

Effective Achievement of Hemoglobin Stability with Once-Monthly C.E.R.A. in Peritoneal Dialysis Patients: A Prospective Study

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Abstract

Background Correction of low hemoglobin (Hb) levels is associated with improved survival and greater quality of life in dialysis patients, but frequent administration of erythropoiesis stimulating agent (ESA) therapy is unsatisfactory for peritoneal dialysis patients.

Objective The objective of this study was to assess Hb stability in an unselected population of maintenance peritoneal dialysis patients receiving once-monthly treatment with C.E.R.A., a continuous erythropoietin receptor activator.

Methods In a prospective, non-interventional, single-arm study at 33 Germany dialysis centers, peritoneal dialysis patients with or without ESA treatment prior to study entry received once-monthly treatment with C.E.R.A. Hb stability was assessed by the proportion of patients for whom all measured Hb values during months 6–8 (the evaluation phase) were within the range 11–12, 11–13, 10–12 or 11–12.5 g/dL.

Results 220 patients received at least one dose of C.E.R.A. During the evaluation phase, 185 patients provided ≥ 1 Hb measurement (efficacy population) and 162 patients provided ≥ 2 Hb measurements (the modified efficacy

population). The mean (SD) time between C.E.R.A. doses was 28.2 (7.2) days and mean (SD) C.E.R.A. dose was 109 (57) μg per application. Mean (SD) Hb level was 11.1 (1.4) g/dL at baseline and 11.5 (1.3) g/dL at the end of the study (modified efficacy population). The primary efficacy variable, all measured Hb values in the range 11–12 g/dL, was 18.4 % (34/185) and 14.8 % (24/162) in the efficacy and modified efficacy populations, respectively. The mean (SD) maximum intra-individual fluctuation in Hb level was 0.56 (0.50) g/dL in the efficacy population and 0.58 (0.49) g/dL in the modified efficacy population, with maximum intra-individual fluctuation ≤ 1 g/dL in 85.4 % (158/185) and 83.3 % (135/162) of patients, respectively. No adverse drug reactions were reported during the study.

Conclusion In this large population of maintenance peritoneal dialysis patients, once-monthly administration of C.E.R.A. achieved a high degree of Hb stability and was well-tolerated.

1 Introduction

Anemia is a well-recognized complication of end-stage renal disease, arising from inadequate production of erythropoietin by the failing kidney in response to declining hemoglobin (Hb) concentration. By the time dialysis is required, approximately three-quarters of patients are anemic [1]. In addition to the classic symptom of fatigue [2], the presence of anemia in patients with peritoneal dialysis contributes to increased cardiovascular risk [3], increased insulin resistance [4] and risk of mortality [5]. An analysis of data from almost 14,000 peritoneally dialyzed patients demonstrated that Hb levels below 11.0 g/dL, and particularly levels less than 10 g/dL, were associated with a higher risk of both hospitalization and mortality [5].

On behalf of the BEAM study group. The members of the BEAM study group are listed in [Appendix](#).

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Observational evidence that correction of low Hb levels is associated with improved survival in dialysis patients [6], as well as greater quality of life [7], has led to recommendations that a Hb level of 11–12 g/dL should be targeted in dialysis patients receiving erythropoiesis stimulating agent (ESA) therapy, with the aim of not exceeding 13 g/dL [8]. More recently, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines have proposed that ESA maintenance therapy not be used to maintain Hb levels above 11.5 g/dL in adult patients with CKD, and recommend that ESAs not be used to intentionally increase Hb above 13.0 g/dL [9].

Since the introduction of recombinant human erythropoietin preparations in 1989, the previously widespread problem of severe anemia in end-stage renal disease had been largely overcome. However, such therapies have a relatively short half-life, requiring administration as often as twice or three times a week. For the peritoneal dialysis patient this necessitates regular clinical visits or frequent self-injection at home, which is both unsatisfactory and can affect compliance. Darbepoetin alfa, which has a somewhat longer half-life than epoetin alfa or beta (~ 25 h [10] compared to ≤ 9 h [11]) and is routinely used once a week, has been assessed for once-monthly dosing in peritoneal dialysis patients in small non-comparative series, but was not always adequate to maintain Hb levels [12–14].

