C.E.R.A. Corrects Anemia in Patients with Chronic Kidney Disease not on Dialysis: Results of a Randomized Clinical Trial

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Background and objectives: This study examined the efficacy of C.E.R.A., a continuous erythropoietin receptor activator, for correcting anemia in patients who had chronic kidney disease (CKD) and were not on dialysis.

Design, setting, participants, & measurements: In this open-label, randomized, parallel-group, Phase III study, 324 adult patients with CKD not on dialysis nor receiving treatment with erythropoiesis-stimulating agents (ESAs) were randomly assigned (1:1) to receive subcutaneous C.E.R.A. once every 2 wk or darbepoetin alfa once weekly during an 18-wk correction period and a 10-wk evaluation period. Thereafter, patients receiving C.E.R.A. were randomly assigned to C.E.R.A. once every 2 wk or once monthly, and patients receiving darbepoetin alfa could receive darbepoetin alfa once weekly or once every 2 wk for a 24-wk extension period. Dosage was adjusted to achieve a hemoglobin (Hb) response and to maintain Hb ±1 g/dl of the response level and 11 to 13 g/dl. Primary end points were Hb response rate during correction and evaluation and change in Hb concentration between baseline and evaluation.

Results: Hb response rates were 97.5% for C.E.R.A. and 96.3% for darbepoetin alfa. Adjusted mean changes in Hb from baseline to evaluation were 2.15 g/dl (C.E.R.A.) and 2.00 g/dl (darbepoetin alfa). Analysis showed that C.E.R.A. once every 2 wk was as effective as darbepoetin alfa once weekly for correcting anemia. Hb levels remained stable in all groups during the extension period. C.E.R.A. and darbepoetin alfa were well tolerated.

Conclusions: Subcutaneous C.E.R.A. once every 2 wk corrects anemia in ESA–naïve patients who are not on dialysis.

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Anemia is highly prevalent in patients with chronic kidney disease (CKD) and is associated with significant morbidity and mortality (1–3). The introduction of erythropoiesis-stimulating agents (ESAs) and the development of clinical practice guidelines have been beneficial in managing renal anemia and improving patient outcomes (4–8); however, despite improvements in anemia therapy, many patients still have hemoglobin (Hb) levels below guideline targets (9).

Renal anemia commonly develops before the need for dialysis but is often poorly controlled initially (2,10–15). Despite the improvements in anemia care, many patients still start dialysis therapy with Hb levels below recommended targets (7).

Maintaining anemia control in patients with CKD is time consuming and associated with considerable burden on health care resources (7,16). The demand on renal units is expected to increase with the rising incidence and prevalence of CKD (7,17,18). Hence, there is value in continuing to explore approaches that improve anemia management across the CKD continuum by allowing administration at extended intervals while still providing predictable and stable Hb responses.

C.E.R.A., a continuous erythropoietin receptor activator, has completed Phase III development for anemia correction and stable maintenance of Hb levels at extended administration intervals in patients with all stages of CKD. C.E.R.A. is a chemically synthesized ESA and differs from epoetin beta through the integration of an amide bond between an amino group of epoetin beta and a specific, linear methoxy polyethylene glycol. The average molecular weight of C.E.R.A. is approximately 60 kD. C.E.R.A. exhibits a long half-life of approximately 130 h when administered either intravenously or subcutaneously and low clearance, which, together with its unique receptor-binding properties, result in a different phar-

macologic profile compared with currently available ESAs (19–21). Data presented to date on Phase II studies in patients with CKD on dialysis and not on dialysis suggest that C.E.R.A. can correct anemia and maintain stable Hb levels in most patients when administered up to once monthly (22–24).

The ARCTOS (Administration of C.E.R.A. in CKD Patients to Treat Anemia with a Twice-Monthly Schedule) study was designed to examine whether C.E.R.A. administered subcutaneously once every 2 wk corrects anemia in ESA-naïve patients with CKD not on dialysis. Patients who responded to C.E.R.A. therapy were then eligible for randomization to receive C.E.R.A. either once every 2 wk or once every 4 wk for an additional 24-wk extension period to assess long-term safety. Here we report the results of this Phase III trial.

Materials and Methods

Patients

ESA-naive patients (aged ≥18 yr) who had stage 3 (creatinine clearance 30 to 59 ml/min) or stage 4 CKD (creatinine clearance 15 to 29 ml/min) and were not on dialysis and had Hb 8 to 11 g/dl at baseline were

recruited from Europe, the United States, Canada, and Australia. Major inclusion and exclusion criteria are presented in Table 1.

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

Study Design

ARCTOS was an open-label, randomized, multicenter, darbepoetin alfa–controlled, parallel-group Phase III study to determine whether subcutaneous C.E.R.A., administered once every 2 wk, was as effective and well tolerated as once weekly subcutaneous darbepoetin alfa for anemia correction in ESA-naïve patients who had CKD and were not on dialysis. After a 1- to 2-wk run-in period, patients were randomly assigned (1:1) to receive subcutaneous C.E.R.A. once every 2 wk or subcutaneous darbepoetin alfa once weekly (Figure 1). Patients were assigned to study treatment *via* a central randomization center with stratification by geographic region. The administration interval and initial dosage for patients who were randomly assigned to subcutaneous C.E.R.A. was 0.6 μg/kg per 2 wk, based on results from a Phase II correction study in patients who had CKD and were not on dialysis

Table 1. Major inclusion and exclusion criteria[a]

Inclusion criteria

    Adult patients (≥18 yr of age) who had stage 3 (CrCl 30 to 59 ml/min) or stage 4 CKD (CrCl 15 to 29 ml/min) and did not require dialysis

