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

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STATISTICAL ANALYSIS PLAN

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

STUDY DRUG: Mircera (RO0503821)

VERSION NUMBER: 1

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EUDRACT NUMBER: 2016-004779-39

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted]

DATE FINAL: See electronic date stamp below {XX Month Year}

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STATISTICAL ANALYSIS PLAN APPROVAL

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1. BACKGROUND

The NH19708 study is a pediatric study in patients aged 3 months to 17 years. It is an open-label, single-arm, multi-center study of Mircera administered once every 4 weeks subcutaneously (SC) for the maintenance treatment of anemia in pediatric patients with Chronic Kidney Disease (CKD). This study is the first use of Mircera in children under 6 years of age, and addresses the questions about 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 main objective of the study is to ascertain the starting dose for the SC administration of Mircera 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 [epoetin alfa or epoetin beta or biosimilar] or darbepoetin alfa.

This analysis plan covers the proposed methods for the final analysis following the database lock at the end of the study.

2. STUDY DESIGN

Patients will be screened for eligibility during a screening period of approximately three weeks. During this period, patients will continue to receive epoetin [epoetin alfa or epoetin beta or biosimilar] or darbepoetin alfa at the same weekly dose, route (SC), and interval as before screening. 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.

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 has taken place as described in Section 6.9 of the study protocol.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 OUTCOME MEASURES

2.2.1 Primary Efficacy Endpoints

The primary efficacy endpoint in this study is the change in Hb concentration (g/dL) between the baseline and evaluation periods.

This is first calculated on a per-patient basis, using an Area Under the Curve (AUC) 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 the formula below. This is referred to as the time adjusted average Hb value, as the time at which the Hb values are measured is taken into account.

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

The Hb 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 (all assessments between Visit 8 (Week 17) and Visit 10 (Week 21) inclusive) will be calculated using the same method as for baseline. Subtracting the baseline 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. 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.

2.2.2 Secondary Efficacy Endpoints

1. The number of patients with an average Hb concentration during the evaluation period within ± 1 g/dL of their baseline Hb
2. The number of patients with an average Hb concentration above, within, or below the range of 10-12 g/dL

3. The change in Mircera dose over time, including the change between the starting dose and the evaluation period

The classification of each patient for endpoints 1 and 2 will be based on their average Hb for the baseline and evaluation periods as calculated for the primary endpoint.

2.2.3 Exploratory Endpoints

Assessment of injection pain using a VAS scale 5 minutes following ESA administration will be done by the patient if 4 years or older, the parent/guardian and the nurse/site staff. 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. Mean injection pain scores will be plotted for all patients per assessor category and per visit.

2.2.4 Pharmacokinetic and Pharmacodynamic Endpoints

Serum concentrations of Mircera and Hb will be used to evaluate the pharmacokinetics and pharmacodynamics using non-linear mixed effect modeling. The evaluation of the pharmacokinetic and pharmacodynamic objectives is outside the scope of this statistical analysis plan. The general outline of the analysis is given in the protocol synopsis.

2.2.5 Safety Endpoints

- Occurrence and severity of adverse events
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

Change in vital signs and laboratory parameters will be summarized separately- from baseline to evaluation period and from baseline to the end of study duration (including optional extension period) respectively.

Adverse events will be summarized separately for the core period and the entire study duration (including the optional extension period).

2.3 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. This means that we assume there will be no change in the Hb levels from baseline to the evaluation period.

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.

2.4 ANALYSIS TIMING

Two analyses of this study have been planned:

- Interim Analysis – An interim analysis was performed to assess efficacy, safety, and pharmacokinetics after 12 patients completed 20 weeks of treatment. The analysis was 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. For more details of the related statistical analysis, please refer to the separate Statistical Analysis Plan for the Interim Analysis. The IMC met on 12 Sep 2019 and based on the review of the data and the meeting discussion, it recommended to continue the study unchanged. The IMC recommendation has been documented and filed in the trial master file.
- Final Analysis – The final analysis will be performed at the 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 if the patient participates to the safety extension.

