CLINICAL PHARMACOLOGY REVIEW

BLA	125164
Submission type	PMR Study Reports and Efficacy Supplement
Submission date	10/31/22 and 6/30/23
Brand name	Mircera®
Generic name	methoxy polyethylene glycol epoetin beta
Sponsor	Vifor Pharma
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BACKGROUND

Studies NH19708 and MH40258 were performed to fulfill the following post marketing requirements (PMR):

- PMR 3385-1: Conduct a multi-center, single-arm, clinical trial to confirm the dosing of US licensed Mircera given subcutaneously in pediatric patients with anemia associated with chronic kidney disease on peritoneal dialysis or not yet on dialysis. The trial will be open to enroll pediatric patients 1 year to less than 18 years of age. The trial will evaluate maintenance of hemoglobin concentration, pharmacokinetics, and safety. The sample size will be a minimum of 40 patients. (Study NH19708)
- PMR 3385-2: Submit a summary report and registry data that describes the dosing, aggregate level safety data and hemoglobin concentrations in a cohort of pediatric patients with anemia associated with chronic kidney disease treated with US-licensed Mircera. The cohort will include pediatric patients from 3 months to less than 18 years of

age, on peritoneal dialysis or hemodialysis, and subcutaneous or intravenous route of administration. The sample size for the cohort will be a minimum of 125 patients. (Study MH40258)

Previously, Mircera was labeled for use in adult patients on dialysis and adult patients not on dialysis and pediatric patients 5 to 17 years of age on hemodialysis who are converting from another erythropoietin-stimulating agent (ESA) after their hemoglobin level was stabilized with an ESA. In pediatric patients, Mircera was only to be administered by intravenous administration. This supplement seeks to expand the label to include pediatric patients 3 months to 17 years of age on dialysis or not on dialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA, and it removes the requirement of intravenous administration of Mircera in pediatric patients, now allowing for subcutaneous and intravenous administration. Only Study NH19708 (PMR 3385-1) contained clinical pharmacology-related data; therefore, only Study NH19708 and PMR 3385-1 will be included in this clinical pharmacology review.

RECOMMENDATION

The Office of Clinical Pharmacology has reviewed the results from Study NH19708 and has determined that PMR 3385-1 has been fulfilled. The results from Study NH19708 support the proposed starting doses of Mircera following subcutaneous administration and the subsequent instructions for dose adjustment in pediatric patients 3 months to 5 years of age who are converting from another ESA.

LABELING CHANGES

New labeling changes are proposed by the Applicant. The major proposed labeling changes from the Applicant and updated labeling recommendations as of March and April 2024 are included in the Appendix.

REVIEW – STUDY NH19708

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.

OBJECTIVES AND ENDPOINTS

Efficacy:

- Objective:

    - To ascertain the starting dose of Mircera given subcutaneously (SC) in pediatric patients with chronic kidney disease (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 hemoglobin (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 $\pm$ 1 g/dL of their baseline Hb or above, within or below the range of 10 to 12 g/dL
    - Change in Mircera dose over time, including the change between the starting dose and the evaluation period

Safety:

- Objective:
    - To assess the safety and tolerability of multiple doses of Mircera given SC in pediatric patients
- Endpoints:
    - Occurrence and severity of adverse events
    - Change from baseline in targeted vital signs
    - Change from baseline in targeted clinical laboratory test results

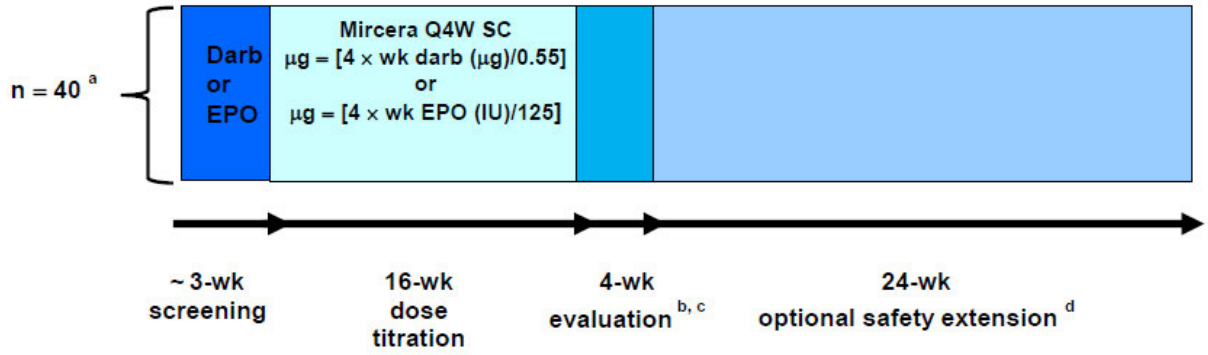
Pharmacokinetics and Pharmacodynamics:

- Objective:
    - To evaluate the pharmacokinetics (PK) and the pharmacodynamics (PD) of Mircera in patients on dialysis or not yet on dialysis who receive the study medication by the SC route of administration
- Endpoint:
    - Serum concentrations of Mircera and Hb will be used to evaluate the PK and PD of Mircera through PK and PK/PD models

DESIGN

This study was an open-label, single-arm, multicenter study to ascertain the optimal starting dose of Mircera given SC for the maintenance treatment of anemia in pediatric patients with CKD on dialysis or not yet on dialysis. This study was performed in 20 centers across 7 countries including Poland, the United States, France, Hungary, Italy, Spain, and Lithuania. Study NH19708 consisted of a screening period of about 3 weeks, a dose titration period (16 weeks) and evaluation period (Weeks 17 to 21) in the core study period, and a 24-week optional safety extension period (Figure 1).

Figure 1. Study Schema



darb = darbepoetin alfa; EPO = epoetin alfa or epoetin beta; Q4W = once 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, was not on dialysis. Available hemodialysis (HD) patients receiving their Erythropoiesis-stimulating agents (ESA) subcutaneously were eligible for enrollment. No more than 10 patients on HD could be enrolled.

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

[c] All patients completed a follow-up visit (Week 21, Visit 10), regardless of whether they continued 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, would be eligible to enter an optional 24-week safety extension period.

Applicant generated figure; Figure 1 in the clinical study report, Report Number 1109997

Population:

Those included in the study were 3 months to 17 years of age with clinically stable chronic renal anemia and CKD with an estimated glomerular filtration rate (eGFR) of < 45 mL/min/1.73 m^2 or dialysis treatment for at least 8 weeks before the first dose of Mircera. A total of 40 patients were enrolled in the core period of the study, and 25 patients entered the 24-week safety extension period. Participants were eligible to join the safety extension period if they completed the 20 weeks of treatment with Hb within ± 1 g/dL of their baseline value and within the target Hb range of 10 to 12 g/dL.

Relevant Inclusion Criteria:

- Baseline Hb concentration 10.0 to 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

Relevant Exclusion Criteria:

- Overt gastrointestinal bleeding within 8 weeks before screening or during the screening period
- Red blood cell (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
- Peritoneal dialysis (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.

