

ORIGINAL PAPER

doi: 10.5455/medarh.2020.74.109-114

MED ARCH. 2020 APR; 74(2): 109-114

RECEIVED: JAN 18, 2020 | ACCEPTED: MAR 30, 2020

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Safety and Efficacy of Methoxy Polyethylene Glycol-epoetin Beta in Anemia Treatment in Patients on Hemodialysis: a Macedonian Experience

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ABSTRACT

Introduction: Anemia in patients with chronic kidney disease (CKD) is present in about 50% in pre-dialysis and over 90% of patients on hemodialysis. Erythropoiesis-stimulating agent (ESA) is a standard therapy for renal anemia, but management of anemia in CKD still remains a challenge from the treatment point of view. **Aim:** To evaluate safety and efficacy of methoxy polyethylene glycol-epoetin beta as continuous erythropoietin receptor activator (C.E.R.A.) in maintenance of haemoglobin (Hb) concentrations in patients with chronic renal anemia in the routine clinical practice. **Methods:** National, multicenter, observational, prospective study in patients with CKD on hemodialysis for maintenance of Hb levels with once-monthly therapy with C.E.R.A. In 8 dialysis centers 184 adult patients were observed and followed up every month during one year. Total number of enrolled patients was 185 from whom 184 patients were observed and 147 patients were followed for 12 months as 37 dropped out from the study earlier. **Results:** Overall mean dose of C.E.R.A. was 115.2 µg with average 4.99 dose modifications per patient. Among 184 patients observed, total number of 121 adverse events (AEs) were identified in 49 of the patients. The most of the AEs were of mild or moderate severity. A few serious AEs were assessed and reported as not related to the drug administration. Mean Hb levels during the study varied but were maintained stable in the range of 100-120 g/l. **Conclusion:** Safety and tolerability of C.E.R.A. was as expected as the frequency and type of AEs was similar to the known pattern from the studies done in other countries and relevant literature. Hb levels as the primary efficacy parameter of C.E.R.A. treatment were maintained stable within the target range during the study.

Keywords: Chronic kidney disease, renal failure, Anemia, Continuous erythropoietin receptor activator, C.E.R.A., Methoxy polyethylene glycol-epoetin beta, tolerability, efficacy.

1. INTRODUCTION

Anemia in patients with chronic kidney disease (CKD) is present in about 50% in pre-dialysis and over 90% of patients on hemodialysis due to endogenous erythropoietin deficiency. Though the erythropoiesis-stimulating agent (ESA) is a standard therapy for renal anemia, management of anemia in CKD still remains a challenge from treatment point of view (1-3).

The reduced oxygen delivery to tissues due to anemia, leads to fatigue and dyspnea, poor health-related quality of life (QoL) and significant morbidity and mortality. Other consequences, such as impaired cognitive function, sleep disorders, depression, depressed immune func-

tion, altered hemostasis, and impaired cardiac function are not uncommon (3-5).

Over the last few decades, several iron and erythropoietin products have been licensed for treating anemia in order to increase survival, decrease hospitalizations and improve QoL of CKD patients. In addition, a number of published articles discussed the benefits and possible risks associated with ESA treatment, especially of long term treatment (3, 6, 7). A number of clinical trials and observational studies in CKD populations demonstrated the benefits of normalizing hemoglobin (Hb) levels followed by frequent revisions of the guidelines for management of CKD anemia (2, 5, 8-12).

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An optimal Hb target for CKD patients is in the range of 110.0 to 120.0 g/L. In CKD patients receiving ESA therapy and iron replacement, the Hb target should not be lower than 90.0 g/l and greater than 130.0 g/l. Individualization of the therapy is reasonable as some patients may have experience improvements in QoL at higher Hb concentration. Correction of Hb concentration should be based on post dialysis values, namely dry Hb concentrations (13-17).

Many guidelines help physicians on how to treat renal anemia patients with ESAs and to ensure safely prescription of dosage and route of administration. It is also important to know how to diagnose and manage complications associated with anemia and ESAs treatment. In addition, guidelines also help define the areas where evidence is lacking and research needed (4, 13, 14, 18, 19).

Three forms of ESAs are available for clinical use: epoetin alpha, epoetin beta (darbepoetin alpha) and methoxy polyethylene glycol-epoetin beta as continuous erythropoietin receptor activator (C.E.R.A. or Mircera®). The treatment of patients on hemodialysis with ESAs has been a major advance for the management of renal anemia (6, 7, 20).

