PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Anemia management with C.E.R.A. in routine clinical practice: OCEANE (Cohorte Mircera® patients non dialysés), a national, multicenter, longitudinal, observational prospective study, in patients with chronic kidney disease not on dialysis
AUTHORS	Frimat, Luc; Mariat, Christophe; Landais, Paul; Koné, Sébastien; Commenges, Bénédicte; Choukroun, Gabriel

VERSION 1 - REVIEW

REVIEWER	Rainer P Woitas Head of Nephrology Division, University Clinics, University of Bonn, Bonn Germany There are no competing interests.
REVIEW RETURNED	25-Sep-2012

THE STUDY	Study design: Non-interventional studies (NIS) are an essential part of the clinical development program of new pharmaceutics. In non-interventional trials patients are treated under real life conditions to investigate the effectiveness of a drug. However, approximately 50% of ESA-naive patients were within the 10-12 g/dL target range at baseline, which in turn means that these patients did not need ESA therapy. In light of the so called endpoint percentage of patients who achieved target hemoglobin (Hb) levels as per European Medicines Agency guidelines (10-12 g/dL) around 6 months of treatment the study population seems not appropriate. The high rate of premature withdrawal (25%) is unexpected and should be clarified. References: the CORDATUS study which was a randomized trial in CKD patients should have been cited also.
RESULTS & CONCLUSIONS	Non-interventional studies (NIS) are an essential part of the clinical development program of new pharmaceutics. In non-interventional trials patients are treated under real life conditions to investigate the effectiveness of a drug. However, 51.6% (n=128) of ESA-naive patients were within the 10-12 g/dL target range at baseline, which in turn means that these patients did not need ESA therapy. In light of the so called endpoint percentage of patients who achieved target hemoglobin (Hb) levels as per European Medicines Agency guidelines (10-12 g/dL) around 6 months of treatment the study population seems not appropriate.
GENERAL COMMENTS	Basically the manuscript could be condensed to a short

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	communication without loss of information. Similarly clarity and arrangement of the data and the informations provided could be improved.

REVIEWER	Daniel Teta, MD, PhD Médecin Adjoint Departement of Nephrology Centre Hospitalier Universitaire Vaudois 1011 Lausanne Switzerland I declare that I do not have any competing interest with the authors and /or with the company producing CERA.
REVIEW RETURNED	07-Oct-2012

THE STUDY	There are non inclusion/exclusion criteria. The way patients were selected is unclear. I doubt that the patients are representative of the population of patients with CKD 4: For instance, there were no patient with cancer, and a relatively low proportion of CKD patients with cardiovascular co-morbidities.
RESULTS & CONCLUSIONS	The authors focussed on the proportion of the patients in the Hb target 10-12 g/dL which was the end-point of the study. However, they did not analyse the subgroup of patients who were below the Hb target of 10 g/dL, i.e. 32% of the patients. The analysis of the latter subgroup would be interesting since there is a real potential to improve the proportion of these patients below the Hb target, rather than the proportion of patients with Hb > 12 g/dL. This study should give more insight in this subgroup (Hb < 10g/dL) in order to identify causal factors of non response that might be improved in the future.
REPORTING & ETHICS	Although the authors report that the study was conducted in accordance with ethical guidelines established by ADELF, it is unclear if the patients received an informed consent and gave their approval.
GENERAL COMMENTS	This observational survey from Frimat et al. gives interesting insights in the treatment of CKD-associated anemia with CERA, in patients not on dialysis and in patients with a kidney transplant. Few data are yet available with this drug in these categories of patients. This is why this report is of interest. The paper is well written, the data are well presented and credible. However, the study has methodological limitations which need to be addressed in detail. In addition, some points need in my opinion to be further analysed in order to improve the interpretation of the data. 1. It is unclear how the investigators have selected the patients to enroll in the study. There was no random selection into the study. Looking at the description of the patients, a selection bias is very likely since for instance no patient have cancer at baseline and a relatively low proportion of patients have cardiovascular co-morbidities. . This might have affected the data in a positive fashion. Thus, the results may be difficult to generalise. The authors shoud give more details with regard to patient selection and comment on this limitation. 2. The proportion of patients with no response, i.e 32% did not achieve the Hb level of at least 10 g/dL has not been analysed. The

