SYNOPSIS OF RESEARCH REPORT (PROTOCOL ML 20952)

COMPANY: **Roche Hellas SA** NAME OF FINISHED PRODUCT: **MIRCERA®** NAME OF ACTIVE SUBSTANCE(S): **methoxy polyethylene glycol-epoetin beta**	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A single arm, open label study to assess the efficacy, safety and tolerability of once-monthly administration of intravenous C.E.R.A. for the maintenance of haemoglobin levels in dialysis patients with chronic renal anaemia / ML20952 / 18 July 2012		
INVESTIGATORS / CENTERS AND COUNTRIES	See section 10.6		
PUBLICATION / POSTER (REFERENCE)	▪ Iatrou C., Once-Monthly Continuous Erythropoietin Receptor Activator (C.E.R.A.) Administration Maintains Hemoglobin Levels in Patients with Chronic Renal Anemia on Hemodialysis. Poster SA-PO2416, ASN 2009 ▪ Siamopoulos K., The Effect of Once Monthly C.E.R.A. administration on Iron Status and Hemoglobin Concentrations in Dialysis Patients with Chronic Renal Anemia. Poster SA-PO2350, ASN 2010		
PERIOD OF TRIAL	January 24, 2008 - September 18, 2009	CLINICAL PHASE	IIIb
OBJECTIVES	**Primary:** To assess the long term maintenance of haemoglobin levels, with once-monthly intravenous administration of C.E.R.A. in 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.		
STUDY DESIGN	This was a single arm, open label, interventional, multicenter study to demonstrate the efficacy, safety and tolerability of MIRCERA when administered intravenous once- monthly for the maintenance of haemoglobin levels in dialysis patients with chronic renal anaemia.		
NUMBER OF SUBJECTS	Enrolled=189, ITT=188, PP=149		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult patients (18 years or older) with chronic renal anaemia who were receiving intravenous epoetin alfa or darbepoetin alfa maintenance treatment		
TRIAL DRUG / STROKE (BATCH) No.	MIRCERA® (C.E.R.A., RO0503821)		
DOSE / ROUTE / REGIMEN / DURATION	Starting dose: the initial dose of intravenous C.E.R.A. was administered by injection of 120, 200 or 360 µg every four weeks, according to the dose of epoetin alpha or darbepoetin alfa administered in the week preceding the first study drug administration. The goal of treatment in this study was to maintain haemoglobin concentrations. Dose adjustment may have been necessary if haemoglobin was increased or decreased in a clinically significant amount. Specific guidance for dose titration in these circumstances was provided.		

REFERENCE DRUG / STROKE (BATCH) No.	N/A
DOSE / ROUTE / REGIMEN / DURATION	N/A
CRITERIA FOR EVALUATION	
EFFICACY:	Key outcomes were assessed during the first 8 weeks following the 16 weeks dose titration period, i.e. during the Efficacy Evaluation Period (EEP). The reference haemoglobin concentration was 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 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
PHARMACODYNAMICS:	N/A
PHARMACOKINETICS:	N/A

SAFETY:	• 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
	  • Dialysis adequacy

STATISTICAL METHODS	All enrolled patients were included in the safety analyses. Patients who had received at least 1 dose of C.E.R.A. (week 0) and for whom data for at least one follow-up variable were available were included in the ITT population. Efficacy data were summarized using descriptive analyses for the endpoints defined above. Descriptive analyses were performed on all adverse events occurring during the study period. The incidence of the adverse events has been 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 was calculated. Information on absolute haemoglobin and rate of haemoglobin change in the 8 weeks preceding SAE's or deaths was analyzed. Patients were followed for safety for 30 days following the last study visit and until death, resolution, or stabilization of any SAE. *Ad hoc* exploratory analyses were carried out on the patient

population or on patient sub-populations.

METHODOLOGY:

The study consisted of four periods: a stability verification period, a dose titration, an efficacy evaluation period, and a short safety follow up period. The safety of C.E.R.A. was evaluated throughout the study.

After written informed consent was obtained, the patients were screened for eligibility during a 4-week period (weeks -4 to -1). During this period, patients continued to receive epoetin alfa or darbepoetin at the same weekly dose, i.v. route and dosing interval (one, two or three times weekly) as before screening. Baseline Hb (mean of all Hb values measured in weeks -4 to 0) for each patient was assessed under stable epoetin alfa/darbepoetin dosage conditions: patients with a stable baseline Hb concentration between 10.0 and 12.0 g/dL were eligible.

After the screening verification period, eligible patients entered the dose titration period and received a starting dose of CERA that was based on the epoetin dose administered during the week preceding the switch to the study drug. A period of 16 weeks (weeks 1 to 16) after the first dose of study drug was used for dose titration and stabilization of Hb concentration.

The dose titration period was followed by an 8-week evaluation period (weeks 17 to 24) to assess the primary efficacy endpoint.

A telephone follow-up visit took place 4 weeks after the evaluation period to capture adverse events.

EFFICACY RESULTS:

A total of 149 patients were included in the PP population. The time adjusted average of haemoglobin at baseline was calculated to be 11.6 g/dl (Std=0.55) and 11.7 g/dl (Std=0.98) during the efficacy evaluation period.

Eighty patients (53.7%) 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 using Pearson-Clopper method for exact confidence bounds was [45.4%, 61.9%]. These results were confirmed by the analyses performed on the ITT population.

PHARMACODYNAMIC RESULTS: N/A

PHARMACOKINETIC RESULTS: N/A

SAFETY RESULTS:

Fifty percent of the patient reported 179 AEs starting during treatment with C.E.R.A.. The most frequently recorded Aes were hypertension (5%), followed by pyrexia (3%) and respiratory tract infection (3%). The most affected body system classes were infections and investigations (15% of all patients), injury, poisoning and procedural complications (10%), and vascular disorders (9%).

An overview of the number of patients with at least one adverse event and number of adverse events is provided in the following table.

Overview of Adverse Events (Safety Population)

Safety Analysis Population	N=188
Any AE (incl. SAE)	93 (50%)
Number of AEs (incl. SAEs)	179
Any SAE	34 (18%)
Number of SAEs	49
Any AE leading to death	4 (2%)
Any AE leading to discontinuation	10 (5%)
Any drug related AE	12 (6%)

CONCLUSIONS:

Conversion of haemodialysis patients with renal anaemia from conventional ESA therapy to monthly C.E.R.A. administration is convenient and offers good control of Hb levels regardless of the previous type of ESA or dosing schedule. These findings, obtained in a large population in 24 centers using pre-filled syringes, confirm that C.E.R.A. offers a practical and effective option for simplified management of anaemia in this population.