**Official Title:** An Open-Label, Single-Arm, Multicenter Study to Ascertain the Optimal Starting Dose of Mircera® Given Subcutaneously for the Maintenance Treatment of Anemia in Pediatric Patients With Chronic Kidney Disease on Dialysis or not yet on Dialysis

**NCT Number:** NCT03552393

**Document Date:** Protocol Version 4: 07-December-2018

# PROTOCOL

**TITLE:** **AN OPEN-LABEL, SINGLE-ARM, MULTICENTER STUDY TO ASCERTAIN THE OPTIMAL STARTING DOSE OF MIRCERA® GIVEN SUBCUTANEOUSLY FOR THE MAINTENANCE TREATMENT OF ANEMIA IN PEDIATRIC PATIENTS WITH CHRONIC KIDNEY DISEASE ON DIALYSIS OR NOT YET ON DIALYSIS**

**PROTOCOL NUMBER:** NH19708

**VERSION NUMBER:** 4

**EUDRACT NUMBER:** 2016-004779-39

**IND NUMBER:** 10158

**TEST PRODUCT:** Mircera® (RO0503821)

**MEDICAL MONITOR:** [redacted], Ph.D.

**SPONSOR:** F. Hoffmann-La Roche Ltd

**DATE FINAL:** Version 1: 19 October 2017

**DATES AMENDED:** Version 2: 19 January 2018
Version 3: 11 July 2018
Version 4: See electronic date stamp below.

## PROTOCOL AMENDMENT APPROVAL

| Approver's Name | Title | Date and Time (UTC) |
|---|---|---|
| [redacted] | Company Signatory | 07-Dec-2018 17:01:54 |

## PROTOCOL AMENDMENT, VERSION 4:
## RATIONALE

Protocol NH19708 has been amended to add an exclusion criterion and provide additional clarification of procedures. The changes made are as follows:

- Requirements for scheduling the screening visits and the approximate length of the screening period have been clarified (Sections 3.1, 4.5, and 4.5.1, and Appendix 1).
- Exclusion Criteria have been amended to exclude patients who have undergone a kidney transplant with use of immunosuppressive therapies known to exacerbate anemia, as inclusion of these patients would add a bias to the studied patient population (Section 4.1.2).
- An explanatory note has been added to the exclusion criterion related to pregnancy testing for patients of childbearing potential (Section 4.1.2).
- Table 3, Mircera Dose Adjustments, has been amended to clarify the dose adjustment rules for Mircera (Section 4.3.2.1.1).
- Language has been added to indicate that assessment of body weight should be performed after dialysis for patients on hemodialysis (Section 4.5.4, Appendix 1, and Appendix 2).
- Section 4.5.6 has been updated with information regarding sample storage and the use of samples after withdrawal of patient consent.
- Text has been modified to account for the fact that special situations (i.e., accidental overdoses and medication errors) are not required to be reported within 24 hours (Sections 5.4 and 5.4.4). Note that serious adverse events associated with special situations are still required to be reported within 24 hours.
- Language has been updated to indicate that therapeutic or elective abortions are not considered adverse events unless performed because of an underlying maternal or embryofetal toxicity. In such cases, the underlying toxicity should be reported as a serious adverse event. Language has also been added to clarify that all abortions are to be reported on the paper Clinical Trial Pregnancy Reporting Form (Section 5.4.3.2).
- Language has been added for consistency with Roche's current data retention policy and to accommodate more stringent local requirements (if applicable) (Section 7.5).
- Language has been added to indicate that the study will comply with applicable local, regional, and national laws (Section 8.1).
- Language has been revised to clarify that redacted CSRs are provided only if requirements of Roche's global policy on data sharing have been met (Section 9.5).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

## TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES

## LIST OF APPENDICES

## PROTOCOL AMENDMENT ACCEPTANCE FORM

| | |
|---|---|
| **TITLE:** | **AN OPEN-LABEL, SINGLE-ARM, MULTICENTER STUDY TO ASCERTAIN THE OPTIMAL STARTING DOSE OF MIRCERA® GIVEN SUBCUTANEOUSLY FOR THE MAINTENANCE TREATMENT OF ANEMIA IN PEDIATRIC PATIENTS WITH CHRONIC KIDNEY DISEASE ON DIALYSIS OR NOT YET ON DIALYSIS** |
| **PROTOCOL NUMBER:** | NH19708 |
| **VERSION NUMBER:** | 4 |
| **EUDRACT NUMBER:** | 2016-004779-39 |
| **IND NUMBER:** | 10158 |
| **TEST PRODUCT:** | Mircera® (RO0503821) |
| **MEDICAL MONITOR:** | [redacted], Ph.D. |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form to the Sponsor or their designee.

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **TITLE:** | **AN OPEN-LABEL, SINGLE-ARM, MULTICENTER STUDY TO ASCERTAIN THE OPTIMAL STARTING DOSE OF MIRCERA® GIVEN SUBCUTANEOUSLY FOR THE MAINTENANCE TREATMENT OF ANEMIA IN PEDIATRIC PATIENTS WITH CHRONIC KIDNEY DISEASE ON DIALYSIS OR NOT YET ON DIALYSIS** |
| **PROTOCOL NUMBER:** | NH19708 |
| **VERSION NUMBER:** | 4 |
| **EUDRACT NUMBER:** | 2016-004779-39 |
| **IND NUMBER:** | 10158 |
| **TEST PRODUCT:** | Mircera® (RO0503821) |
| **PHASE:** | Phase II |
| **INDICATION:** | Chronic renal anemia |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

**Objectives and Endpoints**

This study will ascertain the starting dose of Mircera® given subcutaneously for the maintenance treatment of anemia in pediatric patients with chronic kidney disease (CKD) on dialysis or not yet on dialysis when switching from stable subcutaneous (SC) maintenance treatment with epoetin alfa, epoetin beta, or darbepoetin alfa. Specific objectives and corresponding endpoints for the study are outlined below.

**Table 1 Objectives and Corresponding Endpoints**

| Efficacy Objective | Corresponding Endpoints |
|---|---|
| • To ascertain the starting dose of Mircera given subcutaneously in pediatric patients with CKD on dialysis or not yet on dialysis when switching from stable SC maintenance treatment with epoetin alfa, epoetin beta, or darbepoetin alfa | Primary endpoint:<br>• Change in Hb concentration (g/dL) between the baseline and the evaluation period for each patient<br>Secondary endpoints:<br>• Number of patients with an average Hb concentration during the evaluation period within ±1 g/dL of their baseline Hb or above, within or below the range of 10–12 g/dL<br>• Change in Mircera dose over time, including the change between the starting dose and the evaluation period |
| **Safety Objective** | **Corresponding Endpoints** |
| • To assess the safety and tolerability of multiple doses of Mircera given subcutaneously in pediatric patients | • Occurrence and severity of adverse events<br>• Change from baseline in targeted vital signs<br>• Change from baseline in targeted clinical laboratory test results |

| Pharmacokinetic and Pharmacodynamic Objective | Corresponding Endpoints |
|---|---|
| • To evaluate the pharmacokinetics and the pharmacodynamics of Mircera in patients on dialysis or not yet on dialysis who receive the study medication by the SC route of administration | • Serum concentrations of Mircera and Hb will be used to evaluate the pharmacokinetics and the pharmacodynamics of Mircera through PK and PK/PD models. |

CKD = chronic kidney disease; Hb = hemoglobin; PD = peritoneal dialysis; PK = pharmacokinetic; PK/PD = pharmacokinetic/pharmacodynamic.

**Study Design**

**Description of Study**

This study is an open-label, single-arm, multicenter study to ascertain the optimal starting dose of Mircera given subcutaneously for the maintenance treatment of anemia in pediatric patients with CKD on dialysis or not yet on dialysis.

Following written informed consent from a parent or legal guardian and, if appropriate, assent from the child, the patient will be screened for eligibility during a *screening period of approximately 3 weeks*. During this period, patients will continue to receive epoetin alfa, epoetin beta, or darbepoetin alfa at the same weekly dose, route (SC), and interval as before screening. The total weekly doses 4 weeks before the first Mircera administration should not change > 25% (increase or decrease). Provided that all eligibility criteria are met, including those for hemoglobin (Hb) levels and iron status, the patients will start Mircera administered subcutaneously.

At least 40 pediatric patients 3 months–17 years of age will be enrolled. Approximately 10–15 of these patients will be < 12 years old, with a goal to include as many patients < 5 years old as possible (with a minimum of 3 patients). Approximately 10–15 patients, irrespective of age, will not be on dialysis.

Available hemodialysis (HD) patients receiving their erythropoiesis-stimulating agent (ESA) subcutaneously are eligible for enrollment. No more than 10 patients on HD should be enrolled.

Mircera will be administered subcutaneously once every 4 weeks for the duration of the study. Dose adjustments may be performed every 4 weeks according to dose adjustment rules.

The core study will last for 23 weeks and consists of three periods: screening (3 weeks), dose titration (16 weeks), and evaluation (4 weeks).

Patients completing the 20 weeks of treatment with Hb within ± 1 g/dL of their baseline Hb and within the target range of 10–12 g/dL, will be eligible to enter an optional 24-week safety extension period. Those patients not eligible or not consenting to enter the long-term safety extension should be treated according to clinical practice. All patients must complete the Week 21 visit (Visit 10), regardless of whether they continue in the safety extension period. Visit 10 will serve as the final visit of the core study and the first visit of the safety extension period for patients eligible and willing to continue in the study.

Once 12 patients have completed 20 weeks of treatment (dose titration and evaluation periods), an interim analysis to assess the pharmacokinetics, efficacy, and safety of Mircera will be performed.

**Number of Patients**

Approximately 40 pediatric patients (3 months–17 years of age), who are evaluable for intent-to-treat (ITT) and safety analyses, who have clinically stable chronic renal anemia on dialysis or not yet on dialysis, and who are receiving maintenance SC treatment with an ESA, will be enrolled in this study.

**Target Population**

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Written informed consent from parent/legal guardian and willingness of parent/legal guardian to abide by the requirements of the study
- Written informed consent or assent from child where appropriate

  If required by national legislation, patients <18 years of age at screening who are legally considered to be adults according to national legislation must consent in their own right.
- Pediatric patients 3 months–17 years of age with clinically stable chronic renal anemia
- CKD with estimated glomerular filtration rate (eGFR) of < 45 mL/min/1.73 $m^2$ (determined by the Bedside Schwartz formula) or dialysis treatment for at least 8 weeks before the first dose of Mircera
- For patients on peritoneal dialysis (PD): a weekly Kt/V ≥ 1.8
- For patients on HD: adequate HD, urea reduction ratio (URR) > 65% or Kt/V > 1.2 for patients on HD three times per week.

  Patients with fewer than or more than three HD sessions per week should have a weekly Kt/V ≥ 3.6.
- Baseline Hb concentration 10.0–12.0 g/dL determined from the mean of two Hb values measured at Visit 1 (Week –3) and Visit 2 (Week –1)
- Stable SC maintenance treatment with epoetin alfa, epoetin beta, or darbepoetin alfa with the same dosing interval for at least 6 weeks before the first dose of Mircera
- Stable dose of epoetin alfa, epoetin beta, or darbepoetin alfa treatment with no weekly dose change > 25% (increase or decrease) for at least 4 weeks before the first dose of Mircera
- Adequate iron status defined as ferritin ≥100 ng/mL or transferrin saturation (TSAT) ≥ 20% (or percentage of hypochromic red cells < 10%); mean of two values measured during screening
- For post-pubertal female patients of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or to use acceptable contraceptive methods during the study and for 90 days after the final dose of Mircera

  A female patient is considered to be of childbearing potential if she is postmenarcheal.

  The following are acceptable contraceptive methods: hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Overt gastrointestinal bleeding within 8 weeks before screening or during the screening period
- RBC transfusions within 8 weeks before screening or during the screening period
- Hemoglobinopathies (e.g., homozygous sickle-cell disease, thalassemia of all types)
- Hemolytic anemia
- Active malignant disease
- PD subjects with an episode of peritonitis within the past 30 days prior to screening and/or during the screening period
- Uncontrolled or symptomatic inflammatory disease (e.g., systemic lupus erythematosus)

- Uncontrolled hypertension as assessed by the investigator
- Epileptic seizures within 3 months prior to screening and during the screening period
- Administration of any investigational drug within 4 weeks prior to screening or planned during the study
- *Kidney transplant with use of immunosuppressive therapies known to exacerbate anemia*
- Severe hyperparathyroidism (intact parathyroid hormone [PTH] ≥1000 pg/mL or whole PTH ≥500 pg/mL) or biopsy-proven bone marrow fibrosis
- Known hypersensitivity to recombinant human erythropoietin (EPO), polyethylene glycol, or any constituent of the study drug formulation
- Anti-EPO antibody (AEAB)-mediated pure red cell aplasia (PRCA) or history of AEAB-mediated PRCA or positive AEAB test result in the absence of PRCA
- High likelihood of early withdrawal or interruption of the study (e.g., planned living donor kidney transplant within 5 months of study start)
- Planned elective surgery during the entire study period
- Females who are pregnant or breastfeeding or who intend to become pregnant during the study or within 90 days after the final dose of Mircera
  Note: Patients of childbearing potential must have a negative serum pregnancy test result within 21 days prior to initiation of study drug.

**End of Study**

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur approximately 44 weeks after the last patient is enrolled.

**Length of Study**

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 41 months.

## Investigational Medicinal Products

**Test Product (Investigational Drug)**

The investigational medicinal product (IMP) for this study is Mircera.

Mircera will be administered subcutaneously once every 4 weeks for the duration of the study. Dose adjustments may be performed every 4 weeks according to dose adjustment rules.

The starting dose will be based on conversion factors (CFs) obtained from the dose-finding study (Study NH19707). The initial dose of Mircera will be one of nine starting doses corresponding to the prefilled syringe strengths based on the total weekly ESA dose during the screening period.

## Statistical Methods

**Primary Analysis**

The primary endpoint will be the change in Hb concentration (g/dL) between the baseline and the evaluation period for each patient.

This is calculated on a per-patient basis, using an area under the curve approach to calculate an individual's average for both the baseline and evaluation periods and taking the difference.

The baseline period is defined as all assessments between the day of first study dose and the previous 35 days. If during the baseline period Hb measurements $H_0,\ldots,H_n$ are taken at timepoints $t_0,\ldots,t_n$, a time adjusted average baseline Hb value will be calculated by

$$y = \frac{1}{2(t_n - t_0)} \sum_i (H_i + H_{i-1})(t_i - t_{i-1})$$

The value on the day of the first dose is included in the baseline calculation, as this assessment will be performed before the first dose is given.

The average Hb value for each individual during the evaluation period will be calculated using the same method as for the baseline period. The evaluation period is defined as all assessments between Visit 8 (Week 17) and Visit 10 (Week 21) inclusive. Subtracting the baseline period value from the evaluation period value gives the change in Hb concentration (g/dL) between the baseline and evaluation period.

For patients with no recorded Hb during the evaluation period, the primary endpoint will be missing. Values missing in between non-missing assessments will not be replaced, as these will be interpolated by the trapezoidal rule. To correct for any increase in Hb caused by RBC transfusions, the Hb values measured within 3 weeks after an RBC transfusion will be deleted.

The individual change from baseline will be reported using summary statistics (including mean, standard deviation, and 90% CI of mean change). No formal statistical testing will be performed. Additional analysis will be performed by age category ($<5$, 5–11, $\geq 12$ years), dialysis type (not yet on dialysis, PD, HD) and previous ESA (epoetin alfa, epoetin beta, and darbepoetin alfa), if numbers allow.

**Determination of Sample Size**

This is an exploratory study without a powered statistical group comparison. Therefore, no formal sample size estimation will be performed; however, the calculations below indicate the approximate precision that could be achieved.

