

Official Title: A Randomized, Open Label Study to Assess All-Cause Mortality and Cardiovascular Morbidity in Patients with Chronic Kidney Disease on Dialysis and Those Not on Renal Replacement Therapy Under Treatment with Mircera or Reference ESAs.

NCT Number: **NCT00773513**

Document Date: Protocol Version D 23-Mar-2015

PROTOCOL

TITLE: A RANDOMIZED, CONTROLLED, OPEN-LABEL, MULTI-CENTRE, PARALLEL-GROUP STUDY TO ASSESS ALL-CAUSE MORTALITY AND CARDIOVASCULAR MORBIDITY IN PATIENTS WITH CHRONIC KIDNEY DISEASE ON DIALYSIS AND THOSE NOT ON RENAL REPLACEMENT THERAPY UNDER TREATMENT WITH MIRCERA® OR REFERENCE ESAs

PROTOCOL NUMBER: BH21260/ NCT00773513

VERSION NUMBER: D

EUDRACT NUMBER: 2007-005129-31

IND NUMBER: 10158

TEST PRODUCT: Mircera® (RO0503821)

SPONSOR: F. Hoffmann-La Roche Ltd

DATE FINAL: Version A: 23 April 2008

DATES AMENDED: Version B: 26 November 2008
Version C: 15 November 2011
Version D: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name

██████████

Title

Company Signatory

Date and Time (UTC)

23-Mar-2015 17:36:57

CONFIDENTIAL

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**PROTOCOL AMENDMENT, VERSION D:
RATIONALE**

Protocol BH21260 has been amended to prolong the study by approximately 6 years because of a lower than anticipated event rate (EMA was informed on 8 May 2014, e-CTD seq. 033).

Additional changes to the protocol are as follows:

- Final visit assessments at study end will be modified to match the primary objective of the study to assess cardiovascular morbidity and mortality
- To clarify adverse events reporting on serious adverse event reporting form in the electronic Case Report Form
- Update of Appendix 5 with the revised version of the MIRCERA® Educational Program for anti-erythropoietin antibody-mediated pure red cell aplasia associated with erythropoietin stimulating agent
- Administrative changes in the text of the packaging and labeling
- Administrative changes in the procedures
- Administrative changes in the text in the section of electronic Case Report Form because of a change of data capture system.

No other changes have been made. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION D: SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 3.1: Overview of Study Design and Dosing Regimen

The total length of the study ~~is~~*was* estimated to be 4 years (30 months recruitment and 18 months *of* follow-up on treatment after last patient randomized) until the pre-specified number of outcome events ~~is~~*were* recorded. *Due to an event rate lower than anticipated, it is expected that the study will be prolonged by approximately 4-6 years.*

SECTION 3.1.3: End of Study

The study will end when a total of 1264 endpoint events have been recorded. *Investigators will be informed of the end of study.* Each patient remaining in the study will have a final visit at this time. The end of the study is defined as the date of the last visit of the last patient to complete the study.

SECTION 5.4.1: Clinical Assessments during the Treatment Period

The following clinical information and assessments will be collected/performed during the randomized treatment period and at the final visit:

- ~~– Physical examination at the final visit or early withdrawal, including body weight determination.~~
- Blood pressure: at each study visit, ~~and except at the final visit~~, blood pressure will be measured before blood sampling using standard local techniques; BP should be determined both before and after the dialysis session for HD patients. The same technique (e.g., manual assessment, automated reading) should be used throughout the entire study for every patient. Blood pressure should be measured in the sitting position after at least 5 minutes rest. An appropriate-sized cuff should be used. Both systolic and diastolic blood pressures should be recorded.

SECTION 5.4.2: Laboratory Assessments ~~During the Treatment p~~Period

The total volume of blood loss for laboratory assessments will be approximately ~~2-407~~ mL per visit with safety assessments representing a total of approximately ~~11248~~ mL per year of participation.

The following laboratory assessments will be performed during the randomized treatment period:

- Hematology:
 - Platelet count at study visit 1, ~~and~~ at monthly visit ~~and at the final visit~~.
 - Total white blood cell count at study visit 1, ~~and~~ every 3 months ~~and at the final visit~~.

- Blood chemistry:
 - CRP every 3 months ~~and at the final visit~~.
 - Serum albumin, calcium, phosphorus, potassium at study visit 1; *and* every 3 months ~~and at the final visit~~.
- Cholesterol, triglycerides, HbA1c, glucose at study visit 1; *and* once a year ~~and at the final visit~~.
- 12-lead ECG recording at study visit 1 ~~and at the final visit~~ before dose administration.

SECTION 6.3.2: Packaging and Labeling of MIRCERA®

Study medication will be packaged and provided in an open label fashion. *It will be supplied with either study-specific labels or as commercially available product with additional labeling, if required by national legislation.* Each syringe will be available in an individual blister with a needle for sc or iv administration. The package labels will include the following information: protocol number, study drug name, strength, lot number, re-tests date/used by (as per local guidelines), patient number, administration date and safety precautions for clinical trials.

SECTION 6.3.4: Packaging and Labeling of Reference ESAs

For study centers/countries where reference ESAs will be supplied by Roche, reference ESAs will be packed and labeled according to local specifications, in an open fashion. *It will be supplied with either study-specific labels or as commercially available product with additional labeling, if required by national legislation.* Each PFS will be available blistered in an individual box.

SECTION 6.5: Assessment of Compliance

Theis inventory *and dispensing logs* must be available for ongoing inspection by the Monitor. After injection, all empty blisters of PFS of MIRCERA® or reference ESA will be kept in a container or in the medication box and will be made available for the Roche Monitor to check at each visit. All supplies, including partially used, expired and unused or empty containers and ~~the~~ dispensing logs, must be kept at the study site and ~~returned to~~ *copies of the inventory and dispensing logs will be retrieved by the Roche Monitor periodically* ~~and~~ at the end of the study.

SECTION 6.6: Destruction of the MIRCERA®/Reference ESAs

The unused, partially used or expired MIRCERA®/reference ESA PFS provided by the Sponsor may be destroyed at the site or at the supplying depot following the current Roche and local Standard Operating Procedures as applicable.

Local or institutional regulations may require immediate destruction of used MIRCERA®/reference ESA PFS for safety reasons. In these cases, it may be acceptable for investigational site staff to destroy dispensed MIRCERA®/reference ESA PFS before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped,

dispensed, returned and destroyed. Written authorization must be obtained from the sponsor at study start up before destruction.

Written documentation of destruction must contain the following:

- Quantity of MIRCERA®/reference ESA PFS destroyed
- Date of destruction (*date discarded in designated hazardous container for destruction*)
- Method of destruction (*the site must provide the Sponsor with documentation of their institutional policy and procedures for handling and disposing of drugs*)
- Name and signature of responsible person [or company] who ~~destroyed~~ *discarded the investigational products[s] in a hazardous container for destruction*

SECTION 7.1.1: Clinical AEs

Clinical AEs encountered during the randomized treatment period ~~and considered as serious by the investigator~~ will be recorded on an AE eform of the eCRF (see figure in Appendix 1).

SECTION 7.2.1: Reporting of Serious Adverse Events [immediately reportable]

Any clinical AE or abnormal laboratory test value that is *serious* [as defined in Section 7.1.1.3 above] and which occurs during the course of the study, regardless of the treatment arm, must be reported to Roche within ~~one working day~~ 24 hours of the investigator becoming aware of the event [expedited reporting]. The investigator must complete the *SAE Reporting Form* and forward it to the SAE Responsible.

SECTION 8.2.2: Sample Size

Note: The overall event rate observed during the study is considerably lower than that expected at the planning stage. Changing no other parameters leads to an extended study duration; the occurrence of 1264 events has been estimated to be approximately 10 years after study start.

SECTION 15.4: Electronic Case Report Forms

~~Data for this study will be captured via an Electronic Data Capture (EDC) system by using eCRFs on a laptop. The data is entered on to the laptop using the off line mode. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. The investigator will connect on a regular basis, using an analog phone line, and the data will be transferred directly to the Roche database.~~

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

The investigator should ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports. *All eCRFs should be*

completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee. At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

TABLE 1: Schedule of Assessments

Table 1 has been revised to reflect changes to the protocol.

APPENDIX 5: Educational Program For MIRCERA® Anti-erythropoietin-mediated Pure Red Cell aplasia Associated with Erythropoietin Stimulating Agents

Appendix 5 has been updated with the revised version.

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SYNOPSIS OF POST-AUTHORIZATION SAFETY STUDY PROTOCOL BH21260D

TITLE	A randomized, controlled, open-label, multi-centre, parallel-group study to assess all-cause mortality and cardiovascular morbidity in patients with chronic kidney disease on dialysis and those not on renal replacement therapy under treatment with MIRCERA® or reference ESAs.		
SPONSOR	Hoffmann-La Roche Ltd Global Development	CLINICAL PHASE	IV
INDICATION	Chronic renal anemia		
OBJECTIVES	<p>Primary: to demonstrate non-inferiority of MIRCERA® versus reference ESAs in terms of a composite endpoint of all-cause mortality and non-fatal cardiovascular events (myocardial infarction (MI), stroke)</p> <p>Secondary: to assess the incidence of anti-erythropoietin antibody-mediated pure red cell aplasia (PRCA), gastrointestinal bleeding and thromboembolic events</p>		
TRIAL DESIGN	Randomized, controlled, open-label, multi-centre parallel group, non-inferiority study comparing MIRCERA® to other ESAs		
NUMBER OF SUBJECTS	2800 patients: 1400 patients randomized to MIRCERA®, 1400 patients randomized to other ESAs		
TARGET POPULATION	<p>Adult patients (≥18 years old) with symptomatic anemia associated with CKD (renal anemia) not treated with an ESA (20%) or patients with renal anemia on maintenance ESA therapy (80%).</p> <p>The proportion of patients not on dialysis will be around 20%; approximately 76% of patients are expected to be on hemodialysis and 4% of patients on peritoneal dialysis.</p>		
LENGTH OF STUDY	The total length of the study <i>was</i> estimated to be 4 years (30 months recruitment and 18 months of follow-up on treatment) until the pre-specified number of composite events <i>were</i> recorded. <i>Due to an event rate lower than anticipated, it is expected that the study will be prolonged by approximately 4–6 years.</i>		
END OF STUDY	The study will end when a total of 1264 events of the composite endpoint have been recorded.		
INVESTIGATIONAL MEDICINAL PRODUCT(S) DOSE/ ROUTE/ REGIMEN	<p>Injectable solution of MIRCERA®</p> <ul style="list-style-type: none"> – Patients with renal anemia not treated with an ESA: 0.6 µg/kg body weight, administered once every two weeks as iv or sc injection. – Patients with renal anemia who are on maintenance ESA therapy: the initial monthly dose of MIRCERA® will be one of three starting doses (120, 200 or 360 µg as iv or sc injection) based on the weekly dose of ESA administered prior to the first MIRCERA® administration. <p>MIRCERA® doses will be adjusted to the target Hb levels according to approved label.</p>		

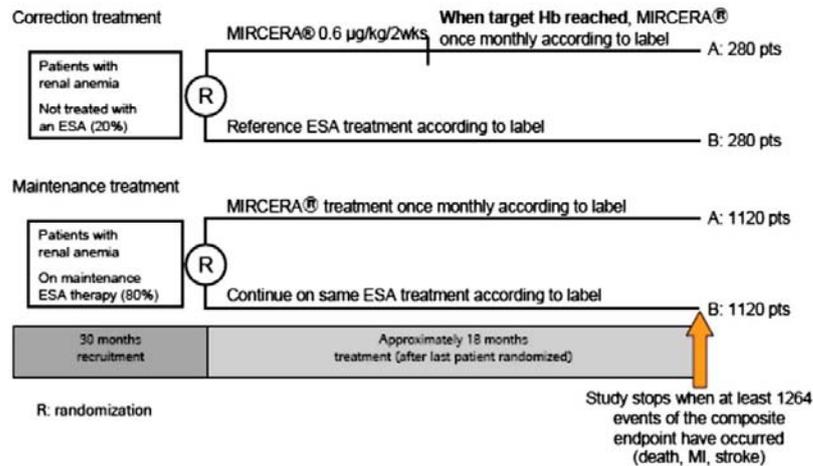
COMPARATOR “DRUG” DOSE/ ROUTE/ REGIMEN	Injectable solution of ESAs: darbepoetin alfa (Aranesp®, Nespo®, Aranest®), epoetin alfa (Eprex®, Epogen®, Epopen®, Erypo®) and epoetin beta (NeoRecormon®, Recormon®). The starting dose, dose adjustment, route and regimen of the reference ESA should be as per local label.
ASSESSMENTS OF:	
- EFFICACY	N/A
- SAFETY	<p>Primary endpoint:</p> <ul style="list-style-type: none"> – time to composite of all-cause mortality and non-fatal cardiovascular events (MI, stroke) <p>Secondary endpoints:</p> <ul style="list-style-type: none"> – time to the individual components of the composite endpoint: the time to death, the time to non-fatal cardiovascular events (MI or stroke), the time to MI and the time to stroke <p>Other clinical parameters:</p> <ul style="list-style-type: none"> – Blood pressure – Adverse Events (AEs) and Serious Adverse Events (SAEs) <p>Laboratory parameters:</p> <ul style="list-style-type: none"> – Iron parameters: serum ferritin, serum iron, serum transferrin or total iron-binding capacity (TIBC); calculated transferrin saturation (TSAT) or percentage of hypochromic RBCs – Hematology: hemoglobin (Hb), white blood cell count, platelet count – Blood chemistry: C-reactive protein (CRP), serum albumin, calcium, phosphorus, potassium – Lipids profile (cholesterol, triglycerides) – Hemoglobin A1c (HbA1c), glucose – ECG recording – Anti-erythropoietin antibody determination – Dialysis adequacy: Kt/V or urea reduction ratio (URR) for hemodialysis patients or weekly Kt/V for peritoneal dialysis patients. Creatinine clearance (CrCl)/glomerular filtration rate [GFR] in patients not on renal replacement therapy.
- PHARMACOKINETICS/ PHARMACODYNAMICS	N/A
- QUALITY OF LIFE/ PHARMACOECONOMICS	N/A
- ROCHE SAMPLE REPOSITORY	All patients who have been enrolled in the study will be asked to participate in the Roche Sample Repository Project in countries where RSR sampling is to be undertaken. The RSR project involves taking a 9 mL blood sample for pharmacogenetic and genetic research. Taking part in the RSR project is entirely optional and is subject to a signature on a separate written informed consent. The RSR study protocol BH21260RG is submitted to the concerned Ethic Committee and is available for Competent Authority upon request.