The pharmacokinetic characteristics of the continuous erythropoietin receptor activator C.E.R.A., including a long half-life (~ 130 h), a relatively low binding affinity for the erythropoiesis receptor and low systemic clearance [15], permit once-monthly dosing. The efficacy of once-monthly C.E.R.A. in hemodialysis patients is similar to shorter-acting ESA agents in terms of maintaining Hb levels [16–18]. Clinical experience in hemodialysis patients suggests that conversion from more frequently administered ESA therapies to once-monthly C.E.R.A. is convenient and maintains good control of Hb levels [19, 20]. Results from the hemodialysis setting, however, are not necessarily applicable to peritoneal dialysis patients. Anemia control with ESA therapy appears to be more readily achieved in peritoneal dialysis patients than in patients receiving hemodialysis [21–25]. A large analysis of US Medicare data from 1995–2000 showed that although ESA therapy was much less frequent in peritoneal dialysis patients (25 versus 80 % of hemodialysis patients), with 50 % lower doses, Hb levels were similar between the two groups [23]. Similarly, a multicenter comparative study in France observed that mean Hb levels were similar in the peritoneal dialysis or hemodialysis subpopulations but that this was achieved in the peritoneally dialyzed patients with a significantly lower dose of ESA at a lower frequency of administration, and with a reduced rate of intravenous iron therapy [24]. In routine practice, both ESA dose [24–26] and use of intravenous iron

[24, 27] is often lower in peritoneal dialysis patients compared to the hemodialysis population. Several factors may be involved in the difference in anemia control between dialysis modalities. Better depuration of erythropoiesis inhibitors during peritoneal dialysis, superior preservation of residual renal function, absence of blood loss from hemodialysis sessions, and greater adequacy of dialysis in terms of frequency and duration may all play a role [28, 29] although their relative contributions are difficult to determine.

The present study was a prospective, multicenter, observational trial undertaken to assess Hb stability in an unselected population of maintenance peritoneal dialysis patients receiving C.E.R.A. therapy once a month.

2 Methods

2.1 Study Design and Conduct

This was a prospective, non-interventional, single-arm study conducted at 33 nephrology centers in Germany during the period April 2009 to March 2011. Following enrolment, all patients received C.E.R.A. therapy once a month. The dose of C.E.R.A. was titrated during the first six months post-baseline (the titration phase), with an evaluation phase during the following three months (months 6–8).

The study was undertaken in accordance with German Medicines Act, as a non-interventional study. The observational plan and the informed consent form were approved by the local ethics committee for the lead investigator (MK) (Ärztchamber Nordrhein, Düsseldorf). All study participants provided written informed consent. Roche Pharma AG (Germany) funded the study, including data analysis by a contract research association, and reviewed the manuscript. All data collection was undertaken by the study investigators.

2.2 Patient Population

Patients were eligible for inclusion if they were receiving peritoneal dialysis and, in the opinion of the investigator, required ESA therapy. Patients were required to have a life expectancy of more than 9 months and to have iron indices within the limits defined by the European Best Practice Guidelines (serum ferritin ≥ 100 ng/mL and transferrin saturation (TSAT) ≥ 20 %) [30]. Exclusion criteria comprised active malignancy, acute infection, acute bleeding, decrease in Hb level within the 4 weeks prior to inclusion (as defined by the investigator), and pregnancy. Patients could be receiving ESA therapy at the time of study entry. Patients were to be withdrawn from the study if an ESA agent other than C.E.R.A. was initiated or if hemodialysis was started.

2.3 Medication

Prior to study entry, any ESA therapy was administered by the physician according to local practice and the summary of product characteristics of the selected ESA. All patients received C.E.R.A. therapy from study entry, prescribed according to local practice. Dose changes were made at the discretion of the investigator.

2.4 Data Collection

Study visits took place at study entry and then monthly up to nine months after the baseline visit. Assessments took place at routine clinical visits. If a patient discontinued C.E.R.A. prematurely or started hemodialysis, a final assessment was carried out but no further data were documented.