Assuming a 30% withdrawal rate (based on the withdrawal rate for the NH19707 study), of the 40 patients evaluable for ITT and safety analysis, more than 26 patients will have data for the evaluation period. Twenty-six patients will be sufficient to provide approximately 90% power that the 90% CI for the Hb change from baseline to the evaluation period is between $-1$ and 1 g/dL, provided the standard deviation is smaller than 1.5 and the optimum dose conversion is able to maintain the Hb at the baseline level.

Approximately 10–15 of the patients will be $<12$ years old, with the objective to include as many patients $< 5$ years old (minimum 3 patients) as possible. Approximately 10–15 patients, irrespective of their age, will not be on dialysis. Available HD patients receiving their ESA subcutaneously are eligible for enrollment. No more than 10 patients on HD should be enrolled.

To achieve the recruitment of the intended number of patients and in case of excessive dropout rate, additional patients may be enrolled to replace patients not treated for a minimum duration of 18 weeks.

**Interim Analyses**

Once 12 patients have completed 20 weeks of treatment, an interim analysis to assess efficacy, safety, and pharmacokinetics will be performed. The analysis will be reviewed by a Roche Internal Monitoring Committee (IMC) with the primary objective of assessing the safety and efficacy of the CFs for starting treatment with SC Mircera. This will be assessed using Hb (the pharmacodynamic marker), changes in dose, and assessment of the pharmacokinetic (PK) data to compare to the available pediatric PK data under IV dosing. The variability of Hb will also be assessed at this time, with regard to protocol assumptions, and the sample size will be revised if necessary.

An individual's Hb response will be based on the mean Hb during the evaluation period (Weeks 17–21) and is defined as a mean Hb change from baseline within $\pm$ 1g/dL. The 90% CI for the average Hb change from baseline will be calculated.

Interim PK and pharmacokinetic/pharmacodynamic (PK/PD) analyses will be conducted, as follows:

- External validation of the existing PK and PK/PD models against preliminary Study NH19708 data to highlight any deviation from the current knowledge of Mircera PK and pharmacodynamic properties; the bioavailability in pediatric patients will be carefully regarded.
- A Bayesian feedback approach will also be used on Mircera serum concentration-time data to get a first assessment of the individual PK parameters in pediatric patients receiving Mircera subcutaneously, especially bioavailability.

The full details of the interim analysis, and any decision criteria, will be specified in separate IMC documents.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| AEAB | anti-erythropoietin antibody |
| AEAB-mediated PRCA | anti-erythropoietin antibody-mediated pure red cell aplasia |
| CF | conversion factor |
| CKD | chronic kidney disease |
| EC | Ethics Committee |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| eGFR | estimated glomerular filtration rate |
| EPO | erythropoietin |
| ESA | erythropoiesis-stimulating agent |
| ESRD | end stage renal disease |
| FDA | Food and Drug Administration |
| Hb | hemoglobin |
| HD | hemodialysis |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICH | International Council for Harmonisation |
| IMC | Internal Monitoring Committee |
| IMP | investigational medicinal product |
| IND | Investigational New Drug (Application) |
| IRB | Institutional Review Board |
| ITT | intent-to-treat |
| IxRS | interactive voice or web-based response system |
| KDOQI | Kidney Disease Outcomes Quality Initiative |
| LPLV | last patient, last visit |
| NAPRTCS | North American Pediatric Renal Trials and Collaborative Studies |
| ObsRO | observer-reported outcome |
| PD | peritoneal dialysis |
| PFS | prefilled syringe |
| PK | pharmacokinetic |
| PK/PD | pharmacokinetic/pharmacodynamic |
| PRCA | pure red cell aplasia |
| PRO | patient-reported outcome |
| PTH | parathyroid hormone |
| SJS | Stevens-Johnson Syndrome |

| Abbreviation | Definition |
|---|---|
| TEN | toxic epidermal necrolysis |
| TSAT | transferrin saturation |
| ULN | upper limit of normal |
| URR | urea reduction ratio |
| USRDS | United States Renal Data System |
| VAS | visual analogue scale |
| VAT | vascular access thrombosis |

# 1. BACKGROUND

## 1.1 BACKGROUND ON CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is characterized by a progressive decline in renal function. As CKD progresses, inadequate levels of erythropoietin (EPO)—mainly synthesized in the kidneys and stimulating the production of red blood cells in the bone marrow—are produced (Caro et al. 1979) and the resulting anemia becomes progressively more severe (Astor et al. 2002; McClellan et al. 2004). If left untreated, anemia impairs quality of life (Klang et al. 1996; Gerson et al. 2004) and may lead to cardiovascular dysfunction (Mitsnefes et al. 2000; Chavers and Herzog 2004), impaired cognition (Pickett et al. 1999), and reduced physical activity (Sietsema et al. 2002; Pattaragarn et al. 2004). The anemia of CKD is also associated with increased hospitalization and mortality rates in both adults and children (Ma et al. 1999; Xia et al. 1999; Warady and Ho 2003).

The mechanism of anemia due to CKD in children is identical to that in adults. Treatment modalities are also identical (KDIGO 2012). Exogenous replacement of EPO by erythropoiesis-stimulating agents (ESAs) is an established method for anemia treatment in CKD in conjunction with iron supplementation (Locatelli et al. 2004). The currently available treatment options include short-acting human recombinant EPOs (epoetin alfa and epoetin beta), requiring several injections per week due to their short half-life, and longer-acting ESAs (hyperglycosylated [darbepoetin alfa] and pegylated [Mircera®]), which need less frequent dosing due to their prolonged half-life. Epoetin alfa/beta and darbepoetin alfa are approved treatments for anemia associated with CKD in pediatric patients. Several studies in pediatric patients with CKD have demonstrated that the safety profile of epoetin alfa/beta or darbepoetin alfa in pediatric patients is similar to that in adults (Gagnadoux et al. 1994; Van Damme-Lombaerts et al. 1994; Burke 1995; Sieniawska and Roszkowska 1997; Brandt et al. 1999; Greenbaum et al. 2000; Morgan et al. 2001; Seeherunvong et al. 2001; Geary et al. 2005; Warady et al. 2006; Warady 2015). The long-term safety and efficacy of darbepoetin alfa were assessed in a prospective registry study of 319 patients treated for up to 2 years (Schaefer et al. 2016). No new safety signals were found for darbepoetin alfa treatment, and anemia was effectively managed in these patients.

Similar to adults with CKD, many children with CKD undergoing hemodialysis (HD) or peritoneal dialysis (PD) require continuous long-term treatment with ESAs to maintain anemia correction. In addition, a significant number of children with reduced kidney function not yet on dialysis (CKD Stage $\geq$ 3b) develop anemia and may need therapy with ESAs to raise hemoglobin (Hb) values (Koshy and Geary 2008).

Data on the epidemiology of CKD in children who are on dialysis are available from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS 2014) and the United States Renal Data System (USRDS 2016). Information regarding pediatric patients who receive maintenance HD or PD has been captured since 1992. Children

with CKD represent a very small percentage of the total CKD population (NAPRTCS 2014 and USRDS 2016).

The 2014 NAPRTCS registry spans more than 25 years and has collected information on the transplants of over 11,186 children. As of 1 January 2014 (database closure for the 2014 report), 12,189 renal transplants had been reported for 11,186 pediatric patients. This represents 586 new transplants and 554 patients with their first registry transplant since the 2010 annual report.

In 2014, the total number of children in the United States who had not yet received a primary kidney transplant and were on maintenance dialysis was 7,045 (NAPRTCS 2014). However, 25% of the primary transplants were preemptive, as these patients had never received maintenance dialysis.

Epidemiology data from the latest USRDS annual report (2016) show that the incidence of end stage renal disease (ESRD) in children has decreased annually between 2008 and 2014 in the United States. In 2014, a total of 1,398 children had a new onset of ESRD, which was 6% less than in 2013. By age, the number of incident cases ranged from a low of 152 in children 5–9 years of age to 555 in young adults 18–21 years of age. Children 18–21 years of age account for 40% of the incident pediatric ESRD population. In terms of rates, incidence ranges from 6.8 per million for children 5–9 years of age to 30.6 per million in children 18–21 years of age. Similarly, as of 31 December 2014, the point prevalence of children with ESRD was 9,721, which represents a 1.6% decrease from the previous year. Prevalence counts do not account for the large number of pediatric patients who have aged into adulthood.

Of the 9,721 children, adolescents, and young adults between the ages of 0 and 21 years with prevalent ESRD as of 31 December 2014, kidney transplant was the most common treatment modality (6,825 [70.2%]), followed by HD (1,745 [18.0%]) and PD (1,122 [11.5%]). Over 80% of prevalent children 5–13 years of age have a kidney transplant. This equates to a point prevalence per million population of 18.5 for HD, 11.7 for PD, and 69.8 for transplant.

## 1.2 BACKGROUND ON MIRCERA

Methoxy polyethylene glycol-epoetin beta (Mircera) is a chemically synthesized continuous EPO receptor activator. Mircera differs from EPO through integration of amide bonds between amino groups and methoxy polyethylene glycol butanoic acid. This results in a calculated molecular weight of approximately 60 kDa.

The available toxicology data suggest excellent safety and tolerability. Single- and multiple-ascending dose studies in healthy volunteers show potent dose-dependent stimulation of erythropoiesis after both IV and SC administration. Mircera has a long elimination half-life (approximately 130 hours after single-dose SC administration and

approximately 90 hours after single-dose IV administration) (Locatelli and Reigner, 2007). The serum concentrations of Mircera are not affected by standard HD or hemofiltration.

In contrast with EPO, Mircera shows a different activity at the receptor level, characterized by a slower association to the receptor, reduced specific activity in vitro with an increased activity in vivo, as well as an increased half-life (Jarsch et al. 2008). These pharmacological properties are relevant in achieving a monthly dosing regimen with Mircera.

The global clinical development program for Mircera included 13 Phase I clinical pharmacology studies and 10 therapeutic studies comprising 4 Phase II and 6 Phase III studies in patients with CKD, including patients on dialysis and not on dialysis (Del Vecchio et al. 2008). 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 ESAs.

Mircera was efficacious in correcting anemia associated with CKD in patients who were on dialysis or not on dialysis and who were not currently treated with an ESA, regardless of route of administration (IV or SC). Mircera, with its effect on erythropoiesis and its long elimination half-life requiring infrequent administration, offers potential benefits compared to other ESAs (Mircera Summary of Product Characteristics and Mircera Prescribing Information)

Data are available on the efficacy and safety of Mircera administered once every 4 weeks by IV application in pediatric patients (64 children, ages 6–17 years old). The completed Phase II Study NH19707 showed that pediatric patients with CKD on HD can be switched from maintenance treatment with epoetin alfa, epoetin beta, or darbepoetin alfa to Mircera using defined conversion factors (CFs) *(Fischbach et al. 2018)* (see Section 1.3).

In addition to Study NH19707, Mircera has been studied in children in two independent investigator-initiated trials. Cano et al. [2011] evaluated the efficacy and safety of Mircera in the management of anemia in 16 pediatric patients (ages 2–14 years) on stable PD receiving EPO who converted to Mircera SC, scheduled every 2 weeks. Wedekin et al. [2011] conducted a study with Mircera administered intravenously every 4 weeks in 12 pediatric patients (ages 6–17 years) in a post-transplant setting. In both studies, no adverse events attributable to Mircera were reported, and Hb levels were effectively controlled. In Study NH19707, the adverse event profile observed during the core study period and in the safety extension period did not reveal any unexpected safety concerns.

Refer to the Mircera Investigator's Brochure for details on nonclinical and clinical studies.

## 1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Most patients with CKD (Stage ≥ 3b) not yet on dialysis or undergoing HD or PD require continuous long-term treatment with ESAs (e.g., epoetin alfa, epoetin beta, or darbepoetin alfa) to correct anemia and to maintain anemia correction. The Phase II and III studies of Mircera in adult $patients\ with\ CKD$ have shown that it is safe and effective in the treatment of anemia in patients not yet on dialysis and in those receiving HD or PD (Del Vecchio et al. 2008). Cumulative exposure to Mircera since it was first licensed in 2007 is estimated to be about 1.5 million patient-years in 2016.

Study NH19707 identified CFs of 4 × previous weekly darbepoetin alfa dose [μg]/0.55 and 4 × previous weekly epoetin alfa/beta dose [IU]/125 to switch from the previous maintenance treatment to once every 4 weeks Mircera IV treatment in HD patients (ages 5–17 years). By using these CFs, patients maintained Hb within target levels during the core and the safety extension periods. The adverse event profile observed during the study did not reveal any unexpected safety concerns.

State-of-the-art pharmacokinetic/pharmacodynamic (PK/PD) models have been developed on a pooled dataset of Phase II and Phase III data from adult patients $with\ CKD$ and the NH19707 Phase II pediatric data. The analysis provided a good understanding of the pharmacokinetic (PK) properties of Mircera; age and body weight captured the differences between adult and pediatric patients. Similarly, the analysis also described the pharmacodynamic properties of Mircera in pediatric patients; it showed no difference in Mircera-specific PK/PD parameters in pediatric and adult patients, thus suggesting the same exposure/response relationship in both populations. In adults, there was neither an impact of dialysis modality nor a difference between IV and SC routes of administration on PK and PK/PD parameters (Chanu et al. 2010). Model-based simulations of clinical outcomes of Mircera, when Mircera is administered subcutaneously once every 4 weeks for the maintenance treatment of anemia in pediatric patients with CKD, support the current dosing strategy. Based on clinical experience in adults and model-based simulations in children, the same initial dose of Mircera can be used intravenously and subcutaneously when switching from epoetin alfa, epoetin beta, or darbepoetin alfa.

This study will address the following questions that remain open following Study NH19707: use of Mircera in younger children (< 6 years old), SC administration of Mircera, its use in patients on PD or not yet on dialysis, and confirmation of the results of the modeling and simulation studies.

The same CFs as identified in the previous pediatric study (Study NH19707) will be tested for Mircera given subcutaneously to patients 3 months–17 years of age who are on dialysis or not yet on dialysis and are switching from stable SC maintenance treatment with epoetin alfa, epoetin beta, or darbepoetin alfa.

## 2. OBJECTIVES AND ENDPOINTS

This study will ascertain the starting dose of Mircera given subcutaneously for the maintenance treatment of anemia in pediatric patients with CKD on dialysis or not yet on dialysis when switching from stable SC maintenance treatment with epoetin alfa, epoetin beta, or darbepoetin alfa. Specific objectives and corresponding endpoints for the study are outlined below (Table 1).

### Table 1 Objectives and Corresponding Endpoints

| Efficacy Objective | Corresponding Endpoints |
|---|---|
| • To ascertain the starting dose of Mircera given subcutaneously in pediatric patients with CKD on dialysis or not yet on dialysis when switching from stable SC maintenance treatment with epoetin alfa, epoetin beta, or darbepoetin alfa | Primary endpoint:<br>• Change in Hb concentration (g/dL) between the baseline and the evaluation period for each patient<br>Secondary endpoints:<br>• Number of patients with an average Hb concentration during the evaluation period within ±1 g/dL of their baseline Hb or above, within or below the range of 10–12 g/dL<br>• Change in Mircera dose over time, including the change between the starting dose and the evaluation period |
| **Safety Objective:** | **Corresponding Endpoints** |
| • To assess the safety and tolerability of multiple doses of Mircera given subcutaneously in pediatric patients | • Occurrence and severity of adverse events<br>• Change from baseline in targeted vital signs<br>• Change from baseline in targeted clinical laboratory test results |
| **Pharmacokinetic and Pharmacodynamic Objective** | **Corresponding Endpoints** |
| • To evaluate the pharmacokinetics and the pharmacodynamics of Mircera in patients on dialysis or not yet on dialysis who receive the study medication by the SC route of administration | • Serum concentrations of Mircera and Hb will be used to evaluate the pharmacokinetics and the pharmacodynamics of Mircera through PK and PK/PD models. |

CKD = chronic kidney disease; Hb = hemoglobin; PD = peritoneal dialysis; PK = pharmacokinetic; PK/PD = pharmacokinetic/pharmacodynamic.