3. STUDY CONDUCT

3.1 RANDOMIZATION

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).

3.2 DATA MONITORING

The IMC reviewed the general safety and efficacy of Mircera in this patient population as well as PK data on 12 September 2019, after 12 subjects completed the core study period (20 weeks of treatment). The IMC consisted of representative(s) from Clinical Science, Drug Safety, Clinical Pharmacology and Biostatistics. The main purpose of the IMC was to assess if the conversion factor from the previous ESA dose to give the starting dose of Mircera SC is appropriate to maintain stable hemoglobin (Hb). The SMT

was recommended to plan and prepare for this interim analysis. The SMT Statistician and the Statistical Programming Analyst performed the interim analyses. Based on the review of the data and the meeting discussion, the IMC recommended to continue the study unchanged. The Development Review Committee (DRC) chair, on behalf of the study team, accepted the IMC recommendations. For detailed description of the role and process of the IMC, please refer to the IMC Agreement.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

4.1.1 Intent to Treat (ITT) Population

The Intent to Treat (ITT) population consists of all patients enrolled in the study.

4.1.2 Per Protocol Population

The Per-Protocol (PP) population is defined as all patients included in the safety population and who have no major protocol deviations as defined below.

1. Patients with less than 3 Hb values during the evaluation period.
2. Patients who miss any application of study medication at week 13 or week 17.
3. Patients with an overdose of Mircera at week 17 captured as a protocol deviation
4. Patient with wrong Mircera starting dose
5. Patients who do not fulfill the inclusion criteria for:
    - hemoglobin
    - iron levels
    - stable dose and dosing interval of SC treatment with epoetin alfa, epoetin beta or biosimilars, or darbepoetin alfa
6. Patients who fulfill any of the exclusion criteria:
    - Hemolytic anemia
    - Use of prohibited therapy

4.1.3 Safety Population

The safety analysis population consists of all patients who received at least one dose of study drug regardless of whether they withdrew prematurely or not.

4.2 ANALYSIS OF STUDY CONDUCT

The summary of patient disposition will give a breakdown of the number and percentage of patients who: enrolled; started, discontinued (with reasons for discontinuation) and completed the core study and the safety extension period.

Premature withdrawals will be listed and summarized by age category and dialysis category.
Patients completing 20 weeks of treatment (having returned for an assessment at study week 21) as defined in the protocol as a key cut-point will also be summarized.

Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results. Protocol deviations related to covid-19 will

be tagged appropriately in the Protocol Deviation Management System (PDMS) and listed separately.

The distribution of patients based on the key strata of age at enrollment (<5, 5-11, ≥12), dialysis status (no dialysis, PD or HD) and previous ESA treatment (epoetin [epoetin alfa or epoetin beta or biosimilar] or darbepoetin alfa) will be summarized and compared by those who completed more than 20 weeks against those who did not.

4.3 EFFICACY ANALYSIS

The primary efficacy endpoint is the change in Hb concentration (g/dL) between the baseline and the evaluation period for each patient. The analysis population for the primary and secondary efficacy analyses will be the ITT population consisting of all enrolled patients.

4.3.1 Primary Efficacy Endpoint

Hb concentration values (g/dL) over time and change in Hb from baseline to evaluation period will be presented in summary tables and graphically. The estimates will be summarized descriptively using means, standard deviation and percentiles.

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, ≥12 years), dialysis type (not yet on dialysis, PD, HD) and previous ESA (epoetin [epoetin alfa or epoetin beta or biosimilar] or darbepoetin alfa), if numbers allow.

The 90% confidence interval (CI) for the average per-patient Hb change from baseline to the evaluation period (weeks 17-21) will be calculated. If the lower limit of the CI is ≥-1 g/dL, the upper limit ≤1 g/dL and the number of dose increases and decreases are approximately balanced across the patients the conversion factor from prior ESA treatment for the first Mircera dose will be considered appropriate.