At study entry, the following data were collected: demographics, concomitant disease, cause of end-stage renal disease, duration of peritoneal dialysis, type of previous ESA therapy during the preceding 16 weeks if relevant, use of C.E.R.A. during the preceding 16 weeks, reason for switch to C.E.R.A., current Hb level prior to C.E.R.A. dose at study entry and laboratory values [iron status, hematology, liver function, estimated glomerular filtration rate (eGFR) calculated by the Modification in Renal Disease (MDRD) formula [31], C-reactive protein, vitamin B12, renal and peritoneal Kt/V (where K is dialyzer clearance of urea, t is dialysis time and V is the volume of distribution of urea), parathyroid hormone and albumin]. At all post-baseline study visits, the following data were recorded: Hb level prior to C.E.R.A. administration, laboratory values and changes in concomitant disease/medication. Adverse drug reactions were to be documented, including duration, severity, whether the event was regarded as serious, and causal relationship with C.E.R.A.

Data were recorded by study investigators on printed forms or electronically. Printed data entries were sent directly to an independent clinical research organization (M.A.R.C.O GmbH & Co KG, 40227 Düsseldorf, Germany), where data were entered to the study database. Electronic data capture contained the same information as the printed forms. The clinical research organization was responsible for clarifying discrepancies on the submitted forms and obtaining additional information from physicians as necessary.

2.5 Statistical Analysis

All data are presented descriptively with no formal statistical analyses, as planned in the study protocol. Stability of Hb was assessed by the proportion of patients for whom all measured Hb values during months 6–8 (the evaluation phase) were within the range 11–12, 11–13, 10–12 or

11–12.5 g/dL. The maximum intra-individual fluctuation in Hb values was defined as the maximum absolute difference from the individual mean Hb value during the evaluation phase.

The safety population comprised all patients who received at least one dose of C.E.R.A. The efficacy population comprised all patients in the safety population who provided at least one post-baseline measurement of Hb concentration. The modified efficacy population consisted of all patients in the efficacy population for whom at least two Hb measurements were available during the evaluation period. A pre-defined subanalysis was performed based on patients in the efficacy population who did not receive C.E.R.A. prior to the study. For patients in whom C.E.R.A. therapy was stopped before the end of the observation period, data were analyzed to the point of discontinuation.

All analyses were descriptive. Statistical analyses were performed using SAS[®] Version 9.1.3 (SAS Institute, Cary, NC, USA)

3 Results

3.1 Patient Population

A total of 223 patients were enrolled; 220 (98.7 %) received at least one dose of C.E.R.A. and formed the safety population. Of these, 219 patients (99.5 %) provided at least one post-baseline Hb measurement and were included in the efficacy population: 185 of these patients provided at least one Hb measurement during the evaluation phase. The modified efficacy population comprised 162/219 patients (74.0 %) (Fig. 1). The nine-month study was completed by 167/220 patients (75.9 %), with the most frequent reason for discontinuation being switch to hemodialysis (Fig. 1).

The mean age of the population was approximately 57 years and slightly more than half the patients (113/220, 51.4 %) were male (Table 1). Concomitant cardiac disorders and diabetes mellitus type 2 were present in 40.9 and 18.1 % of patients, respectively. At time of study entry, the mean duration of peritoneal dialysis was 3.0 years (range 1–15 years). Most patients (135/220, 61.4 %) were receiving continuous ambulatory peritoneal dialysis (CAPD).

Mean (SD) Hb at baseline was 11.1 (1.3) g/dL, with a median value of 11.1 (range 5.4–15.7 g/dL) in the safety population. Sixty patients (27.3 %) were receiving oral iron supplementation and 40 patients (18.2 %) were receiving intravenous iron; a further four patients (0.2 %) were receiving unspecified iron preparations. The last post-baseline values for median serum ferritin and TSAT were 114 ng/mL ($n = 160$) and 26.9 % ($n = 146$), respectively.