- INCLUSION CRITERIA	<ol style="list-style-type: none"> 1. Written informed consent 2. Adult patients (≥ 18 years old) with symptomatic anemia associated with CKD (renal anemia) 3. Patients with renal anemia who are not treated with an ESA: <ul style="list-style-type: none"> - Anemia defined as Hb concentration < 11.0 g/dL (mean of 2 screening values with at least one day and a maximum 2 weeks between measurements) with a clinical indication for ESA treatment or 3. Patients with renal anemia who are on maintenance ESA therapy: <ul style="list-style-type: none"> - If on dialysis: regular long-term hemodialysis or peritoneal dialysis therapy with the same mode of dialysis for at least 3 months before screening - Continuous iv or sc maintenance ESA therapy: darbepoetin alfa (Aranesp[®], Nespo[®], Aranest[®]), epoetin alfa (Eprex[®], Epogen[®], Epopen[®], Erypo[®]) or epoetin beta (NeoRecormon[®], Recormon[®]) administered according to approved label of the same agent and route of administration for at least 2 months before screening - Hb concentration between 10 and 12 g/dL (mean of 2 screening values with at least one day and a maximum of 2 weeks between measurements) 4. Patients with adequate iron status defined as: serum ferritin above or equal to 100 μg/L or transferrin saturation above or equal to 20% (See section 4.4 of the SmPC).
- EXCLUSION CRITERIA	<p><u>Contraindications to ESA treatment</u> (See Section 4.3 of SmPC):</p> <ol style="list-style-type: none"> 1. Uncontrolled hypertension 2. Hypersensitivity to the active substance or any of the excipients of MIRCERA[®] and other ESAs 3. Any other contraindication to ESA therapy <p><u>Conditions known to cause inadequate response to ESA treatment or anemia other than symptomatic anemia associated with CKD, including</u> (See Section 4.4. of the SmPC):</p> <ol style="list-style-type: none"> 4. Hemoglobinopathies (e.g., homozygous sickle-cell disease, thalassemia of all types) 5. Anemia due to hemolysis 6. Pure red cell aplasia (PRCA) <p><u>Other</u></p> <ol style="list-style-type: none"> 7. High likelihood of early withdrawal (e.g. within 1 year) or interruption of the study 8. Pregnancy or breast-feeding 9. Women of childbearing potential without effective contraception 10. Administration of another investigational drug within 1 month before screening or planned during the study period

PROCEDURES (summary):

The study will be a randomized, controlled, open-label, multi-centre parallel group, non-inferiority study comparing MIRCERA® to other ESAs (Figure 1).

Figure 1 Study Design



After written informed consent is obtained, patients will be screened for eligibility. Providing all eligibility criteria are met, patients with renal anemia not treated with an ESA will be randomly allocated 1:1 either to MIRCERA® once every two weeks (group A) or to a reference ESA treatment (group B) according to label for correction of their renal anemia. Once corrected, MIRCERA® patients should be treated with once monthly administration. Patients with renal anemia on stable maintenance ESA therapy will be randomized 1:1 to continue their current ESA treatment (group B) or to change to MIRCERA® treatment (group A) once-monthly. Stratification will be performed by treatment setting (correction/maintenance) and baseline CRP category (≤ 30 mg/L / >30 mg/L).

Pertinent variables to be documented at baseline include demographic parameters, medical history and co-morbidities, co-medications, duration and type of prior ESA, type of vascular access for hemodialysis and time since first dialysis. Baseline laboratory assessments include hemoglobin values, CRP, other laboratory parameters, dialysis adequacy parameters and anti-erythropoietin antibody determination.

During the study, the participants will be treated according to the usual standard of care and current best practice guidelines. The doses of MIRCERA® and reference ESAs should be adjusted according to approved label to achieve and maintain the individual patient's Hb levels within the Hb target range (10-12 g/dL). No further intervention will be done except for monthly visits at which assessments will be performed as specified in the protocol. Information on the components of the composite endpoint

(all-cause mortality, myocardial infarction and stroke) and AEs will be collected on an ongoing basis and recorded at monthly visits.

The total length of the study *was* estimated to be 4 years (30 months recruitment and 18 months *of* follow-up on treatment) until the pre-specified number of composite events *were* recorded. *Due to an event rate lower than anticipated, it is expected that the study will be prolonged by approximately 4–6 years.*

Study oversight will be assured by a steering committee to guide study conduct.

An independent endpoint adjudication committee will provide a blinded assessment of fatal and non-fatal events in the composite endpoint. Suspect events will be recorded by the treating personnel in the participating centers, and the relevant information for the diagnostic coding of the event will be forwarded to the endpoint committee for blinded adjudication. Further details about the role and procedures of the endpoint committee will be provided in a separate document, the Endpoint Adjudication Committee charter. The suspect events will be adjudicated by blinded committee members, with subsequent blinded adjudication in the case of disagreement.

An independent data and safety monitoring board (DSMB) will review the study data, including adjudicated outcomes, and propose continuation or discontinuation of the study according to pre-specified rules recorded in the DSMB charter.

STATISTICAL ANALYSES:

Primary analysis

The primary objective is to demonstrate non-inferiority of MIRCERA® versus reference ESAs in terms of a composite endpoint of all-cause mortality and non-fatal cardiovascular events (MI, stroke), based on a non-inferiority limit of 1.20 for the hazard-ratio of the composite endpoint and a one-sided significance level of 0.025. The model used for the non-inferiority analyses will be a Cox model on time to event with treatment as the independent variable but no co-variables included in the model. The analysis will be performed based on the safety population defined as all patients randomized who receive at least one dose and had at least one post-dose safety assessment.

Secondary analysis

In addition to the primary analysis, Kaplan-Meier methods and frequency tables will be used to describe the time to the composite endpoint as well as the time to the individual components of the composite endpoint for the MIRCERA® versus reference group.

Other analyses

The secondary objectives (incidence of anti-erythropoietin antibody-mediated PRCA, gastrointestinal bleeding and thromboembolic events), as well as hemoglobin over time and dose will be analysed using descriptive statistics and analytical methods such as risk ratios, Cox regression and ANOVA methods.

Demographic and baseline characteristics

Demographic and baseline characteristics (socio-demographic parameters, medical history and co-morbidities, co-medication, laboratory status and dialysis parameters, hemoglobin levels, duration and type of prior ESA treatments) will be summarized and comparability between treatment groups will be assessed descriptively.

Sample size

The stratification will be ensured that 20% of patients will be recruited in the correction setting and 80% in the maintenance switch setting. The expected yearly event rate is approximately 20%, based on

- an expected 25% composite endpoint rate (a mortality rate of approximately 16% [2, 3] and non-fatal cardiovascular morbidity of approximately 9% [4]) in the maintenance setting (80% of patients)
- a 7% rate for the combined endpoint in the correction setting (20% of patients) [CSR BA16738]

Assuming linear recruitment over 30 months and a follow-up time of 18 months after randomization of the last patient, a sample size of 2800 patients, representing approximately 7700 patient-years of exposure, would be adequate to observe 1264 events of the composite endpoint of death and non-fatal cardiovascular events.

1264 events are sufficient to ensure 90% power to establish non-inferiority of MIRCERA® to comparator ESAs in terms of the composite endpoint based on a non inferiority margin of 1.20 and a one-sided significance level of 0.025, assuring that the maximum difference between groups at the upper limit of the CI would be 6.1 % for the composite endpoint and 3.6% for mortality.

Duration (months)	NI limit (HR)	Event rate per year	No. events / Nb patients	Expected Event rate at end of study (%)	Highest event rate based on NI limit (%)	Absolute / relative difference (%)	Absolute and relative difference in deaths (%)
48	1.2	0.2	1264 / 2800	45.2	51.2	6.1 / 13	3.6 / 13

Note: The overall event rate observed during the study is considerably lower than that expected at the planning stage. Changing no other parameters leads to an extended study duration; the occurrence of 1264 events has been estimated to be approximately 10 years after study start.

References

1. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Guideline 4: Evaluation of GFR. Am J Kidney Dis 2002, In: http://www.kidney.org/professionals/kdoqi/guidelines_ckd/p5_lab_g4.htm (accessed Aug 3rd 2006).
2. Cheung AK et al. Cardiac diseases in maintenance hemodialysis patients: Results of HEMO study. Kidney Int 2004;65:2380-2389
3. Excerpts from the USRDS. 2004 Annual Data Report: Atlas of end-stage renal disease in the United States. Am J Kid Dis 2005; 45: Suppl 1
4. Enkoyan G et al. Effect of dialysis dose and membrane flux in hemodialysis. New Engl J Med 2002; 347: 2010-2019

GLOSSARY OF ABBREVIATIONS

AE	Adverse event
BP	Blood pressure
CI	Confidence interval
CKD	Chronic Kidney Disease
CRP	C-reactive protein
CrCl	Creatinine clearance
DCS	Data collection specification
DSMB	Data and Safety Monitoring Board
dL	Deciliter
ECG	Electrocardiogram
eCRF	Electronic Case Report Form(s)
EDC	Electronic Data Capture
eform	Electronic form (page)
ESA	Erythropoiesis-Stimulating Agent
GFR	Glomerular Filtration Rate
Hb	Hemoglobin
HD	Hemodialysis
ICH	International Conference on Harmonization
iDCC	<i>Independent Data Coordinating Center</i>
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
IMP	Investigational Medicinal Product
IU	International Unit
iv	Intravenous
kg	Kilogram
L	Liter
MDRD	Modification of Diet in Renal Disease
µg	Microgram
mL	Milliliter
µmol	Micromole
MI	Myocardial Infarction

GLOSSARY OF ABBREVIATIONS

min	Minute
mmHg	Millimeters of mercury
NT-proBNP	N-terminal pro-brain natriuretic peptide
PD	Peritoneal Dialysis
PFS	Pre-Filled Syringes
PRCA	Pure Red Cell Aplasia
RBC	Red Blood Cell
RSR	Roche Sample Repository
SAE	Serious Adverse Event
sc	Subcutaneous
SmPC	Summary of product characteristics
TIBC	Total iron-binding capacity
TSAT	Transferrin saturation
URR	Urea Reduction Ratio

PART I: STUDY DESIGN AND CONDUCT

1. BACKGROUND AND RATIONALE

1.1 Background

An increased incidence of cardiovascular events has been observed at higher hemoglobin (Hb) levels in recently published studies of anemia correction in patients with chronic kidney disease (CKD) not on dialysis [1, 2]. These studies failed to demonstrate that correction of anemia to a target Hb of 13.5 g/dL or higher in patients with chronic kidney disease not receiving dialysis reduces the risk of cardiovascular events. One study suggested that this degree of correction of Hb level may be associated with an increased risk without incremental improvement in quality of life. Taken together, these findings suggest caution in the full correction of anemia in patients with chronic kidney disease.

The global clinical development program for MIRCERA® included 13 Phase I clinical pharmacology studies and 10 therapeutic studies comprising four Phase II and six Phase III studies in patients with CKD, including patients on dialysis and not on dialysis. Administration of MIRCERA® for the treatment of anemia associated with CKD was generally well tolerated with no difference in the safety profile in comparison to reference erythropoiesis stimulating agents (ESAs) [3, 4].

Data from phase III correction studies show that the Hb response rates in the MIRCERA® group at the end of the correction period were high (93.3% and 97.5% in the studies in patients on dialysis and not on dialysis, respectively) and comparable to comparators (91.3% and 96.3%, respectively). The median time to response was 43 days in the MIRCERA® arm and 29 days in the comparator arm with increases of hemoglobin within the first 6 weeks of 0.2 g/dl/week and 0.3 g/dl/week, respectively.

Four randomized controlled phase III studies were performed in dialysis patients currently treated with darbepoetin alfa or epoetin. Patients were randomized to stay on their current treatment or to be converted to MIRCERA® in order to achieve stable hemoglobin levels. At the evaluation period (week 29-36), the mean and median level of hemoglobin in patients treated with MIRCERA® was virtually identical to their baseline hemoglobin level.

1.1.1 Study Drug

Methoxy polyethylene glycol-epoetin beta (MIRCERA®) is a covalent conjugate of a protein produced by recombinant DNA technology in Chinese Hamster Ovarian cells and conjugated to a linear methoxy-polyethylene glycol (PEG). MIRCERA® is a continuous erythropoietin receptor activator that shows a different activity at the receptor level characterized by a slower association to and faster dissociation from the receptor, a reduced specific activity in vitro with an increased activity in vivo, as well as an increased half-life, in contrast to erythropoietin. The average molecular mass is approximately 60 kDa of which the protein moiety plus the carbohydrate part constitutes approximately 30 kDa.

MIRCERA® stimulates erythropoiesis by interaction with the erythropoietin receptor on progenitor cells in the bone marrow. As primary growth factor for erythroid development, the natural hormone erythropoietin is produced in the kidney and released into the bloodstream in response to hypoxia. In responding to hypoxia, the natural hormone erythropoietin interacts with erythroid progenitor cells to increase red cell production.

The approved reference ESA compounds in the study will be darbepoetin alfa (Aranesp®, Nespo®, Aranest®), epoetin alfa (Eprex®, Epogen®, Epopen®, Erypo®) and epoetin beta (NeoRecormon®, Recormon®).

1.2 Rationale for the Study

As part of the risk management plan, Roche proposes to gain more experience with MIRCERA® administered under clinical practice conditions and according to the approved label by performing a non-inferiority study comparing MIRCERA® to other ESAs in terms of mortality and cardiovascular morbidity.

2. OBJECTIVES

2.1 Primary Objective

The primary objective is to demonstrate non-inferiority of MIRCERA® versus reference ESAs in terms of a composite endpoint of all-cause mortality and non-fatal cardiovascular events (myocardial infarction (MI), stroke).

2.2 Secondary objectives

The secondary objectives are to assess the incidence of anti-erythropoietin antibody-mediated pure red cell aplasia (PRCA), gastrointestinal bleeding and thromboembolic events.

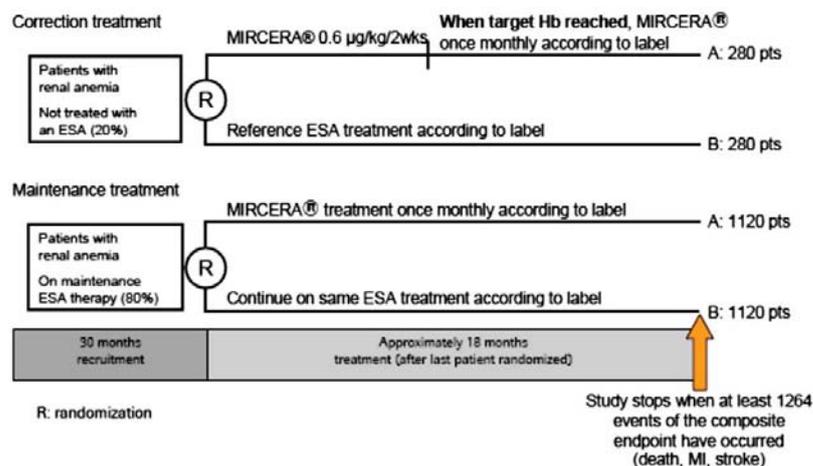
3. STUDY DESIGN

3.1 Overview of Study Design and Dosing Regimen

The study will be a randomized, controlled, open-label, multi-centre parallel group, non-inferiority trial comparing MIRCERA® to other ESAs.

