

ORIGINAL ARTICLE

# Subcutaneous injection pain with C.E.R.A., a continuous erythropoietin receptor activator, compared with darbepoetin alfa

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## ABSTRACT

**Objective:** This study assessed injection site pain following subcutaneous (SC) administration with a continuous erythropoietin receptor activator (C.E.R.A.), compared with darbepoetin alfa in healthy adults.

**Methods:** In a randomized, placebo-controlled, single-centre, single-blind, three-way crossover study, subjects received one of six treatment sequences (ABC/ACB/BAC/BCA/CBA/CAB) involving SC injection of (A) C.E.R.A. 50 µg, (B) darbepoetin alfa 50 µg, or (C) placebo on days 1, 29, and 57. An initial pilot phase ( $n = 12$ ) was used to determine the sample size for the confirmatory phase ( $n = 72$ ), and data were combined for the final analysis ( $n = 84$ ).

**Main outcome measures:** The primary endpoint was pain on the 100 mm visual analog scale (VAS) immediately after dosing. Secondary endpoints included VAS at 1 hour after dosing and pain on

the six-point verbal rating scale (VRS) immediately and at 1 hour after dosing.

**Results:** C.E.R.A. was associated with significantly less pain immediately after SC injection compared with darbepoetin alfa: least squares mean VAS 21.5 (95% confidence interval [CI]: 17.5, 25.5) versus 33.4 (95% CI: 28.4, 38.4) ( $p < 0.0001$ ). Incidence of pain on the VRS was lower with C.E.R.A. compared with darbepoetin alfa immediately after dosing ( $p < 0.0001$ ). One hour after administration, most subjects had no VRS pain. A study limitation is the small sample size and the findings need to be confirmed in a large trial of chronic kidney disease patients.

**Conclusions:** SC injection with C.E.R.A. is significantly less painful than SC darbepoetin alfa in healthy adults. Treatment of anemia in chronic kidney disease with SC injection of C.E.R.A. may provide a lower pain burden compared with darbepoetin alfa.

## Introduction

Anemia is a frequent complication of chronic kidney disease (CKD)<sup>1</sup>. Untreated anemic patients suffer fatigue, reduced quality of life, and an increased risk of cardiovascular events<sup>1-5</sup>. Erythropoiesis stimulating agents (ESAs), such as epoetin alfa and darbepoetin alfa,

are widely used in the management of renal anemia<sup>1</sup>. However, they require frequent dosing to maintain efficacy in patients with CKD. Epoetin alfa requires administration as often as three times weekly<sup>6</sup>, while darbepoetin alfa requires dosing as often as once-weekly<sup>7</sup>.

C.E.R.A. (methoxy polyethylene glycol-epoetin beta), a continuous erythropoietin receptor activator,

is a novel chemically synthesized ESA. C.E.R.A. differs from erythropoietin through integration of an amide bond between an amino group and methoxy polyethylene glycol-succinimidyl butanoic acid<sup>8</sup>. The long half-life of C.E.R.A. (approximately 130 hours)<sup>9-12</sup> allows for once-monthly subcutaneous (SC) or intravenous (IV) dosing. In phase III trials, SC or IV administration of C.E.R.A. once monthly provided comparable tolerability and efficacy to traditional ESAs in maintaining stable hemoglobin levels in patients with CKD with or without dialysis<sup>13-20</sup>. C.E.R.A., approved in Europe for the management of patients with anemia associated with CKD, is currently under review by the US Food and Drug Administration (FDA).

SC is a commonly employed route of administration in the management of renal anemia. This route of administration is convenient, particularly in pre-dialysis patients and in patients receiving peritoneal dialysis treatments who self-administer their treatment at home. In pediatric patients, SC administration is frequently used because most dialysis patients are on peritoneal dialysis.

Injection site pain is a common adverse event with SC administration of ESAs in CKD patients<sup>21-32</sup>, and this is a key consideration in treatment choice. Repeated painful injections in chronically ill patients may affect patient compliance and, thus, the effectiveness of prolonged ESA treatment<sup>21,33</sup>. Previous studies have highlighted differences in injection site pain with SC administration of ESAs, with darbepoetin alfa administration consistently causing more pain than epoetin<sup>34-37</sup>. Studies have also shown that the type of buffer used in the preparation may be associated with differences in subjects' SC injection pain following ESA administration, with citrate-buffered epoetin alfa causing more pain than phosphate-buffered epoetin beta<sup>22-25,27-32</sup>.