Treatments

Mircera was administered SC once every 4 weeks for the duration of the study. The starting dose was based on conversion factors obtained from the dose-finding study in older pediatric patients (Study NH19707, [Report No 1035312]) rounded to the nearest prefilled syringe strengths. The exact conversion factors were 4 x previous weekly darbepoetin alfa dose [µg]/0.55 for darbepoetin alfa and 4 x previous weekly epoetin dose [IU]/125 for epoetin alfa and epoetin beta. Model-based evaluation of the data from Study NH19707 and subsequent simulations, coupled with data from adults suggested the use of same conversion factors for subcutaneous administration in pediatric patients. The initial dose of Mircera was to be one of

nine starting doses corresponding to the prefilled syringe (PFS) strengths based on the total weekly ESA dose during the screening period, as described in Table 1.

Table 1. 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

Applicant generated table from Protocol Number NH19708, Report Nubmer 1109997

The Mircera dose could be adjusted to maintain Hb within a target range of ±1 g/dL of the baseline value and between 10.0 to 12.0 g/dL. Dose adjustments were performed at the scheduled dosing days based on Hb measurements (see Table 2). The Mircera dose could be adjusted no more than once every 4 weeks. Dose adjustment rules for Mircera based on Hb are summarized in Table 2. If participants received a red blood cell transfusion due to worsening anemia secondary to inadequate doses or to poor response to Mircera, the dose was to be adjusted according to the guidelines in Table 2. If participants received a red blood cell transfusion to replace acute blood loss, the dose was not to be changed, and the next dose was to be administered as scheduled.

Table 2. 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. Resume dose at approximately 25% below previous dose (or closest lower PFS strength) at next scheduled dosing day.

Hb = hemoglobin; PFS = prefilled syringe.

Applicant generated table from Protocol Number NH19708, Report Nubmer 1109997

Pharmacokinetic Assessment:

PK sampling was collected throughout the 20-week treatment period. Serum concentrations were used to evaluate the PK and concentration-effect relationships in all patients. Samples were taken at the following timepoints: 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), and at the patient's convenience for one additional sample between 24 hours and 5 days after any one Mircera dose administration. A minimum of one PK sample after treatment initiation was requested for patients younger than 2 years old, and the sample on Week 1 could be omitted in these patients.

Power/Sample Size Calculation:

This study was conducted without a powered statistical group comparison, so no formal sample size estimation was performed. However, based on a previous pediatric study (NH19707), a 30% withdrawal rate was assumed. Of 40 patients evaluable for ITT and safety analysis, more than 26 patients will have data for the evaluation period. 26 patients would 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 less than 1.5 and the optimum dose conversion is able to maintain the Hb at the baseline level.

Pharmacokinetics and Pharmacodynamics Assessments:

Mircera serum concentration-time data and Hb concentration-time data were described with non-linear mixed effect modeling. The influence of covariates on PK and PD parameters were assessed.

The existing PK and PK/PD models were to be challenged against Study NH19708 data to check the predictive performance. These models would be updated by pooling data from Study NH19708 with historical adult and pediatric data. For information on the PK and PK/PD model, please see Appendix 3 for the pharmacometrics review.

Immunogenicity Assessment:

Anti-EPO and anti-Mircera antibodies were measured at baseline (Week 1), at Week 9 (Visit 6), and at the end of the evaluation period (Week 21). In patients who participated in the safety extension period, a sample was also collected at Week 45 (Visit 16). Non-negative findings were documented.

Bioanalytical:

Bioanalytical methods used during Study NH19708 included a method to measure Mircera concentrations. A summary of the method validation for measuring Mircera concentrations and bioanalytical report summary for Study NH19708 is included in Table 3.

Table 3. Summary Method Performance of a Bioanalytical Method to Measure Mircera in Human Serum

Bioanalytical Method Validation Report Name, Amendments, and Hyperlinks	Validation of an ELISA Method for the Determination of RO0503821 in Human Serum Samples (1054621) RO0503821 (Mircera): Validation of an ELISA Method for the Determination of RO0503821 in Human Serum Sample YBS Study YCM/013 (including addendum 1) (1054621)
Method Description	The validated method for the quantification of Mircera in human serum is a sandwich ELISA (1054621). This ELISA is based on the immobilization of rabbit polyclonal anti-EPO antibodies onto microtiter plates to capture Mircera in samples. Mircera is detected by a mouse IgM anti-polyethylene glycol antibody, which in turn, is detected by a goat anti-mouse IgM horse radish peroxidase (HRP) conjugated antibody and reacts with its substrate (tetramethylbenzidine [TMB]/H_2O_2) to generate a photometric readout. The assay could accurately detect Mircera concentrations ranging from 150-4000 pg/mL. The LLOQ (lower limit of quantification) of the ELISA was validated at 150 pg/mL and ULOQ at 4000 pg/mL. Sample concentrations are determined by interpolation from the standard curve, which has been fit using a five-parameter logistic, 1/response^2 weighted, least-squares regression algorithm.
Materials Used for Calibration Curve and Concentration	Reference Standard Mircera (RO0503821) Lot: AW 133; batch: N/A; Concentration: 6.6 mg/mL; Retest Date: (b) (4) Lot: PT1992H01; batch: N/A; Concentration: 6.4 mg/mL; Retest Date: (b) (4) Lot: PZ1602P016; batch: N/A: Concentration: 6.2 mg/mL; Retest Dates: (b) (4) (b) (4) Lot: PZ1602P013; batch: G143.00 Concentration: 5.9 mg/mL; Retest Date: (b) (4)
Validated Assay Range	LLOQ to ULOQ range is 150 to 4000 pg/mL in neat serum
Material Used for QCs and Concentration	Reference Standard Mircera (RO0503821) Lot: AW 133; batch: N/A; Concentration: 6.6 mg/mL; Retest Date: (b) (4) Lot: PT1992H01; batch: N/A; Concentration: 6.4 mg/mL; Retest Date: (b) (4) Lot: PZ1602P016; batch: N/A: Concentration: 6.2 mg/mL; Retest Dates: (b) (4) (b) (4) Lot: PZ1602P013; batch: G143.00 Concentration: 5.9 mg/mL; Retest Date: (b) (4)
MRDs	Final MRD 1:2
Source and Lot of Reagents (LBA)	**Capture reagent** First step: Biotinylated anti-EPO antibodies (Roche Diagnostics, Penzberg) Lot: AW385: Conc.: 8.3 mg/vial; expiry date: 17 Jul 2025 Lot: AW473: Conc.: 8.13 m/vial; expiry date: 21 Jun 2014 Lot: AW875: Conc.: 8.3 mg/vial; expiry date: 17 Jul 2025 Second step: Anti-PEG antibodies (Roche Diagnostics, Penzberg): Lot: AW282: Conc.: 5.34 mg/vial; expiry date: 25 Oct 2024 **Detection reagent** Goat anti-mouse igM POD conjugate (b) (4) Cat no. AP128P: Lot 3199245, received lyophilized (reconstituted to 0.8 mg/mL stock), expiry date 18 Jun 2020 Lot 3417916, received lyophilized (reconstituted to 0.8 mg/mL stock), expiry date 23 Jun 2021 Lot 3682557, received lyophilized (reconstituted to 0.8 mg/mL stock), expiry date 29 Jul 2022 Lot 2290937, received lyophilized (reconstituted to 0.8 mg/mL stock), expiry date 19 Dec 2015
Regression Model and Weighting	5-PL fit, weighted 1/response^2