The total length of the study *was* estimated to be 4 years (30 months recruitment and 18 months *of* follow-up on treatment after last patient randomized) until the pre-specified number of outcome events *were* recorded. *Due to an event rate lower than anticipated, it is expected that the study will be prolonged by approximately 4-6 years.*

Figure 1 Study Design



After written informed consent is obtained, patients will be screened for eligibility. Providing all eligibility criteria are met, patients with renal anemia not treated with an ESA will be randomly allocated 1:1 either to MIRCERA® once every two weeks (group A) or to a reference ESA treatment (group B) according to label for correction of their renal anemia. Once corrected, MIRCERA® patients should be treated with once monthly administration. Patients with renal anemia on stable maintenance ESA therapy will be randomized 1:1 to continue their current ESA treatment (group B) or to change to MIRCERA® treatment (group A) once-monthly.

3.1.1 Rationale for Study Design

1264 events are sufficient to ensure 90% power to establish non-inferiority of MIRCERA® to comparator ESAs in terms of the composite endpoint based on a non-inferiority margin of 1.20 and a one-sided significance level of 0.025, assuring that the maximum difference between groups at the upper limit of the CI would be 6.1 % for the composite endpoint and 3.6% for mortality.

3.1.2 Rationale for Dose Selection

Dosing will be performed as specified in the approved labels.

3.1.3 End of Study

The study will end when a total of 1264 endpoint events have been recorded. *Investigators will be informed of the end of study.* Each patient remaining in the study will have a final visit at this time. The end of the study is defined as the date of the last visit of the last patient to complete the study.

3.2 Number of Subjects/ Assignment to Treatment Groups

2800 patients, [1400 per treatment arm] will be recruited over a planned recruitment period of 30 months. Stratification will be done by treatment setting (correction/maintenance) and baseline CRP category (≤ 30 mg/L / > 30 mg/L).

3.3 Centers

Patients will be recruited in approximately 200-250 centers (around 10 patients per site).

4. STUDY POPULATION

The patient population will consist of adult patients (≥ 18 years old) with symptomatic anemia associated with CKD (renal anemia).

20 percent of the study population will be patients with renal anemia, who are not treated with an ESA and who require correction of anemia.

The remaining 80 percent of the study population will consist of patients with renal anemia who are on maintenance ESA therapy. They will continue their current ESA treatment or change to MIRCERA® treatment once-monthly.

The proportion of patients not on dialysis will be around 20%; approximately 76% of patients are expected to be on hemodialysis and 4% of patients on peritoneal dialysis.

Under no circumstances are patients who enroll in this study permitted to be re-randomized to this study and enrolled for a second course of treatment.

4.1 Inclusion Criteria

Patients must fulfill all of the following inclusion criteria to be eligible for study enrolment.

- Written informed consent
- Adult patients (≥ 18 years old) with symptomatic anemia associated with CKD (renal anemia)
- Patients with renal anemia who are not treated with an ESA:
 - Anemia defined as Hb concentration < 11.0 g/dL (mean of 2 screening values with at least one day and a maximum of 2 weeks between measurements) with a clinical indication for ESA treatment

or

- Patients with renal anemia who are on maintenance ESA therapy:
 - If on dialysis: regular long-term hemodialysis or peritoneal dialysis therapy with the same mode of dialysis for at least 3 months before screening

- Continuous iv or sc maintenance ESA therapy: darbepoetin alfa (Aranesp®, Nespo®, Aranest®), epoetin alfa (Eprex®, Epogen®, Epopen®, Erypo®) or epoetin beta (NeoRecormon®, Recormon®) administered according to approved label of the same agent and route of administration for at least 2 months before screening
- Hb concentration between 10 and 12 g/dL (mean of 2 screening values with at least one day and a maximum of 2 weeks between measurements)
- Patients with adequate iron status defined as: serum ferritin above or equal to 100 µg/L or transferrin saturation above or equal to 20% (See section 4.4 of the SmPC [14])

4.2 Exclusion Criteria

Contraindications to ESA treatment (See Section 4.3 of SmPC [14]): Uncontrolled hypertension

- Hypersensitivity to the active substance or any of the excipients of MIRCERA® and other ESAs
- Any other contraindication to ESA therapy

Conditions known to cause inadequate response to ESA treatment or anemia other than symptomatic anemia associated with CKD, including (See Section 4.4. of the SmPC [14]):

- Hemoglobinopathies (e.g., homozygous sickle-cell disease, thalassemia of all types)
- Anemia due to hemolysis
- Pure red cell aplasia (PRCA)

Other:

- High likelihood of early withdrawal (e.g. within 1 year) or interruption of the study
- Pregnancy or breast-feeding
- Women of childbearing potential without effective contraception
- Administration of another investigational drug within 1 month before screening or planned during the study period

4.3 Concomitant Medication and Treatment

All treatments (medications and medical procedures) are permitted before screening, during the screening period and throughout the treatment period except for:

- Investigational drugs (defined as any material, i.e. placebo or drug, dispensed under the provision of a protocol) within 1 month before screening, during screening or the treatment periods. Participation in studies testing investigational devices should be reported to the sponsor in advance and approved in writing by the sponsor.

All treatments administered within 3 months before the first screening visit and started or stopped at any time during the screening or treatment periods (including those to treat AEs) should be documented in the appropriate sections of the eCRF.

It is expected that patients will be treated according to good clinical practice and current guidelines, particularly with respect to substitution therapy with iron, vitamin B12 and folic acid.

4.3.1 Iron Supplementation

An adequate iron status is a prerequisite to achieve and maintain target Hb levels. Iron deficiency during treatment may cause a reduced erythropoietic response to ESA therapy. In addition, ESA therapy results in increased erythropoiesis that may lead to a depletion of iron stores. The iron status will be monitored throughout the study by assessing serum ferritin and transferrin saturation (TSAT). TSAT will be calculated as described in [Appendix 3](#). The percentage of hypochromic RBCs can be determined instead of TSAT.

Patients should be iron-replete at baseline and should maintain an adequate iron status throughout the randomized treatment period.

Adequate iron status is defined as serum ferritin ≥ 100 $\mu\text{g/L}$ and TSAT $\geq 20\%$ (or percentage of hypochromic red cells $< 10\%$).

Supplemental iron will be administered to prevent iron deficiency during the screening period and during the treatment period, when either serum ferritin is < 100 $\mu\text{g/L}$ or TSAT is $< 20\%$ (or percentage of hypochromic RBCs is $\geq 10\%$).

Iron supplementation will be administered orally or intravenously, according to centre practice. If oral iron is not sufficient to correct iron deficiency, iv iron should be given. If iron treatment is ongoing at the start of the study, it should not be interrupted.

To avoid iron toxicity, iv iron therapy should be temporarily discontinued in patients with serum ferritin > 800 $\mu\text{g/L}$ or TSAT $> 50\%$, until serum ferritin is ≤ 800 $\mu\text{g/L}$ and TSAT is $\leq 50\%$.

In order to obtain accurate measures of the iron parameters, we strongly recommend to follow the European and the NKF-K/DOQI guidelines [6, 7] on the time interval needed between administration of an iv iron dose and the performance of the measurements. This interval depends on the iron preparation and single dose administered: blood sampling for iron parameters should be performed at least 1 week after the administration of a >100 mg/dose of any iv iron preparation.

All oral and iv iron supplementations administered within 3 months before screening and started/stopped at any time during the screening and treatment periods should be documented in the iron supplementation section of the eCRF.

4.3.2 Red Blood Cell Transfusions

All RBC transfusions administered during the study should be documented (i.e., specified by number of units transfused) on the RBC transfusions section of the eCRF. The pretransfusion Hb level should be measured before each RBC transfusion and recorded in the eCRF.

4.3.3 Dialysis

For patients on dialysis, dialysis modality (HD or PD), PD type, the number of HD sessions per week, the type of vascular access for HD, time since first dialysis and dialysis adequacy assessments should be documented in the eCRF.

Dialysis treatment should be performed according to current guidelines [8, 9].

If a patient not on dialysis requires dialysis (HD or PD) due to worsening of renal function, CrCl/GFR should be determined (using either the abbreviated MDRD or the Cockcroft-Gault equations; see [Appendix 3](#)). For the continuation of the study, pre- and post-dialysis blood pressure should be measured at each visit. The start of dialysis and dialysis modality should be documented in the dialysis eform of the eCRF.

4.4 Criteria for Premature Withdrawal

Patients have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study in the event of intercurrent illness, AEs, insufficient therapeutic response, pregnancy, unacceptable toxicity of the study drug or administrative reasons.

In case of kidney transplantation, the patient should be withdrawn from study; the final visit should take place before the transplantation, otherwise there will be no final visit.

The investigator should contact the patient or a responsible relative either by telephone or through an office/clinic visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a subject from the study is an Adverse Event, the principal specific event will be recorded on the eCRF. The subject should be followed until the Adverse Event has resolved, if possible.

An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of subjects should be avoided. Should a subject decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

4.5 Replacement Policy [Ensuring Adequate Numbers of Evaluable Subjects]

4.5.1 For Subjects

No subject prematurely discontinued from the study for any reason will be replaced.

4.5.2 For Centers

A center may be replaced for the following administrative reasons:

- Excessively slow recruitment.
- Poor protocol adherence.

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

Written informed consent must be obtained from the patient before any study-specific assessment or procedure is initiated.

A follow-up (final) visit will be performed for all patients at study end or at any time during the study in case of premature withdrawal. Thereafter patients should be treated according to individual center practice. In case of premature withdrawal due to kidney transplantation, the final visit should necessarily take place before the transplantation, otherwise there will be no final visit.

The schedule of assessments and procedures to be performed during the screening and the randomized treatment periods are described in [Table 1](#).

All the results collected throughout the study should be documented in the eCRF.

Table 1 Schedule of Assessments

	Screening [1]		Randomized treatment period		
	Visit S1	Visit S2	Visit 1 R [2]		Final Visit
Informed Consent	X				
Medical History [3]	X		X		
Pregnancy Test [4]	X				
Physical Examination [5]	X				
Blood Pressure [6]	X	X	X	monthly	
Hb [7]	X	X	X	monthly or twice monthly [7]	X
Platelet Count	X		X	monthly	
CRP	X			every 3 months	
Other Safety Laboratory Parameters [8]			X	every 3 months	
Iron Parameters [9]	X			every 3 months	
Cholesterol, triglycerides, glucose, hemoglobin A1c (HbA1c)			X	once a year	
Cardiac markers [10]				in case of suspected MI	
Coagulation laboratory tests [11]				in case of bleeding adverse events	
Kt/V or URR or CrCl/GFR, serum creatinine [12]			X	every 6 months	
Anti-erythropoietin Antibody			X	once a year	X
12-lead ECG Recording			X		
Concomitant Treatment		X	X	ongoing, recorded at monthly visit	X
Adverse Events			X	ongoing, recorded at monthly visit	X
Composite Endpoint Assessments [13]			X	ongoing, recorded at monthly visit	X
Drug Administration		X	X	ongoing, recorded at monthly visit	

Blood samples should be drawn prior to injection of MIRCERA®/reference ESA.

R = Randomization should be performed before the first scheduled MIRCERA® or reference ESA administration at study visit 1.

1. The second Hb and BP assessments are to be made at a second screening visit with at least one day and a maximum of 2 weeks between first and second screening visit.
2. Study visit 1 should take place on the day of the first MIRCERA® or reference ESA administration and not more than 2 weeks after visit S2.
3. Medical history including demographics, the etiology of CKD, dialysis modality (HD or PD), PD type, number of HD sessions per week, time since first dialysis, type of vascular access for HD for dialysis patients, previous treatments including ESA treatment, anticoagulant during dialysis and iron supplementation, previous and concomitant diseases including risk factors and dialysis-related events (recorded before the first scheduled drug administration at study visit 1) and intercurrent events occurring during screening will be documented before the first scheduled drug administration at study visit 1.
4. Serum pregnancy test only to be performed in female patients of childbearing potential.
5. General physical examination includes height (measured only at screening) and body weight.
6. Systolic and diastolic blood pressure, measured before blood sampling; BP should be determined both before and after the dialysis session for HD patients.
7. Twice monthly Hb measurements until Hb has stabilized, and monthly thereafter.

8. Total white blood cell count, serum albumin, calcium, phosphorus, potassium.
9. Serum iron, serum ferritin, serum transferrin or TIBC, calculated TSAT or percentage of hypochromic RBCs.
10. E.g., troponin T, troponin I
11. E.g., prothrombin time (PT) or INR, thrombin time (TT), partial thromboplastin time (PTT)
12. CrCl/GFR should be estimated for patients not on dialysis either with the abbreviated MDRD or the Cockcroft-Gault equations. Kt/V or URR should be determined for HD patients, and the weekly Kt/V for PD patients.
13. Composite endpoint assessments: deaths, AEs of MI, stroke.

5.1 Screening Examination and Eligibility Screening Form

All subjects must sign and date the most current IRB/IEC-approved written informed consent before any study specific assessments or procedures are performed.

After signed written informed consent is obtained, patients will be screened for eligibility. Patients must fulfill all the entry criteria for participation in the study. During the screening period, patients on ESA treatments will continue to receive their treatment at the same dose, route (iv or sc) and dosing interval as before screening.

An Eligibility Screening Form [ESF] documenting the investigator's assessment of each screened subject with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator.

A screening failure log along with the reasons for screening failure must be maintained by the investigator.

Patients who fail screening may be re-screened if it is considered likely that they could later become eligible. There is a limit of 3 screening attempts for each patient.

5.2 Procedures for Enrolment of Eligible Subjects

At the end of the screening period, patients fulfilling all the inclusion and none of the exclusion criteria will be randomized into the study. The randomization should be performed before the first scheduled ESA or MIRCERA® administration at visit 1. Visit 1 should not be more than 2 weeks after the second screening visit.

Providing all eligibility criteria are met, patients with renal anemia not treated with an ESA will be randomly allocated 1:1 either to MIRCERA® once every two weeks (group A) or to a reference ESA treatment (group B) according to label for correction of their renal anemia. Patients with renal anemia on stable maintenance ESA therapy will be randomized 1:1 to continue their current ESA treatment (group B) or to change to MIRCERA® treatment once-monthly (group A). Stratification will be performed by treatment setting (correction/maintenance) and by baseline CRP category (≤ 30 mg/L/ >30 mg/L).

The subject randomization number will be generated by Roche or its designee and incorporated into a set of subject numbers and associated treatment[s] which will be given to the investigator at the time of individual subject enrolment.

The investigator or designee will use the eCRF with the assigned subject number and enter the corresponding number for allocation to the treatment groups in the appropriate place on each subject's eCRF.

The subject randomization numbers are to be allocated sequentially in the order in which the subjects are enrolled according to the specification document agreed with the external randomization company/centre.

5.3 Assessments during the Screening Period

5.3.1 Clinical Assessments during the Screening Period

The following clinical information and assessments will be collected/performed during the screening period and before first study drug administration:

- Medical history: demographics, the etiology of CKD, dialysis modality (HD or PD), PD type, number of HD sessions per week, time since first dialysis, type of vascular access for HD for dialysis patients, previous treatments including ESA treatment and iron supplementation, previous and concomitant diseases including risk factors and dialysis-related events.
- General physical examination: includes height and body weight determination.
- Blood pressure will be measured before blood sampling using standard local techniques; BP should be determined both before and after the dialysis session for HD patients. The same technique (e.g., manual assessment, automated reading) should be used throughout the entire study for every patient. Blood pressure should be measured in the sitting position after at least 5 minutes rest. An appropriate-sized cuff should be used. Both systolic and diastolic blood pressures should be recorded. BP will be measured at 2 screening visits with at least one day and a maximum of 2 weeks between measurements.
- Intercurrent events occurring during the screening period will be documented before first study drug administration.
- Treatments administered during the screening period including ESA treatment, iron supplementation, antihypertensive treatments and anticoagulation therapy used for HD.