Fig. 1 Patient disposition.
C.E.R.A. continuous erythropoietin receptor activator, *Hb* hemoglobin, *ESA* erythropoiesis stimulating agent

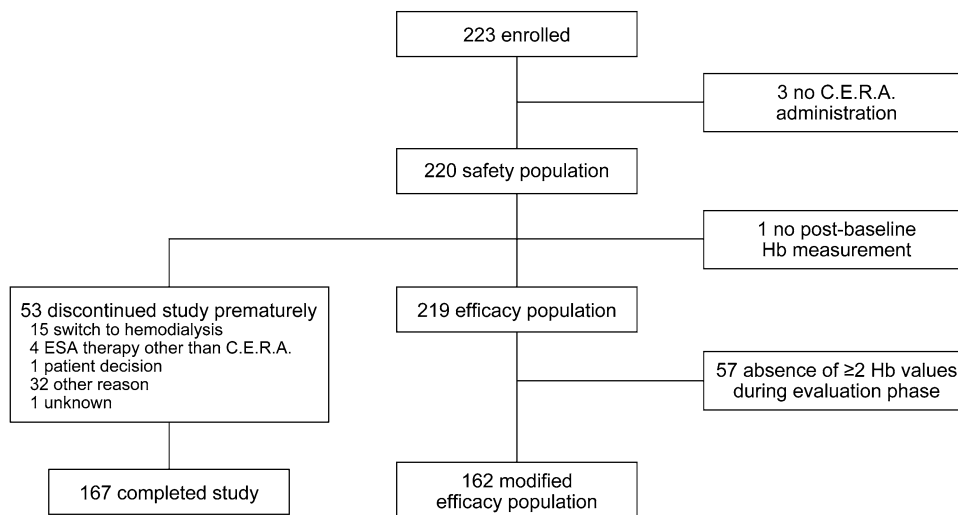


Table 1 Patient characteristics at study entry (safety population, $n = 220$)

Age (years)	
Mean (SD)	56.9 (15.1)
Median (range)	61 (19–93)
Male [n (%)]	113 (51.4)
Body mass index (kg/m ²)	
Mean (SD)	26.0 (4.6)
Median (range)	25.5 (13.7–48.5)
Caucasian [n (%)]	215 (96.4)
Concomitant conditions [n (%)]	
Cardiac disorders	90 (40.9)
Diabetes mellitus (type 2)	40 (18.2)
Duration of peritoneal dialysis (years)	
Mean (SD)	3.0 (2.1)
Median (range)	2.0 (1–15)
Type of peritoneal dialysis [n (%)]	
Continuous ambulatory	135 (61.4)
Ambulatory	65 (29.5)
Intermittent	19 (8.6)
eGFR (mL/min/1.73 m ²)	
Mean (SD)	9.9 (12.5)
Median (range)	7.0 (1.2–76.5)
C-reactive protein (mg/L)	
Mean (SD)	7.2 (9.0)
Median (range)	5.2 (0.5–40.0)
Hb (g/dL)	
Mean (SD)	11.1 (1.3)
Median (range)	11.1 (5.4–15.7)

eGFR estimated glomerular filtration rate, *Hb* hemoglobin, *SD* standard deviation

In the 16 weeks prior to study entry, 75.9 % of patients in the safety population (167/220) had received ESA therapy. Of the 106 patients who received

previous non-C.E.R.A. ESA therapy, this comprised darbepoetin alfa [$n = 72$ (32.7 %)], epoetin beta [$n = 24$ (10.9 %)], epoetin zeta [$n = 15$ (6.8 %)] and epoetin alfa [$n = 11$ (5.0 %)] (more than one ESA therapy was possible). In total, 61 patients in the safety population received C.E.R.A. prior to study entry. In the modified efficacy population, 47 patients had previously received C.E.R.A.

