2. SYNOPSIS

COMPANY: Roche AB

NAME OF FINISHED PRODUCT:
Mircera®,
NAME OF ACTIVE SUBSTANCE(S):
C.E.R.A., RO0503821

TITLE OF STUDY	A single arm, open label study to assess the efficacy, safety and tolerability of once-monthly administration of subcutaneous C.E.R.A. for the maintenance of haemoglobin levels in pre-dialysis patients with chronic renal anaemia

STUDY CENTER(S) and INVESTIGATOR(S)
Among the 25 centers in Sweden, 14 centers recruited patients

Coordinating Investigator:
[redacted]

PUBLICATION (REFERENCE)
None

PERIOD OF TRIAL

28 June 2007 to 16 of november 2009

SPONSOR	Roche AB	CLINICAL PHASE	IIIb

INDICATION	Chronic renal anaemia
OBJECTIVES	**Primary**: To assess the long term maintenance of haemoglobin levels, with once-monthly subcutaneously administration of C.E.R.A. in pre-dialysis patients with chronic renal anaemia. **Secondary:** To evaluate the safety and tolerability of C.E.R.A. once monthly in the treatment of anaemia in patients with chronic kidney disease **Exploratory**: To explore associations between NT-proBNP levels and clinical outcomes observed during the study.
TRIAL DESIGN	A single arm, open label study
NUMBER OF PATIENTS (planned and analyzed)	The study was planned for a total of 200 patients to be recruited at 20 Swedish centers. A total of 39 patients with chronic kidney disease were enrolled from 14 study centres. Twenty nine patients entered the treatment period. Overall, 24 patients (83%) completed the prescribed course of C.E.R.A. medication while 5 patients (17%) prematurely withdrew from the study.
TARGET POPULATION	Adult patients (18 years or older) with chronic renal anaemia who receive subcutaneous darbepoetin alfa maintenance treatment

SELECTION CRITERIA	Inclusion Criteria: • Written informed consent • Age 18 years or older. • Chronic renal anaemia • Haemoglobin concentration between 10.5 g/dl and 12.5 g/dl • Adequate iron status (serum ferritin >100 ng/mL **AND** TSAT>20% **OR** hypochromic red cells <10%) • Continuous subcutaneous maintenance darbepoetin alfa therapy with the same dosing interval during the previous 2 months Exclusion Criteria: • Transfusion of red blood cells during the previous 2 months • Poorly controlled hypertension, i.e. sitting blood pressure exceeding 170/100 despite medication requiring hospitalization or interruption of darbepoetin alfa treatment in the previous 6 months • Significant acute or chronic bleeding such as overt gastrointestinal bleeding • Active malignant disease (except non-melanoma skin cancer) • Haemolysis • Haemoglobinopathies (e.g homozygous sickle-cell disease, thalassemia of all types) • Folic acid deficiency • Vitamin B12 deficiency • Platelet count >500 x 10^9/L or <100 x 10^9/L

SELECTION CRITERIA (continued)	• Pure red cell aplasia
	• Epileptic seizure during previous 6 months
	• Congestive heart failure (NYHA Class IV)
	• Myocardial infarction or stroke, severe or unstable coronary artery disease, severe liver disease during the previous 3 months
	• Uncontrolled or symptomatic secondary hyperparathyroidism
	• Pregnancy or lactation period
	• Women of childbearing potential without effective contraception
	• Participation in a clinical trial or receipt of an investigational compound or an investigational treatment during the previous 3 months
	• Planned (date) elective surgery during the study period except for
	  • cataract surgery
	  • vascular access surgery
	• Known hypersensitivity to recombinant human erythropoietin, polyethylene glycol or to any constituent of the study medication

LENGTH OF STUDY	32 weeks in total, comprising: Stability Verification Period (SVP): 4 weeks Dose Titration Period (DTP): 16 weeks Efficacy Evaluation Period (EEP): 8 weeks Follow Up: 4 weeks
TRIAL DRUG	C.E.R.A. (RO0503821). Starting dose: the initial dose of subcutaneous C.E.R.A. administered by injection of 120, 200 or 360 µg every four weeks, according to the dose of darbepoetin alfa administered in the week preceding first study drug administration. The goal of treatment in this study is to maintain haemoglobin

	concentrations. Dose adjustment may be necessary if haemoglobin increases or decreases in a clinically significant amount. Specific guidance for dose titration in these circumstances is provided.
COMPARATOR DRUG	None
DOSE ROUTE	Subcutaneous C.E.R.A. administered by injection

SAFETY EVALUATION	• Serious and all adverse events and deaths
	• Vital Signs
	• ECG
	• Laboratory parameters
	  • Iron Parameters
	  • Haematology
	  • Hb levels and rate of Hb rise
	  • Blood Chemistry
	  • Anti-erythropoetin antibody determination