5.3.2 Laboratory Assessments during the Screening Period

Normal ranges for the study laboratory parameters must be supplied to Roche before the study starts. Blood sampling should always be performed before ESA administration.

The following laboratory assessments will be performed during the screening period (before first study drug):

- Hematology:
 - Hb: hemoglobin for each patient will be measured at 2 screening visits with at least one day and a maximum of 2 weeks between measurements.
 - Platelet count

- Iron parameters:
 - Serum ferritin, serum iron
 - Serum transferrin (or TIBC)
 - TSAT (or hypochromic RBCs). TSAT will be calculated (see [Appendix 3](#) for calculation).
- CRP
- Serum pregnancy test for female patients of childbearing potential. Patients who are amenorrheic for at least 12 months are not considered of childbearing potential.

5.4 Assessments during the Treatment Period

5.4.1 Clinical Assessments during the Treatment Period

The following clinical information and assessments will be collected/performed during the randomized treatment period and at the final visit:

- MIRCERA® (group A) and ESA (group B) administration.
- Other treatments including iron supplementation, antihypertensive treatments and anticoagulation therapy used for HD.
- Blood pressure: at each study visit, *except at final visit*, blood pressure will be measured before blood sampling using standard local techniques; BP should be determined both before and after the dialysis session for HD patients. The same technique (e.g., manual assessment, automated reading) should be used throughout the entire study for every patient. Blood pressure should be measured in the sitting position after at least 5 minutes rest. An appropriate-sized cuff should be used. Both systolic and diastolic blood pressures should be recorded.
- Adverse events: monitored throughout the randomized treatment period. Serious AEs (SAEs), including composite endpoint assessments, will be monitored up to 30 days after the last study drug administration (see section 7.2).

5.4.2 Laboratory Assessments during the Treatment Period

Normal ranges for the local study laboratory parameters must be supplied to Roche before the study starts.

The total volume of blood loss for laboratory assessments will be approximately 2-40 mL per visit with safety assessments representing a total of approximately 112 mL per year of participation.

Blood sampling during the study should always be performed before MIRCERA® or ESA administration.

The following laboratory assessments will be performed during the randomized treatment period:

- Hematology:
 - Hb at study visit 1, at monthly visit and at the final visit. Hb will be assessed twice monthly until Hb has stabilized.
 - Platelet count at study visit 1 *and* at monthly visit.
 - Total white blood cell count at study visit 1 *and* every 3 months
- Blood chemistry:
 - CRP every 3 months.
 - Serum albumin, calcium, phosphorus, potassium at study visit 1 *and* every 3 months.
- Iron parameters:
 - Serum ferritin, serum iron, serum transferrin or TIBC, TSAT or percentage of hypochromic RBCs every 3 months.
- Cholesterol, triglycerides, HbA1c, glucose at study visit 1 *and* once a year.
- Anti-erythropoietin antibody determination at study visit 1, once a year and at the final visit.
- Patients on HD: Kt/V or URR will be determined at study visit 1 and every 6 months; patients on PD: the weekly Kt/V at study visit 1, every 6 months (see [Appendix 3](#) for definitions).
- Patients not on dialysis: serum creatinine, creatinine clearance/glomerular filtration rate at study visit 1, every 6 months (CrCl/GFR, estimated with the abbreviated MDRD or the Cockcroft-Gault equations [[Appendix 3](#)]).
- 12-lead ECG recording at study visit 1 before dose administration.

The biological samples for specific parameters (anti-erythropoietin antibody determination) which will be analyzed by central laboratories should be classified, packed and shipped as UN 3373 Biological substance, Category B for dispatch purposes, as required by the international regulations and procedures.

5.5 Genomics and Laboratory Biomarkers

5.5.1 Biomarker Sample Repository (BSR)

The collected samples will be stored at Roche for up to 15 years after database closure, after which they will be destroyed. The samples will be used only for research purposes to identify dynamic biomarkers that are predictive of response to ESA treatment in CKD patients with anemia and related diseases.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Dose and Schedule of MIRCERA® and Comparators

MIRCERA® will be injected sc or iv once every two weeks during the correction period or once every month during the maintenance treatment period [3, 4, 14].

Treatment with MIRCERA® has to be initiated under the supervision of a physician experienced in the management of patients with renal impairment.

It is recommended that Hb is monitored every two weeks until stabilized and monthly thereafter.

Patients in the reference group will receive sc or iv injections of ESA according to the approved label during the treatment period [10, 11, 12, 13].

6.1.1 Starting Dose of MIRCERA® and ESA

6.1.1.1 Patients not currently treated with an ESA

The recommended MIRCERA® starting dose for patients not currently treated with an ESA is 0.6 µg/kg body weight, administered once every two weeks as a single iv or sc injection.

The starting dose of the reference ESA should be according to the approved label.

6.1.1.2 Patients currently treated with an ESA

The starting dose of MIRCERA® for each patient in group A will be based on the calculated weekly dose of the ESA administered prior to the switch to MIRCERA® i.e., administered in week-1. The starting doses of MIRCERA® that should be administered at the time of substitution (visit 1) are described in Table 2.

Table 2 MIRCERA® starting doses (µg/month)

Previous weekly darbepoetin alfa intravenous or subcutaneous dose (µg/week)	Previous weekly epoetin intravenous or subcutaneous dose (IU/week)	Monthly MIRCERA® intravenous or subcutaneous dose (µg/once monthly)
<40	<8000	120
40-80	8000-16000	200
>80	>16000	360

Patients randomized to the reference group B will receive reference ESA treatment in week 1 at the weekly dose administered in week-1, at the previous dosing interval and according to the local label during the study period.

The first dose should be given after randomization, at the study visit 1.

6.1.2 Dose Adjustments of MIRCERA® and ESA

6.1.2.1 Patients Not Currently Treated with an ESA

Dose adjustments of MIRCERA® and reference ESA treatments may be made until the individual target Hb level is obtained (Hb range of 10 – 12 g/dL) [3, 4, 10-14].

The MIRCERA® dose may be increased by approximately 25% (or 50% according to approved label in the country) of the previous dose if the rate of rise in Hb is less than 1.0 g/dL over a month. Further increases of approximately 25% (or 50% according to approved label in the country) may be made at monthly intervals until the individual target Hb level is obtained.

If the rate of rise in Hb is greater than 2 g/dL in one month or if the Hb level is increasing and approaching 12 g/dL, the MIRCERA® dose is to be reduced by approximately 25% (or 50% according to approved label in the country). If the Hb level continues to increase, therapy should be interrupted until the hemoglobin level begins to decrease, at which point therapy should be restarted at a MIRCERA® dose approximately 25% below the previously administered dose.

Dose adjustments should not be made more frequently than once a month.

If the desired Hb concentration is reached for the individual patient, MIRCERA® may be administered once monthly using the dose equal to twice the previous once every two weeks dose.

Dose adjustment for the reference ESA should be done according to the approved label [10, 11, 12, 13].

6.1.2.2 Patients Treated with an ESA

If a dose adjustment is required to maintain the Hb concentration of 10 -12 g/dL, the MIRCERA® monthly dose may be increased by approximately 25% [3, 4, 14].

If the rate of rise in Hb is greater than 2 g/dL over a month or if the Hb level is increasing and approaching 12 g/dL, the MIRCERA® dose is to be reduced by approximately 25% (or 50% according to approved label in the country). If the Hb level continues to increase, MIRCERA® therapy should be interrupted until the Hb level begins to decrease, at which point therapy should be restarted at a MIRCERA® dose approximately 25% below the previously administered dose. MIRCERA® Dose adjustments should not be made more frequently than once a month.

Since the treatment experience is limited in patients on peritoneal dialysis, regular Hb monitoring and strict adherence to dose adjustment guidance is recommended in these patients.

Dose adjustment for the reference ESA should be done according to the approved label [10, 11, 12, 13].

6.2 Preparation and Administration of MIRCERA® and Comparator[s]

MIRCERA® in PFS will be administered by sc or iv injection. MIRCERA® sc injection sites are the abdomen, thigh or arm. If two sc injections are necessary (volume of injection >1 mL), then the second injection should be performed on the opposite side of the body (e.g., abdomen right/abdomen left).

In order to assure study drug administration and documentation, MIRCERA® and reference ESAs must be administered by an appropriately trained health care professional; self-administration of study medications is allowed only under the supervision of a health care professional.

Home administration will be allowed when no study visits are planned or blood samples are to be taken. Home administration may be performed under the supervision of appropriately trained medical staff aware of the study procedures.

The reference ESAs will be administered to the patients according to approved labels.

After injection, all empty blisters/medication boxes with patient identification must be retained and made available for the Roche Monitor to check at each visit (see section 6.5).

6.3 Formulation, Packaging and Labeling

Local packaging in some countries may be different.

6.3.1 Formulation of MIRCERA®

MIRCERA® will be provided in sterile single-use injectable solution in PFS containing 0.3 mL or 0.6 mL solution respectively. The MIRCERA® solution contains the following excipients: sodium dihydrogen phosphate monohydrate, sodium sulphate, mannitol (E421), methionine, poloxamer 188, water for injections.

The injectable solution is available in the following strengths (in µg):

PFS	30	50	75	100	120	150	200	250	360
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The PFS should be stored in a refrigerator at 2-8°C and protected from the light. The investigational site is responsible for maintaining a daily temperature log of this refrigerator.

6.3.2 Packaging and Labeling of MIRCERA®

Study medication will be packaged and provided in an open label fashion. *It will be supplied with either study-specific labels or as commercially available product with additional labeling, if required by national legislation.* Each syringe will be available in an individual blister with a needle for sc or iv administration. The package labels will include the following information: protocol number, study drug name, strength, lot number, re-tests date/used by (as per local guidelines), patient number, administration date and safety precautions for clinical trials.

6.3.3 Formulation of Reference ESAs

The formulation of the reference ESAs (Aranesp®, Nespo®, Aranest®, Eprex®, Epogen®, Epopen®, Erypo®, NeoRecormon® and Recormon®) will be according to approved labels [10, 11, 12, 13].

Reference ESAs will be handled and administered according to approved labels. The drug should be stored in a refrigerator (2°C – 8°C). The investigational site is responsible for maintaining a daily temperature log of any refrigerator used for the reference ESAs storage.

6.3.4 Packaging and Labeling of Reference ESAs

The reference ESAs used for the study will be provided either by Roche or by individual study centers, depending on country specifications.

For study centers/countries where reference ESAs will be supplied by Roche, reference ESAs will be packed and labeled according to local specifications, in an open fashion. *It will be supplied with either study-specific labels or as commercially available product with additional labeling, if required by national legislation.* Each PFS will be available blistered in an individual box.

6.4 Blinding and Unblinding

Not applicable, the study is open-label.

6.5 Assessment of Compliance

Accountability and subject compliance will be assessed by maintaining adequate drug dispensing and return records.

A Drug Inventory/Dispensing Log provided by Roche must be kept current and should contain the following information at a minimum:

- the identification of the subject to whom the study medication was dispensed
- the date[s], quantity of the study medication dispensed *to* the subject
- the initials of the person confirming administration of the study medication
- the date[s] and quantity of the study medication returned *by* the subject

The inventory *and dispensing logs* must be available for ongoing inspection by the Monitor. After injection, all empty blisters of PFS of MIRCERA® or reference ESA will be kept in a container or in the medication box and will be made available for the Roche Monitor to check at each visit. All supplies, including partially used, expired and unused or empty containers and dispensing logs, must be kept at the study site and *copies of the inventory and dispensing logs will be retrieved by the Roche Monitor* at the end of the study.

In case of home administrations, for assessment of compliance, subjects will be asked to return empty blisters/medication boxes with the drug administration records at each study visit.

6.6 Destruction of the MIRCERA®/Reference ESAs

The unused, partially used or expired MIRCERA®/reference ESA PFS provided by the Sponsor may be destroyed at the site or at the supplying depot following the current Roche and local Standard Operating Procedures as applicable.

Local or institutional regulations may require immediate destruction of used MIRCERA®/reference ESA PFS for safety reasons. In these cases, it may be acceptable for investigational site staff to destroy dispensed MIRCERA®/reference ESA PFS before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned and destroyed. Written authorization must be obtained from the sponsor at study start up before destruction.

Written documentation of destruction must contain the following:

- Identity [batch numbers or subject numbers] of MIRCERA®/reference ESA [if applicable] destroyed
- Quantity of MIRCERA®/reference ESA PFS destroyed
- Date of destruction (*date discarded in designated hazardous container for destruction*)
- Method of destruction (*the site must provide the Sponsor with documentation of their institutional policy and procedures for handling and disposing of drugs*)
- Name and signature of responsible person [or company] who *discarded the investigational products[s] in a hazardous container for destruction*

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 Adverse Events (AEs) and Laboratory Abnormalities

7.1.1 Clinical AEs

According to the International Conference of Harmonization [ICH], an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign [including an abnormal laboratory finding], symptom, or disease temporally associated with the use of a medicinal [investigational] product, whether or not considered related to the medicinal [investigational] product. Pre-existing conditions which worsen during a study are to be reported as AEs.

Clinical AEs encountered during the randomized treatment period will be recorded on an AE eform of the eCRF (see figure in [Appendix 1](#)).

Kidney transplantation and routine diagnostic procedures/tests are not considered AEs and should therefore not be recorded on an AE eform of the eCRF.

In patients not on dialysis, start of dialysis should not be considered as an AE and should be recorded on a specific eCRF form. If the worsening of kidney function justifying dialysis is faster than expected, the worsening of kidney function may be recorded as an AE term and the dialysis procedure should be recorded in the treatment section of the AE eform.

Cardiac laboratory tests (e.g., troponin I, troponin T) will be assessed in case of suspected MI.

Coagulation laboratory tests (e.g., prothrombin time (PT) or INR, thrombin time (TT), partial thromboplastin time (PTT)) will be assessed in case of bleeding adverse events.

7.1.1.1 Intensity

All clinical AEs encountered during the clinical study will be reported on the AE eform of the eCRF. Intensity of AEs will be graded on a three-point scale [mild, moderate, severe] and reported in detail on the eCRF.

Mild	discomfort noticed but no disruption of normal daily activity.
Moderate	discomfort sufficient to reduce or affect daily activity.
Severe	inability to work or perform normal daily activity

7.1.1.2 Drug - Adverse event relationship

The relationship of the AE to the treatment should always be assessed by the investigator.

The relationship can be one of two possibilities:

- No (unrelated; equals not drug related).
- Yes (the event has a reasonable suspected causal relationship to the drug, or causality is unknown).

The criteria used for determining causality relationship can be found in [Appendix 1](#).

7.1.1.3 Serious Adverse Events [Immediately Reportable to Roche]

A Serious Adverse Event (SAE) is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills at least one of the following criteria:

- is fatal; [results in death**; NOTE: death is an outcome, not an event]
- is life threatening [NOTE: the term "life-threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe].
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;

- is medically significant or requires intervention to prevent one or other of the outcomes listed above.

