720.2)	
C.E.R.A monthly dose (μg)	Mean (SD)	Median
During DTP	87.8 (47.0)	79
During EEP	82.8 (76.3)	68
During LTSP	78.0 (75.1)	60

C.E.R.A.: continuous erythropoietin receptor activator; DTP: dose titration period; EEP: efficacy evaluation period; LTSP: long-term safety period

In the ITT population, 54 patients entered the LTSP. The drug dose needed to be adjusted in 29 patients (54%) (Table 3).

#### Hb concentration from baseline to DTP or LTSP

Between baseline and DTP, the mean (SD) changes in Hb concentration in the PP and ITT populations were 1.8 (0.6) g/dL and 1.6 (0.8) g/dL, respectively. Between baseline and LTSP, the mean (SD) change in Hb concentration was 1.9 (0.8) g/dL in the PP population, and 1.6 (1.2) g/dL in the ITT population (Table 3).

#### Safety results- extent of exposure to trial medication

The mean (SD) cumulative total dose up to week 44 was 1016 (720.2) μg, and the median was 802.5 μg. The mean (SD) C.E.R.A. monthly dose was calculated to be 87.8 (47.0) μg during the DTP, 82.8 (76.3) μg during the EEP, and 78.0 (75.1) during the LTSP. The median dose decreased from 79 μg/mo during DTP, to 68 μg/mo during EEP, and to 60 μg/mo during LTSP (Table 4).

#### Safety results-adverse events (AEs)

Seventy-seven percent of the patients reported 206 AEs starting during treatment. The most frequently recorded AEs were hypertension (20%) and hyperkalemia (12%). A total of 37 drug-related AEs occurred in 21 (28.0%) patients. The most frequently recorded related AEs were hypertension (6.7% of all patients), blood pressure increased (5.3%), hyperkalemia (5.3%), hyperphosphatemia (5.3%), nausea (2.7%) and pruritus (2.7%). All other related AEs were occurred with a frequency less than or equal to 1.3% (Table 5).

Thirty serious adverse events were reported in 24 patients. Edema and thrombocytosis were the two serious adverse events considered to be drug-related, while resolved and re-

**TABLE 5.** Overview of adverse events in safety population (n=75)

Safety Analysis Population	n of AEs	n (%) of patients with AEs
AEs (including SAEs)	206	58 (77.3)
SAEs	30	24 (32.0)
AEs leading to death	-	-
Drug related AEs	37	21 (28.0)
AEs leading drug withdrawal	21	17 (22.7)
AEs with a frequency > 5%	n (%)	
Hypertension	15 (20.0)	
Hyperkalemia	9 (12.0)	
Constipation	7 (9.3)	
Nausea	7 (9.3)	
Metabolic acidosis	7 (9.3)	
Urinary tract infection	6 (8.0)	
Hyperparathyroidism secondary	5 (6.7)	
Pruritus	5 (6.7)	
Blood pressure increased	4 (5.3)	
Hyperlipidemia	4 (5.3)	
Hyperphosphatemia	4 (5.3)	
Back pain	4 (5.3)	
AEs leading drug withdrawal		
Thrombocytosis	1 (1.3)	
Diabetic retinopathy	1 (1.3)	
Nausea	1 (1.3)	
Chest pain	1 (1.3)	
Pyelonephritis acute	1 (1.3)	
Blood creatine increased	2 (2.7)	
Blood creatinine increased	1 (1.3)	
Creatinine renal clearance decreased	1 (1.3)	
Diabetic foot	1 (1.3)	
Hypervolemia	1 (1.3)	
Metabolic acidosis	6 (8.0)	
Renal failure	1 (1.3)	
Renal failure acute	1 (1.3)	
Dyspnea exertional	1 (1.3)	
Hemodialysis	1 (1.3)	

AE: adverse event; SAE: serious adverse event

covered with sequelae, respectively. Twenty-four serious adverse events started during the DTP, four SAEs occurred during the EEP, and two SAEs started during the LTSP.

Seventeen patients withdrew from the study due to adverse events. A summary of all adverse events leading to treatment

withdrawal is provided in Table 5. Twenty-one adverse events in 19 patients led to dose modifications (all screened patients). The most common adverse event leading to dose adjustment was hypertension (11 events).

#### Safety results- hematology, blood biochemistry, iron parameters and other laboratory findings

Compared to baseline Hb values increased by 2 g/dL (mean (SD) from 9.3 (0.5) at baseline to 11.0 (0.8) g/dL at week 48) (Figure 2). For other hematologic laboratory parameters no obvious tendencies in the differences from baseline could be observed during the study. Similarly, no significant changes occurred in blood chemistry and iron parameters during the study (Table 6).