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF THE STUDY

This study is an open-label, single-arm, multicenter study to ascertain the optimal starting dose of Mircera given subcutaneously for the maintenance treatment of anemia in pediatric patients with CKD on dialysis or not yet on dialysis.

Following written informed consent from a parent or legal guardian and, if appropriate, assent from the child, the patient will be screened for eligibility during a *screening period of approximately 3 weeks*. During this period, patients will continue to receive epoetin alfa, epoetin beta, or darbepoetin alfa at the same weekly dose, route (SC), and interval as before screening. The total weekly doses 4 weeks before the first Mircera administration should not change > 25% (increase or decrease). Provided that all eligibility criteria are met, including those for Hb levels and iron status, the patients will start Mircera administered subcutaneously.

At least 40 pediatric patients 3 months–17 years of age will be enrolled. Approximately 10–15 of these patients will be < 12 years old, with a goal to include as many patients < 5 years old as possible (with a minimum of 3 patients). Approximately 10–15 patients, irrespective of age, will not be on dialysis.

Available HD patients receiving their ESA subcutaneously are eligible for enrollment. No more than 10 patients on HD should be enrolled.

Mircera will be administered subcutaneously once every 4 weeks for the duration of the study. Dose adjustments may be performed every 4 weeks according to dose adjustment rules defined in Section 4.3.2.1.1.

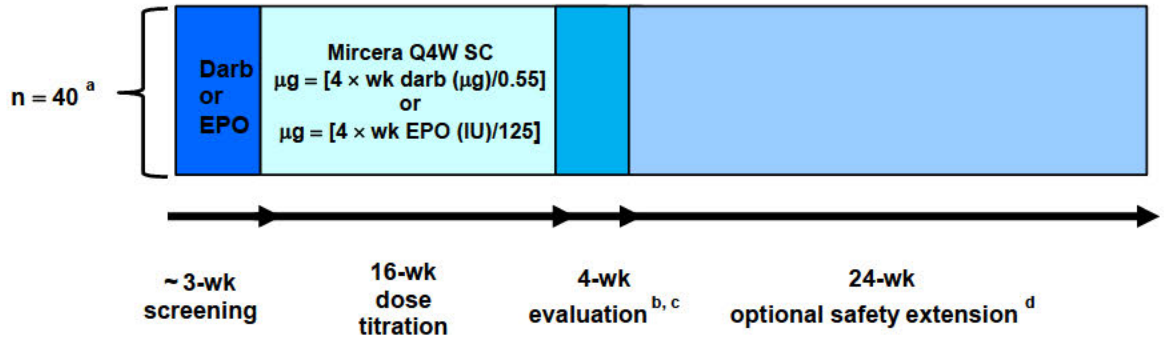
The core study will last for 23 weeks and consists of three periods: screening (3 weeks), dose titration (16 weeks), and evaluation (4 weeks).

Patients completing the 20 weeks of treatment with Hb within ±1 g/dL of their baseline Hb and within the target range of 10–12 g/dL, will be eligible to enter an optional 24-week safety extension period. Those patients not eligible or not consenting to enter the long-term safety extension should be treated according to clinical practice. All patients must complete the Week 21 visit (Visit 10), regardless of whether they continue in the safety extension period. Visit 10 will serve as the final visit of the core study and the first visit of the safety extension period for patients eligible and willing to continue in the study.

Once 12 patients have completed 20 weeks of treatment (dose titration and evaluation periods), an interim analysis to assess the pharmacokinetics, efficacy, and safety of Mircera will be performed (see Section 6.9).

Figure 1 presents an overview of the study design. Schedules of activities are provided in Appendix 1 and Appendix 2.

**Figure 1 Study Schema**




darb = darbepoetin alfa; EPO = *epoetin alfa or epoetin beta*; Q4W = every 4 weeks; wk = week.

[a] Approximately 10–15 of the patients will be < 12 years old, with a goal to include as many patients < 5 years old as possible (with a minimum of 3 patients). Approximately 10–15 patients, irrespective of age, will not be on dialysis. Available HD patients receiving their ESA subcutaneously are eligible for enrollment. No more than 10 patients on HD should be enrolled.

[b] Once 12 patients have completed 20 weeks of treatment (dose titration and evaluation periods), an interim analysis to assess the pharmacokinetics, efficacy, and safety of Mircera will be performed.

[c] All patients will complete a follow-up visit (Week 21, Visit 10), regardless of whether they continue in the safety extension period.

[d] Patients completing the 20 weeks of treatment with Hb within ± 1 g/dL of their baseline Hb and within the target range of 10–12 g/dL, will be eligible to enter an optional 24-week safety extension period.

## 3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur approximately 44 weeks after the last patient is enrolled.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 41 months.

In addition, the Sponsor may decide to terminate the study at any time.

## 3.3 RATIONALE FOR STUDY DESIGN

Most patients with CKD undergoing HD or PD require continuous long-term treatment with ESAs to correct anemia and to maintain anemia correction. The Sponsor has completed Phase II and III studies of Mircera and has shown that it is safe and effective in the treatment of anemia in adult patients *with CKD* not yet on dialysis and in those patients receiving HD or PD. Furthermore, Study NH19707 has shown that pediatric patients with CKD on HD can be safely and effectively switched from maintenance

treatment with IV epoetin alfa, epoetin beta, or darbepoetin alfa to Mircera IV using CFs to define the starting dose. The purpose of this study is to use the same CFs to ascertain the starting dose of Mircera given subcutaneously for the maintenance treatment of anemia with SC ESAs in pediatric patients with CKD on dialysis or not yet on dialysis.

The study design is based on the study design of NH19707 but with fewer visits, as patients on PD or not yet on dialysis visit the nephrology centers less frequently than patients on HD. The similar study design will allow pooling of the data from the two pediatric studies.

### 3.3.1 Rationale for Mircera Dose and Schedule

The completed Phase III program of Mircera in adult $patients\ with\ CKD$ included four studies to assess how to switch patients treated with epoetin alfa, epoetin beta, or darbepoetin alfa to Mircera, administered intravenously or subcutaneously. The CFs that were tested in the Phase II Study NH19707 in pediatric patients were directly derived from the Sponsor's experience in adults receiving Mircera intravenously and from the results of a published study of darbepoetin alfa conducted in pediatric patients (Warady et al. 2006). This completed study identified CFs of 4 $\times$ previous weekly darbepoetin alfa dose [μg]/0.55 for darbepoetin alfa and 4 $\times$ previous weekly epoetin dose [IU]/125 for epoetin alfa and epoetin beta in order to switch from the previous weekly maintenance treatment dose to Mircera IV once every 4 weeks in HD patients. Model-based evaluation of the data from this pediatric study and subsequent simulations, coupled with the data from the adult studies, suggest that these CFs will also be appropriate in the SC setting. Real-world data from independent registries (International Pediatric Dialysis Network) of pediatric patients (3 months and older) treated with Mircera SC and IV confirmed the model-based simulations and the conversion factor identified in Study NH19707. Therefore, the same CFs will be used to identify the starting dose of Mircera administered subcutaneously every 4 weeks.

The patients included in this study are already on stable maintenance doses of SC ESA prior to conversion to Mircera and, assuming a linear relationship across dose ranges, the use of CFs will result in a Mircera dose that is proportional to the previous ESA dose, thus correcting for the higher weight-adjusted dose requirements in pediatric patients.

## 4. MATERIALS AND METHODS

### 4.1 PATIENTS

Approximately 40 pediatric patients, (3 months−17 years of age), who are evaluable for intent-to-treat (ITT) and safety analyses (see Section 6.4 and Section 6.5, respectively), who have clinically stable chronic renal anemia on dialysis or not yet on dialysis, and who are receiving maintenance SC treatment with an ESA, will be enrolled in this study.

Approximately 10–15 of the patients will be < 12 years old, with the objective to include as many patients as possible < 5 years old (with a minimum of 3 patients). Approximately 10–15 patients, irrespective of age, will not be on dialysis. Available HD patients receiving their ESA subcutaneously are eligible for enrollment. No more than 10 patients on HD should be enrolled.

### 4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Written informed consent from parent/legal guardian and willingness of parent/legal guardian to abide by the requirements of the study
- Written informed consent or assent from child where appropriate

  If required by national legislation, patients < 18 years of age at screening who are legally considered to be adults according to national legislation must consent in their own right.
- Pediatric patients 3 months–17 years of age with clinically stable chronic renal anemia
- CKD with estimated glomerular filtration rate (eGFR) of < 45 mL/min/1.73 $m^2$ (determined by the Bedside Schwartz formula [see Appendix 3]) or dialysis treatment for at least 8 weeks before the first dose of Mircera
- For patients on PD: a weekly Kt/V ≥ 1.8
- For patients on HD: adequate HD, urea reduction ratio (URR) > 65% or Kt/V > 1.2 for patients on HD three times per week.

  Patients with fewer than or more than three HD sessions per week should have a weekly Kt/V ≥ 3.6.
- Baseline Hb concentration 10.0–12.0 g/dL determined from the mean of two Hb values measured at Visit 1 (Week –3) and Visit 2 (Week –1)
- Stable SC maintenance treatment with epoetin alfa, epoetin beta, or darbepoetin alfa with the same dosing interval for at least 6 weeks before the first dose of Mircera
- Stable dose of epoetin alfa, epoetin beta, or darbepoetin alfa treatment with no weekly dose change > 25% (increase or decrease) for at least 4 weeks before the first dose of Mircera
- Adequate iron status defined as ferritin ≥100 ng/mL or transferrin saturation (TSAT) ≥ 20% (or percentage of hypochromic red cells < 10%); mean of two values measured during screening
- For post-pubertal female patients of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or to use acceptable contraceptive methods during the study and for 90 days after the final dose of Mircera

  A female patient is considered to be of childbearing potential if she is postmenarcheal.

  The following are acceptable contraceptive methods: hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

### 4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Overt gastrointestinal bleeding within 8 weeks before screening or during the screening period
- RBC transfusions within 8 weeks before screening or during the screening period
- Hemoglobinopathies (e.g., homozygous sickle-cell disease, thalassemia of all types)
- Hemolytic anemia
- Active malignant disease
- PD subjects with an episode of peritonitis within the past 30 days prior to screening and/or during the screening period
- Uncontrolled or symptomatic inflammatory disease (e.g., systemic lupus erythematosus)
- Uncontrolled hypertension as assessed by the investigator (for standard blood pressure reference tables, see Appendix 6)
- Epileptic seizures within 3 months prior to screening and during the screening period
- Administration of any investigational drug within 4 weeks prior to screening or planned during the study
- *Kidney transplant with use of immunosuppressive therapies known to exacerbate anemia (see Section 4.4.5)*
- Severe hyperparathyroidism (intact parathyroid hormone [PTH] ≥1000 pg/mL or whole PTH ≥500 pg/mL) or biopsy-proven bone marrow fibrosis
- Known hypersensitivity to recombinant human EPO, polyethylene glycol, or any constituent of the study drug formulation
- Anti-EPO antibody (AEAB)-mediated pure red cell aplasia (PRCA) or history of AEAB-mediated PRCA or positive AEAB test result in the absence of PRCA
- High likelihood of early withdrawal or interruption of the study (e.g., planned living donor kidney transplant within 5 months of study start)
- Planned elective surgery during the entire study period
- Females who are pregnant or breastfeeding or who intend to become pregnant during the study or within 90 days after the final dose of Mircera

  Note: Patients of childbearing potential must have a negative serum pregnancy test result within 21 days prior to initiation of study drug.

## 4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Patients will be enrolled to receive Mircera once every 4 weeks, and no randomization will be performed. An interactive voice or Web-based response system (IxRS) will be used to track the enrollment and to monitor the disposition of patients with respect to the different subgroups (age group and dialysis type).

Blinding is not applicable; this is an open-label, single-arm study.

## 4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is Mircera.

### 4.3.1 Study Treatment Formulation, Packaging, and Handling

Mircera will be provided by the Sponsor in sterile injectable solution in single-use, prefilled syringes (PFS). The Mircera solution is formulated in sodium phosphate, sodium sulfate, mannitol, methionine, and poloxamer 188, pH 6.2. This formulation does not contain any preservative.

The PFS is available in the following strengths:

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 30 | 50 | 75 | 100 | 120 | 150 | 200 | 250 | µg/0.3 mL |

| | |
|---|---|
| 360 | µg/0.6 mL |

The PFS should be stored in a refrigerator at 2°C–8°C (35.6°F–46.4°F) and protected from light. The investigational site is responsible for maintaining a daily temperature log of this refrigerator.

For information on the formulation and handling of Mircera, see the Mircera Investigator's Brochure and the local prescribing information for Mircera.

### 4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimen is summarized in Section 3.1.

The Mircera PFS should reach room temperature in its outer carton box before injecting. Mircera should be administered subcutaneously using a PFS, and each PFS should be used only once.

The empty PFS blisters/medication boxes with patient identification information must be retained and made available for the Roche Monitor to check at each visit. Once the Roche Monitor has checked the empty PFS blisters/medication boxes with the patient identification, they will be sent back to the Sponsor, or upon approval by the Sponsor, they may be destroyed at the site, either at the end of the study or as required by the site.

All doses administered need to be reported on the Study Drug Administration electronic Case Report Form (eCRF). Any dose modification should be noted on the Study Drug Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.4.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.2.

#### 4.3.2.1 Rationale for Starting Dose Selection

The starting dose will be based on CFs obtained from the dose-finding study (Study NH19707) (see Section 3.3.1). The initial dose of Mircera will be one of nine starting doses corresponding to the PFS strengths based on the total weekly ESA dose during the screening period, as described in Table 2.

**Table 2 Mircera Starting Dose**

| Previous Weekly Epoetin Alfa or Epoetin Beta Dose [IU/Week] | Previous Weekly Darbepoetin Alfa Dose [μg/Week] | Every 4-week Mircera Dose [μg] |
|---|---|---|
| <1300 | <6 | 30 |
| 1300–<2000 | 6–<9 | 50 |
| 2000–<2700 | 9–<12 | 75 |
| 2700–<3500 | 12–<15 | 100 |
| 3500–<4200 | 15–<19 | 120 |
| 4200–<5500 | 19–<24 | 150 |
| 5500–<7000 | 24–<31 | 200 |
| 7000–<9500 | 31–<42 | 250 |
| ≥9500 | ≥42 | 360 |

Once 12 patients have completed 20 weeks of treatment, an interim analysis to assess the pharmacokinetics, efficacy, and safety will be performed (see Section 6.9). If the results of this interim analysis indicate that the starting dose is not appropriate, then it may be changed (see Section 6.9).

#### 4.3.2.1.1 Dose Adjustments of Mircera

Dose adjustments may be performed during the entire study. The dose of Mircera should be adjusted to maintain the individual patient's Hb within a target range of ±1 g/dL of his or her baseline Hb and between 10.0–12.0 g/dL. Baseline Hb is calculated as the mean of Hb values obtained at Visit 1 (Week –3) and Visit 2 (Week –1).

Dose adjustments should be performed at the scheduled dosing days and should be based on the Hb value measured on that day. They should not be performed more often than once every 4 weeks.

Dose adjustment rules for Mircera in response to Hb changes, including those required for safety reasons, are summarized in Table 3.

**Table 3 Mircera Dose Adjustments**

| Hemoglobin Assessment | Compared with the Previous Mircera Dose |
|---|---|
| Hb decreases by more than 1.0 g/dL compared with baseline Hb. | Increase dose by approximately 25% *(or closest higher PFS strength).* |
| Hb is less than 10 g/dL and greater than or equal to 9 g/dL (Hb < 10.0 and ≥ 9.0 g/dL). | Increase dose by approximately 25% *(or closest higher PFS strength).* |
| Hb is less than 9 g/dL (Hb < 9.0 g/dL). | Increase dose by approximately 50% *(or closest to 50% increase PFS strength).* |
| Hb increases by more than 1.0 g/dL compared with the baseline Hb. | Decrease dose by approximately 25% *(or closest lower PFS strength).* |
| *Hb is increasing and is approaching 12 g/dL or Hb is greater than or equal to 12 g/dL (Hb ≥12 g/dL).* | *Decrease dose by approximately 25% (or closest lower PFS strength).* |
| *If Hb* exceeds 12 g/dL *and continues to increase* following a dose reduction. | Stop doses until Hb is less than 12.0 g/dL.<br>Resume dose at approximately 25% below previous dose *(or closest lower PFS strength) at next scheduled dosing day.* |

Hb = hemoglobin*; PFS =prefilled syringe.*.