Table 3. Summary Method Performance of a Bioanalytical Method to Measure Mircera in Human Serum (Continued)

Validation Parameters	Method Validation Summary		Source Location
Calibration Curve Performance During Accuracy and Precision	Number of non-zero standard calibrators from LLOQ to ULOQ	7	Table 2 of YCM/013 Validation Report (1054621)
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-0.7% to 3.3%	Table 2 of YCM/013 Validation Report (1054621)
	Cumulative precision (%CV) from LLOQ to ULOQ	6.2-13.5% CV	Table 2 of YCM/013 Validation Report (1054621)
QCs Performance During Accuracy and Precision	Cumulative accuracy (%bias) in 6 QCs 150, 400, 1600, 3200, 4000 & 300000 pg/mL	Intra assay: -5.7 to 6.7% Inter assay: 8.3-12.5%	Table 3 of YCM/013 Validation Report (1054621) Table 4 of YCM/013 Validation Report (1054621)
	Intra-batch %CV 150, 400, 1600, 3200, 4000 & 300000 pg/mL	1.7-8.1 %	Table 3 of YCM/013 Validation Report (1054621)
	Inter-batch %CV 150, 400, 1600, 3200, 4000 & 300000 pg/mL	7.8-27.7106%	Table 4 of YCM/013 Validation Report (1054621)
	Total Error (TE) 150, 400, 1600, 3200, 4000 & 300000 pg/mL	Intra-assay total error: 1.7-13.6% Inter-assay total error: 10.5-34.9%	Table 3 of YCM/013 Validation Report (1054621) Table 4 of YCM/013 Validation Report (1054621)

Table 3. Summary Method Performance of a Bioanalytical Method to Measure Mircera in Human Serum (Continued)

Validation Parameters	Method Validation Summary	Source Location
Interference and Specificity	EPO at 20 ng/mL with Mircera at 0 ng/mL; no cross-reactivity observed	Table 17 of YCM/013 Validation Report (1054621)
	EPO at 0, 50, 100, 200, 400, 800, 1600, 3200 and 6400 pg/mL with Mircera at LQC of pg/mL. All Mircera results were within 20% of nominal except at 6400 pg/mL EPO which was -22.5% different from nominal. When these concentrations are compared to the back-calculated concentration of the respective QC sample without EPO the difference between the Low QC spiked with 6400 pg/mL EPO (310 pg/mL) and Low QC spiked with 0 pg/mL EPO (349 pg/mL) was -11.2	Table 18 of YCM/013 Validation Report (1054621)
	EPO at 0, 50, 100, 200, 400, 800, 1600, 3200 and 6400 pg/mL with Mircera at MQC of pg/mL. All Mircera results were within 20% of nominal	Table 18 of YCM/013 Validation Report (1054621)
	EPO at 0, 50, 100, 200, 400, 800, 1600, 3200 and 6400 pg/mL with Mircera at HQC of pg/mL. All Mircera results were within 20% of nominal except at 400 pg/mL EPO which was -24.4% different from nominal. When these concentrations are compared to the back-calculated concentration of the respective QC sample without EPO (nominal EPO difference between the High QC spiked with 400 pg/mL (2420 pg/mL) and High QC spiked with 0 pg/mL EPO (2580 pg/mL) was -6.2%. The data demonstrates there is no interference to the analytical method for Mircera from EPO up to 6400 pg/mL of EPO.	Table 18 of YCM/013 Validation Report (1054621)
Hemolysis Effect	One individual normal matrix hemolyzed serum. Observed bias (RE%) calculated at 400 pg/mL= -6.0% Precision (CV%) calculated. at 400 pg/mL = 2.9%	Table 11 of YCM/013 Validation Report (1054621)
Lipemic Effect	PPD: One individual normal matrix lipemic serum Observed bias (RE%) calculated. at 400 pg/mL = -0.5% Precision (CV%) calculated. at 400 pg/mL = 1.5%	Table 10 of YCM/013 Validation Report (1054621)

Table 3. Summary Method Performance of a Bioanalytical Method to Measure Mircera in Human Serum (Continued)

Validation Parameters	Method Validation Summary	Source Location
Dilution linearity	Dilutional linearity was investigated using matrix samples from 3 individuals spiked with Mircera to 300,000 pg/mL (expected C_{max}). Dilutions of x100, x200 and x600 were made All diluted samples were within ±20% of their nominal concentration except one sample at x100 dilution. Since other dilutions for this sample and other samples tested at the same dilution were acceptable; this was attributed to a dilution error. Dilutional linearity up to a maximum dilution factor of x600.	Table 15 of YCM/013 Validation Report (1054621)
Prozone	The prozone or hook effect was investigated by analysing samples from pooled human serum spiked at concentrations of 300,000; 150,000; 75,000; 37,500; 18,800; 9380; 4690 and 2345 pg/mL of RO0503821 and analyzed undiluted. All samples spiked at levels above 4000 pg/mL gave observed concentrations greater than the ULOQ showing that there was no prozone effect.	Table 16 of YCM/013 Validation Report (1054621)
Bench-top/process stability	Mircera in neat serum at LQC (400pgmL) and HQC (3200 pg/mL) and 3000000 pg/mL is stable for at least:24 hours at room temperature % Recovery range: 94.0% to 105.5%	Table 12 of YCM/013 Validation Report (1054621)
Freeze-Thaw stability	Mircera in neat serum at LQC (400pgmL) and HQC (3200 pg/mL) and 3000000 pg/mL is stable for at least 5 F/T cycles at -20°C % Recovery range: 90.3% to 109.3% Extended to 9F/T cycles at -20°C % Recovery range: 99.7% to 102.8%	Table 13 of YCM/013 Validation Report (1054621) Table 16 of YCM/013 Validation Report (1054621)
Long-term stability	Mircera in neat serum at LQC (400pgmL) and HQC (3200 pg/mL) and 3000000 pg/mL is stable for at least 1 month at −20°C Accuracy: 80.0% to 95.0%	Table 14 of YCM/013 Validation Report (1054621)
	Mircera in neat serum at LQC (400pgmL) and HQC (3200 pg/mL) and 3000000 pg/mL is stable for at least 16 months at −20°C Accuracy: 87.2% to 103.4%	Table 8 of YDA/008 Validation Report (1054621)
Parallelism	Not assessed	
Carry over	Not applicable, disposable pipette tips were used for sample dilution and processing	

CV=coefficient of variation; LLOQ=lower limit of quantification; LLQC=lower limit quality check; HQC= higher limit quality check; RDR=Roche Development Report No.; RE=reference; QC=quality check; TE=total error; ULOQ=upper limit of quantification.