    Anemia defined as baseline Hb concentration between 8 and 11 g/dl, determined from the mean of two screening values with at least 1 d between measurements

    Adequate iron status defined as serum ferritin ≥100 ng/ml or TSAT ≥20% (or percentage of hypochromic RBCs <10%); mean of two screening values with at least 1 d between measurements

Exclusion criteria

    Need for dialysis therapy expected in the next 6 mo or rapid progression of CKD (*e.g.*, a CrCl decrease of >20% within 12 wk)

    Previous therapy with any ESA within 12 wk before screening

    Immunosuppressive therapy (other than corticosteroids for a chronic condition, cyclosporine, and monoclonal/polyclonal antibodies) in the 12 wk before screening

    Overt gastrointestinal bleeding or any other bleeding episode necessitating transfusion within 8 wk before screening or during the screening period

    RBC transfusions within 8 wk before screening or during the screening period

    Nonrenal causes of anemia (*e.g.*, hemoglobinopathies [*e.g.*, homozygous sickle cell disease, thalassemia of all types], hemolysis, vitamin B_{12} or folic acid deficiency)

    Active malignant disease (except non-melanoma skin cancer)

    Chronic, uncontrolled or symptomatic inflammatory disease (*e.g.*, rheumatoid arthritis, systemic lupus erythematosus)

    C-reactive protein >15 mg/L

    Poorly controlled hypertension (sitting SBP ≥170 mmHg or DBP ≥100 mmHg)

    Pure red cell aplasia

    Platelets >500 × 10^9/L

    Chronic congestive heart failure (New York Heart Association class IV)

    High likelihood of early withdrawal or interruption of the study (*e.g.*, myocardial infarction, severe or unstable coronary artery disease, stroke, severe liver disease within the 12 wk before screening or occurring during the screening/baseline period)

    Planned elective surgery during the next 7 mo (except laser photocoagulation)

    Life expectancy <12 mo

    [a]CKD, chronic kidney disease; CrCl, creatinine clearance; DBP, diastolic BP; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; RBC, red blood cell; SBP, systolic BP; TSAT, transferrin saturation.
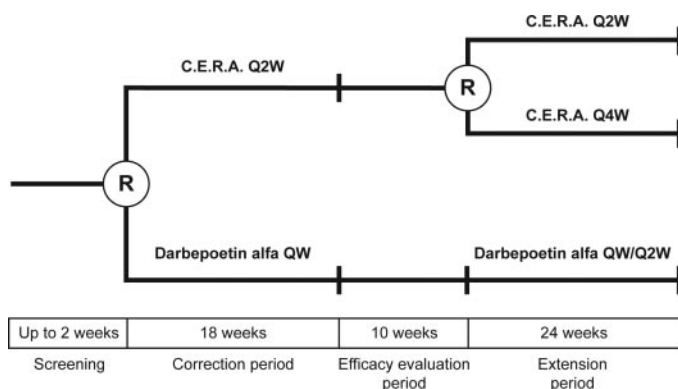
Figure 1. Study design. QW, once weekly; Q2W, once every 2 wk; Q4W, once every 4 wk.

(24). The administration interval and starting dosage of darbepoetin alfa (0.45 μg/kg per wk) was based on published findings (25) and approved treatment recommendations.

The study consisted of an 18-wk correction period (weeks 1 to 18) for dosage titration and Hb correction, followed by a 10-wk evaluation period (weeks 19 to 28) for efficacy assessments. Patients who responded to C.E.R.A. (defined as an increase in Hb $\geq$1.0 g/dl versus baseline and Hb $\geq$11 g/dl without blood transfusion during the first 28 wk after the first dose) were eligible to continue treatment, at the discretion of the investigator, and were randomly assigned to receive subcutaneous C.E.R.A. either once every 2 wk or once every 4 wk for an additional 24-wk extension period to assess long-term safety. Darbepoetin alfa responders were allowed to continue on the drug during the extension period, receiving it either once weekly or once every 2 wk, according to center practice and patient response. The extension period was of an exploratory nature, and no additional confirmatory statistical analyses were preplanned. The safety data collected are part of an ongoing pooled analysis of safety data from the C.E.R.A. clinical development program.

During the dosage titration and evaluation periods, the dosage of study drug was adjusted to achieve a Hb level $\geq$11 g/dl and an increase $\geq$1.0 g/dl versus the individual patient's baseline Hb level. After achievement of response, dosage adjustments were performed to maintain the patient's Hb level within $\pm$1 g/dl of his or her response Hb level and within a target range of 11 to 13 g/dl. During the extension period, Hb levels were to be maintained between 11 and 13 g/dl. Dosage adjustments were performed according to a predefined protocol but no more frequently than once every 4 wk unless safety concerns dictated otherwise. The need for dosage adjustment was based on two consecutive Hb assessments. Up to achievement of response, C.E.R.A. dosages were increased by 50% for Hb increases <1 g/dl in a 4-wk period and by 100% for Hb <9 g/dl and Hb below baseline values. C.E.R.A. dosages were decreased by 50% for Hb increases >2 g/dl in a 4-wk period or for Hb >13.0 and $\leq$14.0 g/dl. After achievement of response, C.E.R.A. dosages were increased by 25% for Hb decreases >1.0 g/dl compared with the response level and for Hb <11.0 g/dl. C.E.R.A. dosages were decreased by 25% for Hb increases >1.0 g/dl compared with the Hb response level or for Hb >13.0 and $\leq$14.0 g/dl. During the extension period, C.E.R.A. dosages were increased or decreased by 25% for Hb <11.0 g/dl and Hb >13.0 and $\leq$14.0 g/dl, respectively, and increased by 100% for Hb <9 g/dl. Patients who were randomly assigned to C.E.R.A. once every 4 wk for the extension period received a dosage that was double the week 27

dosage. Dosage adjustments for darbepoetin alfa were performed as described in the label. Treatment was temporarily interrupted when Hb exceeded 14 g/dl.