Epoetin alpha has relatively short half-life of 8.5 hours and requires frequent administration of two to three times per week. Darbepoetin alpha has longer half-life (25 hours), which allows less frequent dosing to treat anemia in CKD, when administered intravenously (i.v.) or subcutaneously (s.c.) once weekly or once every other week (6, 7). ESA therapy should be tailored to the patient's profile by using the smallest possible dose to control anemia symptoms and achieve Hb target level. It should also be accepted that Hb excursions above and below the target level will occur from time to time which needs frequent ESA dose adjustments (17, 21).

C.E.R.A. is an ESA with long half-life (~130 hours). It allows longer dosing intervals (once monthly) for treatment of renal anemia. The initial drug dose is 6 µg/kg body weight administered as a single i.v. or s.c. injection once every two weeks. Once Hb has been maintained between 100-120 g/l, C.E.R.A. may be administered once monthly using a double dose of 12 µg/kg. C.E.R.A. dosage is based on the total weekly ESA dose at the time of conversion ranging from once monthly dose of 120-360 µg or 60-180 µg once every two weeks. When C.E.R.A. therapy is initiated or adjusted, Hb should be monitored every two weeks until stabilized, and every two to four weeks thereafter (10, 20, 22-24).

In 2007 C.E.R.A. was approved in the EU following the largest and most comprehensive research program ever for a renal anemia drug at initial registration. The data have shown that renal anemia treated with short-acting and frequently administered ESA can be directly switched to once-monthly treatment with C.E.R.A. for smooth and steady erythropoiesis and stable maintenance of Hb levels at extended administration intervals in patients on dialysis directly converted from epoetin or darbepoetin alfa (25-27).

C.E.R.A. improves the convenience and therapeutic utility of the drug resulting in a smooth and steady

rise in hemoglobin levels. Patients with CKD on dialysis who had previously been treated with an ESA maintained stable Hb levels (within ±10 g/l of baseline and within a range of 100–130 g/l) when directly converted to C.E.R.A. administered i.v. or s.c. every 2 or 4 weeks tailored to the clinical response. C.E.R.A. has been administered to more than 2000 CKD patients in clinical studies to date, providing a firm understanding of its efficacy, safety and tolerability (5, 10-12, 22-28).

The European Medicines Agency (EMA) Committee for Human Medicinal Products (CHMP) concluded that the benefits of ESAs products continue to outweigh their risks in the approved indications if used in the treatment of anemia for maintaining the target Hb range for all epoetins of 100-120 g/l. The EMA-CHMP issued Public Statement to healthcare professionals to use ESAs strictly in accordance with their approved Summary of Product Characteristics (SPC) regarding the indications and dosing recommendations. The European Renal Best Practice Guidelines recommend a Hb range 110-120 g/l without intentionally exceeding 130 g/l. In addition, the EMA-CHMP emphasized the need to increase the scientific knowledge on the effects of ESAs and expressed the readiness to continue to review the safety profile of the epoetins within the terms of their currently authorized indications as additional data becomes available (15, 16, 19).

2. AIM

To investigate and evaluate the safety and tolerability, as well as therapeutic efficacy of C.E.R.A. with once-monthly i.v. administration of the drug in hemodialysis patients with chronic renal anaemia treated with intravenous epoetin alfa or beta, regardless of previous dosing intervals.

The main research question and hypothesis was toward expected well tolerability and safety, as well as therapeutic efficacy of C.E.R.A. assessing the AEs and maintenance of Hb concentrations.

3. MATERIAL AND METHODS

Study design and participants

A national, multicenter, observational, prospective study in patients with CKD on hemodialysis receiving once-monthly i.v. therapy with C.E.R.A. for maintenance of Hb levels according to the standard of care and in line with local labelling. The study was a single-arm, open label trial conducted in R.N. Macedonia from 2010 to 2014 in accordance with the local and international ethical standards and regulations (29-30).

Clinical examination and complete laboratory investigations for haematological profile and Hb assessment were made five times during the study, i.e. at enrolment and at week 8, 16, 24 and 48. Adverse events (AEs) and serious adverse events (SAEs) were recorded at every visit post therapy.

Dosing and treatment duration of C.E.R.A. were at the discretion of the investigator. During C.E.R.A. treatment, laboratory assessments were routinely performed. Available data from the medical record relevant for treat-

ment outcome were documented in the case report form (CRF) fulfilled by the investigator during the treatment with C.E.R.A.