**The term sudden death should only be used when the cause is of a cardiac origin as per standard definition (see guidance notes for completing the SAE reporting form [20]). The terms death and sudden death are clearly distinct and must not be used interchangeably.

The study will comply with all local regulatory requirements and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 ([Appendix 2](#)).

7.1.2 Treatment and Follow-up of AEs

AEs, especially those for which the relationship to study medication(s) is not “unrelated”, should be followed up until they have returned to baseline status or stabilized. If after follow-up, return to baseline status or stabilization cannot be established an explanation should be recorded on the eCRF.

7.1.3 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results eform of the eCRF, or appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable. Recommendations for grading adverse events and laboratories abnormalities can be found in [Appendix 4](#).

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AE eform in the eCRF:

Accompanied by clinical symptoms

Leading to a change in study medication [e.g. dose modification, interruption or permanent discontinuation]

Requiring a change in concomitant therapy [e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment].

Any laboratory result abnormality fulfilling the criteria for a serious adverse event [SAE] should be reported as such, in addition to being recorded as an AE in the eCRF.

7.1.3.1 Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

7.2 Handling of Safety Parameters

7.2.1 Reporting of Serious Adverse Events [immediately reportable]

Any clinical AE or abnormal laboratory test value that is *serious* [as defined in Section 7.1.1.3 above] and which occurs during the course of the study, regardless of the treatment arm, must be reported to Roche within 24 hours of the investigator becoming

aware of the event [expedited reporting]. The investigator must complete the *SAE Reporting Form* and forward it to the SAE Responsible.

The investigator must fax the completed SAE reporting form directly to the Roche local country contact person for SAEs (local monitor, see the Administrative and Contact Information).

Related SAEs *MUST* be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

Unrelated SAEs must be collected and reported during the study and for up to 30 days after the last dose of study medication.

This study adheres to the definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2. Complete information can be found in [Appendix 2](#).

As an exception, the following SAEs unrelated to study drug, which are common in the dialysis population, will not be reported in an expedited manner on an SAE reporting form (but will be recorded as SAEs on the AE pages of the eCRF):

- Thrombosis of vascular access for dialysis in HD patients
- Peritonitis in PD patients

All SAEs, including the two categories listed above, occurring during the randomized treatment period or within 30 days after the last injection of MIRCERA® or other ESAs within study, should be documented as SAEs on the AE eforms of the eCRF (See Figure in [Appendix 1](#)).

7.2.2 Pregnancy

No data are available from adequate, controlled studies of MIRCERA® or other ESAs in pregnant women. Therefore, women of childbearing potential must have a serum pregnancy test at screening and must use a reliable method of contraception throughout the study (see [Appendix 3](#)).

A female subject must be instructed to stop taking the study medication and immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies within one working day to the sponsor using the *Pregnancy Reporting Form*. The investigator should counsel the subject, discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to 90 days after the completion of the study medication must also be reported to the investigator.

7.3 Warnings and Precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the SmPC [[14](#)].

7.4 Loss of effect

Hb values will be monitored regularly throughout the study, and dose adjustments to achieve target Hb levels will be made according to protocol guidance (6.1).

Loss of effect is defined as: a decline in Hb of at least 2.8 g/dL in a 4-week period without transfusion *or* requirement for transfusion of one blood unit or more per week for a minimum of two consecutive weeks in the absence of overt bleeding or blood loss, under uninterrupted treatment with study drug and with dose changes according to protocol guidance [18].

If loss of effect is suspected, the cause should be actively sought. Possible causes include: iron deficiency, infection, inflammation, occult blood loss, hyperparathyroidism, myelofibrosis, and malignancy. If a cause for loss of effect is not found, a hematologist should be consulted (bone marrow examination) and an unscheduled blood sample should be obtained for a reticulocyte count and an anti-erythropoietin antibody determination.

If a diagnosis of PRCA is not confirmed, the patient should be maintained on the study drug and other possible causes of loss of effect should be investigated.

If a diagnosis of PRCA is confirmed, treatment with the study drug should be stopped. The patient should not receive another epoetin and causes of PRCA should be investigated. The patient should proceed with the study assessments as scheduled. In addition, reticulocyte counts and anti-erythropoietin antibody testing will be performed every 8 weeks until the end of the study (see [Appendix 5](#)).

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Primary and Secondary Study Endpoints

8.1.1 Primary Endpoints

The primary efficacy endpoint for this study is the time to composite of:

- all-cause mortality
- non-fatal cardiovascular events (MI, stroke)

defined as the time between first dose of study medication and the date of death or non-fatal cardiovascular events (MI, stroke), whatever occurs first. Patients for whom no endpoint event is captured on the clinical database are censored at their last day in the study.

8.1.2 Secondary Endpoints

Secondary endpoints are the time to the individual components of the composite endpoint: the time to death, the time to non-fatal cardiovascular events (MI or stroke), the time to MI and the time to stroke.

8.1.3 Other Safety Endpoints

The safety of the treatment will also be evaluated on the basis of AEs, laboratory tests and vital signs, as described in section [8.2.6](#).

All subjects who receive at least one dose of treatment will be included in the safety evaluation.

8.2 Statistical and Analytical Methods

8.2.1 Statistical Model

8.2.1.1 Primary Endpoint

The analysis of time to event endpoints is based on the survivor function, which is the probability to survive or, more generally, to remain event-free beyond a certain point in time. The primary endpoint will be analyzed with a Cox's proportional hazards model to estimate the hazard ratio and its 95% confidence interval between the two treatment groups. The underlying proportional hazards model is $\lambda(t) = \lambda_0(t)\exp(\beta Z)$. Thereby, β is the coefficient corresponding to the binary vector Z taking the value 0 for patients on the reference arm and the value 1 for patients on the MIRCERA® arm, and $\lambda_0(t)$ is the baseline hazard of the reference treatment. Based on this, the following non-inferiority hypothesis for the hazard ratio ($h_{MR} = \exp(\beta)$) between MIRCERA® and reference will be tested by comparing the upper limit of the 95% confidence interval for the hazard ratio to 1.20:

$$H_0: h_{MR} \geq 1.20 \quad \text{versus} \quad H_1: h_{MR} < 1.20$$

The null hypothesis will be rejected if the upper limit of the confidence interval is below 1.20. The underlying Cox regression model will retain treatment as factor.

In addition, analyses based on Cox models adjusted for the baseline stratification factors and other clinically relevant baseline variables such as CRP at screening, age and baseline risk factors will be reported.

8.2.1.2 Secondary Endpoints

Kaplan-Meier methods and frequency tables will be used to describe the time to the composite endpoint as well as the time to the individual components of the composite endpoint for the MIRCERA® versus reference group. The survival function will be summarized for the 25th percentile, the median, the 75th percentile and their 95% confidence intervals. The plot of Kaplan-Meier estimates for the two treatment groups will be presented. The un-stratified log-rank test will be used to compare survivor functions between the two treatment groups.

In addition, analyses based on Cox models adjusted for the baseline stratification factors (including CRP) and other clinically relevant baseline variables such as age and baseline risk factors will be reported.

8.2.2 Sample Size

The randomization will be stratified by treatment setting (correction/maintenance) and baseline CRP category (≤ 30 mg/L / >30 mg/L). The stratification will ensure that 20% of patients will be recruited in the correction setting and 80% in the maintenance switch setting.

The expected yearly event rate is approximately 20%, based on

- an expected 25% composite endpoint rate (a mortality rate of approximately 16% [15, 16] and non-fatal cardiovascular morbidity of approximately 9% [17]) in the maintenance setting (80% of patients)
- a 7% rate for the combined endpoint in the correction setting (20% of patients) [CSR BA16738]

Assuming linear recruitment over 30 months and a follow-up time of 18 months after randomization of the last patient, a sample size of 2800 patients, representing approximately 7700 patient-years of exposure, would be adequate to observe 1264 events of the composite endpoint of death and non-fatal cardiovascular events.

1264 events are sufficient to ensure 90% power to establish non-inferiority of MIRCERA® to comparator ESAs in terms of the composite endpoint based on a non-inferiority margin of 1.20 and a one-sided significance level of 0.025.

Duration (months)	NI limit (HR)	Event rate per year	No. events / Nb patients	Expected Event rate at end of study (%)	Highest event rate based on NI limit (%)	Absolute / relative difference (%)	Absolute and relative difference in deaths (%)
48	1.2	0.2	1264 / 2800	45.2	51.2	6.1 / 13	3.6 / 13

Note: The overall event rate observed during the study is considerably lower than that expected at the planning stage. Changing no other parameters leads to an extended study duration; the occurrence of 1264 events has been estimated to be approximately 10 years after study start.

8.2.3 Hypothesis Testing

The primary endpoint is the time between first dose of study medication and the date of death or non-fatal cardiovascular events (MI, stroke), whatever occurs first. The hypotheses to be tested are:

$H_0: h_{MR} \geq 1.20$ versus $H_1: h_{MR} < 1.20$

Using the correspondence between tests and confidence intervals, the test for non-inferiority will be based on the upper limit of the two-sided 95% confidence interval for the hazard ratio of the two groups. When the upper confidence interval limit is lower than 1.20, the MIRCERA® group will be regarded as clinically non-inferior to the reference group. The corresponding p-value will be calculated via the standard normal distribution:

$$p = P(t \leq \hat{T}) = \Phi \left(\frac{\ln \hat{h}_{MR} - \ln 1.20}{SE} \right),$$

where SE denotes the standard error of $\ln \hat{h}_{MR}$ and Φ is the cumulative distribution function of the standard normal distribution.

8.2.4 Analysis Populations

The primary analysis will be performed based on the safety population defined as all patients randomized who receive at least one dose and had at least one post-dose safety assessment.

In addition, the primary analysis will be performed based on the intent-to-treat (ITT) population defined as all patients randomized according to the original treatment assignment.

8.2.5 Efficacy Analysis

This is a safety study; no formal efficacy analyses will be performed. Hemoglobin over time and dose will be analyzed descriptively.

8.2.5.1 Interim Analysis

No formal interim analyses are planned. Safety updates will be prepared for review by the DSMB at its scheduled meetings (see section 10.2).

8.2.6 Other Safety Data Analyses

The safety parameters will be vital signs, AEs and the safety laboratory parameters including iron parameters.

Adverse event data will be presented in frequency tables (overall and by intensity) by body system. In tables showing the overall incidence of adverse events, subjects who experienced the same event on more than one occasion are counted only once in the calculation of the event frequency. Adverse events will be summarized throughout the whole study treatment period and up to 30 days after the last administration of study treatment.

Deaths will be listed and summarized descriptively. Vital signs and laboratory data will be analyzed descriptively and will be assessed for clinically relevant abnormalities as well as changes from baseline. The results of the exploratory statistical analysis of NT-proBNP and troponin T will be reported separately.

Demographic and baseline disease characteristics will be summarized by treatment arm for all randomized patients.

The secondary objectives (incidence of anti-erythropoietin antibody-mediated pure red cell aplasia (PRCA), gastrointestinal bleeding and thromboembolic events), will be analyzed using descriptive statistics and analytical methods such as risk ratios, Cox regression and ANOVA methods.

9. DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data are described in the Roche Standard Operational Procedures.

Data for this study will be recorded via an Electronic Data Capture (EDC) system using electronic Case Report Forms. It will be transcribed by the site from the paper source documents onto the eCRF. (In no case is the eCRF to be considered as source data for this trial.)

Accurate and reliable data collection will be assured by verification and cross-check of the eCRFs against the investigator's records by the study monitor [source document verification], and the maintenance of a drug-dispensing log by the investigator.

A comprehensive validation check program utilizing front-end checks in the eCRF and back-end checks in the Roche database will verify the data and discrepancies will be generated accordingly. These are transferred electronically to the eCRF at the site for resolution by the investigator.

Throughout the study the SMT will review data according to the SMT Data Review Plan as described in the Data Quality Plan.

9.1 Assignment of Preferred Terms and Original Terminology

For classification purposes, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF, using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA) terminology for adverse events and diseases and the International Non-proprietary Name (INN) Drug Terms and Procedures Dictionary for treatments and surgical and medical procedures.

10. STUDY COMMITTEES

10.1 Steering Committee

A Steering Committee will be put in place consisting of a group of study investigators and representatives of the Sponsor. The tasks of the Steering Committee include protocol development, review of study conduct, and management of issues arising during the trial.

10.2 DSMB

An independent Data and Safety Monitoring Board (DSMB) consisting of 3 clinical experts in the field and a statistician will be constituted to review the safety data, including adjudicated outcomes, collected during the study. A non-voting clinical scientist representative of Roche will also be available to assist the DSMB with clarification of issues related to the protocol and study management.

The board will review baseline risk factors as specified in section 5.3 and the safety data when approximately 25% (316) of the required events have been recorded and adjudicated. In addition, the board will review the data when 50% (632) and 75% (948) of events have occurred. Following each meeting the DSMB will give recommendations regarding continuation or discontinuation of the study to the sponsor according to pre-specified rules recorded in the DSMB charter.

The Board may recommend stopping the study due to safety reasons, as described in the DSMB charter.

The analyses provided to the DSMB will be prepared by an external independent statistician from the independent data coordinating center (iDCC). Further details about the role and procedures of the DSMB will be provided in the DSMB charter.

10.3 Endpoint Committee

An independent Endpoint Adjudication Committee will be constituted to review all potential endpoint events. The Endpoint Adjudication Committee will consist of at least two cardiologists, one nephrologist and one neurologist with experience in clinical studies and in the adjudication of study endpoints. The committee will provide a blinded assessment of fatal and non-fatal events in the composite endpoint.

Suspect events will be recorded by the treating personnel in the dialysis centers. The Sponsor will supply the Committee members with blinded patient level data for review. For the list of documents see [Appendix 6](#). The suspect events will be adjudicated by blinded committee members, with subsequent blinded adjudication in the case of disagreement.

The Endpoint Committee and the Sponsor will establish the classification definitions in accordance with the study protocol before the adjudication process begins. Further details about the role and procedures of the Endpoint Committee will be provided in a separate document, the Endpoint Adjudication Committee charter.