Dosage adjustments were also permitted in case of blood transfusion for worsening anemia; however, if a transfusion was required to replace acute blood loss, the dosage of study drug was not changed. Iron supplementation during the titration and evaluation periods was initiated or intensified in case of iron deficiency (serum ferritin <100 ng/ml or transferrin saturation [TSAT] <20% [or percentage of hypochromic red blood cells $\geq$10%]) and was temporarily discontinued in patients with serum ferritin >800 ng/ml or TSAT >50% until serum ferritin and TSAT returned to below these levels. Iron supplementation was administered orally or intravenously according to individual center practice. When oral iron was not sufficient to correct iron deficiency, intravenous iron was given.

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, or 400 μg/ml administered via 0.5- and 1.0-ml syringes by a healthcare professional. Darbepoetin alfa was either supplied by F. Hoffmann-La Roche Ltd or obtained from commercial sources by participating sites. Self-administration of either treatment was not allowed.

Assessments

Patients were scheduled for weekly assessments during run-in, once every 2 wk during the correction and evaluation periods, and every 4 wk during the extension period. Week 1 assessments were performed before first administration of study drug. Hb was measured at each assessment. Iron parameters were measured during run-in, at randomization, every 4 wk from weeks 5 to 29, every 8 wk during the extension period, and at the final visit. Quality of life (QoL) was assessed at randomization, at week 13, and at week 29 using the Short Form-36 Health Survey. Anti-C.E.R.A. and anti-erythropoietin antibody testing was carried out at randomization, weeks 13, 25, and 37, and the final visit. Other laboratory safety parameters, physical examination and electrocardiography, adverse events (AEs), red blood cell transfusions, iron supplementation, and concomitant medications were measured or recorded at predefined times throughout the study.

Statistical Analyses

There were two primary efficacy parameters: Hb response rate during the correction and evaluation periods and difference in mean change in Hb concentration between baseline and the evaluation period. Hb response was defined as an increase $\geq$1 g/dl versus baseline and a concentration $\geq$11 g/dl without blood transfusion during the 28 wk after the first dose.

Analysis of the two primary efficacy end points was performed in a hierarchical order to ensure that the overall significance level of 5% would not be exceeded. First, the hypothesis that the Hb response in the C.E.R.A. arm was $\geq$60% was tested. If the lower limit of the 95% confidence interval (CI) was >60%, then it could be concluded that C.E.R.A. once every 2 wk corrected anemia and the noninferiority test was performed. For demonstration of noninferiority, the lower limit of the two-sided 95% CI for the difference between the two groups had to be $\geq$-0.75 g/dl. Primary analysis of Hb response rate was conducted in the intent-to-treat (ITT) population (all patients randomized to treatment), and a confirmatory analysis was performed on the per-protocol (PP) population (all patients without major protocol violations). Primary analysis of change in Hb concentration between baseline and the end of the evaluation period was conducted in the PP population because this is the most conservative approach for a noninferiority test,

and a confirmatory analysis was performed on the ITT population. Analysis of covariance was used to compare the mean change in Hb level between baseline and the evaluation period in both treatment groups using Hb at baseline and geographic region as covariates.

The study sample size was selected to accommodate analysis of both primary end points. A sample size of 126 patients per treatment group was required to provide >90% power to demonstrate that the response rate was ≥60%, assuming that the true response rate was ≥75%. For the noninferiority test, ≥132 patients per group were required to demonstrate that C.E.R.A. once every 2 wk was as effective as darbepoetin alfa once weekly, assuming a noninferiority limit of −0.75 g/dl, a power of 90%, a 5% significance level, a true difference between treatments ≤0.3 g/dl, and that ≤20% of patients would be ineligible for inclusion in the PP population. As a result, 264 patients (132 per group) were required for the analysis of both primary end points. For addressing possible differences regarding effectiveness, randomization was stratified by geographic region.

Secondary efficacy end points, including Hb concentration over time, time to target Hb response evaluated by Kaplan-Meier methods, and incidence of blood transfusions during the first 28 wk, were compared between treatment groups using descriptive methods on the ITT population. Changes from baseline in QoL were analyzed across the two treatment groups in the safety population (all patients who received at least one dose of study medication and had a safety follow-up) using descriptive methods. A clinically meaningful change in QoL score was defined as a change of ≥5 points *versus* baseline. Safety assessments, including AE reporting, safety hematology and blood chemistry (including iron) laboratory tests, C.E.R.A. and erythropoietin antibody testing, monitoring of vital signs, and electrocardiogram, were examined in the safety population, and group summary statistics were calculated.

Results
Patients
Patients were screened at 85 centers in 12 countries. The study began in June 2004 and was completed in January 2006. A total of 324 patients from 82 centers were randomly assigned to C.E.R.A. (n = 162) or darbepoetin alfa (n = 162; ITT population; Figure 2). Most were from Europe (42.9%) and the United States (35.5%), with the remainder from Canada (15.4%) and Australia (6.2%). One patient in the C.E.R.A. group did not subsequently receive any study medication and was excluded from the PP and safety populations.