Table 3. Summary Method Performance of a Bioanalytical Method to Measure Mircera in Human Serum (Continued)

Bioanalytical Report NH19708	YBS Study Number YDA/12	Source Location
Assay passing rate	73.7% (14/19 runs)	Table 1 of YDA/012 (Bioanalytical Report in Final CSR NH19708 [16.2.5, 1109997])
Standard curve performance	Cumulative RE range: -1.3 to 1.6% (non-zero cals, excluding anchor point) Cumulative precision ≤ 8.3% CV (non-zero cals, excluding anchor point)	Table 3 of YDA/012 (Bioanalytical Report in Final CSR NH19708 [16.2.5, 1109997])
QC performance	Cumulative RE range: 3.1 to 5.3% Cumulative precision ≤11.2% CV TE: ≤16.5%	Table 4 of YDA/012 (Bioanalytical Report in Final CSR NH19708 [16.2.5, 1109997])
Method reproducibility	Incurred sample re-analysis was performed in 22/220 (10.0%) of study samples, and 95.5% of the samples met the pre-specified criteria	Table 6 of YDA/012 (Bioanalytical Report in Final CSR NH19708 [16.2.5, 1109997])
Study sample analysis/ stability	Samples and calibration standards/QCs were analyzed within proven frozen stability of 511days at -20°C, the longest sample storage was 431 days. All samples were analyzed within the validated freeze/thaw stability of nine cycles, 4 cycles being the most for any reported study results.	Section 5.5 of YDA/012 (Bioanalytical Report in Final CSR NH19708 [16.2.5, 1109997])
Standard calibration curve performance during accuracy (%RE) and precision runs	100*, 150, 300, 500, 1000, 2000, 3000 and 4000 pg/mL (in 100% human serum). *denotes anchor point, not included in summary statistics	

BAR=bioanalytical report; CV=coefficient of variation; TE=total error.

Applicant-generated table, Table 2, 2.7.1, Appendix 1

RESULTS

Patient Disposition:

A total of 62 patients were screened and 34 patients were enrolled. Among the 28 screen failures, 7 patients were re-screened, 6 patients were enrolled, and 1 patient failed the re-screening. All 40 patients were enrolled in the core period of the study from 20 centers distributed across 7 countries. 38 patients completed the core period, and 2 patients discontinued during the core period due to kidney transplant or use of prohibited medication. Of the 38 patients who completed the core period, 25 eligible patients entered the safety extension period. To enter the extension period, the patients' Hb levels considered were either the Hb value at Week 21 or the mean Hb value during the evaluation period; however, a small variation in the Hb values from the eligibility criteria was accepted if it was deemed by the investigator to provide clinical benefit to the patient. Of the 13 patients who did not enter the safety extension 7 were eligible based on Hb within 10 to 12 g/dL and $\pm$ 1 g/dL of the baseline value. 21 of the 25 patients entering the safety extension completed this period. 4 patients discontinued due to kidney transplant.

Pharmacokinetics:

Sparse PK sampling was collected during Study NH19708. Prior to initiating Study NH19708, a PK model was created. This PK model was updated by pooling Study NH19708 data with historical adult and pediatric PK data. For a review of this model and PK results, please see Appendix 3 for the pharmacometrics review. The model indicated that the bioavailability after SC administration of Mircera in the pediatric and adult patients is 67% and 31%, respectively (Table 4).

In Study NH19708, the median ratio of starting Mircera dose at Week 1 to the dose at Week 17 was 1.44, indicating that there was a decrease in Mircera dose over time. This raises a question of whether the proposed/studied starting doses of Mircera are appropriate for subcutaneous administration. The Applicant states that because the bioavailability (F%) for Mircera is higher in pediatric patients compared to epoetin alfa/beta (Table 4, 67% vs 40%), if at all, the ratio of Mircera dose at Week 1/Week 17 for patients previously treated with epoetin alfa/beta should be higher than for patients transitioning from darbepoetin. However, the results of study NH19708 do not support this since the ratio of Mircera at Week 1/Week 17 is 1.00 and 1.50 for patients previously treated with epoetin alfa/beta and darbepoetin, respectively (Table 4).

Table 4. Absolute Bioavailability (F in %) after Subcutaneous Administration in Adult and Pediatric Patients with Various ESAs and Ratio of Dose at Week 1/Week17 in Study NH19708

ESA	F% in Adults	F% in Pediatrics	Ratio of Mircera Dose at Week1/Week 17 (median)
Mircera	31[3]	67[3]	-
darbepoetin	37[1]	54[1]	1.50[3]
epoetin alfa/beta	32-33[4]	40[2,5]	1.00[3]

ESA= erythropoiesis stimulating agent; F=absolute bioavailability; Mircera= methoxy polyethylene glycol-epoetin beta.

1 ARANESP® US Package Insert 2019.
2 Evans et al. 1991.
3 NH19708 CSR.
4 Halstenson et al. 1991.
5 Heatherington 2003.

Applicant generated table; Table 6 in Type B (Pre-sBLA) Meeting Package submitted September 23, 2024

Pharmacodynamics:

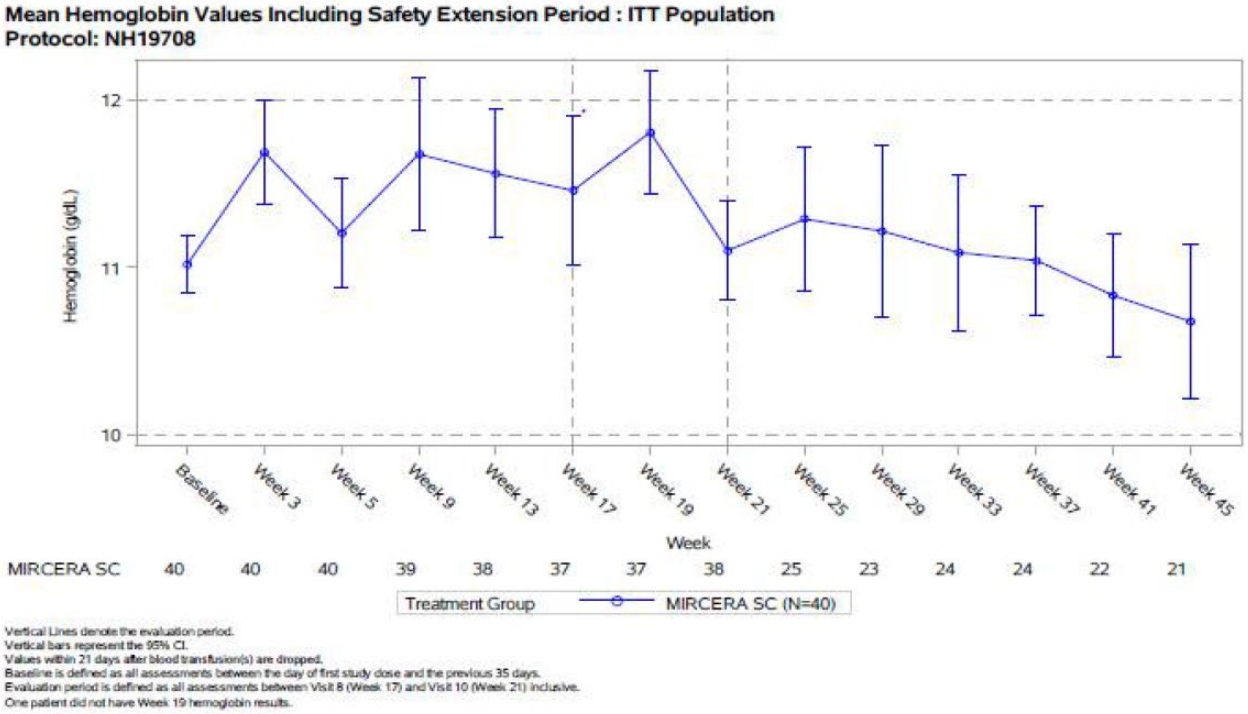
In the core period, the mean (± SD) change in Hb concentration increased by 0.48 (1.03) g/dL above baseline, the 90% CI for the change in mean Hb concentration levels compared to baseline was within the range of ± 1 g/dL, and the SD was < 1.5 (Table 5). Therefore, the primary endpoint was met. A graph of the mean Hb values and change from baseline values are presented in Figures 2 and 3.