#### DISCUSSION

Use of C.E.R.A. at extended intervals has been inherently suitable given its long half-life, slow systemic clearance and low affinity for erythropoietin receptors (4,7). Data from clinical studies (8-13) suggest safe and effective use of C.E.R.A. every 2-4 weeks and once-monthly for correction and maintenance therapy, respectively, in anemic predialysis (8,10,12-17) or dialysis (9,11,18-20) CKD patients.

Data from the ARCTOS (Administration of C.E.R.A. in CKD Patients to Treat Anemia with a Twice-Monthly Schedule) study revealed that once every 2 weeks subcutaneous C.E.R.A. was associated with improved Hb levels and thus amelioration of anemia in ESA-naïve non-dialysis CKD patients, while once-monthly administration maintained stable Hb levels during the 24-week extension period (12). The CORDATUS study (Correction of Renal Anemia in CKD Patients with Subcutaneous Therapy) also showed efficacy of C.E.R.A. in anemia correction in non-dialysis CKD patients along with a safety profile comparable to darbepoetin alpha (10). Efficacy and safety of C.E.R.A. was also reported in predialysis patients with significant increases in Hb levels within 6-12 months of therapy (13,17). Once every 2 week subcutaneous C.E.R.A. in ESA-naïve predialysis CKD patients was reported to be associated with a 2.15 g/dL increase in Hb concentrations within the 28-week follow up along with similar efficacy of the drug within a further 24-week extension period either under every 2 or 4 week regimen (15). Switching of treatment from once weekly darbepoetin alpha to monthly C.E.R.A. was reported to be associated with an increase in the rate for success in correction of anemia in a year from 75.7% to 80% in anemic predialysis patients (16).

Notably, albeit pre-dialysis patients in our cohort were younger (53 years vs. 66-70 years) and composed predomi-

**TABLE 6.** Blood biochemistry and iron parameters in the safety population

	Baseline		Week 48		p
	N	Mean (SD)	N	Mean (SD)	
Albumin (g/L)	75	37.7 (5.7)	46	37.8 (4.1)	0.9177
C reactive protein (mg/L)	70	8.8 (12.8)	40	7.8 (8.7)	0.6615
Creatinine ( $\mu\text{mol}/\text{L}$ )	75	289.6 (104.1)	47	323.8 (133.4)*	0.1163
Phosphate (mmol/L)	71	1.4 (0.3)	45	1.5 (0.3)	0.0829
Potassium (mmol/L)	75	4.9 (0.6)	47	4.9 (0.7)	1.0000
Ferritin ( $\mu\text{g}/\text{L}$ )	73	281.6 (163.2)	43	238.9 (136.6)	0.1518
Iron ( $\mu\text{mol}/\text{L}$ )	75	14.4 (10.3)	46	14.8 (5.7)	0.8096
TIBC ( $\mu\text{mol}/\text{L}$ )	75	44.1 (12.6)	46	44.7 (12.8)	0.8009
TSAT (%)	75	37.2 (42.2)	46	35.4 (17.7)	0.7842

\*last measurement was at week 36 according to the protocol

TIBC: total iron-binding capacity; TSAT: transferrin saturation, SD: standard deviation

nantly of females compared with past studies in pre-dialysis patients (15-17), our findings revealed the similar efficacy of once-monthly subcutaneous C.E.R.A. in the correction and maintenance of Hb levels in pre-dialysis ESA-naïve patients. This seems to indicate the efficacy of C.E.R.A among predialysis anemic patients to be independent of patient demographics including age and gender.

Data from two observational studies indicate the efficacy of C.E.R.A. in treatment of CRA among predialysis CKD patients in real life clinical practice with an increase in Hb levels from  $10.7 \pm 1.4$  g/dL to  $11.5 \pm 1.2$  g/dL (21) and an overall increase of 1 g/dL (22) in ESA-naïve patients during 12-month and 9 months of follow up, respectively.

In fact, 6-month C.E.R.A. treatment was reported to achieve a more marked increase in hemoglobin levels in kidney transplant recipients compared with short-acting ESA (14). Therefore, C.E.R.A treatment seems to be effective in all cases of CRA, regardless of the stage of the disease (17,21,22) or modality selected for renal replacement therapy (9,11,14,18-20).

In our study population, Hb levels improved from the baseline level of 9.4 (0.4) g/dL to the time-adjusted average level of 11.4 (0.7) g/dL in the PP population, while from 9.3 (0.5) g/dL to 11.1 (1.0) g/dL in the ITT population, with a similar change from baseline to EEP of 2.0 (0.7) g/dL and 1.7 (1.1) g/dL, respectively.

Hemoglobin target has been recommended as 11-12 g/dL by 2012 National Kidney Foundation Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines (23), while it is 10-12 g/dL according to the European Medicine Agency (EMA) (24). Notably, time-adjusted average Hb was maintained within the target range of 10.0-12.0 g/dL in 73.2% of our patients in the PP population (95% CI 57.1-85.8%), while only 54.7% of patients (95% CI 42.8-66.2%) in the ITT population. This lower

result in the ITT population can be explained by the possibility of missing a study drug administration for patients in the ITT population, whereas patients in the PP population were not permitted to miss a study drug administration. This seems notable given the suggested potential of achieving stable Hb concentrations in terms of increased health benefits to patients as well as reduction in the frequency of healthcare interventions (4).