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	authors focussed on the proportion of the patients in the Hb target 10-12 g/dL which was the end-point of the study. The analysis of the subgroup of patients not achieving an Hb of 10 g/dL would be interesting since there is a real room for potential improvement in this group of patients, more than in patients with Hb > 12 g/dL. This study should give more insight in this subgroup (Hb < 10g/dL) in order to identify causal factors of non response that might be improved in the future, i.e. iPTH, CRP, iron deficiency etc... 3. Although the authors report that the study was conducted in accordance with ethical guidelines established by ADELF, it is unclear if the patients received a structured information and gave an informed consent. 4. iPTH, a known cause of ESA resistance, is not mentioned. 5. CRP has been measured only at baseline, but not later. 6. How was the adherence to CERA assessed?

VERSION 1 – AUTHOR RESPONSE

Reviewer: Rainer P Woitas
Head of Nephrology Division,
University Clinics,
University of Bonn, Bonn Germany
There are no competing interests.
Study design:
Non-interventional studies (NIS) are an essential part of the clinical development program of new pharmaceutics. In non-interventional trials patients are treated under real life conditions to investigate the effectiveness of a drug. However, approximately 50% of ESA-naive patients were within the 10-12 g/dL target range at baseline, which in turn means that these patients did not need ESA therapy.
In light of the so called endpoint percentage of patients who achieved target hemoglobin (Hb) levels as per European Medicines Agency guidelines (10-12 g/dL) around 6 months of treatment the study population seems not appropriate.
The high rate of premature withdrawal (25%) is unexpected and should be clarified.
Answer:We detailed all reasons of premature withdrawals in the section “Description of the cohort” as requested (see manuscript page 6).

References: the CORDATUS study which was a randomized trial in CKD patients should have been cited also.
Answer:We added the reference of the CORDATUS study (as the reference 17) in the introduction when we mentioned the clinical trials which demonstrated efficacy and safety of C.E.R.A. in patients not on dialysis (see manuscript page 4).

Basically the manuscript could be condensed to a short communication without loss of information. Similarly clarity and arrangement of the data and the information provided could be improved.
Answer:We clarified, completed and improved the manuscriptas requested by the managing editor and reviewers. All changes are in red in the revised manuscript.

Reviewer: Daniel Teta, MD, PhD
MédecinAdjoint
Departement of Nephrology

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Switzerland

I declare that I do not have any competing interest with the authors and /or with the company producing CERA.

There are non inclusion/exclusion criteria. The way patients were selected is unclear.
I doubt that the patients are representative of the population of patients with CKD 4: For instance, there were no patient with cancer, and a relatively low proportion of CKD patients with cardiovascular co-morbidities.
The authors focussed on the proportion of the patients in the Hb target 10-12 g/dL which was the end-point of the study.
However, they did not analyse the subgroup of patients who were below the Hb target of 10 g/dL, i.e. 32% of the patients. The analysis of the latter subgroup would be interesting since there is a real potential to improve the proportion of these patients below the Hb target, rather than the proportion of patients with Hb> 12 g/dL. This study should give more insight in this subgroup (Hb< 10g/dL) in order to identify causal factors of non response that might be improved in the future.
Although the authors report that the study was conducted in accordance with ethical guidelines established by ADELF, it is unclear if the patients received an informed consent and gave their approval.
This observational survey from Frimat et al. gives interesting insights in the treatment of CKD-associated anemia with CERA, in patients not on dialysis and in patients with a kidney transplant. Few data are yet available with this drug in these categories of patients. This is why this report is of interest. The paper is well written, the data are well presented and credible.
However, the study has methodological limitations which need to be addressed in detail. In addition, some points need in my opinion to be further analysed in order to improve the interpretation of the data.