There is minimal information regarding SC injection site pain with different ESA treatments in adults. Therefore, the present study was conducted to assess injection site pain following SC administration of C.E.R.A. compared with darbepoetin alfa in healthy adults.

## Methods

### Subjects

This study enrolled healthy male and female volunteers, 18–65 years of age, with a body mass index of 18–30 kg/m<sup>2</sup>. Healthy subjects were enrolled because it would be unethical to administer placebo, single-dose darbepoetin alfa, or single-dose C.E.R.A. to CKD patients who are stabilized

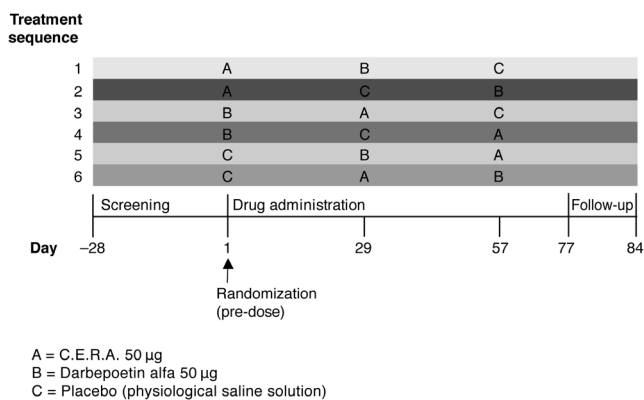
with current ESA therapy. Average hematocrit (packed cell volume) was required to be ≤ 48% for men and ≤ 43% for women, and ferritin had to be within normal limits. Eligible women were surgically sterile, postmenopausal for ≥ 1 year, or had a negative pregnancy test and were using two forms of contraception (including one barrier method). Men were required to use one barrier method of contraception for the duration of the study and for 3 months after the last dose of study drug. All subjects provided written informed consent prior to the study.

Subjects were excluded from study participation if they had a history of clinically significant gastrointestinal, renal, hepatic, bronchopulmonary, neurologic, cardiovascular, hematologic, hypertensive, or allergic disease, or if they had any major illness ≤ 1 month prior to the first dose. Those who smoked > 10 cigarettes per day were not eligible for participation. Administration of any drug between screening and first dose was not allowed, except for paracetamol (≤ 3000 mg per day prior to dosing), vitamin and mineral supplements, and, in women, hormone replacement therapy and hormonal contraception.

### Study design

This was a randomized, placebo-controlled, single-centre, single-blind, three-way crossover study with two components – an initial pilot phase followed by a larger confirmatory phase. Healthy subjects were screened for eligibility ≤ 4 weeks prior to dosing, after which they entered a 4-week washout period. Subjects were then randomized to one of six potential treatment sequences as shown in Figure 1 (ABC/ACB/BAC/BCA/CBA/CAB), involving SC injection on days 1, 29, and 57 of (A) C.E.R.A. 50 µg (vial 100 µg/mL, 0.5 mL); (B) darbepoetin alfa 50 µg (prefilled syringes 100 µg/mL, 0.5 mL); or (C) placebo (physiological saline solution, 0.5 mL). There was a 4-week washout period between each drug administration. The darbepoetin alfa dose chosen was based on the recommended correction dose in patients not on dialysis<sup>38</sup>. The C.E.R.A. dose was based on the correction dose identified from phase III trials of patients not on dialysis. Subjects had a final follow-up visit on day 77–84. The protocol was approved by an Independent Ethics Committee/Institutional Review Board prior to the start of the trial.

Where possible, SC treatment preparations and administration were standardized in the study. C.E.R.A., darbepoetin alfa, and placebo were all administered in a volume of 0.5 mL using 27G needles. For both active drugs, the concentration was



**Figure 1.** Randomized, placebo-controlled, single-center, single-blind, three-way crossover study design. C.E.R.A. = continuous erythropoietin receptor activator

100 µg/mL and the pH of the solution was  $6.2 \pm 0.2$ . Excipients in the C.E.R.A. formulation were sodium dihydrogen phosphate monohydrate, sodium sulfate, mannitol (E421), methionine, poloxamer 188, and water. Darbepoetin alfa contained sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80, and water. The injections were administered in the back of subjects' non-dominant arm and in the same area. Where possible, subjects received drug administration by the same member of staff. Owing to minor differences in the syringes, subjects were blindfolded during treatment administration.