11. REFERENCES

1. Singh AK et al. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006;355:2085-98.
2. Drüeke TB et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006;355:2071-84.
3. MIRCERA®, Core Data Sheet.
4. MIRCERA®, Investigator's Brochure, Ninth Version, September, 2007.
5. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Guideline 4: Evaluation of GFR. *Am J Kidney Dis* 2002, In: http://www.kidney.org/professionals/kdoqi/guidelines_ckd/p5_lab_g4.htm (accessed Aug 3rd 2006).
6. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *Am J Kidney Dis* 2006;47 [Suppl 3]:S11-145.
7. Revised European Best Practice Guidelines for the management of anemia in patients with chronic renal failure. *Nephrol Dial Transplant* 19(suppl 2):Sii1-Sii47, 2004
8. European Best Practice Guidelines on Haemodialysis. *Nephrol Dial Transplant* 22(Suppl 2):ii1-ii120, 2007
9. European Best Practice Guidelines for Peritoneal Dialysis. *Nephrol Dial Transplant* 20(Suppl 9): ix24–ix27, 2005
10. Aranesp® Summary of Product Characteristics, EMEA. In: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000332/human_med_000651.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125#
11. Nespo® Summary of Product Characteristics, EMEA. In: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000333/human_med_000923.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125
12. Eprex® Summary of Product Characteristics (revised text 27 July 2006). In: <http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=889>.
13. NeoRecormon® Summary of Product Characteristics, EMEA. In: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000116/human_med_000921.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125#

14. MIRCERA® Summary of Product Characteristics, EMEA. In:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000739/human_med_000905.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125#
15. Cheung AK et al. Cardiac diseases in maintenance hemodialysis patients: Results of HEMO study. *Kidney Int* 2004;65:2380-2389
16. Excerpts from the USRDS. 2004 Annual Data Report: Atlas of end-stage renal disease in the United States. *Am J Kid Dis* 2005; 45: Suppl 1
17. Enkoyan G et al. Effect of dialysis dose and membrane flux in hemodialysis. *New Engl J Med* 2002; 347: 2010-2019
18. Eckardt KU, Casadevall N. Pure red-cell aplasia due to anti-erythropoietin antibodies. *Nephrol Dial Transplant* 2003;18:865-869.
19. Deicher R, Hörl WH. Heparin: a molecular link between inflammation and anemia. *Nephrol Dial Transplant* 2004;19:521-524.
20. Guidance Notes for Completing SAE Reporting Form (gcp_for000025; version 7.0).

PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

12. ETHICAL ASPECTS

12.1 Local Regulations/Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the “Declaration of Helsinki” or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in “Guideline for Good Clinical Practice” ICH Tripartite Guideline or with local law if it affords greater protection to the subject. For studies conducted in the EU/EEA countries, the investigator will ensure compliance with the EU Clinical Trial Directive [2001/20/EC]. For studies conducted in the USA or under US IND, the investigator will additionally ensure adherence to the basic principles of “Good Clinical Practice” as outlined in the current version of 21 CFR, subchapter D, part 312, “Responsibilities of Sponsors and Investigators”, part 50, “Protection of Human Subjects”, and part 56, “Institutional Review Boards”.

In other countries where a “Guideline for Good Clinical Practice” exists, Roche and the investigators will strictly ensure adherence to the stated provisions.

12.2 Informed Consent

Written Informed Consent from Subjects:

It is the responsibility of the investigator, or a person designated by the investigator [if acceptable by local regulations], to obtain signed informed consent from each subject prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For the subject not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the subject and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject and representative have orally consented to participation in the trial, the witness’ signature on the form will attest that the information in the consent form was accurately explained and understood. The investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The electronic Case Report Forms (eCRFs) for this study contain a section for documenting subject informed consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

For non-US-IND studies:In a life-threatening situation where a patient is unconscious or otherwise unable to communicate, the emergency is such that there is not enough time to obtain consent from the patient's legally acceptable representative, and there is no other or better treatment available, it is permissible to treat the patient under protocol with consent of the investigator, with appropriate documentation that the IEC had approved

the procedures used to enroll patients in such situations. In addition, the patient or his/her legally acceptable representative should be informed about the trial as soon as possible and consent to continue, giving written consent as described above.

12.3 Independent Ethics Committees/Institutional Review Board

Independent Ethics Committees (IECs) [non-US] For EEA member states, the sponsor will submit to the Competent Authority and Ethics Committees the protocol and any accompanying material provided to the subject (such as subject information sheets or descriptions of the study used to obtain informed consent as well as any advertising or compensation given to the subject).

Approval from the committee must be obtained before starting the study, and should be documented in a letter to the investigator specifying the date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of the IEC's approval must be re-submitted by the investigator in the US and by the Sponsor in the EEA member states in accordance with local procedures and regulatory requirements.

When no local review board exists, the investigator is expected to submit the protocol to a regional committee. If no regional committee exists, Roche will assist the investigator in submitting the protocol to the European Ethics Review Committee.

Institutional Review Board [US]: It is the understanding of the sponsor that this protocol [and any modifications] as well as appropriate consent procedures and advertisements, will be reviewed and approved by an Institutional Review Board. This board must operate in accordance with the current Federal Regulations. The sponsor will receive a letter or certificate of approval prior to initiation of the study, and also whenever subsequent amendments/modifications are made to the protocol.

13. CONDITIONS FOR MODIFYING THE PROTOCOL

Requests from investigators to modify the protocol to ongoing studies will be considered only by consultation between an appropriate representative of the sponsor and the investigator [investigator representative[s] in the case of a multicenter trial]. Protocol modifications must be prepared by a representative of the sponsor and initially reviewed and approved by the Clinical Science Leader/Clinical Pharmacologist and Biostatistician.

All protocol modifications must be submitted to the appropriate Independent Ethics Committee or Institutional Review Board for information and approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the change[s] involves only logistical or administrative aspects of the trial [e.g. change in monitor[s], change of telephone number[s]].

14. CONDITIONS FOR TERMINATING THE STUDY

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Roche and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

15. STUDY DOCUMENTATION, eCRFS AND RECORD KEEPING

15.1 Investigator's Files / Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories [1] Investigator's Study File, and [2] subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments, DCS and schedule of assessments, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc. In addition at the end of the study the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data, query resolution correspondence and reasons for changes, in human readable format on CD which also has to be kept with the Investigator's Study File.

Subject clinical source documents [usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs] would include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, EEG, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and subject screening and enrollment logs. The Investigator must keep these two categories of documents (including the archival CD) on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, Roche must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and Roche to store these in a sealed container[s] outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

15.2 Source Documents and Background Data

The investigator shall supply the sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

15.3 Audits and Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Roche Pharma Development Quality Assurance Unit or its designees or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

15.4 Electronic Case Report Forms

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

For each subject enrolled, an eCRF must be completed and electronically signed by the principal investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study [even during a pre-randomization screening period if an eCRF was initiated]. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports. *All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee. At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.*

16. MONITORING THE STUDY

It is understood that the responsible Roche monitor [or designee] will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial [eCRFs and other pertinent data] provided that subject confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor must verify that the subject received the study drug assigned by the randomization center (by controlling the written confirmation of the randomization by IVRS). The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRF. The investigator [or deputy] agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

17. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a subject enrollment log showing codes, names and addresses. The investigator should maintain documents not for submission to Roche, e.g., subjects' written consent forms, in strict confidence.

18. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Roche prior to submission. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, Roche will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Any formal publication of the study in which input of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Roche personnel. Authorship will be determined by mutual agreement.

Appendix 1 AEs Categories for Determining Relationship to Test Drug

UNRELATED

This category is applicable to those AEs which are judged to be clearly and incontrovertibly due only to extraneous causes [disease, environment, etc.] and do not meet the criteria for drug relationship listed under remote, possible, or probable.

RELATED

PROBABLE [must have first three]

This category applies to those AEs which are considered, with a high degree of certainty, to be related to the test drug. An AE may be considered probable, if:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It disappears or decreases on cessation or reduction in dose. [There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; e.g., [1] bone marrow depression, [2] tardive dyskinesias.]
4. It follows a known pattern of response to the suspected medication.
5. It reappears upon rechallenge.

POSSIBLE [must have first two]

This category applies to those AEs in which the connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possible if, or when:

1. It follows a reasonable temporal sequence from administration of the drug.
2. It may have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It follows a known pattern of response to the suspected medication.

REMOTE [must have first two]

In general, this category is applicable to an AE which meets the following criteria:

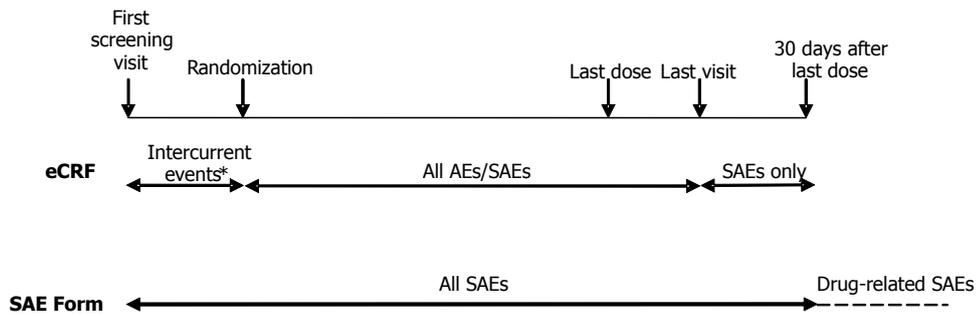
1. It does not follow a reasonable temporal sequence from administration of the drug.
2. It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It does not follow a known pattern of response to the suspected medication.
4. It does not reappear or worsen when the drug is readministered.

In case of a probable, possible or remote relationship to test drug, please indicate the relationship to test drug as "Yes" in the AE eform of the eCRF, and, if it is a serious AE, check and specify "Study treatment" in section 2 "Possible causes of the event" on page 1 of the SAE form.

Appendix 1 AEs Categories for Determining Relationship to Test Drug [Cont.]

	Probable	Possible	Remote	Unrelated
Clearly due to extraneous causes	-	-	-	+
Reasonable temporal association with drug administration	+	+	-	-
May be produced by subject clinical state, etc.	-	+	+	+
Known response pattern to suspected drug	+	+	-	-
Disappears or decreases on cessation or reduction in dose	+	-	-	-
Reappears on rechallenge	+	-	-	-

Timeframes for Adverse Events/Serious Adverse Event Collection



*Intercurrent events should be recorded on the Medical History pages in eCRF

Appendix 2 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills at least one of the following criteria:

- is fatal; [results in death] [NOTE: death is an outcome, not an event]
- is Life-Threatening [NOTE: the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe].
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is medically significant or requires intervention to prevent one or other of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one in which the nature or severity is not consistent with the applicable product information.

Causality is initially assessed by the investigator. For Serious Adverse Events, possible causes of the event are indicated by selecting one or more options. (Check all that apply)

- Pre-existing/Underlying disease - specify
- Study treatment – specify the drug(s) related to the event
- Other treatment (concomitant or previous) – specify
- Protocol-related procedure
- Other (e.g. accident, new or intercurrent illness) - specify

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

**Appendix 2 ICH Guidelines for Clinical Safety Data Management,
Definitions and Standards for Expedited Reporting, Topic E2
[Cont.]**

A serious adverse event occurring during the study or which comes to the attention of the investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, if this is longer, whether considered treatment-related or not, must be reported. In addition, a serious adverse event that occurs after this time, if considered related to test “drug”, should be reported.

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For serious adverse events, the following must be assessed and recorded on the AEs eform of the eCRF: intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the Ethics Review Committee/Institutional Review Board of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

ROCHE LOCAL COUNTRY CONTACT for SAEs: Local Monitor

See attached *Protocol Administrative and Contact Information & List of Investigators form, gcp_for000227*, for details of administrative and contact information.

ROCHE HEADQUARTERS CONTACT for SAEs and other medical emergencies:
Clinical Operations/Clinical Science

See attached *Protocol Administrative and Contact Information & List of Investigators form, gcp_for000227*, for details of administrative and contact information

24 HOUR MEDICAL COVERAGE: Within the US, weekends, holidays and after 5:00 pm, call [REDACTED] and ask for the physician on call. Outside the US, call the local emergency contact number provided by the Monitor.

Appendix 3 Additional Information on Laboratory/Clinical Assessments

– Creatinine Clearance

GFR can be estimated using either the Cockcroft & Gault formula¹ or the simplified or extended MDRD formulae. In general, the MDRD formulae provide a more accurate estimate of GFR in subjects with reduced renal function, regardless of patient weight².

The abbreviated (also called “four-variable” or “simplified”) MDRD Study equation has been validated to estimate CrCl/GFR in CKD patients^{3,4}. It uses age (years), sex (female vs. non-female), race (African-American vs. non-African-American), and serum creatinine.

Abbreviated MDRD formula²

SI Units

$$\text{GFR} = 186.3 \times (\text{serum creatinine } [\mu\text{mol/L}] \times 0.0113)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American})$$

GFR: glomerular filtration rate (mL/min/1.73 m²)
Age (years)

An automatic GFR calculator is available online at the National Kidney Foundation web site: http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm.

Cockcroft & Gault formula¹

SI Units

$$\text{Cr Clearance (mL/min)} = f \times (140 - \text{age}) \times \text{IBW} / (0.81 \times \text{serum Cr } (\mu\text{mol/L}))$$

f = 1.0 for males and 0.85 for females. Age in years, IBW in kg
IBW (male) = [0.9 x Height (cm)] – 88
IBW (female) = [0.9 x Height (cm)] – 92

¹ Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41

² Levey AS, Bosch JP, Breyer Lewis J, Greene T, Rogers N, Roth D & the Modification of Diet in Renal Disease Study Group. A More Accurate Method to Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. *Ann Intern Med.* 1999; 130 (6): 461-470.

³ Levey AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinine. *J Am Soc Nephrol* 2000;11:155A. abstract.

⁴ Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003;139:137-47. [Erratum, *Ann Intern Med* 2003;139:605].

Appendix 3 Additional Information on Laboratory/Clinical Assessments (Cont.)

Note: Because of the current variability in calibration of serum creatinine assays, assays not calibrated in agreement with the kinetic alkaline picrate assay used in the MDRD Study introduce a source of error into GFR estimates.⁵ The MDRD formula was based on serum creatinine measurements calibrated to a serum creatinine standard that measures true serum creatinine. Therefore, the use of non-calibrated serum creatinine values in the formula could result in over-estimation of the GFR at lower serum creatinine concentrations. It is thus recommended to calibrate the measurement of serum creatinine against that of the MDRD core laboratory.⁶ The Roche Laboratory Data Manager will ensure that in collecting the normal ranges for each laboratory participating in this study, there is an indication as to whether the serum creatinine results will be calibrated or not.

It is also recommended to report serum creatinine values as mg/dL to 2 decimal places (e.g., 0.92 mg/dL instead of 0.9 mg/dL) and those reported as $\mu\text{mol/L}$ should be reported as the nearest whole number (e.g., 109 $\mu\text{mol/L}$ instead of 109.3 $\mu\text{mol/L}$). The GFR numeric estimate should be rounded to the nearest whole number, such as “35” (mL/min/1.73 m²).³ The GFR numeric estimate should not be corrected for body surface area.

⁵ Myers GL, Miller WG, Coresh J et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education program. *Clinical Chemistry* 2006;52:1, 5-18.

⁶ Landis JR, Gaughan C, Joffe M. Inter-laboratory serum creatinine (sCr) calibration study. *J Am Soc Nephrol* 2003;14:294A. Abstract.

Appendix 3 Additional Information on Laboratory/Clinical Assessments (Cont.)

– Hemodialysis adequacy

For assessing adequacy of hemodialysis, Kt/V or urea reduction ratio (URR) should be determined according to routine procedures established at each centre.