In total, 297 patients completed the correction and evaluation periods: 144 in the C.E.R.A. group and 153 in the darbepoetin alfa group. Reasons for withdrawal were AEs (n = 8), death (n = 4), refusal of treatment (n = 5), failure to return (n = 4), insufficient therapeutic response (n = 2), and other (n = 4). The incidence of withdrawals for safety-related reasons was similar in both groups (Figure 2). A total of 41 patients in the ITT population were excluded from the PP population, which comprised 283 patients (Figure 2). The main reasons for exclusion were an insufficient number of Hb values (<75% of Hb values up to day 201 or fewer than four Hb values during the evaluation period: C.E.R.A., 11; darbepoetin alfa, 3) and blood transfusions within weeks 1 to 28 (C.E.R.A., 4; darbepoetin alfa, 8).

Baseline characteristics, including causes of CKD, were similar between the two treatment groups (Table 2). Almost all patients (99%) had one or more risk factors for vascular events.
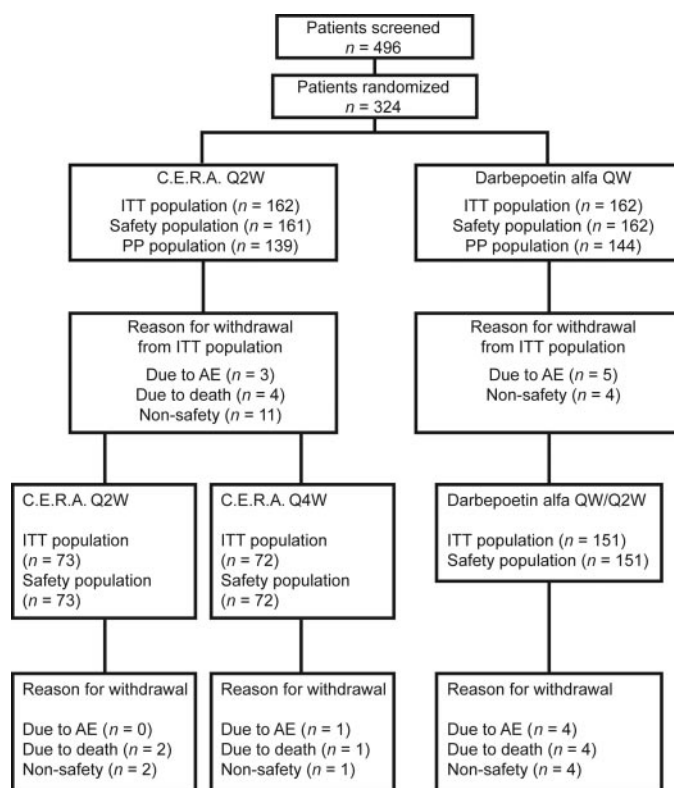

Figure 2. Patient populations and disposition. AE, adverse event; ITT, intent-to-treat; PP, per-protocol.

The most common vascular risk factors in the C.E.R.A. and darbepoetin alfa groups, respectively, were arterial hypertension (97 and 99%), hyperlipidemia (68 and 72%), diabetes (53 and 58%), and ischemic heart disease (28 and 25%). Most patients had at least one other comorbid condition (C.E.R.A., 94%; darbepoetin alfa, 97%).

Mean Hb levels at baseline were similar in the two groups, and similar proportions of patients received iron supplementation at baseline. The most common iron supplements at baseline were ferrous sulfate (C.E.R.A., 20%; darbepoetin alfa, 23%), iron sucrose (14% in both groups), and ferrous gluconate (C.E.R.A., 12%; darbepoetin alfa, 9%). Use of antihypertensive agents was balanced between treatment groups (Table 2).

For the extension period, 73 patients were randomly assigned to C.E.R.A. once every 2 wk and 72 to C.E.R.A. once every 4 wk. A total of 151 patients continued to receive darbepoetin alfa.

Efficacy Evaluation
For the first primary efficacy end point (the response rate within the first 28 wk), Hb response rates in the C.E.R.A. and darbepoetin alfa groups were 97.5 and 96.3%, respectively, in the ITT population (Figure 3). The 95% CI for the C.E.R.A. response rate was 93.80 to 99.32%, and because the lower limit was greater than the predefined 60% response (P < 0.0001), it could be concluded that C.E.R.A. once every 2 wk effectively corrected anemia. Similar results were found in the analysis of the PP population, confirming the robustness of the ITT results (Figure 3).

Table 2. Baseline characteristics and demographic data (ITT population)

Characteristic	C.E.R.A. (n = 162)	Darbepoetin alfa (n = 162)
Male, n (%)	70 (43)	80 (49)
Mean (SD) age, yr	63.9 (14.1)	66.9 (12.8)
Mean (SD) weight, kg	76.8 (16.2)	80.5 (19.5)
Mean (SD) Hb, g/dl	10.2 (0.6)	10.2 (0.7)
Mean (SD) CrCl, ml/min	27.7 (9.7)[a]	27.0 (10.7)
Mean (SD) C-reactive protein, mg/L	6.5 (11.1)[b]	7.0 (14.2)
Mean (SD) albumin, g/L	39.4 (5.2)[c]	38.3 (5.3)[d]
Median (IQR) TSAT (%)	23.7 (20.0–30.7)[a]	23.7 (20.3–29.3)[a]
Median (IQR) ferritin, μg/L	174.7 (107.7–271.3)	185.8 (129.0–284.4)
Iron supplementation at baseline, %	55	54
Mean (SD) SBP, mmHg	139 (18.9)[a]	139 (20.9)[a]
Mean (SD) DBP, mmHg	73 (10.5)[a]	72 (10.7)[a]
Cause of renal failure %,		
diabetes	45	49
hypertension/large vessel disease	40	44
glomerulonephritis	9	12
interstitial nephritis/pyelonephritis	6	6
undefined cause	7	3
polycystic kidney disease	4	6
secondary glomerulonephritis/vasculitis	1	2
other hereditary/congenital diseases	1	1
Previous and concomitant antihypertensive treatments, %		
angiotensin-converting enzyme inhibitors	51	48
calcium channel blockers	39	40
β adrenoceptor antagonists	39	40
angiotensin II receptor blockers	37	35
Race, %		
white	70	81
black	22	12
Asian	4	6
other	4	2
Ethnicity, %		
Hispanic	10	10
non-Hispanic	90	90
Geographic region, %		
United States	35	36
outside United States	65	64