Table 5. 90% Confidence Interval for Hb Values (g/dL) and Change from Baseline in the ITT Population

	MIRCERA SC (N=40)	
	Value at Baseline	Change from Baseline
Evaluation Period (Weeks 17 - 21)		
n	38	38
Mean (SD)	11.05 (0.51)	0.48 (1.03)
90% CI for Mean		(0.20,0.76)

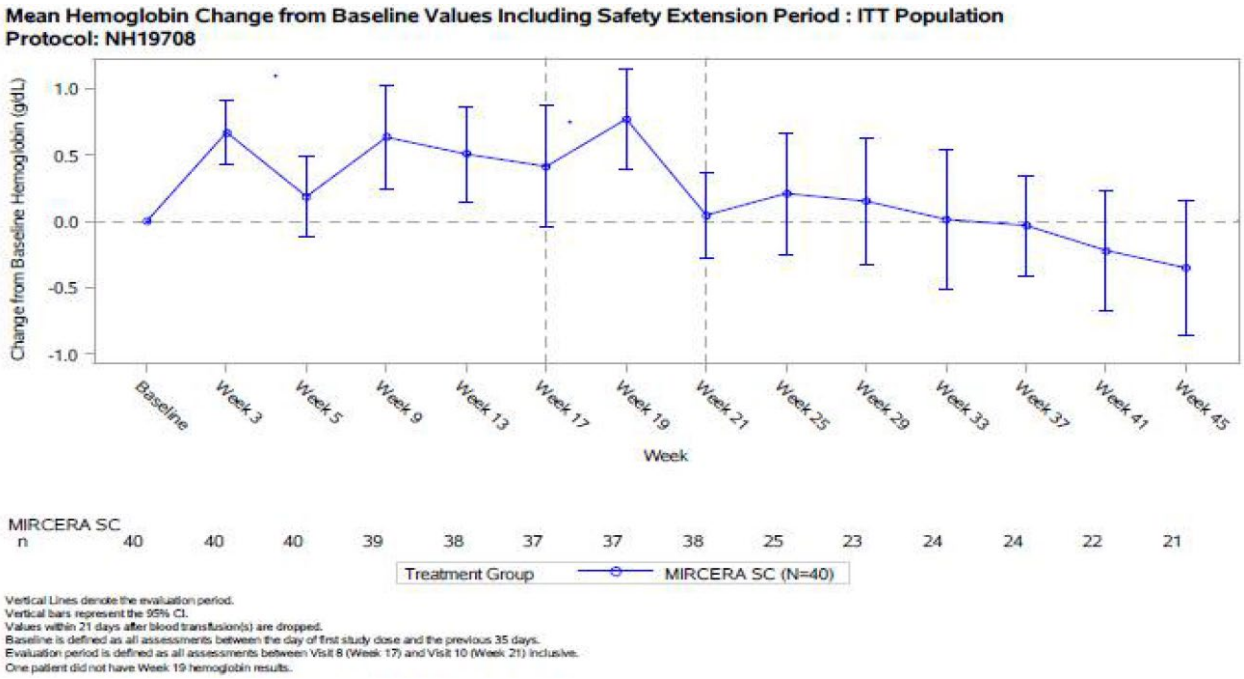
Applicant generated table; Table 13 in the clinical study report, Report Number 1109997

Figure 2. Mean Hb Values throughout Study NH19708 for the ITT Population



Applicant generated figure; Figure 9 in the clinical study report, Report Number 1109997

Figure 3. Mean Hb Change from Baseline for the ITT Population



Applicant generated figure; Figure 10 in the clinical study report, Report Number 1109997

Overall, the results of the mean change in Hb concentration levels by age group, dialysis status at the start of the study, and previous ESA treatment were fairly similar, and were consistent with the results of the primary endpoint during the evaluation period. For secondary endpoints, 24 patients (63.2%) maintained Hb concentration levels within the range of 10 to 12 g/dL, 19 patients (50%) maintained Hb concentration levels within the range of $\pm$ 1 g/dL of the baseline value, and 18 patients (47.4%) maintained Hb concentration levels within both the ranges of 10 to 12 g/dL and $\pm$ 1 g/dL of the baseline Hb concentration levels (Table 6). During the core period, the mean Hb concentration levels were maintained within 10 to 12 g/dL.

During the safety extension period, mean Hb concentrations remained within 10 to 12 g/dL. The Hb concentration levels were maintained within 10 to 12 g/dL in 60.9% to 91.7% of patients and within $\pm$ 1 g/dL of the baseline Hb value in 57.1% to 77.3% of patients from Weeks 25 to 45 (Tables 7 and 8).

Table 6. Summary of Patients Maintaining Stable Hb during the Evaluation Period for the ITT Population

	MIRCERA SC (N=40)
Hb within +/- 1 g/dL of Baseline	
n	38
Above +1 g/dL	15 (39.5%)
Maintained	19 (50.0%)
Below -1 g/dL	4 (10.5%)
Hb within 10-12 g/dL	
n	38
Above 12 g/dL	12 (31.6%)
Maintained	24 (63.2%)
Below 10 g/dL	2 (5.3%)
Hb within +/- 1 g/dL of Baseline and within 10-12 g/dL	
n	38
Yes	18 (47.4%)
No	20 (52.6%)

Applicant generated table; Table 15 in the clinical study report, Report Number 1109997

Table 7. Summary of Patients Maintaining Stable Hb over Time within 10-12 g/dL Including the Safety Extension Period for the ITT Population

		Hemoglobin [g/dL]		
Treatment / Study Week	n	Below 10 g/dL	Maintained	Above 12 g/dL
MIRCERA SC (N=40)				
Baseline (Day -35 to Day 1)	40	0	39 (97.5%)	1 (2.5%)
Week 3	40	1 (2.5%)	19 (47.5%)	20 (50.0%)
Week 5	40	3 (7.5%)	28 (70.0%)	9 (22.5%)
Week 9	39	4 (10.3%)	18 (46.2%)	17 (43.6%)
Week 13	38	4 (10.5%)	20 (52.6%)	14 (36.8%)
Week 17	37	4 (10.8%)	22 (59.5%)	11 (29.7%)
Week 19	37	2 (5.4%)	17 (45.9%)	18 (48.6%)
Week 21	38	4 (10.5%)	27 (71.1%)	7 (18.4%)
Evaluation Period (Weeks 17 - 21)	38	2 (5.3%)	24 (63.2%)	12 (31.6%)
Week 25	25	2 (8.0%)	18 (72.0%)	5 (20.0%)
Week 29	23	3 (13.0%)	14 (60.9%)	6 (26.1%)
Week 33	24	3 (12.5%)	19 (79.2%)	2 (8.3%)
Week 37	24	0	22 (91.7%)	2 (8.3%)
Week 41	22	3 (13.6%)	17 (77.3%)	2 (9.1%)
Week 45	21	5 (23.8%)	13 (61.9%)	3 (14.3%)