– Peritoneal dialysis adequacy

The total weekly Kt/V should be determined for assessing adequacy of peritoneal dialysis as follows:

Kt/V	K = urea clearance (mL/min) t = time of weekly dialysis (usually 7 days expressed as minutes, i.e. 10080 minutes) V = V _D = volume of urea distribution in the total body water (mL)
K = C _{Du} + C _{Ru}	C _{Du} = dialytic urea clearance (mL/min) C _{Ru} = renal urea clearance (mL/min)
C _{Du} = $\frac{U_d \times V_d}{U_p}$	U _d = dialysate urea concentration (mg/mL) V _d = dialysate flow rate (mL/min) U _p = serum urea concentration (mg/mL)
C _{Ru} = $\frac{U_u \times V_u}{U_p}$	U _u = urine urea concentration (mg/mL) V _u = urine flow rate (mL/min) U _p = serum urea concentration (mg/mL)

The volume of urea distribution in the body water (V_D) is estimated according to Watson nomogram, which takes into account sex, age, height, and lean body mass (LBM):

For Men: V_D (liters) = 2.447 + 0.3362 x LBM (kg) + 0.1074 x Height (cm) - 0.09516 x Age (years)
For Women: V_D (liters) = -2.097 + 0.2466 x LBM (kg) + 0.1069 x Height (cm)

LBM can be calculated as follows⁷:

LBM (men) = (1.10 x Weight (kg)) - 128 x (Weight²/(100 x Height (m))²)
LBM (women) = (1.07 x Weight (kg)) - 148 x (Weight²/(100 x Height (m))²)

⁷ <http://www.halls.md/body-mass-index/leanbody.htm>

Appendix 3 Additional Information on Laboratory/Clinical Assessments (Cont.)

– Hemolysis

Acute hemolysis is usually associated with low haptoglobin and high lactate dehydrogenase levels. Reticulocytes may increase but this is masked in patients receiving erythropoietic agents since these agents stimulate reticulocyte production. Hemolysis may be confirmed by the following assessments:

- Decline in haptoglobin below 30 mg/dL
- Presence of free Hb in blood (>1% of total Hb)
- Increased lactate dehydrogenase

Conditions that result in chronic hemolytic anemia include but are not limited to:

- Thalassemias
- Homozygous sickle-cell disease (excluding sickle cell trait)
- Autoimmune hemolytic anemias
- Hereditary spherocytosis, elliptocytosis
- Red blood cell (RBC) enzyme deficiencies (e.g. glucose-6-phosphate Dehydrogenase G6PD deficiency)

– For United Kingdom only: Women of Childbearing Potential Without Effective Contraception

Effective methods of contraception include oral, injectable or implantable contraceptives (e.g. pill, 3-month injection, hormonal depot preparation), intrauterine devices in combination with a barrier method (e.g. condom, diaphragm) and/or spermicidal gel or absolute abstinence.

– Transferrin Saturation

Transferrin saturation (TSAT) should be calculated using one of the following formulas (US units)⁸:

$$\text{TSAT [\%]} = \frac{\text{Serum iron } [\mu\text{g/dL}] \times 70.9}{\text{Serum transferrin } [\text{mg/dL}]}$$

$$\text{TSAT [\%]} = \frac{\text{Serum iron } [\mu\text{g/dL}] \times 100}{\text{Total iron binding capacity } [\mu\text{g/dL}]}$$

The conversion factors for iron and transferrin from SI units to US units are as follows:

$$\begin{array}{l} \text{Iron:} \quad \quad \quad \mu\text{mol/L} \xrightarrow{\times 5.59} \mu\text{g/dL} \\ \text{Transferrin:} \quad \quad \mu\text{mol/L} \xrightarrow{\times 7.96} \text{mg/dL} \end{array}$$

⁸ Wick M, Pinggera W, Lehmann P. Iron Metabolism, Anemias Diagnosis and Therapy, 4th edition, 2000, Springer-Verlag Wien - New York, 160-161

Appendix 4 Recommendations for Grading of Adverse Events and Laboratory Abnormalities

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE
<u>HEMATOLOGY</u>			
Hemoglobin	8.0 - 9.4 gm/dL	7.0 - 7.9 gm/dL	6.5 - 6.9 gm/dL
Absolute Neutrophil Count	1000 - 1500 /mm ³	750 - 999 /mm ³	500 - 749 /mm ³
Platelets	75,000 - 99,000 /mm ³	50,000 - 74,999 /mm ³	20,000 - 49,999 /mm ³
<u>CHEMISTRIES</u>			
Creatinine	1.1 - 1.5 x upper normal limit	1.6 - 3.0 x upper normal limit	3.1 - 6 x upper normal limit
Creatinine Phosphokinase (unrelated to exercise)	> 1.0 - 2.0 x upper normal limit	> 2.0 - 4.0 x upper normal limit	> 4.0 - 6.0 x upper normal limit
<u>SODIUM</u>			
Hyponatremia	130 - 135 meq/L	123 - 129 meq/L	116 - 122 meq/L
Hypernatremia	146 - 150 meq/L	151 - 157 meq/L	158 - 165 meq/L
<u>POTASSIUM</u>			
Hypokalemia	3.0 - 3.4 meq/L	2.5 - 2.9 meq/L	2.0 - 2.4 meq/L
Hyperkalemia	5.6 - 6.0 meq/L	6.1 - 6.5 meq/L	6.6 - 7.0 meq/L
<u>PHOSPHOROUS</u>			
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 - 1.9 mg/dL	1.0 - 1.4 mg/dL

Appendix 4 Recommendations for Grading of Adverse Events and Laboratory Abnormalities (Cont.)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE
CALCIUM			
(corrected for albumin)			
Hypocalcemia	7.8 - 8.4 mg/dL	7.0 - 7.7 mg/dL	6.1 - 6.9 mg/dL
Hypercalcemia	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL
BILIRUBIN			
Hyperbilirubinemia	1.1 - 1.5 x upper normal limit	1.6 - 2.5 x upper normal limit	2.6 - 5 x upper normal limit
GLUCOSE			
Hypoglycemia	55 - 64 mg/dL	40 - 54 mg/dL	30 - 39 mg/dL
Hyperglycemia	116 - 160 mg/dL	161 - 250 mg/dL	251 - 500 mg/dL
URIC ACID			
Hyperuricemia	7.5 - 10.0 mg/dL	10.1 - 12.0 mg/dL	12.1 - 15.0 mg/dL
LIVER TRANSAMINASE (LFTs)			
AST (SGOT) or ALT (SGPT)	1.25 - 2.5 x upper normal limit	2.6 - 5 x upper normal limit	5.1 - 10 x upper normal limit
LDH	1.25 - 2.5 x upper normal limit	2.6 - 5 x upper normal limit	5.1 - 10 x upper normal limit
Alkaline Phosphatase	1.25 - 2.5 x upper normal limit	2.6 - 5 x upper normal limit	5.1 - 10 x upper normal limit

Appendix 4 Recommendations for Grading of Adverse Events and Laboratory Abnormalities (Cont.)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE
PANCREATIC ENZYMES			
Amylase	1.1 - 1.5 x upper normal limit	1.6 - 2.0 x upper normal limit	2.1 - 5.0 x upper normal limit
Pancreatic Amylase	1.1 - 1.5 x upper normal limit	1.6 - 2.0 x upper normal limit	2.1 - 5.0 x upper normal limit
Lipase	1.1 - 1.5 x upper normal limit	1.6 - 2.0 x upper normal limit	2.1 - 5.0 x upper normal limit
URINALYSIS			
PROTEINURIA			
Spot Urine	1+	2 - 3+	4+
24 Hour Urine	200 mg - 1 g loss/day OR < 0.3% OR < 3 g/l	1 - 2 g loss/day OR 0.3 - 1.0% OR 3 - 10 g/l	2 - 3.5 g loss/day OR > 1.0% OR > 10 g/l
Gross hematuria	Microscopic only	Gross, no clots	Gross + clots
CARDIAC			
Cardiac Arrhythmia	-----	Asymptomatic; transient dysrhythmia, no Rx required	Recurrent/persistent dysrhythmia; symptomatic Rx required
Hypertension	Transient increase > 20 mmHg, no Rx	Recurrent; chronic increase > 20 mmHg, Rx req	Requires acute Rx: out-patient hospitalization possible
Hypotension	Transient orthostatic hypotension; no Rx	Symptoms correctable with oral fluid Rx	Requires i v fluids; no hosp required

Appendix 4 Recommendations for Grading of Adverse Events and Laboratory Abnormalities (Cont.)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE
Pericarditis	Minimal effusion	Mild/mod asymp Effusion, no Rx	Symptomatic effusion, pain, EKG changes
Hemorrhage, Blood Loss	-----	Mildly symptomatic, no Rx required	Gross blood loss or 1 - 2 units transfused
<u>RESPIRATORY</u>			
Cough - for aerosol studies	Transient - no Rx	Treatment associated cough; inhaled bronchodilator	Uncontrolled cough; systemic Rx required
Bronchospasm	Transient; no Rx; < 70% - 70% predicted FEV ₁ (or peak flow)	Req Rx, normalizes with bronchodilator; predicted FEV ₁ 50% - 70% (or peak flow)	No normalization w/bronchodilator; predicted FEV ₁ 25% - 50% (or peak flow), retractions
Dyspnea	Dyspnea on exertion	Dyspnea with normal activity	Dyspnea at rest
<u>GASTROINTESTINAL</u>			
Oral Discomfort / Dysphagia	Mild discomfort; no difficulty swallowing	Difficulty swallowing but able to eat and drink	Unable to swallow solids
Nausea	Mild or transient; reasonable intake maintained	Mod discomfort or intake decreased for < 3 days	Severe discomfort or minimal intake for ≥ 3 days
Vomiting	Mild or transient; 2 - 3 episodes per day or mild vomiting lasting < 1 week	Mod or persistent; 4 - 5 episodes per day or vomiting lasting ≥ 1 week	Sever vomiting of all food/fluids in 24 hrs or orthostatic hypotension or i v Rx req

Appendix 4 Recommendations for Grading of Adverse Events and Laboratory Abnormalities (Cont.)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE
Diarrhea	Mild or transient; 3 - 4 loose stools per day or mild diarrhea lasting < 1 week	Mod or persistent; 5 - 7 loose stools per day or diarrhea lasting ≥ 1 week	Bloody diarrhea; or orthostatic hypotension; or > 7 loose stools/day or i v Rx required
Constipation	Mild	Moderate	Severe
<u>NEUROLOGIC</u>			
Neuro-Cerebellar	Slight Incoordination Or Dysdiadochokinesia	Intention Tremor Or Dysmetria Or Slurred Speech Or Nystagmus	Ataxia Requiring Assistance To Walk Or Arm Incoordination Interfering With Adls
Neuro-Psych/Mood	-----	-----	Severe mood changes requiring medical intervention
Paresthesia (burning, tingling, etc)	Mild discomfort; no Rx required	Mod discomfort; non-narcotic analgesia required	Severe discomfort; OR narcotic analgesia required with symptomatic improvement
Neuro-Motor	Mild weakness in muscles of feet but not able to walk and/or mild increase or decrease in reflexes	Mod weakness in feet (unable to walk on heels and/or toes), mild weakness in hands, still able to do most hand tasks and/or loss of previously present reflex or development of hyperreflexia and/or unable to do deep knee bends due to weakness	Marked distal weakness (foot drop or unable to dorsiflex toes), and mod proximal weakness, e g , in hands, interfering with ADLs and/or requiring assistance to walk and/or unable to rise from chair unassisted

Appendix 4 Recommendations for Grading of Adverse Events and Laboratory Abnormalities (Cont.)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE
Neuro-Sensory	Mild impairment (dec sensation, e g vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution	Mod impairment (mod dec sensation, e g vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	Severe impairment (dec or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i e upper and lower extremities)
<u>OTHER PARAMETERS</u>			
Fever; oral > 12 hours	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F
Headache	mild, no Rx	Mod, or non-narcotic analgesia, Rx	Severe; or responds to initial narcotic therapy
Fatigue	Normal activity reduced 25%	Normal activity decr 25 - 50%	Normal activity decr > 50%; can't work
Allergic Reaction Cutaneous/Rash/Dermatitis	Pruritis w/o rash Erythema, pruritis	Localized urticaria Diffuse maculopapular rash or dry desquamation	Generalized urticaria angioedema Vesiculation or moist desquamation or ulceration
Myositis	mild symptoms with an increased CK or asymptomatic with increased CK plus a positive EMG or biopsy	positive EMG or muscle biopsy and either - mild symptoms with an increased CK > 4 wks or moderate myalgias for < 4 weeks requiring non-steroidal anti-inflammatory agents; or difficulty with mobility	positive EMG or muscle biopsy and either moderate to severe myalgias for > 4 weeks non-steroidal anti-inflammatory agents; or needs some assistance walking
Local Reaction (2* parenteral Rx not vaccination or skin test)	Erythema	Induration ≤ 10 mm or inflammation or phlebitis	Induration > 10 mm or ulceration

Appendix 5 Educational Program For *MIRCERA*[®] Anti-erythropoietin-mediated Pure Red Cell aplasia Associated with Erythropoietin Stimulating Agents

*Educational Program for *MIRCERA*[®]
(methoxy polyethylene glycol-epoetin beta)*

Physician's Guide

***Diagnosing and reporting of adverse drug reactions
associated with *MIRCERA*[®]***

Anti-erythropoietin antibody-mediated pure red cell aplasia
associated with erythropoietin stimulating agent

Contents

1. *MIRCERA and anti-erythropoietin-mediated pure red cell aplasia (AEAB-mediated PRCA)*
2. *What is the objective of this educational program?*
3. *Loss of effect of ESA treatment*
 - 3.1 *If an ESA loses its effect after having been effective in a patient what should I do?*
 - 3.2 *What are the most frequent causes?*
4. *What happens in AEAB-mediated PRCA?*
 - 4.1 *Findings in blood and bone marrow*
 - 4.2 *Timing of onset*
 - 4.3 *Discontinuation of ESAs*
5. *Diagnosis of PRCA*
 - 5.1 *Haemoglobin drop*
 - 5.2 *Antibody testing*
 - 5.3 *Bone marrow examination*
6. *Follow up after PRCA diagnosis*
7. *Adverse drug reaction reporting*
8. *Questionnaire*
9. *How to obtain further information*
Supporting Information

1. MIRCERA and anti-erythropoietin-mediated pure red cell aplasia (AEAB-mediated PRCA)

MIRCERA is an erythropoietin-stimulating agent or ESA.

A very rare side effect of ESAs is “anti-erythropoietin antibody-mediated pure red cell aplasia” or AEAB-mediated PRCA.

This side effect is an important identified risk in the EU risk management plan for MIRCERA.

2. What is the objective of this educational program?

The objective of this booklet and the educational program is:

- *to increase early awareness and knowledge of AEAB-mediated PRCA associated with ESAs*
- *to encourage doctors to report adverse drug reactions to MIRCERA, especially AEAB-mediated PRCA*
- *to improve understanding of the importance of collecting detailed information on AEAB-mediated PRCA - through a questionnaire completed by the physician*
- *to inform about Roche’s offer for free antibody testing after having received a report of a suspected case of AEAB-mediated PRCA. This includes where loss of effect of unknown cause is associated with MIRCERA.*

For full details on this topic, look at the MIRCERA Physician’s Prescribing Information (Summary of Product Characteristics). Look in particular at the section:

- *“Special warnings and special precautions for use” relating to important facts about erythropoietin-stimulating agents / MIRCERA and AEAB-mediated PRCA.*

3. Loss of effect of ESA treatment

3.1 If an ESA loses its effect, after having been effective in a patient what should I do?

Investigate the main possible causes:

- *haemolysis*
- *malnutrition*
- *iron deficiency*
- *aluminium toxicity*
- *chronic blood loss*
- *inadequate dialysis*
- *inflammatory disorders*
- *multiple myeloma, myelofibrosis*
- *other malignancies*
- *hyperparathyroidism / osteitis fibrosa*
- *vitamin deficiencies – such as folate or vitamin B₁₂*
- *haemoglobinopathies – such as alpha- and beta-thalassaemias or sickle cell anemia*
- *adverse effects of concomitant drugs – such as cytotoxic and immunosuppressive agents and angiotensin-converting enzyme (ACE) inhibitors.*

If none of these conditions are diagnosed, anaemia should be fully investigated (see [Section 5](#)).