IQR, interquartile range.
[a]n = 161 patients with evaluable measurements.
[b]n = 159 patients with evaluable measurements.
[c]n = 158 patients with evaluable measurements.
[d]n = 160 patients with evaluable measurements.

For the second primary efficacy end point, mean changes in Hb concentration between baseline and the evaluation period were comparable in the C.E.R.A. and darbepoetin alfa groups (2.12 *versus* 2.02 g/dl) in the PP population. After adjustment for covariates (baseline Hb levels and geographic region), the mean change in Hb from baseline to the evaluation period in the PP population was 2.15 g/dl with C.E.R.A. and 2.00 g/dl with darbepoetin alfa. The mean (95% CI) difference in the change in Hb between the two groups was 0.16 g/dl (−0.05 to 0.35) in the PP population. The lower limit of the 95% CI was well above the prespecified level of −0.75 g/dl, demonstrating that C.E.R.A. once every 2 wk is as effective as darbepoetin alfa once weekly for anemia correction ($P < 0.0001$; Figure 4). These results were confirmed by analysis of the ITT population (Figure 4).

In the analysis of secondary efficacy end points, mean Hb increased in both treatment groups during the correction period (Figure 5), with a maximum mean Hb level in the
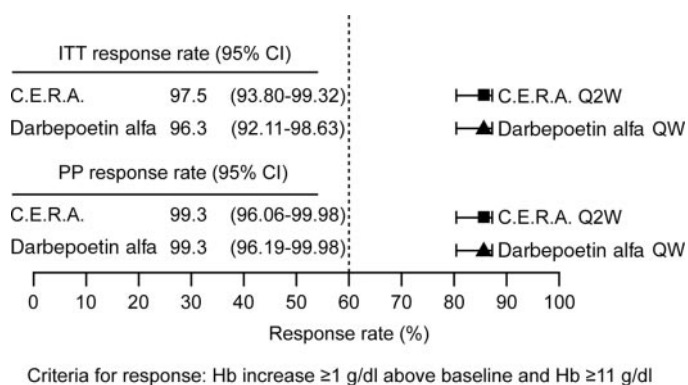
Figure 3. Response rates to C.E.R.A. and darbepoetin alfa during the correction and evaluation periods (ITT and PP populations). CI, confidence interval.

C.E.R.A. group (12.59 g/dl) observed at week 18 compared with week 12 in the darbepoetin alfa group (12.83 g/dl). Hence, the median time to response was 43 d for C.E.R.A. and 29 d for darbepoetin alfa ($P < 0.0001$). A Kaplan-Meier plot of the time to Hb response is shown in Figure 6. At the end of the evaluation period, mean Hb was 12.18 g/dl in the C.E.R.A. group and 12.01 g/dl in the darbepoetin alfa group.

The difference in the time to Hb response between the two treatment groups was investigated further in an exploratory analysis of patients with Hb >13 g/dl. A total of 12.4% of patients who were taking C.E.R.A. and 33.5% who were taking darbepoetin alfa experienced at least one Hb value >13 g/dl during the first 8 wk ($P < 0.0001$). In the correction and evaluation period (weeks 1 to 28), 67.7% of patients who were taking C.E.R.A. and 80.6% who were taking darbepoetin alfa experienced at least one Hb value >13 g/dl ($P < 0.0082$).

Fewer patients who were treated with C.E.R.A. (2.5%) required one or more red blood cell transfusions during the correction and evaluation periods compared with darbepoetin alfa (6.8%).

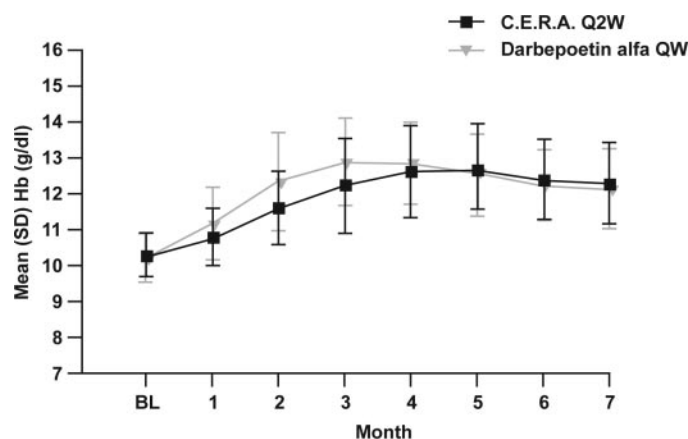An assessment of treatment dosages during the study in the

Figure 4. Difference in change in mean adjusted Hb with C.E.R.A. and darbepoetin alfa between baseline and evaluation (ITT and PP populations).