3.2 C.E.R.A Administration

The mean (SD) dose of C.E.R.A. per application was 109 (57) μg throughout the study, equivalent to 3.5 (2.1) $\mu\text{g}/\text{day}$ [total cumulative dose 1,040 (625) μg]. The most frequent initial doses were 50 μg (38/220, 17.3 %), 75 μg (48/220, 21.8 %) and 100 μg (43/220, 19.5 %). The mean dose of C.E.R.A. per application remained stable from baseline [110 (63) μg] to month 9 [103 (61) μg]. During the nine-month study period, 138 patients (62.7 %) required one or more C.E.R.A. dose change, while the remaining 82 patients (37.3 %) remained on their initial dose. The proportions of patients receiving a dose increase (106/220, 48.2 %) or a dose decrease (111/220, 50.5 %) were similar, with a mean of 0.9 dose increases and 0.8 dose decreases per patient during the study. In total, the mean (SD) number of dose changes per patient during the study was 1.7 (1.8).

Of the 2,097 C.E.R.A. doses administered during the study, 1,972 (94.0 %) were given subcutaneously and 92 (4.4 %) intravenously (route was unknown for 33 doses). Doses were administered in the clinic (85/220 patients, 38.6 %), at home (78/220, 35.5 %) or both (57/220, 25.9 %).

The mean (SD) time between C.E.R.A. doses was 28.2 (7.2) days.

3.3 Efficacy

Mean (SD) Hb level was 11.1 (1.4) g/dL at baseline and 11.5 (1.3) g/dL at the end of the study (modified efficacy population) (Fig. 2). A small initial rise after study entry was attributed to the 53 patients who were not previously receiving ESA therapy prior to study, in whom mean (SD) Hb increased from 11.0 (1.4) g/dL at baseline to 11.5 (1.4) g/dL one month after initiation of C.E.R.A. therapy and 11.3 (1.5) g/dL at month 9. For the 106 patients who were receiving non-C.E.R.A. ESA treatment prior to the study, mean (SD) Hb level was 11.3 (1.3) g/dL at baseline, 11.5 (1.2) g/dL after one month and 11.7 (1.0) g/dL at month 9.

Figure 3 illustrates the proportion of patients with all available Hb values within pre-specified ranges during the evaluation phase. The proportion of patients in the range 11–12 g/dL during the evaluation phase, i.e. the primary efficacy variable, was 18.4 % (34/185) of patients in the efficacy population for whom Hb measurements were provided, and 14.8 % (24/162) in the modified efficacy population. During the evaluation phase, approximately 40 % of patients in the efficacy and the modified efficacy populations had all measured Hb levels within the 10–12 or 11–13 g/dL ranges (Fig. 3). Among the 115 patients in the modified efficacy population who did not receive C.E.R.A. prior to study entry, 13.9 % (16/115), 38.3 % (44/115) and 38.3 % (44/115) had all Hb values within the ranges 11–12, 10–12 and 11–13 g/dL, respectively. During the evaluation period, approximately 83 % of patients had all Hb values ≥ 10 g/dL and 87 % of patients had all Hb values ≤ 13 g/dL in both the efficacy and modified efficacy populations (Fig. 3).

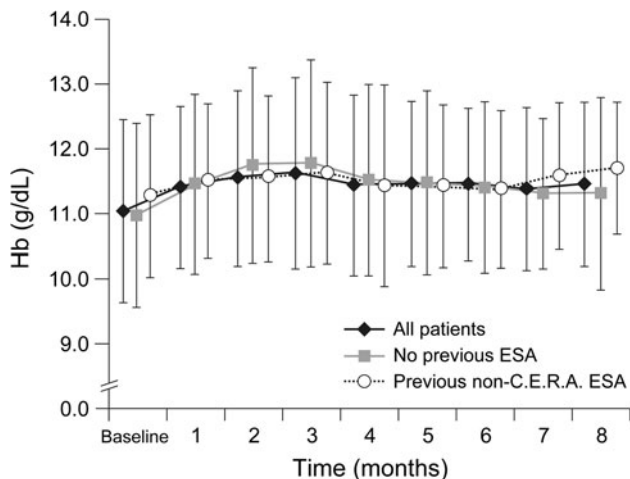


Fig. 2 Mean (SD) hemoglobin level in all patients, in patients without any erythropoiesis stimulating agent (ESA) therapy prior to study entry, and in patients who received an ESA therapy other than continuous erythropoietin receptor activator (C.E.R.A.) prior to study entry (modified efficacy population, $n = 162$)