#### 4.3.2.1.2 Dose Adjustments in Case of Red Blood Cell Transfusion

In case of an RBC transfusion due to worsening anemia secondary to inadequate doses or to poor response to Mircera, the dose (administered at the next scheduled dosing day, if possible) should be adjusted according to the guidelines in Table 3.

In case of an RBC transfusion to replace acute blood loss, the dose should not be changed, and the next dose should be administered as scheduled.

### 4.3.3 Investigational Medicinal Product Accountability

All IMPs (Mircera) required for completion of this study will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

### 4.3.4 Continued Access to Mircera

Currently, the Sponsor does not have any plans to provide the Roche IMP (Mircera) or any other study treatments or interventions to patients who have completed the study. The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

## 4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment within 3 months before screening. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

### 4.4.1 Permitted Therapy

All treatments (medications and medical procedures) are permitted before screening, during the screening period, and throughout the 20-week treatment period, except for those listed in Section 4.4.5.

### 4.4.2 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 epoetin therapy. In addition, epoetin 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 TSAT. TSAT will be calculated as described in Appendix 3. The percentage of hypochromic red cells can be determined instead of TSAT.

Adequate iron status is defined as follows:

Serum ferritin $\geq 100$ ng/mL

or

TSAT $\geq 20\%$ (or percentage of hypochromic red cells $< 10\%$)

Patients must be iron-replete at baseline to be enrolled in this study and should maintain an adequate iron status throughout the treatment period. For baseline, iron status should be assessed using the mean of two values measured during screening (Weeks $-3$ and $-1$).

Supplemental iron will be administered to prevent iron deficiency during the screening period and during the study, and to maintain adequate iron status. Therefore, oral or IV iron will be given during the entire study period (screening, dose titration, and evaluation periods) according to center practice. If iron treatment is ongoing at the start of the study, it should not be interrupted.

To avoid iron toxicity, caution is suggested in patients with serum ferritin $> 500$ ng/mL or TSAT $> 30\%$.

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.

### Iron Loading

In case of inadequate iron stores at the end of screening, the patient should receive iron loading according to center practice. After completion of the iron loading, the patient will be allowed to be re-screened. New assessment of iron stores should be performed at least 1 week after iron loading.

### 4.4.3 Red Blood Cell Transfusions

RBC transfusions may be given during the treatment period in case of medical need, that is, in severely anemic patients with recognized symptoms or signs of anemia (e.g., in patients with acute blood loss or in patients whose Hb has declined to critical levels). Every reasonable effort should be made to avoid RBC transfusions in patients with Hb concentrations above 8 g/dL.

All RBC transfusions administered during the study should be documented (i.e., specified by type, number of units transfused, and total volume transfused) in the RBC transfusions section of the eCRF. The pre-transfusion Hb level must be measured before each RBC transfusion and recorded on the appropriate page in the eCRF.

The indication for the RBC transfusions (e.g., the etiology of the acute blood loss or worsening of anemia if no other etiology is known) should be recorded as an adverse event on the eCRF page and the RBC transfusions listed as treatment on the same eCRF page.

### 4.4.4 Dialysis

Dialysis modality at study start (HD, PD, or none), number of HD sessions per week, the type of vascular access for HD, PD type, time since first dialysis, and dialysis adequacy assessments should be documented in the dialysis section of the eCRF.

In the event that a patient not previously on dialysis requires emergent or long-term dialysis treatment due to worsening of renal function, the patient should be kept in the study, whenever possible, until the final visit. The route of administration for Mircera should stay the same (SC). The start of dialysis and dialysis modality should be documented in the dialysis page of the eCRF.

Dialysis modality changes (i.e., switch from PD to HD) may be performed during the treatment period in case of medical need. If a switch from PD to HD during the study becomes necessary, the patient can continue to participate in the study as long as the SC route of administration is maintained. The visits should occur on the day of the mid-week dialysis. The change of dialysis should be documented in the dialysis page of the eCRF.

### 4.4.5 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- *Other* IMPs (defined as any material [i.e., placebo or drug] dispensed under the provision of a protocol) within 4 weeks before screening, during screening, or during the treatment periods.

  Participation in studies testing investigational devices or dialysis solutions should be reported to the Sponsor in advance and approved by the Sponsor.
- Non-Food and Drug Administration (FDA) or European Medicines Agency-approved biosimilar ESAs within 12 weeks before screening or during screening
- RBC transfusions within 8 weeks before screening or during screening (see also Section 4.4.3)
- Immunosuppressive therapies known to exacerbate anemia, such as cyclophosphamide, sirolimus, tacrolimus, azathioprine, and mycophenolate mofetil, administered the last 12 weeks before the first screening visit

- Whenever possible, intermittent treatment (i.e., start or stop) or dose change of medications known to influence Hb concentration should be avoided.

    These medications include androgens (known to improve anemia), angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and immunosuppressive therapies, except for corticosteroids for a chronic condition, cyclosporine, and monoclonal /polyclonal antibodies

If drugs that are highly bound to RBCs (e.g., cyclosporine) are given during the study, blood levels of these drugs should be monitored and their dosage adjusted as the Hb rises.

## 4.5 STUDY ASSESSMENTS

The schedules of activities to be performed during the study are provided in Appendix 1 and Appendix 2. All activities must be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

Throughout the screening period and the 20-week treatment period (dose titration and evaluation periods), the study visits should be scheduled*, if possible,* on the same day of the week. For patients undergoing HD or patients converting to HD, the visits should occur on the day of the mid-week dialysis.

A follow-up visit will be performed for all patients at study end (Week 21) or at any time during the study in case of premature withdrawal. In case of premature withdrawal due to kidney transplantation, the follow-up visit must take place before the transplantation; otherwise, there will be no follow-up visit.

Patients completing the 20 weeks of treatment with Hb within $\pm 1$ g/dL of their baseline Hb and within the target range of 10–12 g/dL will be eligible to enter an optional 24-week safety extension period.

### 4.5.1 Informed Consent Forms and Screening Log

Written informed consent from the parent/legal guardian and willingness of the parent/legal guardian to abide by the requirements of the study, and written informed consent or assent from the child where appropriate, must be obtained before performing any study-related procedures (including screening evaluations). If required by national legislation, patients $< 18$ years of age at screening who are legally considered to be adults according to national legislation must consent in their own right.

Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Eligibility will be assessed during an initial screening period. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Patients who fail screening may be re-screened if it is considered likely that they could later become eligible. Patients who are not eligible will be allowed to undergo a maximum of two new rounds of screening assessments. All eligibility criteria have to be reassessed during the new screenings.

Provided that the efficacy and safety profiles for the patient are acceptable, at least 2 weeks prior to the follow-up visit (Visit 10, Week 21), the investigator should discuss with the parents/legal guardians and, if appropriate, with the patient, the possibility of continuing with an optional safety extension period. A new signature on the informed consent (and, if indicated, on the assent) should be obtained at this time. The clinical and laboratory assessments at Week 21 (Visit 10, follow-up visit) of the core study period are also used as initial assessments for the optional safety extension period.

### 4.5.2 Medical History, Concomitant Medication, and Demographic Data

The following information will be collected during the screening period:

- Medical history includes etiology of CKD, dialysis modality (HD,PD or none), number of HD sessions per week, the type of vascular access for HD, anticoagulant treatment during HD, PD type, date of first dialysis treatment, dialysis adequacy assessments, previous ESA treatments, and iron supplementation. It also includes risk factors and dialysis-related events, as well as clinically significant diseases.
- In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 3 months prior to screening will be recorded.
- Demographic data will include age, sex, and self-reported race/ethnicity (where permissible).
- Reproductive status and smoking history will be collected.

### 4.5.3 Physical Examinations

A complete physical examination, performed at screening (Week −3, Visit 1),at the follow-up visit (Week 21, Visit 10), and at the final safety extension visit (Week 45), should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified should be recorded on the corresponding page of the eCRF.

### 4.5.4 Height and Body Weight

Height will be collected at Week 1, Visit 3, at the follow-up visit (Week 21, Visit 10), and at the final safety extension visit (Week 45). Body weight will also be recorded throughout the study *(after dialysis for patients on HD)*.

### 4.5.5 Vital Signs

Vital signs will be measured regularly throughout the study. They include measurements of systolic and diastolic blood pressure and pulse rate while the patient is if possible in a seated position, and they will be measured before blood sampling (see Appendix 5). The blood pressure should be measured at least twice and the average of these measurements should be recorded. An appropriate-sized cuff should be used. Blood pressure should be determined before and after the dialysis session for HD patients.

### 4.5.6 Laboratory Assessments

*For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.*

*Biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exception:*

- *Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.*

*When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.*

*Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.*

#### 4.5.6.1 Safety Assessments

Normal ranges for the study laboratory parameters should be supplied to Roche before the study starts. Blood sampling should always be performed before ESA administration and for patients on HD before the dialysis. The following laboratory assessments will be performed throughout the study at selected visits (see the schedules of activities in Appendix 1 and Appendix 2) and analyzed at the study site's local laboratory:

- Hematology: Hb, RBC, absolute reticulocyte count
- Safety laboratory: leukocytes plus differential, AST, ALT, serum albumin, ALP, C-reactive protein, potassium, phosphorus, calcium, and platelets
- Serum creatinine: measured only for patients not on dialysis

  eGFR will be calculated using the Bedside Schwartz formula (see Appendix 3).

- Iron parameters: serum ferritin, serum iron, and TSAT. TSAT will be calculated as described in Appendix 3 with either serum transferrin or total iron-binding capacity. The percentage of hypochromic red blood cell may be determined instead of TSAT.
- Serum pregnancy test for post-pubertal female patients of childbearing potential
- Kt/V for patients on PD

  Frequency will follow current Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (2006).
- Kt/V or URR for patients on HD

  Frequency will follow current KDOQI guidelines (2006).

Per individual, the trial-related blood loss (including any losses in the maneuver) should not exceed 3% of the total blood volume during a period of four weeks and should not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90 ml/kg body weight; 3% is 2.4 ml blood per kg body weight (DG SANTE 2008). Blood sampling to assess the different laboratory parameters should be done routinely at the site but should not exceed the recommended maximal volume of 2.4 ml per kg per four weeks.

Samples for the following laboratory tests will be sent to one or several bioanalytical laboratories for analysis:

- Serum samples will be collected to evaluate the pharmacokinetics of Mircera administered subcutaneously (see Section 4.5.6.2).
- Anti-EPO and anti-Mircera antibody will be determined at Week 1, Visit 3, at Week 9 (Visit 6), and follow-up visit (Week 21, Visit 10). An additional sample will be collected at Week 45 (Visit 16) for the patients participating in the safety extension period.

For the patients participating in the optional safety extension period, laboratory assessments will be performed every 4 weeks (see the schedules of activities in Appendix 1 and Appendix 2).

### 4.5.6.2 Pharmacokinetic Assessments

PK sampling will be performed in all patients throughout the 20-week treatment period (dose titration and evaluation periods). Serum concentrations of Mircera will be used to evaluate the pharmacokinetics and the concentration-effect relationships in all patients. The timing of all PK and hematology samples needed for this study will coincide as much as possible with regularly scheduled visits.

Samples taken at the following timepoints will be sent to one or several bioanalytical laboratories for analysis:

- Week 1 (Visit 3) before the first Mircera dose administration
- Week 3 (Visit 4)
- Week 9 (Visit 6) before the Mircera dose administration

- Week 17 (Visit 8) before the Mircera dose administration
- Week 19 (Visit 9)
- At the patient's convenience, one additional sample between 24 hours and 5 days after any one Mircera dose administration should be collected.

A minimum of one PK sample after treatment initiation is requested in patients younger than 2 years old; the sample on Week 1 can be omitted in these patients.

The exact time of PK blood sampling must be recorded on the lab requisition form and the exact time of the preceding Mircera administration must be recorded on the appropriate page in the eCRF.

PK samples must be handled according to the procedures described in a separate document.

The standard laboratory parameters should be measured locally at the study site. PK and antibody samples will be shipped to one or several bioanalytical laboratories for measurement.

### 4.5.7 Patient-Reported, Observer-Reported, and Clinician-Reported Outcomes

Patients 4 years or older, along with their parent/guardian and nurse/site staff member, will assess pain from the ESA injection and the Mircera injection. Patients who receive an ESA injection during either or both of the screening visits will assess injection pain. Assessments of the Mircera injection will occur at Week 1 (Visit 3) and Week 9 (Visit 6).

#### Patient-Reported Injection Pain

Patients 4 years old or older will be asked to assess their pain from the injection 5 minutes after the injection takes place. Pain will be rated on a visual analogue scale (VAS) consisting of a 10-cm horizontal line ranging from ″did not hurt at all″ to ″as painful as it could be,″ as in Schmitt et al. (2006). Scores out of 10 will be determined by measuring the mark on the line. For young children ($\geq$ 4 years old and $<$ 10 years old), five cartoon faces ranging from ″neutral″ to ″very distressed″ will be added as a guide. Children under the age of 4 will not be asked to rate their own pain, as reliability is questionable in very young patients.

#### Parent-Reported Injection Pain

Parents or guardians will be asked to rate observed pain. Pain will be rated on a VAS consisting of a 10-cm horizontal line ranging from ″did not hurt at all″ to ″as painful as it could be.″ Scores out of 10 will be determined by measuring the position of the mark on the line. As much as possible, the same parent/guardian should rate pain at every visit.

### Nurse-Reported Injection Pain

The nurse or site staff member administering the ESA or Mircera doses will be asked to rate observed pain. Pain will be rated on a VAS consisting of a 10-cm horizontal line ranging from ″did not hurt at all″ to ″as painful as it could be.″ Scores out of 10 will be determined by measuring the position of the mark on the line. As much as possible, the same nurse/site staff member will rate each patient across all visits.

## 4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

### 4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Pregnancy
- Kidney transplantation
- AEAB-mediated PRCA

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

In this study, if a patient discontinues study treatment for the reasons mentioned above, he or she will be discontinued from the study. See Section 4.6.2 for additional possible reasons for patient discontinuation from study.

### 4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

In case of premature withdrawal, patients will return to the clinic for a follow-up visit (all assessments for Visit 10, see Appendix 1 for details). In case of premature withdrawal due to a kidney transplantation, the follow-up visit must take place before the transplantation; otherwise, there will be no follow-up visit.

The primary reason for withdrawal from the study should be documented on the appropriate eCRF page. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

Additional patients may be enrolled to replace patients who withdraw early, before the Week 17 (Visit 8).

### 4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

### 4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

## 5. ASSESSMENT OF SAFETY

### 5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with Mircera in completed and ongoing studies. The anticipated important safety risks for Mircera are outlined below. Please refer to the Mircera Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

### 5.1.1 Risks Associated with Mircera

#### 5.1.1.1 Hypertension and Hypertensive Encephalopathy

Observational studies and registry data show that more than half of children with CKD have high blood pressure based upon a casual blood pressure reading.

ESA treatment may increase blood pressure in patients with CKD, possibly due to effects on the vasoactive hormone axes. The role of blood viscosity remains uncertain.

During development trials in adults, hypertension was reported as an adverse event in 23.6% of patients receiving Mircera and 22.6% of patients receiving reference ESAs.

In Study NH19707, around 50% of patients had hypertension reported as a preexisting condition at baseline, and 58% of patients were receiving—or had previously received—antihypertensive and/or diuretic agents. During the core study, 13% of patients required an increase in antihypertensive treatment. Of 8 patients with hypertension reported as an adverse event during the core study, all had hypertension and/or had received antihypertensive therapy prior to enrollment.