### Pain assessments

Subjects assessed their SC injection site pain immediately after dosing and 1 hour after dosing on two scales – the visual analog scale (VAS) and the verbal rating scale (VRS)<sup>39</sup>. On the 100 mm VAS, subjects rated their pain from 0 mm ('no pain') to 100 mm ('pain as bad as it could be'). The six-point VRS was a categorical scale where 0 = 'no pain', 1 = 'minimal pain', 2 = 'slightly painful', 3 = 'moderately painful', 4 = 'very painful', and 5 = 'extremely painful'.

### Safety assessments

All adverse events were recorded during the study, including incidence, nature, severity, relationship to study medication, and frequency of any resultant treatment discontinuations. Serious adverse events were defined as fatal, life-threatening, requiring hospitalization, resulting in persistent or significant disability or incapacity, medically significant, or requiring intervention. Vital signs, physical examination, electrocardiogram, and clinical laboratory safety (hematology, biochemistry, and urinalysis) were also assessed.

### Endpoints

The primary endpoint was pain VAS immediately after SC administration. Secondary endpoints were pain VAS 1 hour after dosing, pain VRS immediately and at 1 hour after dosing, and safety and tolerability.

### Statistical analysis

The trial had a pilot phase and a confirmatory phase. Results from the pilot phase were used to determine the sample size required for the confirmatory phase, based on a clinically relevant effect size in the VAS range of 10–20 mm. Planned subject numbers were  $n = 12$  for the pilot phase and an additional maximum of  $n = 72$  for the confirmatory phase. For the final analysis, data from the two phases were combined. The study was powered to detect a difference of 10 mm in VAS score (when tested at  $\alpha = 0.05$  level) with at least 80% probability.

An analysis of variance (ANOVA) model, adjusting for treatment, gender, and period as fixed effects, and subject as random effect, was applied to the untransformed VAS scores. The chosen model allowed for different variances with respect to treatment (heteroscedasticity). The secondary endpoint, pain VRS immediately after dosing, was analyzed by means of a Wilcoxon signed rank test. No statistical analyses were performed on the other secondary endpoints.

## Results

### Subject disposition and baseline demographics

A combined total of 84 healthy volunteers (42 men and 42 women) were recruited in the pilot ( $n = 12$ ) and confirmatory ( $n = 72$ ) phases of this trial. Three female subjects withdrew prematurely from the study owing to serious adverse events, which are described below. At baseline, 83 of the 84 subjects were Caucasian, and mean  $\pm$  standard deviation (SD) age was  $33.5 \pm 11.4$  years (Table 1).

### Pain VAS

For the primary endpoint, C.E.R.A. was associated with significantly less pain VAS immediately after the SC injection compared with darbepoetin alfa. The least squares (LS) mean VAS was 21.5 (95% confidence interval [CI]: 17.5, 25.5) following SC administration of C.E.R.A. compared with 33.4 (95% CI: 28.4, 38.4) following SC darbepoetin alfa. The estimated difference between darbepoetin alfa and C.E.R.A. of 11.9 (95% CI: 6.35, 17.4) was statistically significant ( $p < 0.0001$ ) (Figure 2, Table 2). Placebo

**Table 1.** Subject baseline demographics

Subject demographics	All subjects (n = 84)
Gender, n (%)	
Male	42 (50)
Female	42 (50)
Race, n (%)	
Caucasian	83 (99)
Other	1 (1)
Age, years	
Mean ± SD	33.5 ± 11.4
Median	30.0
Range	18.0–65.0
Weight, kg	
Mean ± SD	69.0 ± 10.4
Median	68.4
Range	49.8–94.0
Height, cm	
Mean ± SD	170.4 ± 8.5
Median	170.0
Range	155.0–187.0
BMI, kg/m <sup>2</sup>	
Mean ± SD	23.7 ± 2.6
Median	23.7
Range	18.7–29.3
Tobacco use, n (%)	45 (54)

BMI = body mass index; SD = standard deviation

was associated with the lowest LS mean VAS value of 16.0 (95% CI: 12.4, 19.7), which was significantly lower than that for darbepoetin alfa ( $p < 0.0001$ ) or C.E.R.A. ( $p = 0.015$ ).

In most subjects, pain VAS 1 hour after administration was 0 mm ('no pain'). The highest VAS score was 25 mm in one subject following darbepoetin alfa.