1. It is unclear how the investigators have selected the patients to enroll in the study. There was no random selection into the study. Looking at the description of the patients, a selection bias is very likely since for instance no patient have cancer at baseline and a relatively low proportion of patients have cardiovascular co-morbidities. . This might have affected the data in a positive fashion. Thus, the results may be difficult to generalise. The authors should give more details with regard to patient selection and comment on this limitation.
Answer:
- We rewrote the paragraph “Screening of patients” to clarify how the investigators selected the patients as requested(see manuscript page 5).
- We agree with the second comment about the selection of patients. Indeed, the selection process should have introduced a selection bias, affecting the data in a positive fashion as no patient with cancer and a relatively low proportion of CKD patients with cardiovascular co-morbidities were enrolled in our study. As OCEANE was a non-interventional study, each physician had to consecutivelyinclude patients fulfilling inclusion criteria during routine follow-up visits without any selection guided by co-morbidities. Additionally, patients with canceror with severe cardiovascular co-morbidities are more likely to be followed-up by oncologists or cardiologists, respectively, rather than nephrologists. We strengthened the section of the discussion with this limitation of the study (see manuscript page 11).

2. The proportion of patients with no response, i.e 32% did not achieve the Hb level of at least 10 g/dL has not been analysed. The authors focussed on the proportion of the patients in the Hb target 10-12 g/dL which was the end-point of the study.
The analysis of the subgroup of patients not achieving an Hb of 10 g/dL would be interesting since

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there is a real room for potential improvement in this group of patients, more than in patients with Hb> 12 g/dL. This study should give more insight in this subgroup (Hb< 10g/dL) in order to identify causal factors of non response that might be improved in the future, i.e. iPTH, CRP, iron deficiency etc...
Answer:We agree with this comment about the point of identifying causal factors of non response to C.E.R.A. However, as the OCEANE study focused on patients achieving a Hb level within the target level of 10-12 g/dL at the request of the French National Authority for Health (Haute Autorité de Santé, or HAS), we are not able to provide statistical analyses of the subgroup of patients not achieving an Hb level under 10g/dL.

3. Although the authors report that the study was conducted in accordance with ethical guidelines established by ADELF, it is unclear if the patients received astructured information and gave an informed consent.
Answer: as mentioned above, we added a paragraph on Ethics statement in the revised manuscript (see manuscript page 5).

4. iPTH, a known cause of ESA resistance, is not mentioned.
Answer: We mentioned that other causes of hyporesponsivess to ESAs, in particular high plasma intact parathyroid hormone (iPTH) concentrations, were not reported in the OCEANE study, as requested (see manuscript page 10).

5. CRP has been measured only at baseline, but not later.
Answer: CRP was measured at inclusion in the study in 54% of patients not on dialysis and 67% of kidney transplant patients, and screened at each quarterly visit (M3, M6, M9, M12) in some patients. CRP was stable during the study as shown below (Results expressed as medians, mg/L):
- Patients not on dialysis: Inclusion : 5 [q1-q3 : 2-10], M3 : 5 [q1-q3 : 2-11], M6 : 5 [q1-q3 : 2-10], M9 : 5 [q1-q3 : 2-9] et M12 : 5 [q1-q3 : 2-10].
- Kidney transplant patients: Inclusion : 4 [q1-q3 : 2-7], M3 : 5 [q1-q3 : 2-8], M6 : 4 [q1-q3 : 2-9], M9 : 4 [q1-q3 : 2-6] et M12 : 5 [q1-q3 : 2-7].
In this paper, we focused on results regarding end-points:
- Main endpoint: percentage of patients with a Hb level within 10-12 g/dL (as per 2007 EMA guidelines) around 6 months of C.E.R.A. treatment, and therapeutic modalities for treating anemia (dose, route of administration, conditions of administration) until the follow-up visit around 6 months.
- Secondary endpoints: percentage of patients with Hb levels within 10-12 g/dL around 12 months of C.E.R.A. treatment, change in Hb levels, hematocrit and laboratory parameters used to monitor anemia and CKD, and tolerability of C.E.R.A.