Figure 5. Mean Hb values during the correction and evaluation periods with C.E.R.A. and darbepoetin alfa (ITT population).

safety population showed that median dosages were 0.6 μg/kg per 2 wk and 0.45 μg/kg per wk in the C.E.R.A. and darbepoetin alfa groups, respectively, at both baseline and the time of response. Median dosages in the C.E.R.A. and darbepoetin alfa groups decreased during the course of the study, reaching 0.34 μg/kg per 2 wk for C.E.R.A. and 0.19 μg/kg per wk for darbepoetin alfa by the end of the evaluation period.

In the extension period, median Hb levels remained stable in the ITT population of all three treatment groups. Median Hb levels for the whole extension period were 11.8 g/dl for C.E.R.A. once every 2 wk, 11.7 g/dl for C.E.R.A. once every 4 wk, and 12.1 g/dl for darbepoetin alfa once weekly and once every 2 wk (Figure 7). Patients who received at least one blood transfusion represented 2.7, 0, and 2.6% of each group, respectively.

QoL
Relative to baseline, mean scores increased on each of the eight subscales and summary scores in both treatment groups, representing an improvement in each parameter (Figure 8). Clinically meaningful improvements from baseline to weeks 13 and 29 (an increase of ≥5 points) were observed for C.E.R.A. once every 2 wk in general health, vitality, role emotional, role physical (week 13 only), and social functioning and for darbepoetin alfa in vitality, role emotional, and role physical.

Safety and Tolerability
The overall incidence of AEs, serious AEs, and AEs that led to withdrawal for the complete study period are presented in Table 3. The number of patients who experiencing one or more AE was similar between treatment groups and typical of this patient population. The most commonly reported AEs included hypertension, peripheral edema, diarrhea, and nasopharyngitis and were similar for the correction/evaluation period *versus* the complete study period. Most events were mild or moderate in intensity, and very few were considered treatment related (C.E.R.A., 7.5%; darbepoetin alfa, 5.6%).

Serious AE were reported more frequently in the darbepoetin alfa group (35.8%) than in the C.E.R.A. group (30.4%); few were
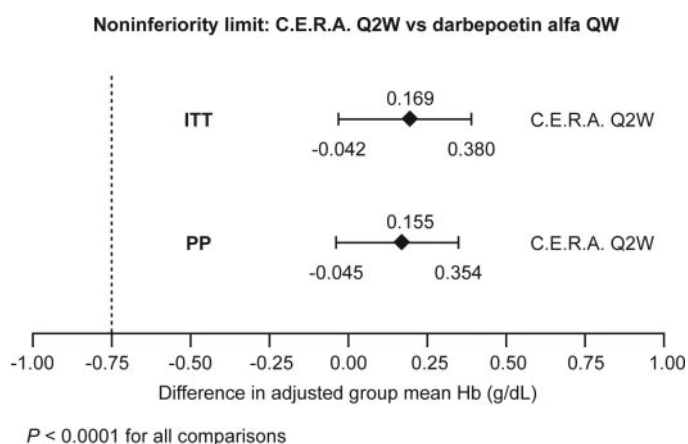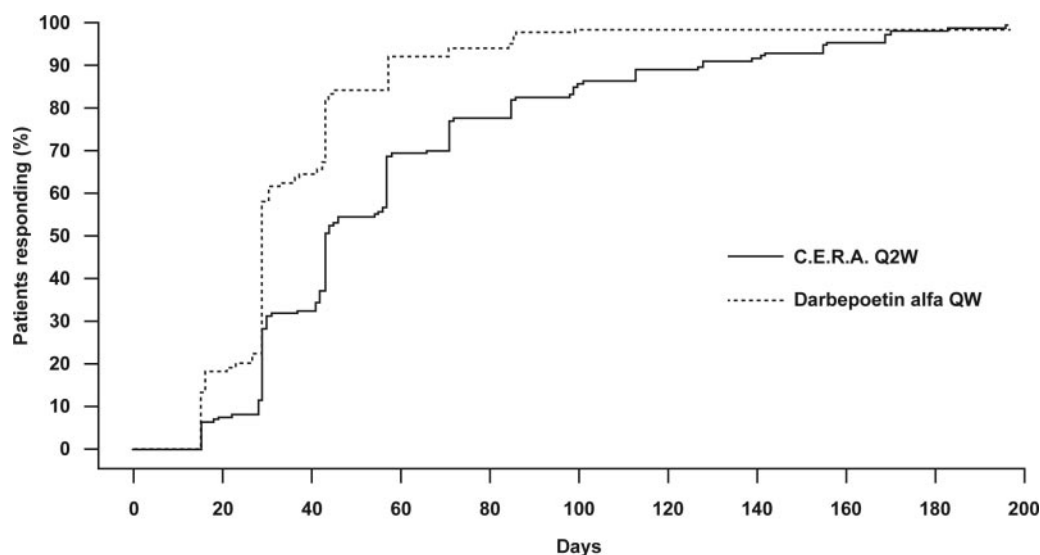
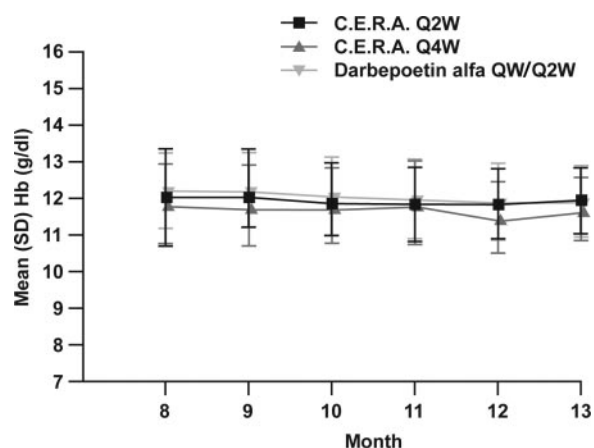*Figure 6.* Kaplan-Meier plot of responders over time (ITT population).