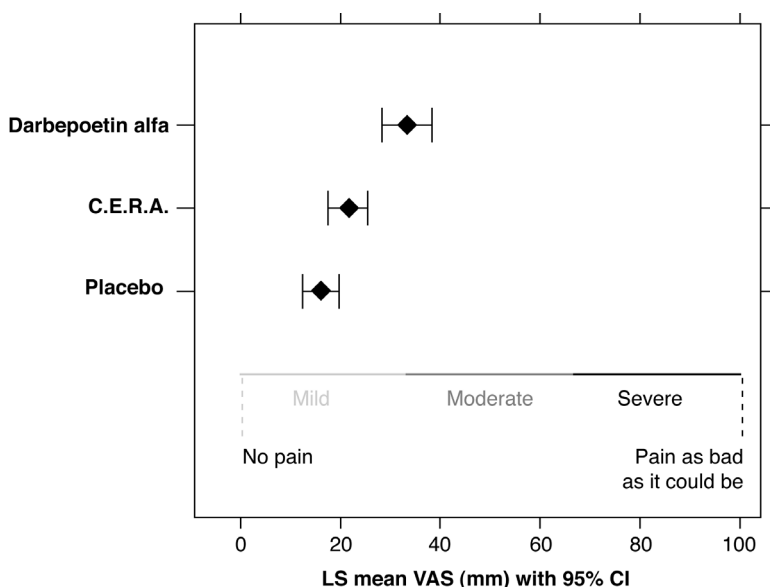
### Pain VRS

Immediately after SC administration, C.E.R.A. was associated with a lower incidence of pain VRS compared with darbepoetin alfa ( $p < 0.0001$ , Wilcoxon Signed Rank Test). In total, 28 subjects experienced the same level of pain following either C.E.R.A. or darbepoetin alfa, as depicted by the varying subject numbers in the main diagonal in Figure 3A. Only 10 subjects rated C.E.R.A. with a higher VRS score than darbepoetin alfa. In contrast, 43 subjects rated darbepoetin alfa with a higher VRS score than C.E.R.A. None of the C.E.R.A.-treated subjects gave a rating of 'very painful' (VRS score 4) compared with 11 subjects who were administered darbepoetin alfa.

One hour following administration of C.E.R.A. or darbepoetin alfa, most subjects rated their pain VRS as 0 ('no pain'); the highest VRS score was 1 ('minimal pain') in three subjects (Figure 3B).

### Adverse events

Table 3 summarizes the incidences of adverse events during the trial. The overall rate of adverse events was



$p < 0.0001$  for C.E.R.A. versus darbepoetin alfa according to the ANOVA model

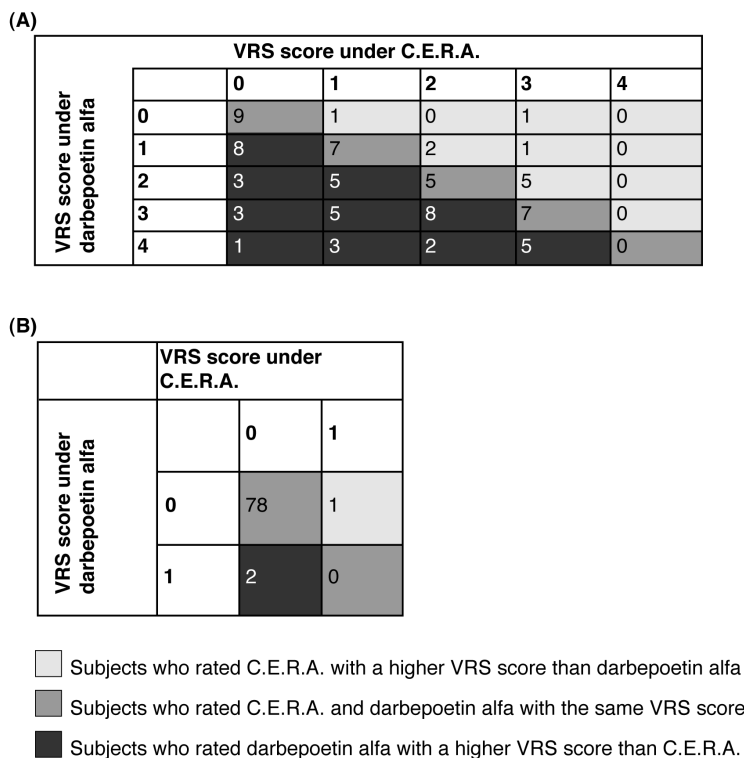
**Figure 2.** Least squares (LS) mean for pain visual analog scale (VAS) immediately following subcutaneous administration of continuous erythropoietin receptor activator (C.E.R.A.), darbepoetin alfa, and placebo.  $p < 0.0001$  for C.E.R.A. versus darbepoetin alfa according to the analysis of variance mode. CI = confidence interval