Hypertensive encephalopathy describes a syndrome of neurological dysfunction induced by severe hypertension. Less than 1% of patients with hypertension experience a hypertensive crisis at any time. During clinical development studies in adults, hypertensive encephalopathy was reported in 0.3% of patients receiving Mircera and in 0.1% of patients receiving reference ESAs. No patients in Study NH19707 experienced hypertensive encephalopathy.

Instructions for recording blood pressure values and adverse events of high blood pressure and hypertension are provided in Section 5.3.5.6.

#### 5.1.1.2 Anti-Erythropoietin Antibody-Mediated Pure Red Cell Aplasia

AEAB-mediated PRCA is a very rare adverse effect of ESA treatment, caused by the formation of AEABs that neutralize endogenous EPO. The condition is characterized by severe, progressive, refractory anemia, low reticulocyte count, and absent erythroid precursor cells in bone marrow. Patients typically develop ESA resistance following initial response to treatment, and become transfusion-dependent. No cases of AEAB-mediated PRCA have been observed in patients receiving Mircera during clinical trials. Cumulatively to 19 July 2016, there have been 8 cases of confirmed AEAB-mediated PRCA following exclusive use of Mircera in the postmarketing setting, all involving adult patients $with\ CKD$. Total cumulative exposure to Mircera is currently more than 1.5 million patient-years.

Detailed information on recognition and diagnosis of AEAB-mediated PRCA is provided in Appendix 4.

#### 5.1.1.3 Low Platelet Count

During development trials in adults, platelet values below $100 \times 10^9$/L were observed in 9.7% of patients treated with Mircera versus 6.7% of patients treated with reference ESAs. The incidence of thrombocytopenia reported as an adverse event was similar in both groups (approximately 0.22% vs. 0.32%, respectively).

In Study NH19707, platelet count at baseline ranged from $80–518 \times 10^9$/L. Median platelet count decreased slightly during the core study period in both dose groups. No events of bleeding were reported in any patients in association with low platelet counts. Thrombocytopenia was reported as an adverse event in 2 patients, in both cases classified as mild.

Instructions for recording platelet count values and adverse events of low platelet count and thrombocytopenia are provided in Section 5.3.5.

#### 5.1.1.4 Vascular Access Thrombosis

Vascular access thrombosis (VAT) is a frequent and potentially serious problem in HD patients. Arteriovenous grafts are at greater risk of VAT than fistulas. Other possible risk factors include high hematocrit, hypercoagulability, and decreased blood flow (e.g., due to low cardiac output, hypovolemia, hypotension, or compression). During development trials, events suggestive of VAT were reported in 13.2% of patients receiving Mircera and 11.6% of patients receiving reference ESAs. In Study NH19707 involving pediatric patients on HD, during the core period, 4 patients reported 5 events of VAT.

#### 5.1.1.5 Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

There has been only one case of Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN) in which available information was suggestive of a possible causal role of Mircera, based primarily on temporal course and reappearance of typical symptoms after re-challenge. No cases suggestive of SJS/TEN or other severe cutaneous adverse reactions caused by Mircera were observed during clinical trials.

### 5.1.2 Management of Patients Who Experience Adverse Events

#### 5.1.2.1 Anti-Erythropoietin Antibody-Mediated Pure Red Cell Aplasia

ESAs should be discontinued in any patient with confirmed AEAB-mediated PRCA. The physician should investigate for the presence of anti-EPO and anti-Mircera antibodies and perform a bone marrow examination. An additional blood sample should also be stored for an anti-PEG antibody determination after the assay has been developed.

Patients must not be switched to another recombinant ESA because of the risk of cross-reactivity of antibodies with endogenous and all recombinant ESAs (see Appendix 4 for further detailed information on recognition and management of AEAB-mediated PRCA).

## 5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

### 5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.8 and Section 5.3.5.9 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., invasive procedures such as blood sampling, discontinuation of medications)

Kidney transplantation and routine diagnostic procedures/tests are not considered adverse events and should therefore not be recorded on an Adverse Event eCRF page.

The start of dialysis or the change in dialysis modality should not be considered an adverse event and should be recorded on a specific eCRF page (see Section 5.3.5.11).

### 5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life-threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.12)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" (Section 5.3.3) and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe); the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Seriousness is a regulatory criterion for adverse event reporting. It should be considered in determining whether a case needs to be reported as a serious adverse event or not (e.g., a headache may be severe in terms of interfering significantly with a patient's usual function but would not be classified as serious, unless it met one of the criteria for seriousness described above).

Severity and seriousness need to be independently assessed for each adverse event recorded on the Adverse Event eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

As an exception, the following serious adverse events, which are common in the dialysis population, will not be reported in an expedited manner if unrelated to study drug, but will be recorded as serious adverse events on the Adverse Event pages of the eCRF:

- Thrombosis of vascular access for HD
- Peritonitis due to PD

### 5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

## 5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6. The investigator is also responsible for reporting medical device complaints (see Section 5.4.5).

For each adverse event recorded on the Adverse Event page of the eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

### 5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as blood sampling, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

### 5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

### 5.3.3 Assessment of Severity of Adverse Events

The World Health Organization (WHO) toxicity grading scale (see Appendix 7) will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed or are not appropriate (e.g., due to the disease under study or age of the patient) in the WHO toxicity grading scale.

**Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale**

| Grade | Severity |
|---|---|
| 1 | Mild; transient or mild discomfort (<48 hours); no medical intervention or therapy required |
| 2 | Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required |
| 3 | Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible |
| 4 | Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable |

Notes: Developed by the Division of Microbiology and Infectious Diseases.

Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

### 5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 5):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study

- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

**Table 5 Causal Attribution Guidance**

| Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment? | |
|---|---|
| YES | There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge. |
| NO | An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug). |

### 5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

#### 5.3.5.1 Injection Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of injection reaction).

#### 5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than injection reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the

single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

#### 5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

#### 5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

#### 5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

#### 5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

#### 5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either *as a serious adverse event* or an adverse event of special interest (see Section 5.4.2).

#### 5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of CKD.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of CKD, the term "chronic kidney disease" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

#### 5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

#### 5.3.5.10 Loss of Effect

Hb values will be monitored regularly throughout the study, and dose adjustments to achieve target Hb will be made according to protocol guidance (see Section 4.3.2.1.1).

Loss of effect is defined as follows: a decline in Hb of at least 2.8 g/dL in a 4-week period without transfusion or requirement for transfusion of 1 blood unit or more per week for a minimum of 2 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 (Eckardt and Casadevall 2003). If loss of effect is suspected, the cause should be actively sought. Possible causes include the following: 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 (possible bone marrow examination), and an unscheduled blood sample should be obtained for a reticulocyte count and an anti-EPO and anti-Mircera antibody determination. An additional blood sample should also be stored for an anti-PEG antibody determination after the assay has been developed.

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

If a diagnosis of PRCA is confirmed, treatment with the IMP should be stopped. The patient should not receive another epoetin, and causes of PRCA should be investigated. Reticulocyte counts and anti-EPO, anti-Mircera, and anti-PEG antibody testing will be performed every 8 weeks until the end of the study (see Appendix 4 for further, detailed guidance).

#### 5.3.5.11 Progression of Kidney Disease

Events that are clearly consistent with the expected pattern of progression of the patient's underlying kidney disease should not be recorded as adverse events. Kidney transplantation should not be recorded as an adverse event. Start of dialysis or change of dialysis modality should not be considered an adverse event and should be reported on the dialysis eCRF. If the worsening of kidney function is faster than expected, the worsening of kidney function may be recorded as an adverse event term. Every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

#### 5.3.5.12 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not experienced an adverse event.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

#### 5.3.5.13 Patient-Reported or Observer-Reported Outcome Data

Adverse event reports will not be derived from patient-reported outcome (PRO) or observer-reported outcome (ObsRO) data by the Sponsor, and safety analyses will not be performed using PRO or ObsRO data. Sites are not expected to review the PRO or ObsRO data for adverse events.

## 5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (as defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Medical device complaints (see Section 5.4.5 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board or Ethics Committee (IRB/EC).

### 5.4.1 Emergency Medical Contacts

**Medical Monitor Contact Information for All Sites**

Medical Monitor/Roche Medical Responsible: [redacted], Ph.D. (Primary)

Telephone No.: [redacted]

Medical Monitor/Roche Medical Responsible: [redacted], M.D. (Secondary)

Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day,

7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

### 5.4.2 Reporting Requirements for Serious Adverse Events and Adverse events of special interest

#### 5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

#### 5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur >28 days after the final dose of study treatment are provided in Section 5.6.

### 5.4.3 Reporting Requirements for Pregnancies

#### 5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 90 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the

pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

#### 5.4.3.2 Abortions

*A spontaneous* abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

*If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.*

*All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.*

#### 5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

### 5.4.4 Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For Mircera, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with Mircera, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

### 5.4.5 Reporting Requirements for Medical Device Complaints

In this study, the single-use, prefilled syringe is considered a medical device. The investigator must report all medical device complaints to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study patient, the event

must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

## 5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

### 5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

### 5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

## 5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the final dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

## 5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Mircera Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Certain adverse events are anticipated to occur in the study population at some frequency independent of study drug exposure and, if unrelated to study drug, will be excluded from expedited reporting. These anticipated events include, but are not limited to, the following:

- Peritonitis due to PD
- Thrombosis of vascular access for HD patients

# 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

## 6.1 DETERMINATION OF SAMPLE SIZE

This is an exploratory study without a powered statistical group comparison. Therefore, no formal sample size estimation will be performed; however, the calculations below indicate the approximate precision that could be achieved.

Assuming a 30% withdrawal rate (based on the withdrawal rate for the NH19707 study), of the 40 patients evaluable for ITT and safety analysis, more than 26 patients will have data for the evaluation period. Twenty-six patients will be sufficient to provide approximately 90% power that the 90% CI for the Hb change from baseline to the evaluation period is between $-1$ and 1 g/dL, provided the standard deviation is smaller than 1.5 and the optimum dose conversion is able to maintain the Hb at the baseline level.

Approximately 10–15 of the patients will be $< 12$ years old, with the objective to include as many patients $< 5$ years old (minimum 3 patients) as possible. Approximately 10–15 patients, irrespective of their age, will not be on dialysis. Available HD patients receiving their ESA subcutaneously are eligible for enrollment. No more than 10 patients on HD should be enrolled.

To achieve the recruitment of the intended number of patients and in case of excessive dropout rate, additional patients may be enrolled to replace patients not treated for a minimum duration of 18 weeks.

## 6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the core study and the safety extension period will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

## 6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, height, weight, laboratory parameters, and previous ESA therapy) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall, by age group, by dialysis type (on PD, HD or not yet on dialysis), and previous ESA therapy (EPO alfa and beta combined vs. darbepoetin alfa).

## 6.4 EFFICACY ANALYSES

All efficacy variables (original values and change from baseline) over time will be presented in summary tables and graphically. The estimates will be summarized descriptively using means, standard deviations, and percentiles.

The analysis population for the primary and secondary efficacy analyses will be the ITT population consisting of all enrolled patients.

An additional analysis will be performed based on the per-protocol population, which will be precisely defined in the statistical analysis plan, before database closure, as the subset of the ITT population without major protocol deviations.

### 6.4.1 Primary Efficacy Endpoint

The primary endpoint will be the change in Hb concentration (g/dL) between the baseline and the evaluation period for each patient.

This is calculated on a per-patient basis, using an area under the curve approach to calculate an individual's average for both the baseline and evaluation periods and taking the difference.

The baseline period is defined as all assessments between the day of first study dose and the previous 35 days. If during the baseline period Hb measurements $H_0,\ldots,H_n$ are taken at timepoints $t_0,\ldots,t_n$, a time adjusted average baseline Hb value will be calculated by

$$y = \frac{1}{2(t_n - t_0)} \sum_i (H_i + H_{i-1})(t_i - t_{i-1})$$

The value on the day of the first dose is included in the baseline calculation, as this assessment will be performed before the first dose is given.

The average Hb value for each individual during the evaluation period will be calculated using the same method as for the baseline period. The evaluation period is defined as all assessments between Visit 8 (Week 17) and Visit 10 (Week 21) inclusive. Subtracting the baseline period value from the evaluation period value gives the change in Hb concentration (g/dL) between the baseline and evaluation period.

For patients with no recorded Hb during the evaluation period, the primary endpoint will be missing. Values missing in between non-missing assessments will not be replaced, as these will be interpolated by the trapezoidal rule. To correct for any increase in Hb caused by RBC transfusions, the Hb values measured within 3 weeks after an RBC transfusion will be deleted.

The individual change from baseline will be reported using summary statistics (including mean, standard deviation, and 90% CI of mean change). No formal statistical testing will be performed. Additional analysis will be performed by age category ($<5$, 5–11, $\geq 12$ years), dialysis type (not yet on dialysis, PD, HD) and previous ESA (epoetin alfa, epoetin beta, and darbepoetin alfa), if numbers allow.

### 6.4.2 Secondary Efficacy Endpoints

The number of patients with an average Hb concentration during the evaluation period within $\pm 1$ g/dL of their baseline Hb or above, within, or below the range of 10–12 g/dL will be summarized.

The change in Mircera dose over time, including the change between the starting dose and the evaluation period, will be analyzed descriptively.

### 6.4.3 Exploratory Analyses

The patient if 4 years or older, the parent/guardian, and the nurse/site staff member who gives the injection will assess injection pain using a VAS scale 5 minutes following ESA administration, as appropriate. The assessments will take place during the screening period for all patients who received an ESA injection during either or both of the visits, and at Week 1 (Visit 3) and Week 9 (Visit 6). Injection pain data will be plotted by visit for each patient and analyzed in an exploratory manner.

## 6.5 SAFETY ANALYSES

Safety data for the whole study including the safety extension period will be presented. The safety analysis population will consist of all patients who received at least one dose of study drug regardless of whether they withdrew prematurely or not.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to a four-point scale (see Section 5.3.3).

Tables with group summary statistics will be provided for all safety parameters (vital signs, adverse events, and safety laboratory parameters). Vital signs and safety laboratory parameters will be assessed for clinically significant abnormalities as well as shifts from baseline. For safety analyses, baseline is defined as the last value before first study medication.

Most safety endpoints will include data from the whole study period, including the optional safety extension period. Selected outputs may be prepared for the core and extension periods separately.

## 6.6 PHARMACOKINETIC ANALYSES

Mircera serum concentration-time data will be described using non-linear mixed effect modeling. The previously developed model was a one-compartment model with first order absorption and elimination processes. It will be updated with Study NH19708 data. The influence of covariates (e.g., age, body weight) on PK parameters will be studied.

PK analysis will be performed in two steps:

- The existing PK model will be challenged against Study NH19708 data to check its predictive performance and to highlight any deviation from the current knowledge of Mircera pharmacokinetics. The results of the interim PK analysis will guide the change in bioavailability in pediatric versus adult patients.
- The PK model will be updated by pooling Study NH19708 data with historical adult and pediatric PK data; estimation of the bioavailability of the SC formulation in pediatric patients will be performed.

## 6.7 PHARMACODYNAMIC ANALYSIS

Hb concentration-time data will be described, using non-linear mixed effect modeling. The previously developed PK/PD model was a life-span type of longitudinal model (Chanu et al. 2010). It will be updated with Study NH19708 data. The influence of covariates (e.g., previous ESA dose) on pharmacodynamic parameters will be studied.

Pharmacodynamic analysis will be performed in two steps:

- The existing pharmacodynamic model will be challenged against Study NH19708 data to check its predictive performance and to highlight any deviation from the current knowledge of Mircera PD properties.
- The PK/PD model will be updated by pooling Study NH19708 data with historical adult and pediatric pharmacodynamic data. Sensitivity analysis will be performed by re-estimating the PK/PD model parameters on pediatric data only.

## 6.8 IMMUNOGENICITY ANALYSES

Anti-EPO and anti-Mircera antibodies will be measured at baseline, at Week 9 (Visit 6), and at end of study. An additional sample will be collected at Week 45 (Visit 16) for the patients participating in the safety extension period. Any non-negative findings will be documented.