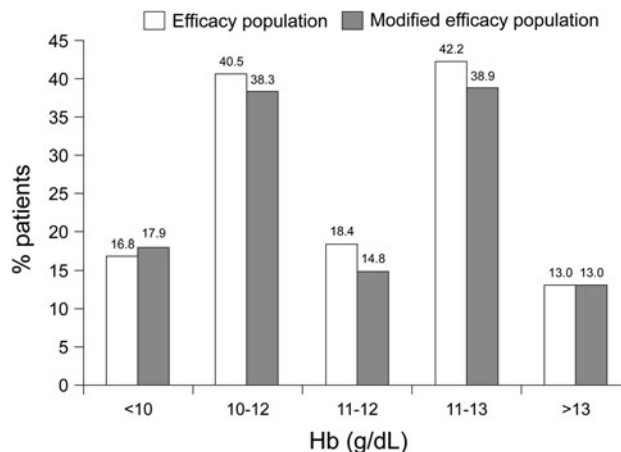


Fig. 3 Proportion of patients within pre-specified hemoglobin (Hb) ranges during the evaluation phase (months 6–8). The efficacy population consisted of patients with at least one Hb value during the evaluation phase ($n = 185$). The modified efficacy population consisted of all patients in the efficacy population for whom at least two Hb measurements were available during the evaluation period ($n = 162$)

The mean (SD) maximum intra-individual fluctuation in Hb level during the evaluation period was 0.56 (0.50) g/dL in the efficacy population and 0.58 (0.49) g/dL in the modified efficacy population. The maximum intra-individual fluctuation during the evaluation phase was ≤ 1 g/dL in 85.4 % (158/185) and 83.3 % (135/162) of patients in the efficacy and modified efficacy populations, respectively.

3.4 Safety and Tolerability

No adverse drug reactions were reported during the study. No clinically relevant changes in laboratory values or vital signs were noted during the study.

4 Discussion

In this large population of maintenance peritoneal dialysis patients, once-monthly administration of C.E.R.A. achieved a high degree of Hb stability and was well-tolerated when administered according to local practice. Conversion from more frequently-administered ESA therapies to C.E.R.A.—or introduction of C.E.R.A. as de novo therapy—proved convenient, with relatively few doses changes and approximately 65 % of patients administering at least one dose at home.

Maintaining Hb levels within a narrow target range in dialysis patients is notoriously challenging due to the high degree of Hb variability observed in dialysis populations [32]. Indeed, one retrospective study in the

Netherlands, which included 56 hemodialysis patients and 12 peritoneal dialysis patients, found that none remained within the target range of 11–12 g/dL over a one-year period during ESA therapy [33]. The current real-life population is likely to have included more challenging patients than in randomized controlled trials which, for example, frequently specify a baseline Hb range and maximum limits for Hb fluctuation as part of the inclusion criteria. Against this background, the finding that only approximately 15 % of patients in the modified efficacy population achieved the primary variable of all Hb levels within 11–12 g/dL during the three-month evaluation phase is not unexpected. Perhaps more relevantly, few patients had Hb values <10 g/dL (approximately 17 %). Importantly, only 13 % had a single Hb value above 13 g/dL during the evaluation period, consistent with recent recommendations from KDIGO [9].

The initial doses of C.E.R.A prescribed by the managing physicians were appropriate, as indicated by the largely unchanged mean dose and the similar proportion of dose increases and dose decreases during the study. Multicenter studies in which hemodialysis patients were converted from shorter-acting ESA preparations to monthly C.E.R.A. have reported similar findings [20, 34]. It is encouraging that almost 40 % of patients required no dose changes over the 9-month study, with an overall mean of fewer than two dose changes per patient. This is consistent with findings from a pooled analysis of three comparative Phase III trials of C.E.R.A. twice- or once-monthly versus shorter-acting ESAs in hemodialysis patients, in which significantly fewer dose changes were required in the C.E.R.A. treated patients [35], and previous observational data in peritoneally dialyzed patients [36]. More frequent ESA dose changes show an association with increased Hb fluctuation [33, 36], a relationship that appears to be causal [36], so a low rate of dose alterations may support stable Hb control. Data from dialysis populations [37, 38] have suggested that fluctuation from target Hb range to values below 11 g/dL are associated with increased mortality. Here, the mean fluctuation in Hb levels over the nine-month study was ~1.5 g/dL, which compares favorably with published data [33]. A retrospective, single-center analysis reported a trend to fewer excursions from Hb target range in C.E.R.A.-treated peritoneal dialysis patients versus those receiving epoetin beta, although complete Hb cycles were similar in both groups [36]. The authors concluded that fewer dose changes with C.E.R.A. may offer a small advantage in reducing the degree of Hb variability [36].