**Table 2.** Estimated population least squares means of subcutaneous injection site pain VAS following administration of C.E.R.A., darbepoetin alfa, and placebo

Pain assessment	Placebo (n = 82)	C.E.R.A. (n = 84)	Darbepoetin alfa (n = 81)
Pain VAS, LS mean (95% CI)			
Immediate*	16.0 (12.4, 19.7)	21.5 (17.5, 25.5)	33.4 (28.4, 38.4)
1 hour post-dose	0.82 (0.20, 1.43)	0.26 (0.02, 0.51)	0.82 (-0.01, 1.64)

\* $p < 0.0001$  for darbepoetin alfa versus C.E.R.A.,  $p < 0.0001$  for darbepoetin alfa versus placebo, and  $p = 0.015$  for C.E.R.A. versus placebo, according to the analysis of variance model

C.E.R.A. = continuous erythropoietin receptor activator; CI = confidence interval; LS = least squares; VAS = visual analog scale



**Figure 3.** All possible combinations for verbal rating scale (VRS) following subcutaneous administration of darbepoetin alfa (vertical) and continuous erythropoietin receptor activator (C.E.R.A.) (horizontal) (A) immediately after dosing and (B) 1 hour after dosing. Each subject belongs to one field only

In the six-point VRS, 0 = 'no pain', 1 = 'minimal pain', 2 = 'slightly painful', 3 = 'moderately painful', 4 = 'very painful', and 5 = 'extremely painful'. None of the subjects had a rating of 5. Example: dark shaded fields (10 fields in [A]) correspond to more pain following darbepoetin alfa than following C.E.R.A.

lower following administration of C.E.R.A. ( $n = 29$ , 35%) than darbepoetin alfa ( $n = 33$ , 41%), and was lowest following placebo ( $n = 24$ , 29%). Most adverse events were mild to moderate in intensity. Two subjects following administration of C.E.R.A. experienced events that were severe in intensity. These were food poisoning, which was considered unrelated to treatment, and an increase in transaminases (observed 37 days after the single dose), which was considered to have a remote possibility that it was related to treatment. Adverse

events experienced by  $\geq 2\%$  of subjects following C.E.R.A. or darbepoetin alfa administration were headache (13% vs. 14%), nasopharyngitis (5% vs. 5%), sensation of heaviness (2% vs. 2%), and wound (0% vs. 2%), respectively. Adverse events that were considered possibly or probably related to treatment occurred with a similar frequency following C.E.R.A. (8%) or darbepoetin alfa (7%); these were headache (both 6%), sensation of heaviness (both 1%), and vomiting (1% with C.E.R.A. only).

**Table 3.** Incidence of adverse events in all subjects, n (%)

Adverse event	Placebo (n = 82)	C.E.R.A. (n = 84)	Darbepoetin alfa (n = 81)
All adverse events	24 (29)	29 (35)	33 (41)
Adverse events with $\geq 2\%$ incidence			
Headache	9 (11)	11 (13)	11 (14)
Nasopharyngitis	2 (2)	4 (5)	4 (5)
Sensation of heaviness	1 (1)	2 (2)	2 (2)
Wound	0	0	2 (2)
Treatment-related adverse events*	1 (1)	7 (8)	6 (7)
Headache	0	5 (6)	5 (6)
Sensation of heaviness	1 (1)	1 (1)	1 (1)
Vomiting	0	1 (1)	0
Serious adverse events	0	3 (4)	0
Discontinuations owing to adverse events	0	3 (4)	0

\*Possibly/probably related to study treatment

C.E.R.A. = continuous erythropoietin receptor activator

Serious adverse events were reported in three women, all of whom were withdrawn from the study. The first subject received C.E.R.A. on day 1 and placebo on day 29 before being withdrawn because of ventricular extrasystoles; this serious adverse event was due to hyperthyroidism related to pre-existing Basedow disease and was considered unrelated to study drug. Although technically a protocol violator, Basedow disease was not diagnosed during screening owing to absence of clinical symptoms or laboratory evidence. The second subject received C.E.R.A. on day 1 and then was withdrawn owing to the severe increase in transaminases, described above, observed 37 days after the single dose; relation to treatment was considered remote. The third subject to be withdrawn experienced a second-degree atrioventricular block 30 days after receiving C.E.R.A. on day 1; relation to treatment was considered remote. Additional cardiac examinations showed that the second-degree atrioventricular block was intermittent and possibly related to an underlying vagotonia condition.