The end of study was the date of the last visit of the last subject undergoing the study.

Patients were recruited and observed during the routine clinical practice in 8 dialyses centers in R.N. Macedonia with a minimum recruitment of 10 patients per center. The first subject was enrolled on June 22, 2010. Re-gratuation period lasted till December 24, 2012. Data were collected till January 24, 2014. Target population were adult subjects on dialysis with CKD who were receiving C.E.R.A. treatment for maintenance of Hb levels, followed for the duration of their treatment with C.E.R.A. up to one year observation period.

Patients who enrolled and completed a period of treatment earlier in accordance with the protocol, or who discontinued prematurely from the study were not permitted to re-enrol.

Patients at week 0 had to fulfil eligibility criteria for inclusion related to age, duration of haemodialysis, renal anaemia with Hb concentration from 100.0 to 120.0 g/l, previous ESAs treatment, as well as written informed consent. Main exclusion criteria related to transfusion of red blood cells during the previous 2 months, hypertension exceeding 170/100 mmHg despite medication, gastrointestinal bleeding, active malignant disease, haemolysis, haemoglobinopathies, congestive heart failure, myocardial infarction or stroke, pregnancy or lactation period etc.

Total number of enrolled patients on dialysis was 185 from whom 184 patients data were analyzed and 147 patients were followed for 12 months as 37 dropped out from the study earlier. Eligibility was confirmed prior to the first planned dose of study medication. Data were collected from patient records using a CRF of each patient fulfilled by the investigator. Average age of the patients was 58.0±10.9 years with minimum 27 years and maximum 82 years. According to the gender structure 57.6% of the patients were male and 42.4% were female. Average patients' height was 164.4±10.0 cm with minimum 130.0 cm and maximum 188.0 cm (±SD 10.038). Average patients' weight was 67.0±17.7 kg with minimum 39.0 kg and maximum 121.0 kg (±SD 14.659).

Approach for safety and efficacy evaluation

Route of administration and dose of C.E.R.A. per injection, as well as concomitant treatment for anemia like iron and incidence of AEs during the study were recorded and evaluated. Correction of anemia and maintenance of Hb was evaluated in patients with Hb<100 g/l at enrolment and determined by the percentage of these patients achieving, and the time required to achieve, target Hb range of 100-120 g/l. Maintenance of target Hb was evaluated by the mean time spent in target Hb range. Endpoints of the study for safety of C.E.R.A. relate to AEs and SAEs during treatment course, especially the frequency, outcome and relation to the therapy of SAEs. Endpoints for efficacy of C.E.R.A. relate to C.E.R.A. doses and dose adjustments during the study, Influence of patient demographics, patient compliance, co-mor-

bidity and baseline clinical variables on the levels and maintenance of HB within the target level in various periods during the study.

Statistical analysis

Collected data for safety and efficacy parameters were processed using the standard descriptive and analytic methods for qualitative (ratio, proportions, rates and statistical significance of differences - Difference test) and quantitative statistical series (n, mean, SD, median, range and 95% significance difference with Mann-Whitney U test at confidence interval p<0.05). Statistical significance of differences in Hb values during the correction period was analysed with Analysis of Variance - ANOVA.

4. RESULTS

The main results related to safety and therapeutic efficacy of C.E.R.A. are presented in logical order, as well as in tables and graphics.

Participants

Total number of enrolled patients on dialysis was 185. One CRF wasn't completed and couldn't be evaluated. In the safety analysis set were included 184 patients on dialysis from 8 centers. For the planned 12 month period 147 (79.9%) of the patients were followed during 12 month period and 37 (20.1%) were withdrawn from the study prematurely due to various reasons. The reasons for treatment interruption are presented in Figure 1.

The number of patients who died was 10, but by the discretion of the investigator this event was not related to the drug administration.