Applicant generated table; Table 23 in the clinical study report, Report Number 1109997

Table 8. Summary of Patients Maintaining Stable Hb over Time within Baseline ± 1 g/dL Including the Safety Extension Period for the ITT Population

		Hemoglobin [g/dL]		
Treatment / Study Week	n	Below -1 g/dL	Maintained	Above +1 g/dL
MIRCERA SC (N=40)				
Week 3	40	1 (2.5%)	29 (72.5%)	10 (25.0%)
Week 5	40	3 (7.5%)	30 (75.0%)	7 (17.5%)
Week 9	39	2 (5.1%)	21 (53.8%)	16 (41.0%)
Week 13	38	3 (7.9%)	23 (60.5%)	12 (31.6%)
Week 17	37	4 (10.8%)	22 (59.5%)	11 (29.7%)
Week 19	37	3 (8.1%)	18 (48.6%)	16 (43.2%)
Week 21	38	6 (15.8%)	24 (63.2%)	8 (21.1%)
Evaluation Period (Weeks 17 - 21)	38	4 (10.5%)	19 (50.0%)	15 (39.5%)
Week 25	25	5 (20.0%)	15 (60.0%)	5 (20.0%)
Week 29	23	2 (8.7%)	16 (69.6%)	5 (21.7%)
Week 33	24	4 (16.7%)	18 (75.0%)	2 (8.3%)
Week 37	24	4 (16.7%)	17 (70.8%)	3 (12.5%)
Week 41	22	3 (13.6%)	17 (77.3%)	2 (9.1%)
Week 45	21	6 (28.6%)	12 (57.1%)	3 (14.3%)

Applicant generated table; Table 24 in the clinical study report, Report Number 1109997

Immunogenicity:

A total of 131 samples were tested for anti-Mircera and anti-EPO antibodies. There were 2 positive samples for anti-Mircera antibodies, and 4 positive samples for anti-EPO antibodies in 2 patients.

One patient had a positive sample for both anti-Mircera and anti-EPO antibodies at Week 21, with titers of 1:1.56 and 1:29.8, respectively. The Week 9 sample was negative for both anti-Mircera and anti-EPO antibodies. The baseline (Week 1) and end-of-study (Week 45) samples for this patient were unfit for analysis due to incorrect handling, so the initial or final status for this patient is unknown. The patient continued to receive Mircera treatment after the end of the study. The patient was recalled for an additional ADA sample about 7 months after the end of the study visit, and they tested negative for both anti-Mircera and anti-EPO antibodies.

One patient had a positive sample for anti-Mircera antibodies at Week 1, with a titer of 1:1.32 and 1:1.56 for anti-Mircera antibodies and anti-EPO antibodies, respectively. Although the patient was positive for anti-Mircera antibodies, they had never been treated with Mircera before. This patient also tested positive for anti-EPO antibodies at Weeks 9 and 21 with titers of 1:3.20 and 1:8.77, respectively. Tests for anti-Mircera antibodies were negative at these timepoints. Samples taken at Week 45 were negative for both anti-Mircera and anti-EPO antibodies.

Per the Applicant, neither patient had evidence of anti-erythropoietin antibody-mediated pure red cell aplasia, and both patients continued to show response to Mircera treatment.

Safety:

During the core period, the pattern of adverse events (AEs) was similar to the established safety profile of Mircera in patients older than 6 years of age. No new safety signals were detected. 32 patients (80%) experienced at least one AE. 106 AEs were reported during the core period. 13 patients (32.5%) experienced serious AEs (SAEs); however, the investigator did not consider any of these SAEs related to Mircera treatment, and none resulted in withdrawal, dose modification, or dose interruption. 6 patients (15%) had AEs of severe intensity. 2 patients (5%) each reported AEs leading to dose modification/interruption. 1 patient (2.5%) required blood transfusion.

During the safety extension period, 16 patients (64%) experienced at least 1 AE. 53 AEs were reported in the safety extension period. 3 patients (12%) each experienced SAEs and AEs of severe intensity. 1 patient (4%) experienced an AE considered by the investigator related to Mircera. 1 patient (4) required a blood transfusion. No patient experienced an AE leading to treatment withdrawal, dose modification, or dose interruption during the safety extension period.

CONCLUSION

The Applicant concludes that the primary endpoint was met, as the mean (± SD) change in Hb concentration during the evaluation period showed a 0.48 (1.03) g/dL increase above the baseline

level, the 90% CI for change in Hb concentration levels from baseline was within the range of ± 1 g/dL, and the SD was < 1.5. In the core period, 63.2% of patients maintained Hb concentration levels within the range of 10 to 12 g/dL, 50% maintained Hb concentration levels within the range of ± 1 g/dL of the baseline value, 47.4% maintained Hb concentration levels within both the ranges of 10 to 12 g/dL and ± 1 g/dL of the baseline Hb concentration levels, and the mean Hb concentration levels overall were maintained within 10 to 12 g/dL. During the safety extension period, mean Hb concentrations remained within 10 to 12 g/dL, Hb concentration levels were maintained within 10 to 12 g/dL in 60.9% to 91.7% of patients, and 57.1% to 77.3% of patients maintained Hb within ± 1 g/dL of baseline from Weeks 25 to 45. The AE profile observed during the core study period or the optional safety extension did not reveal any unexpected safety concerns. Therefore, the Applicant concludes that pediatric patients with CKD on dialysis or not yet on dialysis can be safely and effectively switched from previous treatment with epoetin alfa/beta or darbepoetin to Mircera administered subcutaneously for maintenance treatment of anemia.

The review team evaluated the appropriateness of the starting doses. Although the data showed patients with Hb >12 g/dL at Weeks 3, 5, or 9 (timepoints following the transition to Mircera), indicative of the Mircera starting doses being higher, this was not a significant concern for safety, as the risk for cardiovascular events are not necessarily applicable to pediatric patients whose Hb levels are generally higher compared to adults (also refer to clinical review). Moreover, any increase in Hb is expected to be transient, as Mircera starting doses can be titrated subsequently based on response. Therefore, the proposed Mircera starting doses and the instructions for dose adjustment are acceptable for subcutaneous administration in pediatric patients converting from another ESA.

Based on the results from this study, the Applicant proposed (b) (4) however, the Applicant did not submit data to support (b) (4) (b) (4) Safety could not be extrapolated, so FDA recommended to the Applicant that Mircera should be labeled so pediatric patients younger than 6 years of age should maintain the same route of administration as that of their previous ESA while transitioning to Mircera. This is to ensure pediatric patients younger than 6 years of age do not transition from the subcutaneous to the intravenous route of administration while transitioning from another ESA to Mircera. The Applicant agreed and updated the label accordingly.