The Hb change from baseline is calculated on a per-patient basis, using an Area Under the Curve (AUC) approach to calculate an individual's average for both the baseline and evaluation periods and taking the difference. This per-patient change is then averaged over all patients and the confidence interval calculated.

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 or imputed. 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.

4.3.2 Secondary Efficacy Endpoints

4.3.2.1 Number of patients within stable range of Hb

The 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 and those who fulfill both criteria will be summarized. The classification of each patient will be based on their average Hb for the baseline and evaluation periods as calculated for the primary endpoint.

4.3.2.2 Change in Mircera dose over time

The change in Mircera dose over time, including the change between the starting dose and the evaluation period, will be analyzed descriptively, overall and by age-group. The ratio of starting dose (Week 1) to the dose at the evaluation period (Week 17) will be summarized by using mean, median, minimum and maximum.

A dose change is defined as a change in the administered dose strength compared to the preceding dose. The number of patients with dose increases, dose decreases and both increases and decreases will be tabulated.

4.3.2.3 Average Hb and Change from Baseline

Average Hb values will also be summarized by Hb levels: < 10 g/dL, between 10 and 12 g/dL, and > 12 g/dL. The number and percentage of patients within each Hb level will be presented. The Hb level at evaluation period, at baseline and the change from baseline to evaluation period will be listed for all the patients.

4.3.2.4 Patients with Dose adjustments

Patients with dose adjustments during the core study period will be summarized descriptively, overall and by age-group.

4.3.3 Exploratory Efficacy Endpoints

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 separately for patient reported, nurse reported, and parent reported assessments. Descriptive summary statistics for the pain score assessed by nurse/ site staff, patient and parent respectively will be presented by visit. A plot of mean pain scores per assessor category per visit will be produced.

4.3.4 Sensitivity Analyses

Sensitivity analysis may be carried out for the primary efficacy endpoint based on the number of patients who do not respond to increasing doses of Mircera over the study duration. Sensitivity analysis for data exploration may also be done for the primary efficacy endpoint if a large volume of data is missing.

4.3.5 Subgroup Analyses

The main subgroups used for analysis in this pediatric study will be the age groups (based on age at study start) used for stratification:

1. Age groups:
   - < 5 years
   - 5-11 years
   - ≥ 12 years

Additionally, the other stratification factor that may be used for subgroup analyses:

2. Previous ESA treatment
   - epoetin alfa or epoetin beta or biosimilar
   - darbepoetin alfa
3. Dialysis type at study start
   - Not yet on dialysis
   - PD
   - HD

Analyses of the primary endpoint & the dose over time will be repeated by these subgroups.

4.4 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. The safety parameters will include vital signs, adverse events and the safety laboratory parameters including iron.

4.4.1 Exposure of Study Medication

Exposure to study drug will be summarized, overall and by visit. The treatment duration (in weeks) and number of doses will be summarized using descriptive statistics such as mean, median, minimum and maximum. The average dose (ug), average dose per kg of body weight and average dose per body surface area (BSA) will be summarized descriptively, both overall as well as by visit (using weight at that visit as reference).

4.4.2 Adverse Events

All AEs recorded in the CRF will be listed and classified by System Organ Class (SOC) and Preferred Term (PT). Events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Adverse event severity will be graded according to the WHO Toxicity Grading Scale for determining the severity of adverse events (refer to Appendix 7 of the study protocol for details). AEs that occurred during the treatment period: from the first treatment dose until 28 days after last dose or until the final visit (whichever is latest) will be summarized. Standard safety analyses for all AEs, related AEs, serious AEs, fatal AEs and AEs leading to study drug modification or discontinuation or withdrawal from study will be performed in terms of frequency tables by event and patient.

All adverse events of special interest (AESI) will be presented. AESI include but are not limited to the following:

- 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 of study protocol)
- 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.