## 6.9 PLANNED INTERIM ANALYSIS

Once 12 patients have completed 20 weeks of treatment, an interim analysis to assess efficacy, safety, and pharmacokinetics will be performed. The analysis will be reviewed by a Roche Internal Monitoring Committee (IMC) with the primary objective of assessing the safety and efficacy of the CFs for starting treatment with SC Mircera. This will be assessed using Hb (the pharmacodynamic marker), changes in dose, and assessment of the PK data to compare to the available pediatric PK data under IV dosing. The variability of Hb will also be assessed at this time, with regard to protocol assumptions, and the sample size will be revised if necessary.

An individual's Hb response will be based on the mean Hb during the evaluation period (Weeks 17−21) and is defined as a mean Hb change from baseline within ±1g/dL. The 90% CI for the average Hb change from baseline will be calculated.

Interim PK and PK/PD analyses will be conducted, as follows:

- External validation of the existing PK and PK/PD models against preliminary Study NH19708 data to highlight any deviation from the current knowledge of Mircera PK and pharmacodynamic properties; the bioavailability in pediatric patients will be carefully regarded.
- A Bayesian feedback approach will also be used on Mircera serum concentration-time data to get a first assessment of the individual PK parameters in pediatric patients receiving Mircera subcutaneously, especially bioavailability.

The full details of the interim analysis and any decision criteria will be specified in separate IMC documents.

# 7. DATA COLLECTION AND MANAGEMENT

## 7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO and ClinRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

## 7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of 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.

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.

## 7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/ EC review. The study site must also allow inspection by applicable health authorities.

## 7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

## 7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms and child assent forms (if applicable), laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

*Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.*

# 8. ETHICAL CONSIDERATIONS

## 8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the *applicable* laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) *and applicable local, regional, and national laws.*

## 8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal

health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

## 8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

## 8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

### 8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

## 9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

### 9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

### 9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

### 9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

## 9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 35 sites globally will participate to enroll approximately 40 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

## 9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses, *in clinical trial registries,* and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. *Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met.* For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. 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, the Sponsor 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.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

## 9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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# Appendix 1
# Schedule of Activities Core Period (Week –3 to Week 21)

| Study Period | Screening Period ~ 3 weeks [a] | | Dose Titration Period 16 weeks | | | | | Evaluation Period 4 weeks | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Visit Number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Name of the Visit Day (start of Week ...) [b] | Week –3 [a] | Week –1 [a] | Week 1 [c] | Week 3 | Week 5 | Week 9 | Week 13 | Week 17 | Week 19 | Week 21 Follow-Up Visit [d] |
| Informed consent | x | | | | | | | | | |
| Medical history [e] | x | | | | | | | | | |
| Physical examination [f] | x | | | | | | | | | x |
| Pregnancy test [g] | x | | | | | | | | | |
| Vital signs, weight [h] | x | x | x | | x | x | x | x | | x |
| Height | | | x | | | | | | | x |
| Hematology [i] | x | x | x | x | x | x | x | x | x | x |
| Serum creatinine [j] | x | | x | | | | | | | x |
| Iron parameters [k] | x | x | | | | x | | x | | x |
| Kt/V for patients on PD | x | | | | | | | | | x |
| Kt/V or URR for patients on HD | x | | x | | x | x | x | x | | x |
| Safety laboratory [l] | x | | | | | x | | | | x |
| Anti-EPO and anti-Mircera antibody [m] | | | x | | | x | | | | x |
| Injection pain questionnaire [n] | (x) [o] | (x) [o] | x | | | x | | | | |
| Concomitant therapy [p] | Recorded throughout screening, dose titration and evaluation periods | | | | | | | | | |

# Appendix 1
# Schedule of Activities Core Period (Week –3 to Week 21) (cont.)

| Study Period | Screening Period ~ 3 weeks [a] | | Dose Titration Period 16 weeks | | | | | Evaluation Period 4 weeks | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Visit Number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Name of the Visit Day (start of Week ...) [b] | Week –3 [a] | Week –1 [a] | Week 1 [c] | Week 3 | Week 5 | Week 9 | Week 13 | Week 17 | Week 19 | Week 21 Follow-Up Visit [d] |
| Adverse events [q] | | | Recorded throughout the dose titration and evaluation periods | | | | | | | |
| ESA administration | x [r] | | | | | | | | | |
| Mircera administration | | | x [c] | | x [c] | x [c] | x [c] | x [c] | | |
| Iron supplementation | As needed to maintain iron stores | | | | | | | | | |
| PK sampling [s] | | | x | x | | x | | x | x | |

CKD = chronic kidney disease; eCRF = electronic Case Report Form; eGFR = estimated glomerular filtration rate; EPO = erythropoietin; ESA = erythropoietin-stimulating agent; Hb = hemoglobin; HD = hemodialysis; PD = peritoneal dialysis; PK = pharmacokinetic; TSAT = transferrin saturation; URR = urea reduction ratio.

[a] *Visits 1 and 2 should be 2 weeks apart (±3 days). The ESA dosing interval needs to be taken into account when planning Visits 1, 2, and 3, i.e., the number of days between Visits 2 and 3 should be based on the dosing interval of the ESA drug, which may result in a screening period of up to a maximum of 4 weeks.*

[b] Visit window ± 3 days. *All study visits should be scheduled based on the date of the first Mircera dose at Visit 3 (Week 1).* For patients under HD or patients converting to HD, the study visits should occur on the day of the mid-week dialysis.

[c] Mircera is administered every 4 weeks during dose titration and evaluation periods.

[d] Follow-up visit assessments should be performed before resuming *epoetin alfa, epoetin beta, or darbepoetin alfa dose*.

[e] Medical history includes demographics, other diseases, etiology of CKD, details of dialysis, previous treatments including ESA treatments, and iron supplementation.

[f] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified should be recorded on the corresponding page of the eCRF.

[g] Serum pregnancy test should be performed in post-pubertal female patients of childbearing potential. If a pregnancy is suspected, the serum pregnancy test must be repeated during the course of the study.

# Appendix 1
# Schedule of Activities Core Period (Week –3 to Week 21) (cont.)

[h] *Systolic* and diastolic blood pressure and pulse rate will be recorded while the patient is if possible in a seated position, and they will be measured before blood sampling. The blood pressure should be measured at least twice and the average of these measurements should be recorded. An appropriate-sized cuff should be used. Blood pressure should be determined before and after the dialysis session for patients with HD. Body weight will also be recorded *(after dialysis for patients on HD)*.

[i] Includes Hb, RBC, and absolute reticulocyte count. Samples should always be obtained on the same day of the week*, if possible*, prior to injection of Mircera and, for patients on HD, before dialysis.

[j] Serum creatinine should be measured only for patients not on dialysis. eGFR will be calculated using the Bedside Schwartz formula (see Appendix 3).

[k] Includes serum ferritin, serum iron and TSAT. TSAT will be calculated as described in Appendix 3 with either serum transferrin or total iron-binding capacity. The percentage of hypochromic red blood cells may be determined instead of TSAT.

[l] Includes leukocytes plus differential, AST, ALT, serum albumin, ALP, C-reactive protein, potassium, phosphorus, calcium, and platelets.

[m] Anti-EPO and anti-Mircera antibody samples should be collected prior to study drug administration.

[n] Injection pain will be assessed by the patient, parent/guardian, and nurse/site staff member as appropriate. Children under the age of 4 will not be asked to rate their own pain. As much as possible, the same nurse/site staff member should rate pain at every visit. The assessments will take place approximately 5 minutes after study drug injection. Assessment of ESA injection pain during the screening period will be assessed in all patients who receive an ESA injection during either or both of the screening visits.

[o] Parentheses indicate that the assessment is optional. The assessment at the screening visit is only necessary if ESA drug has been injected on that day. Therefore, not all patients will assess injection pain.

[p] All concomitant therapy administered within 3 months before screening or during the screening or treatment periods should be reported.

[q] Prior to initiation of study drug, report only serious adverse events caused by a protocol-mandated intervention.

[r] *Treatment with ESAs should continue during the screening period at the previous dosing interval. Note that depending on the dosing interval, ESA treatment may or may not be administered the same day as the screening period visit.*

[s] At Visit 3 (Week 1), Visit 6 (Week 9), and Visit 8 (Week 17), samples should be drawn before the Mircera dose. At the patient's convenience, a sixth PK sample between 24 hours and 5 days after any one Mircera dose administration should also be collected. A minimum of one PK sample after treatment initiation is requested in patients younger than 2 years old; the sample on Week 1 can be omitted in these patients. The exact time of PK blood sampling must be recorded on the lab requisition form and the exact time of the preceding Mircera administration must be recorded on the appropriate page in the eCRF.

# Appendix 2
# Schedule of Activities for Optional Safety Extension Period (Week 21 to Week 45)

| Study Period | Safety Extension Period 24 Weeks | | | | | | |
|---|---|---|---|---|---|---|---|
| Visit Number | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
| Name of the Visit Day (start of Week ...) [a] | Week 21 [b] | Week 25 | Week 29 | Week 33 | Week 37 | Week 41 | Week 45 Final Safety Extension Visit [c] |
| Informed consent | x | | | | | | |
| Physical examination [d] | x | | | | | | x |
| Vital signs, weight [e] | x | x | x | x | x | x | x |
| Height | x | | | | | | x |
| Hematology [f] | x | x | x | x | x | x | x |
| Serum creatinine [g] | x | | | | | | x |
| Iron parameters [h] | x | | x | | x | | x |
| Kt/V for patients on PD | x | | | | | | x |
| Kt/V or URR for patients on HD | x | x | x | x | x | x | x |
| Safety laboratory [i] | x | | | x | | | x |
| Anti-EPO and anti-Mircera antibody [j] | x | | | | | | x |
| Concomitant therapy | Recorded throughout the safety extension period | | | | | | |
| Adverse events | Recorded throughout the safety extension period | | | | | | |
| Mircera administration | x | x | x | x | x | x | |
| Iron supplementation | As needed to maintain adequate iron stores | | | | | | |

# Appendix 2
# Schedule of Activities for Optional Safety Extension Period (Week 21 to Week 45) (Cont.)

eCRF = electronic Case Report Form; EPO = erythropoietin; HD = hemodialysis; PD = peritoneal dialysis; URR = urea reduction ratio.

[a] Visit window ± 3 days.

[b] Visit 10, Week 21 corresponds to the follow-up visit of the core study period (see Appendix 1).

[c] Final assessments should be performed before resuming *epoetin alfa, epoetin beta, or darbepoetin alfa dose*.

[d] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified should be recorded on the corresponding page of the eCRF.

[e] Every 4 weeks, systolic and diastolic blood pressure and pulse rate will be recorded while the patient is if possible in a seated position, and they will be measured before blood sampling. The blood pressure should be measured at least twice and the average of these measurements should be recorded. An appropriate-sized cuff should be used. Blood pressure should be determined before and after the dialysis session for patients on HD. Body weight will also be recorded *(after dialysis for patients on HD)*.

[f] Includes Hb, RBC, and absolute reticulocyte count. *Samples should always be taken* on the same day of the week*, if possible*, prior to the injection of Mircera and, for patients on HD, before dialysis.

[g] Serum creatinine should be measured only for patients not on dialysis. eGFR will be calculated using the Bedside Schwartz formula (see Appendix 3).

[h] Includes serum ferritin, serum iron and TSAT. TSAT will be calculated as described in Appendix 3 with either serum transferrin or total iron-binding capacity. The percentage of hypochromic red blood cells may be determined instead of TSAT.

[i] Includes leukocytes plus differential, AST, ALT, serum albumin, ALP, C-reactive protein, potassium, phosphorus, calcium, and platelets.

[j] Anti-EPO and anti-Mircera antibody samples should be collected prior to study drug administration.

# Appendix 3
# Formula Guidelines for Calculation of Dialysis Adequacy, Transferrin Saturation, and eGFR

## HEMODIALYSIS AND PERITONEAL DIALYSIS ADEQUACY

For assessing adequacy of hemodialysis and peritoneal dialysis, Kt/V or urea reduction ratio should be determined according to routine procedures established at each center.

## TRANSFERRIN SATURATION

Transferrin saturation (TSAT) should be calculated using one of the following formulas[1]:

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

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

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

Iron: $\mu\text{mol/L} \xrightarrow{\text{x } 5.59} \mu\text{g/dL}$

Transferrin: $\mu\text{mol/L} \xrightarrow{\text{x } 7.96} \text{mg/dL}$

## ESTIMATED GLOMERULAR FILTRATION RATE CALCULATION

Estimated glomerular filtration rate determined by the Bedside Schwartz formula [2]

Scr in Conventional Units:

$$\text{eGFR} = \frac{0.413 \times h}{\text{Scr}}$$

eGFR = estimated glomerular filtration rate (mL/min/1.73 m2); *h* = height (cm); Scr = serum creatinine (mg/dL).

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[1] Wick M, Pinggera W, Lehmann P. Iron metabolism, anemias diagnosis and therapy. 4th ed. Springer-Verlag Wien: New York, 2000:160–1.

[2] Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20:629–37.

# Appendix 3
# Formulae Guidelines for Calculation of Dialysis Adequacy, Transferrin Saturation, and eGFR (cont.)

Scr in SI Units:

$$eGFR = \frac{36.2 \times h}{Scr}$$

eGFR = estimated glomerular filtration rate (mL/min/1.73 $m^2$);
h = height (cm); Scr = serum creatinine (μmol/L).

Measured creatinine should be in steady state. This formula may be most accurate in the range of 15 to 75 mL/min per 1.73 $m^2$.

This formula applies to enzymatic serum creatinine measurements calibrated to reference measurements by isotope dilution mass spectroscopy (IDMS), but not to alkaline picrate ("Jaffe") methods, even those traceable to IDMS.

# Appendix 4
# Educational Program for Anti-Erythropoietin Antibody–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**

# Appendix 4
# Educational Program for Anti-Erythropoietin Antibody–Mediated Pure Red Cell Aplasia Associated with Erythropoietin-Stimulating Agents (cont.)

10. Supporting information
    - 10.1 Need and clinical importance of adverse drug reaction reporting
    - 10.2 Important facts about EAB-mediated PRCA and ESAs
    - 10.3 Testing approaches
    - 10.4 Literature

## 1. MIRCERA AND ANTI-ERYTHROPOIETIN ANTIBODY–MEDIATED PURE RED CELL APLASIA (AEAB-MEDIATED PRCA)

Mircera is an erythropoietin-stimulating agent (ESA).

A very rare side effect of ESAs is anti-erythropoietin antibody–mediated pure red cell aplasia (AEAB-mediated PRCA).

This side effect is an important identified risk in the E.U. risk management plan for Mircera.

## 2. WHAT ARE THE OBJECTIVES OF THIS EDUCATIONAL PROGRAM?

The objectives of this booklet and the educational program are as follows:

- 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 with use of 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.

Full details on the risks of potential PRCA can be found in the following section of Mircera Physician's Prescribing Information (Summary of Product Characteristics): "Special warnings and special precautions for use" relating to important facts about ESAs, Mircera, and AEAB-mediated PRCA.

# Appendix 4
# Educational Program for Anti-Erythropoietin Antibody–Mediated Pure Red Cell Aplasia Associated with Erythropoietin-Stimulating Agents (cont.)

## 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:

- Hemolysis
- Malnutrition
- Iron deficiency
- Aluminum toxicity
- Chronic blood loss
- Inadequate dialysis
- Inflammatory disorders
- Multiple myeloma, myelofibrosis
- Other malignancies
- Hyperparathyroidism or osteitis fibrosa
- Vitamin deficiencies such as folate or vitamin B12
- Hemoglobinopathies such as alpha- and beta-thalassemias or sickle cell anemia
- Adverse effects of concomitant drugs such as cytotoxic and immunosuppressive agents and angiotensin-converting enzyme inhibitors

If none of these conditions are diagnosed, anemia should be fully investigated (see Section 5 of the protocol).