Monthly C.E.R.A therapy was also shown to achieve Hb levels of 10-12 g/dL in the evaluation period in 50% of predialysis patients with CRA (17). Given the lower likelihood of increasing Hb levels beyond the recommended targets ( $>13$  g/dL) in pre-dialysis patients within the first 8-weeks of C.E.R.A (12.4%) than darbepoetin alpha (33.5%) treatment (15), C.E.R.A treatment of anemia seems to retain the range of targeted Hb levels by offering a more gradual increase in Hb levels (20) as well as more stabilized Hb levels (15,17).

Given the percent of patients who needed dose changes during EEP (56.1% in PP and 49.1% in ITT population) and LTSP (59.0% in PP and 54.0% in ITT population) in the present study, our findings seem consistent with data on the maintenance of stable target Hb levels (11-12 g/dL) under C.E.R.A. within a 12-month extension period with no need for dose adjustments in nearly 30% of patients (4).

In this regard, our findings related to requirement of dose adjustment during the DTP in 85.4% and 82.7% of patients in the PP and ITT populations, respectively with the need for an increase as well as a decrease in dose during the titration period in 46.3% and 49.3% of patients, respectively, emphasize the role of careful titration of the drug dose for adequate treatment.

Increased risk for hypertension, thrombosis and cardiovascular events has been considered amongst the potential non-erythropoietic effects of C.E.R.A therapy in CKD patients (25-27). In this regard, the lack of abnormalities in other laboratory parameters investigated in our patients during the course of C.E.R.A. therapy seems to indicate the target Hb concentration used in our study population to be appropriate in terms of risk/benefit assessment (28).

In a past meta-analysis in anemic CKD patients treated with recombinant human erythropoietin, a higher Hb target of 12-16 g/dL was reported to be associated with increased risk of all-cause mortality, arterio-venous access thrombosis and poorly controlled hypertension (28). Hence, it is worth noting that hypertension was the most frequently encountered adverse event in our population.

In general, C.E.R.A. was documented to be well tolerated, with no association of the pattern of AEs with the dosage or schedule of regimen (4). In a recent meta-analysis of phase II-III data on C.E.R.A treatment, C.E.R.A was determined to

be associated with significantly lower rates of AEs and SAEs as compared with other ESAs (29). Likewise, our study confirmed the good safety and tolerability profile of C.E.R.A with the mean cumulative total dose up to week 44 of 1016 (720.2) µg and there were 206 adverse events in 58 (77.3%) patients overall. Thirty SAEs were recorded in 24 (32.0%) patients, two of which were identified to be drug-related. Notably, metabolism and nutrition disorders (10.7%), metabolic acidosis in particular (8.0%), were the adverse events most commonly associated with treatment withdrawal. The occurrence of gradual rather than abrupt increase in Hb levels and stabilization in the follow up seems to have a role in the good safety profile offered by C.E.R.A.

Management of anemia has been considered challenging, involving the frequent administration of conventional ESAs along with the need for Hb monitoring and dose adjustments (4,26,27). Given the complexity of clinical management of dialysis patients, the introduction of extended administration intervals and less frequent dose changes has been considered to offer a simplified and less time-consuming care and thus to allow the fair distribution of healthcare resources along with a reduction in healthcare costs (4,30).

Certain limitations to this study should be considered. Firstly, the lack of a placebo or comparison group consistent with a single-arm open-label design of the study seems to be the major limitation. The inclusion of patients followed by nine different centers located in diverse geographical regions of our country and high statistical power (100%) in the post-hoc power analysis increase the ability of our study results to reflect the pre-dialysis patients countrywide, whereas high premature discontinuation rates and predominance of female patients in our cohort limits the extension of the knowledge achieved in the current study other and racial differences should also be considered while interpreting our results for other populations. Secondly, one must remain prudent when interpreting our findings on the safety and tolerability profile, given the inclusion of a very homogeneous patient population with GFR<30 mL/min and the relatively small sample size. Nevertheless, limiting the likelihood of the introduction of selection bias for more responsive or unresponsive patients, patients with CRA were treatment-naïve in terms of RRT and ESA treatment prior to C.E.R.A. and our findings provide data on the effect of C.E.R.A. in a very homogeneous population (only patients with GFR <30 mL/min) of patients with predialytic CKD, and thus represent a valuable contribution to the available literature.

In conclusion, our findings demonstrate that the use of once-monthly subcutaneous C.E.R.A. is effective in the correction and maintenance of Hb levels in pre-dialysis CRA patients.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of İstanbul University İstanbul School of Medicine.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

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