Figure 7. Mean Hb values during the extension period with C.E.R.A. and darbepoetin alfa (ITT population).

considered related to study medication (C.E.R.A. one [0.6%], maculopapular rash; darbepoetin alfa two [1.2%], angioneurotic edema, hypertension). A total of 15 patients were withdrawn as a result of AEs (including 10 during the correction/evaluation period): three AEs in the C.E.R.A. group (peripheral edema, skin discoloration, and maculopapular rash) and one in the darbepoetin alfa group (angioneurotic edema) were considered treatment related (Table 3).

A total of 17 deaths occurred during the complete study period: eight (5%) in the C.E.R.A. group and nine (6%) in the darbepoetin alfa group. None of the deaths was considered treatment related. Cardiovascular causes accounted for seven deaths in the C.E.R.A. group, and the cause of the remaining death was intracranial hemorrhage. In the darbepoetin alfa group, five deaths were due to cardiovascular causes, and the causes of the other deaths were multiorgan disorder, multiorgan failure, gastrointestinal hemorrhage, and thrombotic thrombocytopenic purpura.

Antibodies to C.E.R.A. were not detected in any patient. A single case of non-neutralizing anti-erythropoietin antibodies was detected in the darbepoetin alfa group. There were no clinically relevant changes in vital signs or iron or laboratory parameters during the complete study period. During the correction and evaluation periods, greater variation was seen in median systolic BP than in median systolic BP in both treatment groups; however, both of these parameters remained relatively stable for the complete study period.

Discussion

ARCTOS is the first large-scale study to demonstrate that anemia can be corrected in ESA-naive patients who have CKD and are not on dialysis with once every 2 wk administration of subcutaneous C.E.R.A. at a starting dosage of 0.6 μg/kg per 2 wk. A total of 97.5% of patients who received C.E.R.A. once every 2 wk achieved a Hb response during the 28-wk correction and evaluation period. A similar proportion (96.3%) of patients responded to once-weekly darbepoetin alfa; this response rate is somewhat higher than previously reported (25). When ARCTOS was compared with the darbepoetin alfa study, we found that the baseline characteristics of the two studies differed, and this included higher baseline Hb in the darbepoetin alfa study compared with those in ARCTOS. It is possible that differences in baseline characteristics between the two studies could account for the seemingly higher response rate in ARCTOS than in the darbepoetin alfa study. In ARCTOS, although the time to response was slightly longer in the C.E.R.A. arm, the proportion of patients with at least one Hb value >13 g/dl was significantly lower compared with the darbepoetin alfa group ($P < 0.0082$).

This study demonstrated that the C.E.R.A. starting dosage of 0.6 μg/kg once every 2 wk was effective for anemia correction in this patient population and that AEs were similar to darbepoetin alfa. These data are consistent with a previous smaller
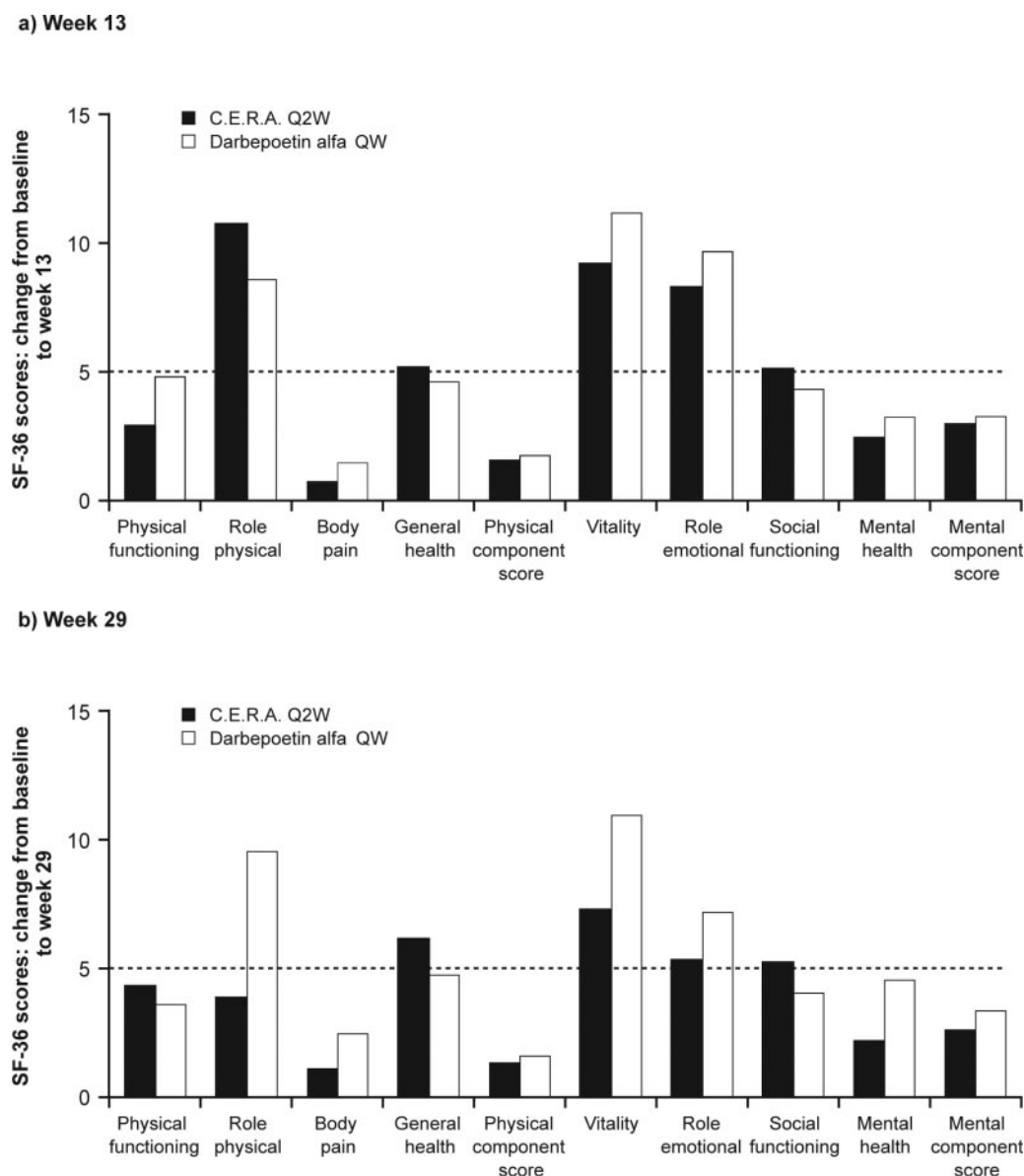
Figure 8. Changes in quality of life from baseline to weeks 13 and 29 measured by the Short Form-36 (SF-36) questionnaire. A clinically meaningful change is defined as a change of ≥5 points *versus* baseline.