## Discussion

The study results showed that C.E.R.A., a novel, chemically synthesized, once-monthly ESA, was associated with significantly less SC injection site pain compared with darbepoetin alfa in healthy adults. This observed difference might be due to the nature of the injected ESA compounds. However, contribution

of the excipients of the active drug formulations cannot be excluded. These findings provide important information for physicians choosing ESA therapy for the management of patients with anemia of CKD. The improved SC tolerability and once-monthly dosing schedule of C.E.R.A. may reduce patients' experience of pain and enhance convenience leading to improved adherence to C.E.R.A. compared with darbepoetin alfa.

Previous studies have explored differences in injection site pain with SC administration of ESAs. Several pediatric studies showed that pain following SC injection of darbepoetin alfa is higher than with SC epoetin<sup>34-36</sup>. In 14 children with chronic renal failure receiving darbepoetin alfa for 6 months after previous use of epoetin, eight of them retrospectively indicated that injection site pain with darbepoetin alfa was more severe<sup>35</sup>. In another study, SC injections of darbepoetin alfa were reported to be more painful than those of epoetin in the majority of pediatric dialysis patients<sup>36</sup>. The first crossover study comparing SC injection site pain with ESAs in healthy adults showed that darbepoetin alfa was significantly more painful than epoetin beta ( $n = 40$ )<sup>37</sup>. Pain scores were significantly higher immediately after SC injection with darbepoetin alfa compared with epoetin beta for both median verbal pain score (2 [95% CI: 0.0, 3.0] vs. 0 [95% CI: 0.0, 1.0];  $p < 0.0001$ ) and VAS (2.0 [95% CI: 1.4, 4.2] vs. 0.5 [95% CI: 0.0, 1.5];  $p < 0.0001$ ). The proportion of subjects reporting moderate to severe pain immediately after injection was also higher following darbepoetin alfa than

epoetin beta (37.5% vs. 5.4%). Of note is that the previous studies showing that SC administration of darbepoetin alfa was more painful than SC epoetin were conducted before a formulation change was introduced for darbepoetin alfa in June 2006. The present study was conducted after the formulation change and demonstrated that pain following SC injection of darbepoetin alfa was higher than with SC C.E.R.A. in healthy adults.

The design of this trial (randomized, single-blind, three-way crossover) ensured that any observed differences would not be a result of variation in subjects' pain perception. In addition, the trial methodology was standardized where possible to ensure that any observed differences in pain perception between SC treatments were unlikely to result from properties of the final preparation (e.g., drug concentration, injection volume) or injection procedure (e.g., needle size or sharpness, location of injection site, and staff's administration technique).

The inclusion of a placebo in this trial demonstrated that SC injection of physiological saline solution was associated with pain, and that this pain was less than that following either of the active drug formulations. Therefore, the differences in pain perception observed between placebo, darbepoetin alfa, and C.E.R.A. resulted from either the nature of the injected ESA compounds or the excipients of the active drug formulations. Given the differences in the excipients of the active drug formulations, their contribution to the variation in SC injection site pain experienced by subjects cannot be ruled out. C.E.R.A. contained sodium dihydrogen phosphate monohydrate, sodium sulfate, mannitol (E421), methionine, and poloxamer 188, whereas darbepoetin alfa contained sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, and polysorbate 80.

In the present study, serious adverse events occurred in three subjects, all of whom had received C.E.R.A. on day 1 – ventricular extrasystoles due to pre-existing Basedow disease, increased transaminases, and intermittent second-degree atrioventricular block possibly related to an underlying vagotonia condition. The relationship of these serious adverse events to study drug was considered remote or unrelated. Data from phase III trials have shown that C.E.R.A. once monthly provided comparable tolerability to traditional ESAs in patients with CKD with or without dialysis<sup>13-20</sup>.

Some limitations associated with this trial should be noted. This study sample of healthy subjects was relatively small, and the findings need to be confirmed in a large trial of patients with CKD. Chronically ill patients may be more susceptible to pain and psychological distress from receiving repeated injections.

## Conclusions

SC administration of C.E.R.A. is significantly less painful than SC darbepoetin alfa in healthy adults. Treatment of anemia of CKD with once-monthly SC injection of C.E.R.A. may provide a lower total pain burden compared with darbepoetin alfa.

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