### 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 approximately 5% of cases)
- Idiopathic (in approximately 50% of cases)

# Appendix 4
# Educational Program for Anti-Erythropoietin Antibody–Mediated Pure Red Cell Aplasia Associated with Erythropoietin-Stimulating Agents (cont.)

## 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 in which erythropoiesis is inhibited by erythropoietin-specific neutralizing antibodies.

### 4.1. FINDINGS IN BLOOD AND BONE MARROW

The current diagnostic criteria for PRCA have been defined as follows:

- Decrease in hemoglobin of approximately 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, $<$ 1% erythroblasts (occasionally up to 5% proerythroblasts or basophilic erythroblasts), normal myeloid cells, and megakaryocytes

### 4.2. TIMING OF ONSET

The shortest and longest intervals of onset of PRCA after the start of treatment were reported within 2 months and 90 months, respectively.

### 4.3 DISCONTINUATION OF ESAS

There is consensus that ESAs should be discontinued in any patient with confirmed AEAB-mediated PRCA. The physician should do the following:

- Investigate for the presence of anti-erythropoietin antibodies
- Perform a bone marrow examination

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

## 5. DIAGNOSIS OF PRCA

### 5.1. HEMOGLOBIN DECREASE

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

- Has a sudden, rapid decrease in hemoglobin (Hb) concentration of approximately 0.5–1 g/dL/week despite ongoing ESA treatment; or
- Requires transfusions of 1–2 units of RBCs per week to maintain the Hb level

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

### 5.2. ANTIBODY TESTING

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

Sampling instructions will be sent to the physician (see Section 9 How to Obtain Further Information).

### 5.3. BONE MARROW EXAMINATION

A bone marrow examination should be performed in the case of a rapid and sustained decrease in the reticulocyte count.

PRCA is characterized by the following:

- Normal cellularity
- $<1\%$ erythroblasts
- Occasionally erythroblasts up to 5% with evidence of a red cell precursor maturation block
- Normal myeloid and megakaryocytic lineages

Bone marrow findings help to distinguish PRCA from aplastic anemia 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

The physician should check reticulocyte count regularly during a follow-up. This is the best laboratory marker of RBC production. The reticulocyte count indicates bone marrow activity with regard to daily RBC production. A decrease in hemoglobin level will be preceded by a change in the rate of RBC production. An unchanged reticulocyte count suggests that treatment is effective.

Any decrease 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.

# Appendix 4
# Educational Program for Anti-Erythropoietin Antibody–Mediated Pure Red Cell Aplasia Associated with Erythropoietin-Stimulating Agents (cont.)

## 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.

An adverse drug reaction report should be considered when 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 a follow-up on updated investigational results and updated results of continued monitoring of these patients.
- Reports of unexplained loss of effect, especially:
- After exclusion of alternative causes of PRCA (see Section 3 Loss of Effect of ESA Treatment)
- If a patient previously had a stable hemoglobin 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.

Suspected AEAB-mediated PRCA or the unexplained loss of therapeutic effect should be investigated through anti-erythropoietin antibody testing and hematological consultation.

## 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, “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 available information.

If appropriate, these collected data will support communication of a substantial change—for example, via a label update.

# Appendix 4
# Educational Program for Anti-Erythropoietin Antibody–Mediated Pure Red Cell Aplasia Associated with Erythropoietin-Stimulating Agents (cont.)

The questionnaire will collect data such as the following:

- Diagnostic results to confirm the diagnosis or clinical suspicion
- Relevant comorbidities or concomitant drugs
- Alternative conditions to explain a sudden decrease in hemoglobin
- Exposure to epoetin brands with regard to the onset of first signs or symptoms suggestive of AEAB-mediated PRCA

This guided questionnaire is used only when adverse drug reaction reports are received for the use of Mircera outside of a clinical study. In clinical studies, the study protocol will provide guidance on 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

**For further information on antibody sampling and shipment:**

Please address the local Roche affiliate

**For further information on Mircera including literature:**

Please address the local Roche affiliate

## 10. SUPPORTING INFORMATION

### 10.1. 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 is needed for a signal. As detection of rare adverse effects is increased and accelerated, the more physicians contribute to spontaneous reporting of adverse reactions (Meyboom et al. 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 postmarketing 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 et al. 1999).

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

## 10.2. 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 three-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, referring to treatment in several million patients (Bergrem et al. 1993; Peces et al. 1996; Prabhakar and Muhlfelder 1997). Since 1998, there has 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 United States (Eprex), with a peak in reports in 2001 and 2002 (Rossert et al. 2004).

## 10.3. TESTING APPROACHES

Two testing approaches were used during the development program of Mircera, and will be applied for investigations for future postmarketing experience. The first test is a bridging ELISA test, the method for quantification of anti-erythropoietin (anti-EPO) antibodies and of anti-methoxy polyethylene glycol-epoetin beta (anti-Mircera) antibodies. The second type of testing is a neutralizing antibody assay, a functional assay based on the use of a standard in vitro assay to detect EPO or Mircera activity. This assay measures the EPO or Mircera–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-Mircera antibodies reduces or suppresses cell proliferation. This assay can be optionally applied to samples with discrepancies between antibody titer

determined by antibody enzyme-linked immunosorbent assay (ELISA) and clinical diagnosis. Since the antibody ELISAs has a several-fold higher sensitivity compared with the neutralizing antibody assay, the neutralizing antibody assay is not expected to provide additional clinically relevant information for samples with low antibody titers or confirmed PRCA.

## 10.4. LITERATURE

### Practical and basic guidance on patient evaluation

The list below shows the relevant publications that are grouped according to the practical and basic guidance on patient evaluation. The detailed aspects of the topic are summarized for each publication:

- **Which patients should be evaluated and when the work-up should begin, investigations for appropriate work-up of anemia in CKD, and diagnosis of renal anemia:** Revised European best practice guidelines on anaemia management (Section I: anaemia evaluation). Nephrol Dial Transplant 2004;19(Suppl 2):ii2–5.
- **Failure to reach or maintain target hemoglobin, criteria to suspect anti-erythropoietin antibody-mediated pure red cell aplasia (AEAB-mediated PRCA), and criteria to confirm AEAB-mediated PRCA:** Revised European best practice guidelines on anaemia management (Section IV: failure to respond to treatment). Nephrol Dial Transplant 2004;19(Suppl 2):ii32–6.
- **Recommendations for diagnostic approach including discussions on potential findings:** Casadevall N, Cournoyer D, Marsh J, et al. Recommendations on haematological criteria for the diagnosis of epoetin-induced pure red cell aplasia. Eur J Haematol 2004;73:389–96.

### Further readings

- **Description of worldwide collection of reports of AEAB-mediated PRCA emphasizing the need of spontaneous reporting by physicians in order to document a change in the occurrence rate:** Bennett CL, Luminari S, Nissenson AR, et al. Pure red-cell aplasia and epoetin therapy. N Engl J Med 2004; 351:1403–8.
- **Information on treatment and long-term follow-up of 191 patients with AEAB-mediated PRCA:** Bennett CL, Cournoyer D, Carson KR, et al. Long-term outcome of individuals with pure red cell aplasia and anti-erythropoietin antibodies in patients treated with recombinant epoetin: a follow-up report from the Research on Adverse Drug Events and Reports (RADAR) Project. Blood 2005;106:3343–7.

# Appendix 4
# Educational Program for Anti-Erythropoietin Antibody–Mediated Pure Red Cell Aplasia Associated with Erythropoietin-Stimulating Agents (cont.)

- **Clinical characterization of 13 patients with AEAB-mediated PRCA:** Casadevall N, Nataf J, Viron B, et al. Pure red-cell aplasia and antierythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med 2002;346: 469–75.
- **Diagnosis and causes of AEAB-mediated PRCA:** Eckardt K-U, Casadevall N. Pure red-cell aplasia due to anti-erythropoietin antibodies. Nephrol Dial Transplant 2003;18:865–9.
- **Diagnosis, assays, epidemiology, and risk factors:** Rossert J, Casadevall N, Eckardt K-U. Anti-erythropoietin antibodies and pure red cell aplasia. J Am Soc Nephrol 2004;15:398–406.
- **Consequences of antibody formation:** Schellekens H. Factors influencing the immunogenicity of therapeutic proteins. Nephrol Dial Transplant 2005;20(Suppl 6):vi3–9.
- **Effects of antibodies on endogenous protein production, clinical effects of antibodies, and factors influencing immunogenicity:** Schellekens H. Immunogenicity of therapeutic proteins: clinical implications and future prospects. Clin Ther 2002;24:1720–40.

# Appendix 4
# Educational Program for Anti-Erythropoietin Antibody–Mediated Pure Red Cell Aplasia Associated with Erythropoietin-Stimulating Agents (cont.)

## REFERENCES


Bergrem H, Danielson BG, Eckardt K-U, et al. A case of antierythropoietin antibodies following recombinant human erythropoietin treatment. In: Bauer C, Koch KM, Scigalla P, et al. editors. Erythropoietin: molecular physiology and clinical applications. New York: Marcel Dekker, 1993:265–73.

Meyboom RH, Egberts AC, Gribnau, FW, et al. Pharmacovigilance in perspective. Drug Saf 1999;21:429–47.

Peces R, de la Torre M, Alcázar R, et al. Antibodies against recombinant human erythropoietin in a patient with erythropoietin-resistant anemia. N Engl J Med 1996;335:523–4.

Prabhakar SS, Muhlfelder T. Antibodies to recombinant human erythropoietin causing pure red cell aplasia. Clin Nephrol 1997;47:331–5.

Rossert J, Casadevall N, Eckardt K-U. Anti-erythropoietin antibodies and pure red cell aplasia. J Am Soc Nephrol 2004;15:398–406.

Schellekens H. Immunogenicity of therapeutic proteins: clinical implications and future prospects. Clin Ther 2002;24:1720–40.

Stephens M. Introduction. In: Talbot J, Waller P, editors. Stephen's detection of new adverse drug reactions. Chichester: Wiley, 2004:1–2.

Waller PC, Evans SJ. A model for the future conduct of pharmacovigilance. Pharmacoepidemiol Drug Saf 2003;12:17–29.

# Appendix 5
# Blood Pressure Measurements in Children

The preferred method of blood pressure measurement is auscultation. Oscillometric devices are convenient and minimize observer error, but they do not provide measures that are identical to auscultation. The blood pressure in children should be measured with a standard clinical sphygmomanometer, using a stethoscope placed over the brachial artery pulse, proximal and medial to the cubital fossa, and below the bottom edge of the cuff (i.e., about 2 cm above the cubital fossa). The use of the bell of the stethoscope may allow softer Korotkoff sounds to be heard better. The use of an appropriately sized cuff may preclude the placement of the stethoscope in this precise location, but there is little evidence that significant inaccuracy is introduced, either if the head of the stethoscope is slightly out of position or if there is contact between the cuff and the stethoscope.

Preparation of the child for standard measurement can affect the blood pressure level just as much as technique. Ideally, the child whose blood pressure is to be measured should have avoided stimulant drugs or foods, have been sitting quietly for 5 minutes, and seated with his or her back supported, feet on the floor and right arm supported, cubital fossa at heart level. The right arm is preferred in repeated measures of blood pressure for consistency and comparison to standard tables and because of the possibility of coarctation of the aorta, which might lead to false (low) readings in the left arm.

Correct measurement of blood pressure in children requires use of a cuff that is appropriate to the size of the child's upper right arm. The equipment necessary to measure blood pressure in children, ages 3 through adolescence, includes child cuffs of different sizes and must also include a standard adult cuff, a large adult cuff, and a thigh cuff. The latter two cuffs may be needed for use in adolescents.

Two advantages of automatic devices are their ease of use and the minimization of observer bias or digit preference. Use of the automated devices is preferred for blood pressure measurement in newborns and young infants, in whom auscultation is difficult.

The blood pressure should be measured at least twice and the average of these measurements should be recorded.

Hypertension is defined as average SBP or DBP that is greater than or equal to the 95th percentile for sex, age, and height on at least three separate occasions. Reference tables including 95th percentiles by sex, age and height have been included in Appendix 6.

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Source: Falkner B, Daniels SR, Flynn JT, et al. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004;114(2 III):555-76.

# Appendix 6
# Blood Pressure Levels According to Age and Height

The following blood pressure standard reference tables are for children and adolescents, aged 3 to 17 years, as compiled from the German Health Interview and Examination Survey for Children and Adolescents (Neuhauser et al. 2011).

| Age (Year) | Blood pressure from boys (95th percentile) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **3,5** | Height (cm) | 95 | 96 | 98 | 101 | 104 | 106 | 108 |
| | syst. (mm Hg) | 109 | 109 | 109 | 110 | 110 | 111 | 111 |
| | diast (mm Hg) | 69 | 69 | 69 | 70 | 70 | 71 | 71 |
| **4,5** | Height (cm) | 101 | 103 | 105 | 108 | 111 | 114 | 115 |
| | syst. (mm Hg) | 109 | 109 | 110 | 110 | 111 | 111 | 111 |
| | diast. (mm Hg) | 69 | 69 | 70 | 70 | 71 | 71 | 71 |
| **5,5** | Height (cm) | 107 | 109 | 111 | 115 | 118 | 121 | 123 |
| | syst. (mm Hg) | 109 | 109 | 110 | 111 | 111 | 112 | 112 |
| | diast. (mm Hg) | 70 | 70 | 70 | 71 | 71 | 72 | 72 |
| **6,5** | Height (cm) | 113 | 115 | 118 | 121 | 125 | 128 | 130 |
| | syst. (mm Hg) | 110 | 110 | 111 | 111 | 112 | 113 | 113 |
| | diast. (mm Hg) | 70 | 71 | 71 | 71 | 72 | 72 | 72 |
| **7,5** | Height (cm) | 119 | 121 | 124 | 128 | 131 | 135 | 137 |
| | syst. (mm Hg) | 111 | 111 | 112 | 113 | 113 | 114 | 114 |
| | diast. (mm Hg) | 71 | 71 | 72 | 72 | 72 | 73 | 73 |
| **8,5** | Height (cm) | 124 | 126 | 130 | 134 | 138 | 141 | 143 |
| | syst. (mm Hg) | 112 | 113 | 113 | 114 | 115 | 116 | 116 |
| | diast. (mm Hg) | 72 | 72 | 72 | 73 | 73 | 74 | 74 |
| **9,5** | Height (cm) | 129 | 131 | 135 | 139 | 143 | 147 | 149 |
| | syst. (mm Hg) | 114 | 114 | 115 | 116 | 117 | 118 | 118 |
| | diast. (mm Hg) | 73 | 73 | 73 | 74 | 74 | 74 | 75 |
| **10,5** | Height (cm) | 133 | 136 | 140 | 144 | 149 | 153 | 155 |
| | syst. (mm Hg) | 115 | 116 | 117 | 118 | 119 | 120 | 121 |
| | diast. (mm Hg) | 74 | 74 | 74 | 75 | 75 | 76 | 76 |
| **11,5** | Height (cm) | 137 | 140 | 144 | 149 | 154 | 159 | 162 |
| | syst. (mm Hg) | 117 | 118 | 119 | 120 | 122 | 123 | 124 |
| | diast. (mm Hg) | 75 | 75 | 75 | 76 | 76 | 77 | 77 |
| **12,5** | Height (cm) | 142 | 145 | 150 | 155 | 161 | 166 | 169 |
| | syst. (mm Hg) | 120 | 121 | 122 | 124 | 125 | 126 | 127 |
| | diast. (mm Hg) | 76 | 76 | 77 | 77 | 78 | 78 | 78 |
| **13,5** | Height(cm) | 149 | 152 | 157 | 163 | 169 | 174 | 177 |
| | syst. (mm Hg) | 124 | 124 | 126 | 127 | 129 | 130 | 131 |
| | diast. (mm Hg) | 77 | 78 | 78 | 78 | 79 | 79 | 79 |