6. How was the adherence to CERA assessed?
Answer: Less than 10% of patients with at least one available self-questionnaire declared to have forgotten or postponed the C.E.R.A. injection at least once during follow-up (patients not on dialysis: 6%, 18 patients out of 291; kidney transplant patients: 7.5%, 4 patients out of 53).
Additionally, 17% of predialysis and 21% of transplanted patients stopped C.E.R.A. temporarily over the 6 months following the first injection (only one temporary discontinuation per patient in most cases). The main causes were: Hb concentration value (68% of cases) and non-compliance with treatment (14%).
Over the 1-year follow-up, the main reason of temporarily discontinuation were due to Hb levels (72% of cases in predialysis and 88% of cases in transplanted patients) and patient non-compliance with treatment (28% of cases in predialysis and 12% of cases in transplanted patients).

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VERSION 2 – REVIEW

REVIEWER	PD Dr Daniel Teta, MD, PhD Médecin Adjoint Service de Néphrologie Centre Hospitalier Universitaire Vaudois Lausanne, Suisse I declare that I have neither competing interest nor conflit of interest regarding the matter treated in this manuscript
REVIEW RETURNED	24-Nov-2012

THE STUDY	CKD patients included in this study were somewhat selected as anticipated by my comment during my 1st revision of the manuscript. The authors admitted that selection and have aknowledged this point in the revised version.
GENERAL COMMENTS	The authors have revised the manuscript, with respect to the points raised by my review. All the questions have been treated in detail and the responses provided are satisfactory. I have just a single request. I think that the data on adhererence/compliance to CERA, revealed by the authors in their reponse, should be important enough to see the light in the manuscript itself. The importance of compliance is massive in the management of anemia in this setting.

VERSION 2 – AUTHOR RESPONSE

Response to the comments and concerns raised by the Reviewer
Reviewer: PD Dr Daniel Teta, MD, PhD
Médecin Adjoint
Service de Néphrologie
Centre Hospitalier Universitaire Vaudois
Lausanne, Suisse

I declare that I have neither competing interest nor conflit of interest regarding the matter treated in this manuscript

CKD patients included in this study were somewhat selected as anticipated by my comment during my 1st revision of the manuscript. The authors admitted that selection and have aknowledged this point in the revised version.

The authors have revised the manuscript, with respect to the points raised by my review. All the questions have been treated in detail and the responses provided are satisfactory.

I have just a single request. I think that the data on adhererence/compliance to CERA, revealed by the authors in their reponse, should be important enough to see the light in the manuscript itself. The importance of compliance is massive in the management of anemia in this setting.

Answer :
As requested, we added the data on adherence/compliance to C.E.R.A. (see below) in the manuscript at the end of the section on “CERA treatment” (see page 8):

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“Regarding adherence to C.E.R.A. treatment, less than 10% of patients with at least one available self-questionnaire declared to have forgotten or postponed the C.E.R.A. injection at least once during follow-up (patients not on dialysis: 6%, 18 patients out of 291; kidney transplant patients: 7.5%, 4 patients out of 53). Additionally, 17% of not on dialysis patients and 21% of transplanted patients stopped C.E.R.A. temporarily over the 6 months following the first injection (only one temporary discontinuation per patient in most cases). The main causes were: Hb concentration value (68% of cases) and non-compliance with treatment (14%). Over the 1-year follow-up, the main reasons of temporarily discontinuation were due to Hb levels (72% of cases among not on dialysis patients and 88% of cases among transplanted patients) and patient non-compliance with treatment (28% of cases among not on dialysis patients and 12% of cases in transplanted patients).”

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