Phase II study of subcutaneous C.E.R.A. in ESA-naïve patients who had CKD and were not on dialysis (26).

Both C.E.R.A. and darbepoetin alfa improved QoL, and this is consistent with the equivalent efficacy of both regimens in the correction of Hb levels. While many similar trials have shown improvements in QoL with increasing Hb concentrations, recent studies have raised concerns regarding higher Hb targets. In the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study of 1432 patients with CKD, which was terminated early, there was a 34% increased risk for a composite of death and cardiovascular complications for patients with Hb targets of 13.5 g/dl *versus* those with targets of 11.3 g/dl ($P < 0.03$) (27). In addition, there was no difference in improvements in QoL between the two groups; however, the optimal upper Hb limit in patients with CKD, including its impact on QoL, continues to be debated.

Both treatments were generally well tolerated throughout the 52-wk study; most AEs were consistent with those commonly associated with this patient population and were comparable between treatment groups. The frequency of serious AEs was slightly lower for patients who received C.E.R.A. Treatment-related AEs and serious AEs were detected in <8 and 1% of patients, respectively. The number of deaths was balanced between the two treatment groups, and none were related to study treatment. There were no significant changes in any laboratory parameter or vital sign, and no antibodies to C.E.R.A. were detected.

The characteristics of our patients indicated that our study population was representative of many patients who are regularly seen in renal units; therefore, similar efficacy and safety results should be expected with C.E.R.A. in daily clinical practice. In addition, the results of the extension phase of ARCTOS

Table 3. Overall and most frequent AE (≥5% of patients) during the complete study period (safety population)

Parameter	% of Patients with AEs	
	C.E.R.A. (n = 161)	Darbepoetin alfa (n = 162)
Hypertension	16	15
Peripheral edema	9	18
Diarrhea	9	15
Nasopharyngitis	12	12
Constipation	7	11
Upper respiratory tract infection	8	10
Headache	6	9
Urinary tract infection	7	8
Dizziness	9	6
Hyperkalemia	7	7
Renal impairment	9	4
Back pain	7	6
Pain in extremity	4	9
Vomiting	4	8
Gout	6	5
Influenza	5	6
Hypotension	3	7
Nausea	2	9
Cough	6	3
Any AE	90.1	91.4
Serious AE	30.4	35.8
AE leading to withdrawal	3.1	6.2
Arteriovenous thromboembolic events		
Limb venothrombosis	0	<1
Pulmonary embolism	0	0
Myocardial infarction	2	0
Stroke	<1	0
Deaths	5	6

are consistent with other Phase III comparative studies that have demonstrated the efficacy C.E.R.A. administered intravenously or subcutaneously up to once monthly for the maintenance of Hb levels in patients who were on dialysis and were switched from epoetin one to three times weekly (28,29).

Two published studies previously evaluated the efficacy and safety of initiating treatment of anemia with darbepoetin alfa once every 2 wk in ESA-naive patients who had CKD and were not on dialysis (25,26). However, fundamental differences in study design (no randomization and no control group) and different definitions of response rate in these two studies compared with ours make it inappropriate to draw any conclusions.

The investigators acknowledge certain limitations of the ARCTOS study. First, Hb was used as a surrogate end point for anemia efficacy evaluations because low Hb is the established parameter that defines the condition. Second, we note that the open-label design of this study may have an impact on the data, most particularly the QoL end points and the incidence and severity of any patient-reported AEs.

Conclusions

The results of ARCTOS demonstrate that C.E.R.A., administered subcutaneously at extended administration intervals of once every 2 wk in ESA-naïve patients who have CKD and are not on dialysis, provides a smooth and steady increase in Hb in accordance with current guidelines. In addition, C.E.R.A. maintained Hb levels during the extension period of the study. C.E.R.A. once every 2 wk was safe and effective for anemia correction in these patients.

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Disclosures

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