Another 9-month observational study with a similar protocol has been conducted in 924 hemodialysis patients [20]. Baseline Hb levels were broadly similar to the current population [mean (SD) 11.4 (1.2) g/dL compared to 11.1 (1.3) g/dL here] [20]. During the evaluation phase in the hemodialysis patients, Hb parameters were consistently similar to those seen in the current peritoneal dialysis population, including mean Hb levels, the proportion of patients within pre-specified Hb ranges, the mean intra-individual Hb fluctuation and the proportion of patients with a maximum intra-individual fluctuation ≤ 1 g/dL. In the hemodialysis patients, however, the mean dose of C.E.R.A. over the nine-month study was 124 μ g compared to 109 μ g in the current peritoneal dialysis population. Carrera et al. [39] described an initial mean C.E.R.A. dose of 159 μ g, titrated upwards by protocol to 260 μ g. These data are in line with published data showing that higher ESA doses are often required in hemodialysis patients to achieve the same level of Hb control as in peritoneally dialyzed patients [21–25].

With regards the safety profile of C.E.R.A., no adverse drug reaction was reported in this series of over 200 patients during the eight-month period.

5 Conclusions

Once-monthly C.E.R.A. was effective and well-tolerated when used in routine clinical practice for the treatment of anemia in peritoneal dialysis patients either following conversion from more frequently-dosed ESA therapies or as de novo treatment. Results in this largely unselected population of peritoneally dialyzed patients suggest that the effectiveness of once-monthly C.E.R.A. in peritoneally dialyzed patients is similar to that observed in hemodialysis patients but that this may be achieved at a slightly lower dose.

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Disclosures *Author contributions:* All authors contributed to the study design, collected clinical data, evaluated the data, critically assessed the manuscript and gave final approval for submission.

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Conflict of interest MK and WT have no conflicts of interest to declare. DF has received consulting and speaker's honoraria from Amgen, Roche Pharma AG and Ortho Biotech.

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Appendix: The BEAM Study Investigators

All locations are in Germany.

Samih Al-Sarraf, Augsburg; Volker Becker, Heusenstamm; Lucia Bittorf-Rollenhagen, Berlin; Gunnar Bücker, Osnabrück; Theo Busch, Moers; Ernst-Gerhard Danneemann, Gelsenkirchen; Tilman David-Walek, Kiel; Ralf Desselberger, Greifswald; Robert Dunst, Reutlingen; Hans-Herbert Echterhoff, Bielefeld; Danilo Fliser, Homburg; Björn Friedrich, Leonberg; Christian Friedrichsohn, Villingen-Schwenningen; Klaus Fromm-herz, St. Wendel; Georg Georges, Tübingen; Gerd Hetzel, Düsseldorf; Martin Kimmel & Niko Braun, Stuttgart; Rüdiger Knaup, Siegen; Michael Koch, Mettmann; Axel Krieter, München; Heike Martin, Zwickau; Uta Neuhäuser-Piduhn, Dortmund; Rainer Nowack, Lindau; Susanne Pawlow-Handt & Manfred Schlöcker, Wolfenbüttel; Sylvia Petersen, Berlin; Jörg Radermacher, Minden; Andreas Raffelsiefer, Warendorf; Thomas Rath, Kai-serslautern; Peter Rawer, Wetzlar; Manfred Schmitt, Speyer; Frank Seibt & Erika Eger, Berlin; Wolfgang Treiber & Thomas Sures, Neuwied; Sibille Tröster, Westerstede; Volker Vielhauer, München.

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