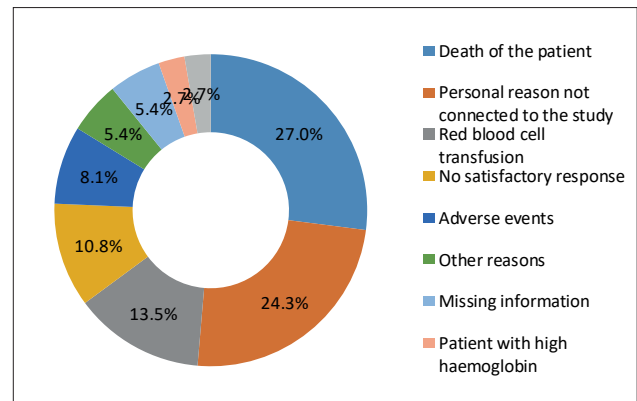


Figure 1. Title: Reasons for treatment interruption and early withdrawal of patients from the study

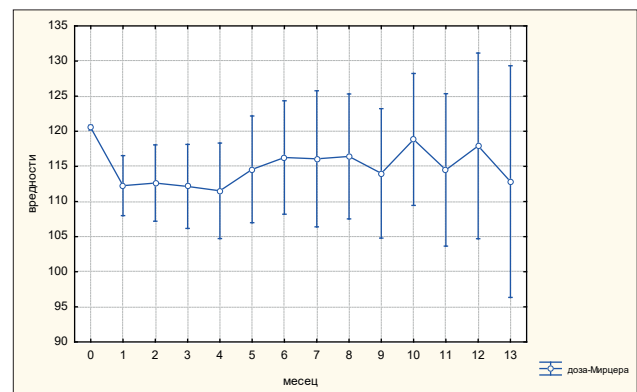


Figure 2. Mean dose of C.E.R.A. in µg given during the 12 month period

Week no.	No.of patients	Mean Hb	Minimum	Maximum	±Stand.Dev
Enrollment	184	110.3	81.0	129.0	8.671274
Week 8	179	110.8	84.0	148.0	13.31517
Week 16	155	111.3	75.0	151.0	14.97250
Week 24	161	111.2	69.0	157.0	14.93382
Week 48	130	111.4	70.0	151.0	13.5594

Table 1. Mean Hb level at enrollment and at the week 8, 16, 24 and 48

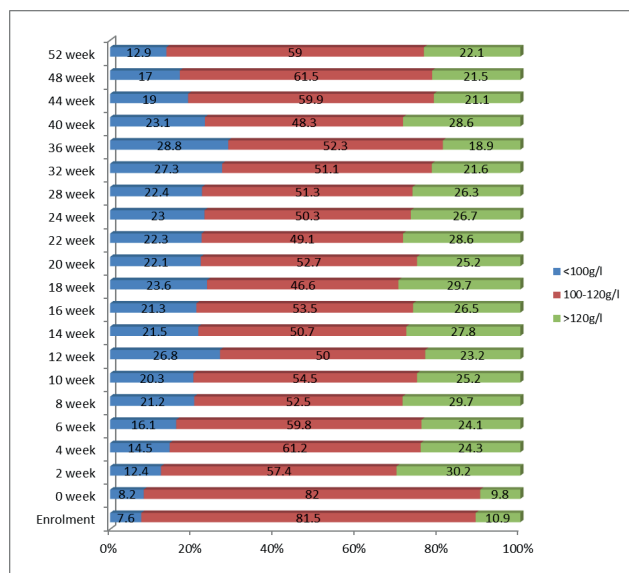


Figure 3. Distribution of patients according hemoglobin levels during the study, in three intervals: <100g/l, 100-120g/l and >120g/l

Primary and concomitant diseases

The most common primary diseases for renal impairment were: unknown cause for CKD 42 (22.8%), hypertension 35 (19.0%), nephroangiosclerosis 30 (16.3%), glomerulonephropathy 28 (15.1%), interstitial nephropathy 20 (10.9%), adult polycystic kidney disease 18 (9.7%); diabetes mellitus 17 (9.2%) etc. The most common concomitant diseases noted by the investigator were: hypertension (24.5%), anaemia (19.6%), renal osteodystrophy (19.6%), cardiomyopathy (13.6%), hepatitis C (6.5%), gastritis (6.0%), polyarthralgia (5.4%), diabetes mellitus (4.9%), angina pectoris and arrhythmia (4.3%). All other diseases were represented with less than 2%. According to the anaemia therapy before enrolment, 182 patients were treated with erythropoietin and 107 with Fe (some of them with both).

Dosage and administration of C.E.R.A.

Mean dose of C.E.R.A. at the beginning of the study was 120.5 µg. During the 6 months titration period, mean doses for the following applications were 112.3, 112.6, 112.1, 111.5, 114.6 and 116.3 µg, respectively. Mean dose of C.E.R.A. at the end of the study was 117.9 µg and overall mean dose was 115.2 µg (Figure 2).