Adverse events related to covid-19 will be identified using the special covid-19 SMQ containing a narrow basket of preferred terms (PTs) to provide a more targeted list of events related to the SARS-CoV-2 virus. Only events occurring in the pandemic timeframe (1 Dec 2019 onwards) will be included in this list. A listing of such adverse events associated with covid-19 will be provided. For those patients with confirmed covid-19 infection or positive PCR test (9 preferred terms from the above SMQ) any other AEs occurring within <=7 days before and <=30 days after start date of the AE will also be considered as covid-19 associated events.

4.4.3 Laboratory Data

For all safety laboratory parameters (including iron parameters), the change in average lab parameter values, from baseline to evaluation period will be summarized using descriptive statistics (mean, standard deviation, minimum, maximum and quartiles). For all safety laboratory parameters, the baseline is defined as last value before the first study drug administration. For the iron and selected hematology parameters (reticulocytes, red blood cells count, serum ferritin, serum iron, and Transferrin Saturation (TSAT)), baseline is defined using all the assessments between day -35 and the day of first study dose (day 1 pre-dose). For these parameters, baseline value is calculated using the time adjusted approach described in Section 4.3.1.

For safety labs, the assessment corresponding to Week 21 will be used as evaluation assessment. For Iron parameters (serum iron, serum ferritin, TSAT), the average of assessments done in evaluation period (i.e. all assessments between Week 17 and Week 21) will be used as evaluation assessment. For hematology labs (Hb, reticulocytes, RBC), the average value for each individual during the evaluation period will be calculated using the same method (time adjusted average) as for the baseline period.

Sites have the possibility to enter one of two alternative parameters: TSAT or hypochromic RBCs; transferrin or total iron binding capacity (TIBC). The same parameter should be recorded for a patient all the way through the study. For all patients, transferrin saturation will be recalculated as the ratio (%) of serum iron to serum transferrin (where available) or serum iron and TIBC if transferrin is not available using the formulae given below. Summaries will be based on the calculated values. Listings will contain both the calculated TSAT values and those provided on the CRF where available.

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

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

Selected safety laboratory parameters (AST, ALP, ALT, leucocytes, serum albumin, c-reactive protein, potassium, phosphorus, calcium, platelets) will be assessed for clinically significant abnormalities as well as shifts from baseline to worst post-baseline values.

4.4.4 Vital Signs

Vital signs (systolic and diastolic blood pressure and pulse rate) will be summarized descriptively at baseline and each pre-defined time point per protocol using summary statistics such as mean, std. dev., minimum, maximum and quartiles. To summarize the

data from this pediatric population, normalized Z- scores will be used to assess if the population values are above or below age, sex and development stage-specific norms.

For patients on hemodialysis, pre and post hemodialysis assessments of vital signs will be summarized descriptively.

Normalized Z-scores

Normalized Z-scores will be calculated for height, weight and blood pressure. These standardize the data relevant to a reference population using ranges based on age and sex (and additionally for blood pressure, height). This standardization makes results comparable across ages and allows meaningful calculation of summary statistics. A Z-score of 0 indicates that a patient's value is average for their sex and age (and development). In the standard normal distribution 68%, 95% and 99% of values fall within a Z-score of ±1, ±2 and ±3 respectively. Values outside of ±2 are therefore often considered as low/high, as in the reference population only 5% of comparable children have values this extreme. Percentiles corresponding to the Z-scores can also be used for summaries. Z-scores of -1.89, -1.65, -1.28, -0.68, 0, 0.68, 1.28, 1.65, and 1.89 correspond to the 3rd, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 97th percentiles respectively.

Height and Weight

In this short study growth and development over time will not be assessed, but normalized scores will be used to summarize the population. The reference to be used is the US CDC (Centers for Disease Control and Prevention) Growth Charts.
The method for calculating a standardized score is referred to as the 'LMS method' [1], which utilizes Box-Cox transformations to normalize the data. The Z-score for a given X (the height or weight value of interest), can be calculated as:

$$Z = \frac{\left(\frac{X}{M}\right)^{L} - 1}{LS}$$

Where: L is the skewness parameter, M the median and S the generalized coefficient of variation. The L, M, S parameters are sex & age (in months) specific and can be obtained from the CDC website.