Table 9. Summary of the Pediatric Studies and Number of Patients Contributing PK and Hb Data into the Analysis

Study	Phase	Route	Treatment setting	Age Groups	Number of patients not on dialysis	Number of patients on Peritoneal dialysis	Number of patients on hemodialysis
NH19707	II	IV	Maintenance	2-6 y	-	-	1
				7-11 y	-	-	24
				12-18 y	-	-	38
NH19708	II	SC	Maintenance	3mo-2y	3	1	-
				2-6 y	4	4	-
				7-11 y	3	2	1
				12-18 y	7	11	4
				3mo-2y	9	3	-
(Combined)	II	IV or SC	Maintenance	2-6 y	12	12	3
				7-11 y	9	6	75
				12-18 y	21	33	126

IV: intravenous; SC: subcutaneous. NH19707 had a total of 63 patients with PK and Hb data. NH19708 had a total of 40 patients with PK and Hb data.

Applicant generated table; Table 3-2 in Certara Reference No: ROCH-PMX-MIRCERA-2969 Final Report

Considering the results from study NH19708, PMR 3385-1 has been fulfilled.

17 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX 3 – PHARMACOMETRICS REVIEW

1. POPULATION PK ANALYSIS

1.1 Review Summary

In general, the applicant's population PK (PopPK) analysis is considered acceptable for the purpose of characterizing the PK profile of MIRCERA (methoxy polyethylene glycol-epoetin beta) in adult patients on dialysis and not on dialysis, pediatric patients 3 months to 17 years of age on dialysis or not on dialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA. The applicant's analyses were verified by the reviewer, with no significant discordance identified. More specifically, the model was used to support the current submission as outlined in **Table 1.**

Table 1. Specific Comments on Applicant's Final Population PK model

Utility of the final model			Reviewer's Comments
Support applicant's proposed labeling statements about intrinsic and extrinsic factors	**Intrinsic factor**	Same as original label: The pharmacokinetics of methoxy polyethylene glycol-epoetin beta were not altered by age (range: 6 to 89 years), gender, race, severe hepatic impairment (Child-Pugh Class C), site of subcutaneous injection (abdomen, arm or thigh), or the use of dialysis. Added in current supplement: A population pharmacokinetic analysis was performed with data from 103 pediatric patients ages 6 months to 17 years and 524 adult patients. Pediatric patients received Mircera intravenously (N=63, all on hemodialysis) or subcutaneously (total N=40, n=17 on pre-dialysis, n=18 on peritoneal dialysis and n=5 on hemodialysis). The covariate analysis showed a positive body weight effect on clearance (CL) and volume of distribution (V), and a positive age effect on V. Once those covariate effects were taken into account together with the addition of a pediatric subcutaneous bioavailability of 67%, compared to 31% in adults, no differences could be observed in the pharmacokinetic properties of Mircera in pediatric patients compared to adult patients.	The reviewer agrees with the proposed added language in current supplement. See Section 1.4 for details. There is no patient enrolled with the age ranging from 3 months to 2 years old and receiving the MIRCERA via IV route, which may limit the PopPK model accuracy when describes this specific patient population. Considering there is potential difference in bioavailability between pediatric and adult (2.18 fold higher in pediatric for SC route), it is better to switch with the same route of administration for patients whose hemoglobin have been stabilized by treatment with an ESA.
	Extrinsic factor	N/A	N/A

1.2 Introduction

The primary objectives of applicant's analysis were to:

- To update the adult population PK model for MIRCERA by pooling data from Phase II (BA16260, BA16528) and Phase III (BA16736, BA16739, BA16740) studies in adult patients with the IV pediatric NH19707 and SC pediatric NH19708 studies, to assess the PK properties of MIRCERA in pediatric patients, and especially to assess the relative bioavailability of the SC versus the IV administrations;
- To generate population PK posthoc estimates to be used in the sequential PK/PD analysis;
- To update the previous PK/PD analysis for MIRCERA by including NH19708 pediatric SC data in patients that are on hemo-, peritoneal or not yet on dialysis and to assess whether PD properties of MIRCERA in pediatric patients differ from those seen in adults;
- To compare the clinical trial data from NH19708 and PK/PD model predictions to real world data obtained through the IPDN registry (study MH40258).

1.3 Model development

Data

The PopPK model previously developed based on adult Phase II/III + NH19707 was first challenged against Study NH19708 data to check its predictive performance and to highlight any deviation from the current knowledge of Mircera PK. Then the PK model was updated by pooling Study NH19708 data with historical adult and pediatric PK data and the estimation of the bioavailability of the SC formulation in pediatric patients was performed. The PK dataset comprised 6727 data points in 627 patients, which includes 5883 data points from 524 adults and 881 data points from 103 children. Brief descriptions of the studies included are presented in **Table 2**.

The PopPK analysis was performed using Phoenix NLME (nonlinear mixed effect) (build 8.3.0.4720) with the FOCE-ELS engine. PopPK model qualification was simulated with Phoenix VPC procedure. Exploratory data analyses and post-processing of model and simulation outputs were performed using R® Version 4.1.0. PopPK model qualifications were simulated using Phoenix VPC procedure. The simulations were then post processed using the R package tidyvpc 1.0. **Table 3** provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 2. Summary of Studies with PK Sampling Included in Population PK Analysis

Study	Phase	Route	Treatment Setting	Number of Patients with PK and Hb data	Number of Patients not on dialysis	Number of Patients on Peritoneal dialysis	Number of Patients on hemodialysis

Adult							
BA16260	II	SC	Correction	59	--	19	40
BA16528	II	SC	Correction	65	65	--	--
BA16736	III	IV	Correction	135	--	3	132
BA16739	III	IV	Maintenance	122	--	--	122
BA16740	III	SC	Maintenance	143	--	11	132
Pediatric							
				Age Groups			
NH19707*	II	IV	Maintenance	2-6 years	--	--	1
				7-11 years	--	--	24
				12-18 years	--	--	38
NH19708*,#	II	SC	Maintenance	3 mo-2 years	3	1	--
				2-6 years	4	4	--
				7-11 years	3	2	1
				12-18 years	7	11	4

**: The starting dose is calculated using conversion factor as below:*

Mircera starting dose=4×previous weekly epoetin dose [IU]/125

or

Mircera starting dose=4×previous weekly darbepoetin dose [μg]/0.55

Then the dose of Mircera is adjusted upwards or downwards in each patient based on the Hb concentration measured every four weeks for the maintenance of Hb concentration.

#: In Table 3-2 of PopPK report, there is a mistake in subject number counting in the row of "combined" which ideally should provide sum of the patient's number of two pediatric studies #19707 and 19708. However, the applicant provided sum patient number did not match with the add up of two studies. The reviewer verified with information in applicant proposed labeling and Table 3-3 that the individual subject counting for each study is correct. The original "combined" column is removed by reviewer.