Variations of mean C.E.R.A. dose during the study were observed. The difference between mean doses has no statistical significance for p<0.05. During the observational period of 12 months, total number of 919 dose modifications in 184 patients was done, which is average of 4.99 dose modifications per patient in order to maintain Hb level within the target range of 100-120 g/l.

Safety and tolerability evaluation

Safety analysis was performed on population of 184 patients. Total number of 121 AEs was identified in 49 of the patients. Investigators reported only 5 AEs as related to the drug administration as follows: rash 2, hypotension 1, facial erythema with dyspnea and lumbalgia 1 and thrombosis of the femoral catheter 1. All related AEs were resolved except hypotension, listed in the SPC (28).

Serious adverse events (SAEs) were reported at 22 (11.96%) of the patients during the treatment course. By the investigators opinion all SAEs were related to cardiovascular diseases and other comorbidities and complications and not to the drug administration. Out of 22 SAEs, 6 were defined as resolved, 2 as persisting, 4 as improved and 10 were fatal (5.4%). The most common SAEs were death related to comorbidities and complications in advanced age (4 cases died due to myocardial infarction with average age of about 64 years, 2 patients died due to cerebrovascular accident with an average age of about 72 years etc.). By the discretion of the investigator/s none of the SAEs was assessed as related to C.E.R.A.

Therapeutic efficacy evaluation

Complete laboratory investigations were performed five times during the study, i.e. at enrolment and at week 8, 16, 24 and 48. The average level of Hb at inclusion was 110.3 ± 8.7 g/l and at week 48 was 111.4 ± 13.6 g/l (Table 1). Change of mean Hb level between baseline and 6 month (24 week) was 0.8% (from 110.3 to 111.2 g/l). Distribution of patients according Hb levels during the study in three intervals (<100g/l; 100-120g/l and >120g/l) is shown in Figure 3. More than a half of the patients in the interval of 12 months after initiation of the treatment with C.E.R.A. were with mean Hb level from 100-120 g/l; 53.5% at week 16; 46.6% at week 18; 52.7% at week 20; 49.1% at week 22; 50.3% at the end of the titration period, week 24, and 61.5% at the end of observation period, week 48 (twelfth month). Mean Hb levels during the study varied but were always in the range of 100-120g/l. At the start (week 0) mean Hb level was 110.3 g/l, at the end of titration period (week 24) was 111.2 g/l and at the end of the study (week 48) was 111.4 g/l. The difference between the mean Hb values is statistically insignificant for p<0.05, which means that hemoglobin levels maintained stable within the target range.

5. DISCUSSION

Among 185 patients on hemodialysis enrolled in this study, who have switched from a previous ESA to C.E.R.A., 184 were analyzed for safety and efficacy of C.E.R.A. with mean dose of 120.5 µg at the beginning of the study, and overall mean dose of 115.2 µg and with av-

erage 4.99 dose modifications per patient. Results of our study confirm the known safety profile and tolerability, as well as the efficacy of C.E.R.A. in anemia management in CKD patients on dialysis. Main findings about safety of C.E.R.A. show that the total number of 121 AEs were identified in 49/184 of the patients. SAEs were reported in 22 (11.96%) of the patients during the treatment course. Concerning seriousness, 7 SAEs were followed by initial/prolonged hospitalization, 5 were medically significant and 10 (5.4%) resulted in death. It should be mentioned that the clinical profile of CKD patients is complex with advanced age and present comorbidities and possible resistance factors to ESAs treatment. By the investigators opinion all SAEs weren't related to the drug administration but to comorbidities and complications (cerebrovascular accidents, myocardial infarction etc). Results from some other studies showed that C.E.R.A. was generally well tolerated, with the most AEs being of mild to moderate severity, associated with co-morbidities and identified risk factors for vascular disease or hemorrhage at baseline in this group of patients seen in routine nephrology practice. Adverse events associated with the use of C.E.R.A. usually include hypertension, diarrhea, nasopharyngitis, upper respiratory tract infection, headache, muscle spasms, procedural hypotension, fluid overload etc. (2, 8, 22, 27). The frequency and type of AEs and SAEs in our study was similar to the known patterns of AEs and SAEs, as well as the patients who died (5,4% in our study population) as noted in the SPC (5,7 - 6.1%) and other clinical trials (2, 5, 10, 11, 23, 28).