Blood Pressure

Normalized scores for blood pressure are calculated using the methodology described in "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" [2]. Blood pressure standards are based on a child's sex, age and height.
An expected blood pressure value for a child of age y with a height Z-score Zht (computed with the CDC method above) is calculated using the following equation.

$$\mu = \alpha + \sum_{j=1}^{4} \beta_j (y - 10)^j + \sum_{k=1}^{4} \gamma_k (Zht)^k$$

The α,β,γ parameter values are given in the reference document, with different values for systolic and diastolic blood pressure for males and females. A normalized Z-score is then calculated by taking the observed value minus this expected value and dividing by a sex and systolic/diastolic specific standard deviation. Reference to the standard normal distribution gives the corresponding percentiles for these Z-scores.
Pediatric patients can be classified as hypertensive (above the 95th percentile on 3 or more occasions), or pre-hypertensive (above the 90th percentile) based on these percentiles.

4.4.5 Deaths

Details of any deaths will be presented in the form of an individual patient listing, patient narratives as well as a frequency table by cause of death.

4.4.6 Patient Narratives

All patients with Confirmed/Suspected COVID-19 serious adverse events will be included as patient narratives. Additional listings of medical history, demographic and baseline characteristics in patients with confirmed/ suspected covid-19 may be provided to support the narratives.

4.5 MISSING DATA

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. 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.

4.6 INTERIM ANALYSES

Once 12 patients have completed 20 weeks of treatment, an interim analysis to assess efficacy, safety, and pharmacokinetics was performed. The analysis was 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 was 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 was also assessed at this time, with regards to protocol assumptions.
An individual's Hb response was 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 was calculated.
The full details of the interim analysis and any decision criteria have been specified in separate IMC documents. The statistical analysis has been detailed in a separate Interim analysis SAP.

4.7 OPTIONAL SAFETY EXTENSION

In the majority of cases efficacy endpoints are defined based on data from the core study period only; additional outputs containing related data from the safety extension period will be produced.

The following analysis of key data from the optional safety extension period will be performed:

1. Patient disposition: patients entering, ongoing, withdrawing (with reason) and completing the extension period
2. Summary of Hb over time
3. Change in vital signs
4. Change in laboratory parameters
5. Listing of blood transfusions
6. Adverse events
    a. Number of deaths, all AEs, SAEs
    b. Listing of AEs
    c. Summary of AEs

Generally, for outputs displaying summaries over time (e.g. laboratory parameters, vital signs) all time points for the complete trial will be displayed in a single output (core and extension periods combined), so no special distinction between periods is required.

For Adverse Events in most cases, for each summary classification, 3 outputs will be produced based on different time periods – core study, extension study and the complete study.

Note: to have the option to participate in the safety extension period patients were required to have stable Hb levels (within ± 1 g/dL of their baseline Hb and within the target range of 10-12 g/dL).

5. REFERENCES

1. Centers for Disease Control and Prevention, National Center for Health Statistics. CDC growth charts: United States. http://www.cdc.gov/growthcharts/. May 30, 2000.

2. “The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents” https://www.nhlbi.nih.gov/sites/default/files/media/docs/hbp_ped.pdf

Appendix 1
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: • Change in Hb concentration (g/dL) between the baseline and the evaluation period for each patient Secondary endpoints: • 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 • 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 • Change from baseline in targeted vital signs

	• 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

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

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, ≥ 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.

Appendix 2
Schedule of Assessments

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									

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.

[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 of protocol).

[k] Includes serum ferritin, serum iron and TSAT. TSAT will be calculated as described in Appendix 3 of protocol 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.

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						

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 of protocol).

[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 of protocol).

[h] Includes serum ferritin, serum iron and TSAT. TSAT will be calculated as described in Appendix 3 of protocol 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.