## Appendix 6
## Blood Pressure Levels According to Age and Height (cont.)

| Age (Year) | Blood pressure from boys (95th percentile; cont.) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **14,5** | Height (cm) | 157 | 160 | 165 | 170 | 176 | 181 | 184 |
| | syst. (mm Hg) | 128 | 129 | 130 | 132 | 133 | 135 | 136 |
| | diast. (mm Hg) | 79 | 79 | 79 | 80 | 80 | 81 | 81 |
| **15,5** | Height (cm) | 163 | 165 | 170 | 175 | 180 | 185 | 187 |
| | syst. (mm Hg) | 132 | 133 | 134 | 136 | 137 | 138 | 139 |
| | diast. (mm Hg) | 80 | 80 | 81 | 82 | 82 | 82 | 82 |
| **16,5** | Height (cm) | 166 | 169 | 173 | 178 | 182 | 186 | 189 |
| | syst. (mm Hg) | 135 | 136 | 137 | 139 | 140 | 142 | 143 |
| | diast. (mm Hg) | 82 | 82 | 82 | 83 | 83 | 84 | 84 |
| **17,5** | Height (cm) | 167 | 170 | 174 | 179 | 183 | 187 | 189 |
| | syst. (mm Hg) | 138 | 139 | 141 | 142 | 144 | 145 | 146 |
| | diast. (mm Hg) | 83 | 84 | 84 | 84 | 85 | 85 | 85 |

| Age (Year) | Blood pressure from girls (95th percentile) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **3,5** | Height (cm) | 94 | 95 | 97 | 100 | 102 | 105 | 106 |
| | syst. (mm Hg) | 108 | 108 | 109 | 109 | 110 | 111 | 111 |
| | diast (mm Hg) | 70 | 70 | 70 | 71 | 71 | 72 | 72 |
| **4,5** | Height (cm) | 100 | 102 | 104 | 107 | 110 | 113 | 114 |
| | syst. (mm Hg) | 108 | 109 | 109 | 110 | 111 | 111 | 112 |
| | diast. (mm Hg) | 70 | 70 | 71 | 71 | 71 | 72 | 72 |
| **5,5** | Height (cm) | 107 | 108 | 111 | 114 | 117 | 120 | 122 |
| | Syst. (mm Hg) | 109 | 109 | 110 | 111 | 112 | 113 | 113 |
| | diast. (mm Hg) | 71 | 71 | 71 | 71 | 72 | 72 | 72 |
| **6,5** | Height (cm) | 112 | 114 | 117 | 121 | 124 | 127 | 129 |
| | syst. (mm Hg) | 110 | 110 | 111 | 112 | 113 | 114 | 115 |
| | diast. (mm Hg) | 71 | 71 | 72 | 72 | 72 | 73 | 73 |
| **7,5** | Height (cm) | 118 | 120 | 123 | 127 | 130 | 133 | 135 |
| | syst. (mm Hg) | 111 | 112 | 113 | 114 | 115 | 116 | 116 |
| | diast. (mm Hg) | 71 | 72 | 72 | 72 | 73 | 73 | 73 |
| **8,5** | Height (cm) | 123 | 125 | 128 | 132 | 136 | 140 | 142 |
| | syst. (mm Hg) | 113 | 113 | 114 | 115 | 116 | 118 | 118 |
| | diast. (mm Hg) | 72 | 72 | 73 | 73 | 74 | 74 | 74 |
| **9,5** | Height (cm) | 128 | 130 | 134 | 138 | 142 | 146 | 149 |
| | syst. (mm Hg) | 114 | 115 | 116 | 117 | 118 | 120 | 120 |
| | diast. (mm Hg) | 73 | 73 | 73 | 74 | 74 | 75 | 75 |

## Appendix 6
## Blood Pressure Levels According to Age and Height (cont.)

| Age (Year) | Blood pressure from girls (95th percentile; cont.) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **10,5** | Height (cm) | 133 | 136 | 140 | 144 | 149 | 153 | 155 |
| | syst. (mm Hg) | 116 | 117 | 118 | 119 | 121 | 122 | 123 |
| | diast. (mm Hg) | 74 | 74 | 74 | 75 | 75 | 75 | 76 |
| **11,5** | Height (cm) | 140 | 142 | 146 | 51 | 156 | 160 | 162 |
| | syst. (mm Hg) | 119 | 119 | 121 | 122 | 123 | 124 | 125 |
| | diast. (mm Hg) | 75 | 75 | 75 | 76 | 76 | 76 | 76 |
| **12,5** | Height (cm) | 146 | 149 | 153 | 157 | 162 | 166 | 168 |
| | syst. (mm Hg) | 121 | 122 | 123 | 124 | 125 | 126 | 127 |
| | diast. (mm Hg) | 75 | 76 | 76 | 76 | 77 | 77 | 77 |
| **13,5** | Height (cm) | 150 | 153 | 157 | 161 | 166 | 170 | 172 |
| | syst. (mm Hg) | 123 | 124 | 125 | 126 | 127 | 128 | 128 |
| | diast. (mm Hg) | 77 | 77 | 77 | 78 | 78 | 78 | 78 |
| **14,5** | Height (cm) | 153 | 156 | 159 | 164 | 168 | 172 | 174 |
| | syst. (mm Hg) | 125 | 125 | 126 | 127 | 128 | 129 | 129 |
| | diast. (mm Hg) | 78 | 78 | 78 | 79 | 79 | 79 | 80 |
| **15,5** | Height (cm) | 155 | 157 | 161 | 165 | 169 | 173 | 176 |
| | syst. (mm Hg) | 126 | 126 | 127 | 128 | 129 | 129 | 130 |
| | diast. (mm Hg) | 79 | 79 | 79 | 80 | 80 | 81 | 81 |
| **16,5** | Height (cm) | 155 | 157 | 161 | 165 | 170 | 174 | 176 |
| | syst. (mm Hg) | 127 | 127 | 128 | 129 | 129 | 130 | 130 |
| | diast. (mm Hg) | 80 | 80 | 81 | 81 | 82 | 82 | 82 |
| **17,5** | Height (cm) | 155 | 157 | 161 | 166 | 170 | 174 | 176 |
| | syst. (mm Hg) | 128 | 129 | 129 | 129 | 130 | 130 | 131 |
| | diast. (mm Hg) | 82 | 82 | 82 | 83 | 83 | 83 | 83 |

### REFERENCE

Neuhauser HK, Thamm M, Ellert E, et al. Blood pressure percentiles by age and height from nonoverweight children and adolescents in Germany. Pediatrics 2011;127:e978–e988.

# Appendix 7
# WHO Toxicity Grading Scale for Determining the Severity of Adverse Events

| **HEMATOLOGY** | | | | |
|---|---|---|---|---|
| Item | Grade 1 Toxicity | Grade 2 Toxicity | Grade 3 Toxicity | Grade 4 Toxicity |
| Hemoglobin | 9.5–10.5 g/dL | 8.0–9.4 g/dL | 6.5–7.9 g/dL | $<$6.5 g/dL |
| Absolute neutrophil count | 1000–1500/$mm^3$ | 750–999/$mm^3$ | 500–749/$mm^3$ | $<$500/$mm^3$ |
| Platelets | 75000–99999/$mm^3$ | 50000–74999/$mm^3$ | 20000–49999/$mm^3$ | $<$20000/$mm^3$ |
| Prothrombin time (PT) | 1.01–1.25 × ULN | 1.26–1.5 × ULN | 1.51–3.0 × ULN | $>$3 × ULN |
| Activated partial thromboplastin (APPT) | 1.01–1.66 × ULN | 1.67–2.33 × ULN | 2.34–3 × ULN | $>$3 × ULN |
| Fibrinogen | 0.75–0.99 × LLN | 0.50–0.74 × LLN | 0.25 - 0.49 × LLN | $<$0.25 x LLN |
| Fibrin split product | 20–40 mcg/mL | 41–50 mcg/mL | 51–60 mcg/mL | $>$60 mcg/mL |
| Methemoglobin | 5%–9.9% | 10.0%–14.9% | 15.0%–19.9% | $>$20% |
| **LIVER ENZYMES** | | | | |
| AST (SGOT) | 1.25–2.5 × ULN | 2.6–5 × ULN | 5.1–10 × ULN | $>$10 × ULN |
| ALT (SGPT) | 1.25–2.5 × ULN | 2.6–5 × ULN | 5.1–10 × ULN | $>$10 × ULN |
| GGT | 1.25–2.5 × ULN | 2.6–5 × ULN | 5.1–10 × ULN | $>$10 × ULN |
| Alkaline phosphatase | 1.25–2.5 × ULN | 2.6–5 × ULN | 5.1–10 × ULN | $>$10 × ULN |
| Amylase | 1.1–1.5 × ULN | 1.6–2.0 × ULN | 2.1–5.0 × ULN | $>$5.0 × ULN |

## Appendix 7
## WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

| **CHEMISTRIES** | | | | |
|---|---|---|---|---|
| Hyponatremia | 130–135 mEq/L | 123–129 mEq/L | 116–122 mEq/L | < 116 or mental status changes or seizures |
| Hypernatremia | 146–150 mEq/L | 151–157 mEq/L | 158–165 mEq/L | > 165 mEq/L or mental status changes or seizures |
| Hypokalemia | 3.0–3.4 mEq/L | 2.5–2.9 mEq/L | 2.0–2.4 mEq/L or intensive replacement Rx required or hospitalization required. | < 2.0 mEq/L or paresis or ileus or life-threatening arrhythmia |
| Hyperkalemia | 5.6–6.0 mEq/L | 6.1–6.5 mEq/L | 6.6–7.0 mEq/L | > 7.0 mEq/L or life-threatening arrhythmia |
| Hypoglycemia | 55–64 mg/dL | 40–54 mg/dL | 30–39 mg/dL | < 30 mg/dL or mental status changes or coma |
| Hyperglycemia (note if fasting) | 116–160 mg/dL | 161–250 mg/dL | 251–500 mg/dL | > 500 mg/dL or ketoacidosis or seizures |
| Hypocalcemia (corrected for albumin) | 8.4–7.8 mg/dL | 7.7–7.0 mg/dL | 6.9–6.1 mg/dL | < 6.1 mg/dL or life-threatening arrhythmia or tetany |
| Hypercalcemia (correct for albumin) | 10.6–11.5 mg/dL | 11.6–12.5 mg/dL | 12.6–13.5 mg/dL | > 13.5 mg/dL life-threatening arrhythmia |
| Hypomagnesemia | 1.4–1.2 mEq/L | 1.1–0.9 mEq/L | 0.8–0.6 mEq/L | < 0.6 mEq/L or life-threatening arrhythmia |
| Hypophosphatemia | 2.0–2.4 mg/dL | 1.5–1.9 mg/dL or replacement Rx required | 1.0–1.4 mg/dL intensive Rx or hospitalization required | < 1.0 mg/dL or life-threatening arrhythmia |

# Appendix 7
# WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

| | | | | |
|---|---|---|---|---|
| **CHEMISTRIES continued** | | | | |
| Hyperbilirubinemia | 1.1–1.5 × ULN | 1.6–2.5 × ULN | 2.6–5 × ULN | > 5 × ULN |
| BUN | 1.25–2.5 × ULN | 2.6–5 × ULN | 5.1–10 × ULN | > 10 × ULN |
| Creatinine | 1.1–1.5 × ULN | 1.6–3.0 × ULN | 3.1–6 × ULN | > 6 × ULN or required dialysis |
| **URINALYSIS** | | | | |
| Proteinuria | 1+ or < 0.3% or < 3g/L or 200 mg–1 g loss/day | 2–3+ or 0.3–1.0% or 3–10 g/L 1–2 g loss/day | 4+ or > 1.0% or > 10 g/L 2–3.5 g loss/day | nephrotic syndrome or > 3.5 g loss/day |
| Hematuria | microscopic only | gross, no clots | gross + clots | obstructive or required transfusion |
| **CARDIAC DYSFUNCTION** | | | | |
| Cardiac Rhythm | | asymptomatic, transient signs, no Rx required | recurrent/persistent; no Rx required | requires treatment |
| Hypertension | transient increase > 20 mm; no Rx required | recurrent, chronic, > 20 mm, Rx required | requires acute Rx; no hospitalization required | requires hospitalization |
| Hypotension | transient orthostatic hypotension, no Rx | symptoms correctable with oral fluids Rx | requires IV fluids; no hospitalization required | requires hospitalization |
| Pericarditis | minimal effusion | mild/moderate asymptomatic effusion, no Rx required | symptomatic effusion; pain; EKG changes | tamponade; pericardiocentesis or surgery required |
| Hemorrhage, Blood Loss | microscopic/occult | mild, no transfusion | gross blood loss; 1–2 units transfused | massive blood loss; > 3 units transfused |

# Appendix 7
# WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

| | | | | |
|---|---|---|---|---|
| **RESPIRATORY** | | | | |
| Cough | transient; no Rx | treatment-associated cough local Rx | uncontrolled | |
| Bronchospasm, Acute | transient; no Rx $<$80%–70% $FEV_1$ (or peak flow) | requires Rx normalizes with bronchodilator; $FEV_1$ 50%–70% (or peak Flow) | no normalization with bronchodilator; $FEV_1$ 25%–50% (or peak flow retractions) | cyanosis: $FEV_1$ $<$25% (or peak flow) or intubated |
| **GASTROINTESTINAL** | | | | |
| Stomatitis | mild discomfort; no limits on activity | some limits on eating/drinking | eating/talking very limited | requires IV fluids |
| Nausea | mild discomfort; maintains reasonable intake | moderate discomfort; intake decreased significantly; some activity limited | severe discomfort; no significant intake; activities limited | minimal fluid intake |
| Vomiting | transient emesis | occasional/moderate vomiting | orthostatic hypotension or IV fluids required | hypotensive shock or hospitalization required for IV fluid therapy |
| Constipation | mild | moderate | severe | distensions w/vomiting |
| Diarrhea | transient 3–4 loose stools/day | 5–7 loose stools/day | orthostatic hypotension or $>$7 loose stools/day or required IV fluids | hypotensive shock or hospitalization for IV fluid therapy required |

# Appendix 7
# WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

| | | | | |
|---|---|---|---|---|
| **NEURO AND NEUROMUSCULAR** | | | | |
| Neuro-cerebellar | slight incoordination dysdiadochokinesis | intention tremor, dysmetria, slurred speech; nystagmus | locomotor ataxia | incapacitated |
| Mood | mild anxiety or depression | moderate anxiety or depression and therapy required | severe anxiety or depression or mania; needs assistance | acute psychosis; incapacitated, requires hospitalization |
| Neuro control (ADL = activities of daily living) | mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected | moderate confusion/agitation some limitation of ADL; minimal Rx | severe confusion/agitation needs assistance for ADL; therapy required | toxic psychosis; hospitalization |
| Muscle strength | subjective weakness no objective symptoms/signs | mild objective signs/symptoms no decrease in function | objective weakness function limited | paralysis |
| **OTHER PARAMETERS** | | | | |
| Fever: oral, > 12 hours | 37.7°C –38.5°C or 100.0°F–101.5°F | 38.6°C–39.5°C or 101.6°F–102.9°F | 39.6°C–40.5°C or 103°F–105°F | > 40°C or > 105°F |
| Headache | mild, no Rx therapy | transient, moderate; Rx required | severe; responds to initial narcotic therapy | intractable; required repeated narcotic therapy |
| Fatigue | no decrease in ADL | normal activity decreased 25%–50% | normal activity decreased > 50% can't work | unable to care for self |
| Allergic Reaction | pruritus without rash | localized urticaria | generalized urticaria; angioedema | anaphylaxis |

# Appendix 7
# WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (cont.)

| **OTHER PARAMETERS continued** | | | | |
|---|---|---|---|---|
| Local Reaction | tenderness or erythema | induration < 10 cm or phlebitis or inflammation | induration > 10 cm or ulceration | necrosis |
| Mucocutaneous | erythema; pruritus | diffuse, maculopapular rash, dry desquamation | vesiculation, moist desquamation, or ulceration | exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery |

NOTE: For coding purposes, the following toxicity grades may be used interchangeably: 1 = mild; 2 = moderate; 3 = severe; 4 = life threatening.