The EMEA in 2007 reviewed the safety of epoetins due to previous clinical trials data about unexplained excess mortality in patients with anemia associated with cancer and with CKD who have been treated with epoetins to achieve relatively high target Hb concentrations. As a consequence, it increased the risk of mortality and cardiovascular morbidity. Additional explanation from EMEA was that trials have shown a small unexplained excess mortality related to high target Hb concentrations without significant benefits from ESAs administration to increase Hb concentration beyond the level necessary to control symptoms of anemia and to avoid blood transfusion (15, 16).

Main findings about efficacy show that the mean Hb levels during the study varied but, for majority of the patients (61.5% at the end of observation period, week 48), were maintained stable within the target range of 100-120g/l. The hypothesis was affirmed as once monthly i.v. administration of C.E.R.A. represented a safe treatment option for patients as the AEs reported in this study are consistent with the established safety profile of C.E.R.A. In addition, the results of the study proved the efficacy of C.E.R.A. in management of renal anemia in CKD patients on dialysis with i.v. application once monthly providing stable Hb responses. Such results were confirmed with some other clinical studies (8, 10, 20, 23, 30). Some studies proved that more than 90% of patients experienced Hb cycling with amplitude 25.1 ± 9 g/l and duration of Hb excursions >8 weeks (17, 21).

This Macedonian study expanded the volume and diversity of clinical safety experience and knowledge about therapeutic efficacy of C.E.R.A. in order to inform future clinical practice and to demonstrate the safety and efficacy of C.E.R.A. in the context of the EMEA guidelines (16, 28). Results from some other studies proved that C.E.R.A. administration i.v. or s.c., every 2 or 4 weeks, is highly effective and maintain successfully baseline Hb level in range of 110 to 120 g/l with average oscillations of about 10 g/l within the evaluation period. C.E.R.A. dosage is based on the total weekly ESA dose at the time of conversion ranging from once monthly dose of 120-360 µg or once every two weeks dose of 60-180 µg (2, 8, 10, 22-24).

The MAXIMA study was the first-ever clinical study that examined the direct conversion to a once-monthly dosing regimen regardless of previous dosing intervals. This ability to switch patients from ESAs directly to C.E.R.A. may help to simplify anaemia management and to reduce the renal unit workload, as well as to free up valuable time that could be used by staff to focus on other aspects of patient care (9, 26, 27). The AEs during dose-titration after conversion to C.E.R.A. were not higher than those with an unchanged regimen of epoetin therapy (9, 26).

Limitation of the study

The study was observational, non-interventional, open label trial where patients were followed during standard clinical practice in 8 dialysis centres in R.N. Macedonia. This study depicts the situation in a short period of time (12 months) in a limited territory of R.N. Macedonia. Even though, the study reflects the observations in the routine clinical practice and the results might be generalized to the treatment of renal anemia patients. Possible biases in reported results might arise from the patients, physicians, and dialysis unit staff due to observational character of the study and some differences in local clinical practice in various dialysis centers.

6. CONCLUSION

Results from our study increased the scientific knowledge and expanded the volume and diversity of clinical safety experience and efficacy of C.E.R.A. and filled the gap for data in anemia management in CKD patients on dialysis in R.N. Macedonia. In patients with anemia associated with CKD on dialysis (previously treated with ESAs), C.E.R.A. was well tolerated as traditional ESA treatments, maintaining stable Hb levels within the target range when administered once monthly. In addition, C.E.R.A. is convenient for a simplified regimen of anemia management with monthly dosing schedule as compared to traditional frequently administered ESAs. Doctors should use C.E.R.A. and epoetins, in general, strictly in accordance with their approved SPC, regarding the indications and dosing recommendations.

- **Acknowledgements:** The authors acknowledge the efforts and cooperation of the principal and other investigators, as well as extend thankfulness to patients and staff of eight study centers of dialysis and related public hospitals and health centers in R.N. Macedonia.

We also acknowledge Prof. Rozalinda Isjanovska for statistical analyses of data. Finally, we acknowledge support and cooperation with the Hoffmann La Roche Ltd. Basel, Representative Office Skopje, employee and staff.

- **Authors contribution:** Each author were included equally in all steps of preparation of this article. Final proof reading was made by the first author.
- **Conflict of interest:** None declared.
- **Financial support and sponsorship:** The study was funded by the Hoffmann La Roche Ltd. Basel, Representative Office Skopje, R.N. Macedonia, and study honoraria were provided for principal investigators and other external collaborators and experts.

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