3.2 What are the most frequent causes?

For acquired PRCA, the following are the most frequent causes:

- *lymphoproliferative disorders*
- *infections – such as parvovirus B19*
- *systemic autoimmune disease – such as systemic lupus, rheumatoid arthritis*
- *drugs – such as azathioprine, isoniazid, phenytoin*
- *thymoma - in about 5% of cases*
- *idiopathic - in about 50% of cases.*

4. What happens in AEAB-mediated PRCA?

Epoetin permits terminal maturation of erythroid precursor cells and thus treats anemia due to chronic kidney disease. AEAB-mediated PRCA is an acquired immune disease where erythropoiesis is inhibited by erythropoietin-specific neutralising antibodies.

4.1 Findings in blood and bone marrow

The current diagnostic criteria for PRCA have been defined as:

fall in haemoglobin of about 0.1 g/dL/day

reticulocyte count below 10 or $20 \times 10^9/L$

no major changes in white cell count, platelet count, or differential leukocyte count

normal cellularity of bone marrow, less than 1% erythroblasts (occasionally up to 5%

proerythroblasts or basophilic erythroblasts), normal myeloid cells and

megakaryocytes.

4.2 Timing of onset

The shortest interval of onset of PRCA after treatment starts was reported within 2 months and the longest as 90 months.

4.3 Discontinuation of ESAs

There is consensus that ESAs should be discontinued in any patient with confirmed AEAB-mediated PRCA. You should:

- investigate for the presence of anti-erythropoietin antibodies*
- perform a bone marrow examination.*

Patients must not be switched to another recombinant ESA. This is because of cross-reactivity of antibodies with endogenous and all recombinant ESAs molecules.

5. Diagnosis of PRCA

5.1 Haemoglobin drop

European Best Practice Guidelines suggest to strongly suspect PRCA if a patient treated with an ESA:

- has a sudden, rapid decline in Hb concentration of approximately 0.5-1 g/dL/week despite ongoing ESA treatment or
- requires transfusions of 1-2 units of red blood cells per week to maintain the Hb level.

In these cases, do a complete blood count with blood film examination and reticulocyte count. A reticulocyte count below 10 or $20 \times 10^9/L$ strongly suggests a PRCA.

5.2 Antibody testing

On request from a physician, Roche will offer testing or re-testing of serum samples in a reference laboratory. This is free of charge service for cases of suspected or confirmed AEAB-mediated PRCA or unexplained loss of effect (as documented in an ADR report and the questionnaire).

Sampling instructions will be send to the physician, for details see [Section 9](#) "How to obtain further information".

5.3 Bone marrow examination

A bone marrow examination should be triggered by a rapid and sustained decrease in the reticulocyte count.

PRCA is characterised by:

- normal cellularity
- < 1% erythroblasts
- occasionally erythroblasts up to 5% with evidence of a red cell precursor maturation block
- myeloid and megakaryocytic lineages are normal

Bone marrow findings help to distinguish PRCA from aplastic anaemia and myelodysplastic syndrome. If no bone marrow examination is possible, a suspected diagnosis could suffice, but the level of confidence of the diagnosis may be lower.

6. Follow up after PRCA diagnosis

You should check reticulocyte count regularly during follow-up. This is the best laboratory marker of red blood cell production. The reticulocyte count tells us about bone marrow activity with regard to daily red cell production. A drop in haemoglobin will be preceded by a change in the rate of red cell production. An unchanged reticulocyte count suggests that treatment is effective.

Any decline in reticulocyte count should be investigated. As one of the proposed diagnostic criteria for AEAB-mediated PRCA an absolute reticulocyte count below 10 or $20 \times 10^9/L$ was suggested.

7. Adverse drug reaction reporting

We need to know as much as possible about suspected case reports of AEAB-mediated PRCA potentially associated with MIRCERA treatment.

You should consider an adverse drug reaction report where there are:

confirmed report of AEAB-mediated PRCA – such as positive AEAB findings or bone marrow examination showing PRCA

suspected AEAB-mediated PRCA with insufficient or inconclusive results. This includes follow-up on updated investigational results and updated results of continued monitoring of these patients

reports of **unexplained** loss of effect, especially:

- after excluding alternative causes of PRCA (see [Section 3](#))
- if a patient previously had a stable haemoglobin concentration after having had established the MIRCERA dose (i.e. not during titration). Loss of effect could be reflected by findings such as “refractory anemia,” massive dose increase of the already established dose of MIRCERA, or a decrease in drug effect.

Investigate through anti-erythropoietin antibody testing and haematological consultation in suspected AEAB-mediated PRCA or the unexplained loss of therapeutic effect.

8. Questionnaire

After receiving an adverse drug reaction report for AEAB-mediated PRCA or loss of effect, Roche will send the reporting physician a guided questionnaire.

This questionnaire is called:

“Erythropoietin Stimulating Agents (ESAs) questionnaire on adverse event of anti-erythropoietin-mediated pure red cell aplasia, inadequate response to ESA treatment, anemia refractory to ESA treatment, and unexplained loss of effect of ESA treatment.”

The questionnaire will be updated with information already received.

If appropriate, these collected data will support communication of a substantial change (e.g., via a label update).

The questionnaire will collect data such as:

- *diagnostic results to confirm the diagnosis or clinical suspicion*
- *relevant comorbidities or concomitant drugs*
- *alternative conditions to explain a sudden drop in haemoglobin*
- *exposure to epoetin brands with regard to the onset of first signs/symptoms suggestive of AEAB-mediated PRCA.*

This guided questionnaire is only for when MIRCERA is used outside a clinical study. In clinical studies, the study protocol will guide how to follow up a report of potential AEAB-mediated PRCA or loss of effect.

9. How to obtain further information

For further information on adverse drug reaction reporting including the Questionnaire:

Please address the local Roche affiliate [Address]

For further information on antibody sampling and shipment:

Please address the local Roche affiliate [Address]

For further information on MIRCERA including literature:

Please address the local Roche affiliate [Address]

Supporting Information

Need and clinical importance of adverse drug reaction reporting

The aim of pharmacovigilance is the detection, assessment, and prevention of adverse reactions. A critical number of case reports are needed for a signal. Detection of rare adverse effects is increased and accelerated the more physicians contribute to spontaneous reporting of adverse reactions [Meyboom 1999]. According to Waller and Evans [2003], spontaneous adverse reaction reporting could be defined as an approach to collate individual case reports of clinical suspicion of an adverse drug reaction with the main aim of detecting unknown serious potential drug toxicity. The primary role of spontaneous reporting from post-marketing experience is signal generation for type 'A' effects (dose-related pharmacological effects of the drug) and type 'B' effects (e.g., allergic or idiosyncratic reactions, AEAB-mediated PRCA) [Meyboom 1999].

ADR reporting for a drug newly introduced to the market is not only identification and quantification of unexpected adverse drug reactions but also the identification of subgroups of patients at particular risk (e.g., related to comorbidities, age, gender, and dose). After introducing a drug to the market, safety is further continuously monitored to ensure that the benefit/risk assessment remains acceptable and to communicate appropriate information to health professionals [Talbot 2004]. Spontaneous ADR reporting is understood as a cornerstone of pharmacovigilance [Waller 2003].

Important facts about AEAB-mediated PRCA and ESAs

All exogenous proteins could be potentially immunogenic. With therapeutic proteins, the reported incidence of antibody formation varies considerably depending on, for example, genetic background of the patient, the type of disease, type of protein, the route of administration, dose frequency, and duration of treatment, in addition, manufacturing, handling and storage might introduce contaminants, or alter the 3-dimensional structure of the protein via oxidation or aggregate formation [Schellekens 2002].

During the first 10 years (1988–1998) of epoetin treatment, three reports of AEAB-mediated PRCA were published [Bergrem 1993, Peces 1996, Prabhakar 1997] referring to treatment in several million patients. Since 1998, there had been a sudden upsurge of reports of AEAB-mediated PRCA in patients with chronic kidney disease. The majority of these were reported in patients treated subcutaneously with the human serum albumin-free epoetin alfa formulation marketed outside the U.S. (Eprex) with a peak in reports in 2001 and 2002 [Rossert 2004].

Testing approaches

Two testing approaches were utilised during the development program of MIRCERA and will be applied for investigations for future post-marketing experience. The first test is a bridging ELISA test that is the method for quantification of anti-EPO antibodies and of anti-methoxy polyethylene glycol-epoetin beta (anti-MIRCERA) antibodies. The second type of testing is a neutralising antibody assay, which is a functional assay based on the use of a standard in vitro assay to detect EPO or methoxy polyethylene glycol-epoetin

beta activity. This assay measures EPO- or methoxy polyethylene glycol-epoetin beta-stimulated proliferation of an EPO receptor-expressing cell line in the presence and absence of patient serum. The presence of neutralizing anti-EPO or anti-methoxy polyethylene glycol-epoetin beta antibodies reduces or suppresses cell proliferation. This assay can optionally be applied to samples with discrepancies between antibody titer determined by antibody ELISA and clinical diagnosis. Since the antibody ELISA assays have a several fold higher sensitivity compared with the neutralizing antibody assay, this assay is not expected to provide additional clinically relevant information for samples with low antibody titers or confirmed PRCA.

Literature

A brief summary indicates main aspects of the publications, which are grouped according to the aspect of practical and basic guidance on patient evaluation and detailed aspects of the topic as briefly indicated in a summary for each publication.

Practical and Basic Guidance on Patient Evaluation

- Revised European Best Practice Guidelines on Anaemia Management (Section I. Anaemia evaluation) *Nephrol Dial Transplant*, 2004; 19(Suppl 2): ii2-ii5.
 - Which patients should be evaluated and when should the work-up begin.
 - Investigations for appropriate work-up of anaemia in CKD.
 - Diagnosis of renal anaemia.
- Revised European Best Practice Guidelines on Anaemia Management (Section IV. Failure to respond to treatment) *Nephrol Dial Transplant*, 2004; 19(Suppl 2): ii32-ii36.
 - Failure to reach or maintain target haemoglobin.
 - Criteria to suspect antierythropoetin-mediated pure red cell aplasia (AEAB-mediated PRCA).
 - Criteria to confirm AEAB-mediated PRCA.
- Casadevall N., Cournoyer D., et al. Recommendations on haematological criteria for the diagnosis of epoetin-induced pure red cell aplasia. *Eur J Haematol* 2004; 73:389-396.
 - Recommendations for diagnostic approach including discussions on potential findings.

Further Reading / These publications are available on request

- Bennett CL., Luminari S., et al. Pure Red-Cell Aplasia and Epoetin Therapy. *N. Engl. J. Med.*, September 30, 2004; 351(14): 1403-1408.
 - Description of worldwide collection of reports of AEAB-mediated PRCA emphasising the need of spontaneous reporting by physicians in order to document a change in the occurrence rate.

- Bennett CL., Cournoyer D. et al. Long-term outcome of individuals with pure red cell aplasia and antierythropoietin antibodies in patients treated with recombinant epoetin: a follow-up report from the Research on Adverse Drug Events and Reports (RADAR) Project. *Blood*. 2005;106:3343-3347.
 - Information on treatment and long-term follow-up of 191 patients with AEAB-mediated PRCA.
- Casadevall N., Nataf J., et al. Pure Red-Cell Aplasia and Antierythropoietin Antibodies in Patients Treated with Recombinant Erythropoietin. *N Engl J Med* 2002; 346(7): 469-475.
 - Clinical characterization of 13 patients with AEAB-mediated PRCA.
- Eckardt K-U., Casadevall N. Pure red-cell aplasia due to anti-erythropoietin antibodies. *Nephrol Dial Transplant* 2003; 18: 865-869.
 - Diagnosis, causes of AEAB-mediated PRCA.
- Rossert J., Casadevall N., et al. Anti-Erythropoietin Antibodies and Pure Red Cell Aplasia. *J Am Soc Nephrol* 2004; 15: 398-406.
 - Diagnosis, assays, epidemiology, risk factors.
- Schellekens H. Factors influencing the immunogenicity of therapeutic proteins. *Nephrol Dial Transplant*. 2005; 20 (Suppl 6):vi3-9.
 - Consequences of antibody formation.
- Schellekens H. Immunogenicity of Therapeutic Proteins: Clinical Implications and Future Prospects. *Clin Ther* 2002; 24:1720-1740.
 - Effects of antibodies on endogenous protein production, clinical effects of antibodies, factors influencing Immunogenicity.

Further references mentioned in the text

- Bergrem H., Danielson BG., et al. A Case of Antierythropoietin Antibodies Following Recombinant Human Erythropoietin Treatment. In: Bauer C, Koch KM, Scigalla P, Wiczorek L, eds. *Erythropoietin: Molecular physiology and clinical applications*. New York: Marcel Dekker. 1993; 265-273.
- Cavill I., Williams JD. Benefits of recombinant human erythropoietin. *Lancet* 2002; 360 Nov 16: 1606 -1607.
- Meyboom RHB., Egberts AC., et al. Pharmacovigilance in Perspective. *Drug Safety*, December 1999, 21(6): 429-447.
- Peces R., de la Torre M., et al. Antibodies against recombinant human erythropoietin in a patient with erythropoietin-resistant anemia. *N Engl J Med*. 1996; 335: 523-524.
- Prabhakar SS., Muhlfelder T. Antibodies to recombinant human erythropoietin causing pure red cell aplasia. *Clin Nephrol*. 1997; 47:331-335.
- Talbot J., Waller P. *Steven's Detection of New Adverse Drug Reactions, Chapter 1 Introduction*, pp1-2, 5th ed. 2004.

- *Waller PC., Evans SJW. A model for the future conduct of pharmacovigilance. Pharmacoepidemiol Drug Safety 2003; 12: 17-29.*
- *Weber G., Gross J., et al. Allergic Skin and Systemic Reactions in a Patient with Pure Red Cell Aplasia and Anti-Erythropoietin Antibodies Challenged with Different Epoetins. J Am Soc Nephrol 2002; 13:2381-2383.*

Appendix 6 Endpoints Documentation Checklist

- 1. Updated eCRF**
- 2. Serious Adverse Event Forms**
- 3. Ancillary documents (when applicable):**
 - a) Copies of pertinent laboratory, imaging and cardiac testing reports
 - b) Copies of hospital admission notes and all pertinent hospital records and progress notes surrounding the event (physician and nursing notes)
 - c) Copies of surgical, consultant and pathology reports
 - d) Hospital discharge summary
 - e) Certified death/autopsy summary (if applicable)