EFFICACY EVALUATION	Key outcomes will be assessed during the first 8 weeks following the 16 weeks dose titration period, i.e. during the Efficacy Evaluation Period (EEP). The reference haemoglobin is defined as the mean of the five assessments recorded during the SVP (weeks -4,-3,-2,-1, 0). For the purposes of efficacy assessment the target haemoglobin concentration range will be defined as ± 1 g/dL of the reference haemoglobin concentration and within the range 10.5 – 12.5g/dL. <u>Primary Efficacy Endpoint</u> • The proportion of patients maintaining average haemoglobin concentration during the EEP within the target range <u>Secondary Efficacy Endpoints</u> • Change in haemoglobin concentration between reference (SVP) and the EEP • The proportion of patients maintaining haemoglobin concentration within the haemoglobin range 10.5-12.5 g/dL throughout the EEP • Mean time spent in haemoglobin range of 10.5-12.5 g/dL <u>During the dose titration and efficacy evaluation periods</u> • Proportion of patients requiring any dose adjustment • The incidence of red blood cell transfusions <u>Additional Endpoints</u> • Serum NT-proBNP levels and potential clinical associations
STATISTICAL METHODS	All enrolled patients will be included in the safety analyses. Patients who have received at least 1 dose of C.E.R.A. (week 0) and for whom data for at least one follow-up variable are available will be included in the ITT population. Efficacy data will be summarized using descriptive analyses for the endpoints defined above. Descriptive analyses will be performed on all adverse events occurring during the study period. The incidence of the adverse events will be tabulated by frequency and organ systems. The upper limit for the 95% one-sided confidence interval for the incidence of the most frequent adverse event will be calculated. Information on absolute haemoglobin and rate of haemoglobin change in the 8 weeks preceding SAE's or deaths will be analyzed. Patients will be followed for safety for 30 days following the last study visit and until death, resolution, or stabilization of any SAE. *Ad hoc* exploratory analyses may be carried out on the patient population or on patient sub-populations.

SUMMARY	Due to the slow recruitment rate the enrolment was stopped after 39 patients were screened and 29 patients were treated. Contrary to the instructions given in the study protocol only two different patient populations were defined: intention-to-treat, and safety. Due to early termination of recruitment no confirmatory analysis was performed. The main analysis was performed on the intent-to-treat population.
EFFICACY RESULTS	Primary Efficacy variable The primary efficacy parameter in study ML20944 was the proportion of patients maintaining their mean hemoglobin concentration (g/dL) within ±1 g/dL of their reference Hb and between 10.5 and 12.5 g/dL during the EEP. A total of 29 patients were treated with C.E.R.A. The time adjusted average of hemoglobin at baseline was calculated to be 11.7g/dl (Std=0.52) and 11.4 g/dl (Std=1.09) during the efficacy evaluation period. Fifteen out of 29 patients (51.7%) were maintaining their mean hemoglobin concentration within ±1 g/dL of their reference hemoglobin value and between 10.5 and 12.5 g/dL during the EEP. The 95% confidence interval calculated with Pearson-Clopper method was [32.5%, 70.6%]. Secondary efficacy variable The mean change of the time adjusted average of haemoglobin between baseline (SVP) and the EEP was calculated to be -0.3g/dl (Std=1.04). The proportion of patients maintaining the hemoglobin concentration within the target range of 10.5 - 12.5 g/dl throughout the EEP was 58.6% with a 95% confidence interval from 38.9% to 76.5%. The time spent in the target range of 10.5 - 12.5 g/dl was calculated to be 31 days (Std=17.2). After a 4 weeks stability verification period patients switched form darbepoetin alfa to C.E.R.A. The starting dose of C.E.R.A. was based on the dose of darbepoetin alfa administered in the week preceding the switch to C.E.R.A.. During the titration phase dose adjustment was necessary in 18 patients (62%). In eight patients the dose was only decreased and in three patients only increased. In 7 patients the dose has to be increased and decreased during the 16 weeks of the titration period. Twenty six patients entered the efficacy evaluation period. The dose of C.E.R.A. needed to be increased in eight patients (31%). No dose decrease was necessary during the 8 weeks of the EEP. The mean C.E.R.A. monthly dose during the dose titration period was calculated to be 123.6 µg (Std=34.3) and 113.5 µg (Std=81.7) during the efficacy evaluation period. The median monthly dose was 120 µg for both periods. Exploratory variable At this moment, no further analyses were done due to the low number of patients.
SAFETY RESULTS	Adverse events Seventy six percent of the patient reported 64 AEs starting during treatment with C.E.R.A.. The most frequently recorded AE were dizziness (10%), fatigue (10%) and nausea (10%), followed by anemia

	(7%), arthralgia (7%), headache (7%), hypotension (7%), and nasopharyngitis (7%). The most affected body system classes were infections and investigations (35% of all patients), general disorders and administration site conditions (24%), nervous system disorders (24%), and musculoskeletal and connective tissue disorders (17%). <u>Serious adverse events</u> No death was documented. For nine patients (31%) a total of 11 serious adverse events were reported. All serious adverse events were definitively not drug related.
CONCLUSION	This study has been performed to investigate the efficacy, safety and tolerability of once monthly administration of C.E.R.A. to patients with chronic renal anemia for correction and subsequent maintenance of hemoglobin concentrations. The purpose of of this study was to expand the volume and diversity of clinical safety and efficacy experience with 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 new EMA Hb guidelines. A total of 39 patients with chronic kidney disease were enrolled into study ML20944 between October 10, 2007 and March 16, 2009. This is far less than planned by protocol, but after 1, 5 year of inclusion, it was judged appropriate to close the study. Finally, data from 29 patients could be analysed in the intention to treat analysis and presented in this report for efficacy parameters and all 39 patients for safety. Several issues with this study can be raised making it difficult to draw any solid conclusion about data collected. However, the main issue is the actual numbers of patients enrolled was 39 instead of 200 patients planned to be enrolled. This leaves us with very few data to be analysed in depth and for any solid statistical power calculation possibilities. More than expected protocol violations were collected for so few patients further reducing the correctly treated patients. However, only 2 patients were withdrawn due to protocol violations, out of 12, two more patients dropped out due to kidney transplantations and one due to adverse event. Besides these issues we can conclude that Mircera is effective in correcting and maintaining haemoglobin levels in patients with chronic kidney disease not in dialysis. Furthermore, no significant safety concerns arose during the study. These findings are in line with the results and the data seen in the clinical phase III program seen with Mircera.
APPENDICIES	1. Study protocol dated 08 june 2007, [redacted]/version 3 2. Statistical report dated December 08th, 2009
DATE OF REPORT	2011-04-15