Source: Table adapted from Table 3-1, 3-2, and 3-3, Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis of MIRCERA in Pediatric Patients (Study No. NH19708 (Skipper) and MH40258, No. ROCH-PMX-MIRCERA-2969

Table 3. Summary of Baseline Demographic Covariates for Analysis*

	NH19707			NH19708			
	2-6 y (N=1)	7-11 y (N=24)	12-18 y (N=38)	3mo-2y (N=4)	2-6 y (N=8)	7-11 y (N=6)	12-18 y (N=22)
Dialysis							
pre	0 (0%)	0 (0%)	0 (0%)	3 (75.0%)	4 (50.0%)	3 (50.0%)	7 (31.8%)
peritoneal	0 (0%)	0 (0%)	0 (0%)	1 (25.0%)	4 (50.0%)	2 (33.3%)	11 (50.0%)
hemo	1 (100%)	24 (100%)	38 (100%)	0 (0%)	0 (0%)	1 (16.7%)	4 (18.2%)
Weight (kg)							
Mean (SD)	24.3 (NA)	26.8 (5.53)	44.2 (13.5)	7.81 (0.731)	13.5 (2.44)	24.8 (4.85)	49.1 (16.1)
Median	24.3	26.5	42.7	7.97	14.0	26.5	47.6
[Min, Max]	[24.3,24.3]	[17.7,41.6]	[19.3,85.4]	[6.90, 8.40]	[9.10,16.3]	[17.0,29.8]	[26.6,90.0]
Age (years)							
Mean (SD)	6.00 (NA)	9.21 (1.47)	14.8 (1.44)	0.975 (0.608)	3.64 (0.521)	9.42 (1.80)	14.7 (2.31)
Median[Min,	6.00	9.00	15.0	1.00	3.50	10.2	15.0
Max]	[6.00, 6.00]	[7.00, 11.0]	[12.0, 17.0]	[0.400,1.50]	[3.10, 4.60]	[6.40, 11.0]	[11.1, 17.7]
Sex							
Female	1 (100%)	9 (37.5%)	20 (52.6%)	1 (25.0%)	4 (50.0%)	3 (50.0%)	9 (40.9%)
Male	0 (0%)	15 (62.5%)	18 (47.4%)	3 (75.0%)	4 (50.0%)	3 (50.0%)	13 (59.1%)

mo = months of age; y = years of age; SD = Standard Deviation
**The applicant did not provide the summary of baseline covariates for clinical studies in adults, which is the basis of approval of original application BLA 125164 in 11/14/2007. These data were combined with pediatric data and also used in current PopPK analysis.*
Source: Table 3-3, Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis of MIRCERA in Pediatric Patients (Study No. NH19708 (Skipper) and MH40258, No. ROCH-PMX-MIRCERA-2969

The applicant also conducted a real-world clinical study #MH40258 "Real Word Evidence of Safety and Dosing of MIRCERA in Children with Chronic Kidney Disease", which was used to compare the predication from PK/PD model. The patient information in the real-world study is listed in **Table 4** below.

Table 4. Summary of real-world patient data

Study	Route	Treatment setting	Age Groups	Number of patients on Peritoneal dialysis	Number of patients on hemodialysis	All Patients
MH40258	IV	Maintenance	3mo-2y	1		1
			2-6 y	18	3	21
			7-11 y	7	15	22
			12-18 y	14	31	45
	SC	Maintenance	3mo-2y	10		10
			2-6 y	5		5
			7-11 y	14		14
			12-18 y	38	1	39

IV: intravenous; SC: subcutaneous. Patients with more than one Route of administration or with missing Route of administration were excluded.
Source: Table 3-4, Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis of MIRCERA in Pediatric Patients (Study No. NH19708 (Skipper) and MH40258, No. ROCH-PMX-MIRCERA-2969

Base model

The PK model previously developed based on adult and Pediatric NH19707 data was a 1-compartment model with first order absorption rate (Ka) and elimination rate (Ke), which was developed based on 5 adult Phase II/III studies and NH19707 study. The previous PopPK model was challenged against study NH19708 data, then updated by pooling study NH19708 with historical adult and pediatric PK data. The estimation of the bioavailability of the SC formulation in pediatric patients was also performed. Please see details of previous PopPK model in clinical pharmacology review dated 5/21/2018[1].

Covariate analysis

The covariates search focused on the relative bioavailability in pediatric versus adult patients. Difference between pediatric and adults was investigated by using either a pediatric flag or an effect of age on the relative bioavailability. The investigation of the effect of the following covariates including age, sex, treatment setting, dialysis modality and route of administration were conducted graphically using the random effect (ETAs).

1.4 Final Model

The parameter estimates for the final covariate model are listed in **Table 5**. The model described the observed data adequately, as seen in the goodness-of fit plots (**Figure 1**).

Table 5. Parameter estimates of the final PopPK model

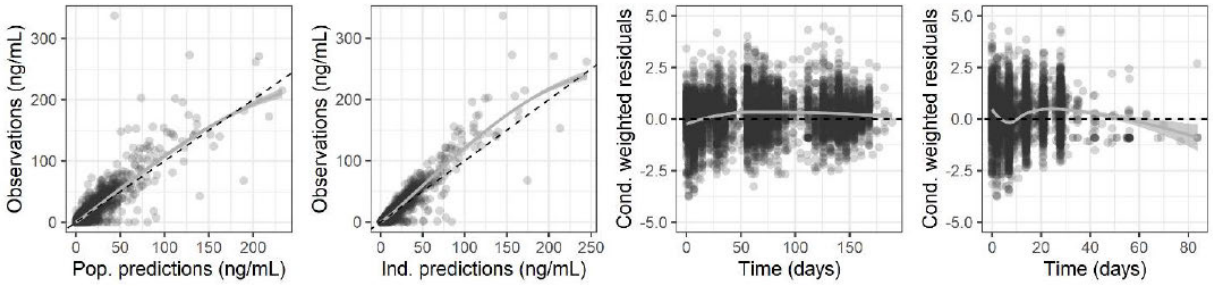
Parameter	Unit	Estimate	SE	RSE (%)	Variability (%)	Shrinkage (%)
Fixed Effects						
CL	L/day	0.718	0.0179	2		
V	L	3.452	0.1278	4		
Ka-Ke	1/day	0.276	0.0398	14		
F		0.308	0.0177	6		
Random Effects (variance)						
BSV CL		0.225	0.036	16	47	8
BSV V		0.125	0.017	13	35	23
BSV Covariance CL-V		0.097	0.020	21	correlation 0.58	
IOV CL		0.0193	0.003	17	13	
Covariate effects					**Covariate form**	
Body weight on CL		0.772	0.058	8	x(Weight/67.5)^dCLdWeight	
Body weight on V		0.625	0.061	10	x(Weight/67.5)^dVdWeight	
Age on V		0.233	0.032	14	x(Age/18)^dVdAge	
Pediatric Effect on F		0.780	0.119	15	x exp((ped==1)*dFdped)	
Pediatric Frel		**0.671**			**F x exp(0.780)= F x 2.18**	
Residual variability			**CObs = 0.15 + C + CEps* (C+0.15*CMixRatio)**			
Proportional (%)		0.379	0.009	2	Modified double exponential error	
tvCMixRatio		1.473	0.080	5	model with 0.15 as correction factor	
Additive part variance		0.678			Add var = (0.379*tvCMixRatio^2)^2	

RSE%: relative standard error; Pediatric Frel: pediatric flag
Source: Table 4-1, Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis of MIRCERA in Pediatric Patients (Study No. NH19708 (Skipper) and MH40258, No. ROCH-PMX-MIRCERA-2969

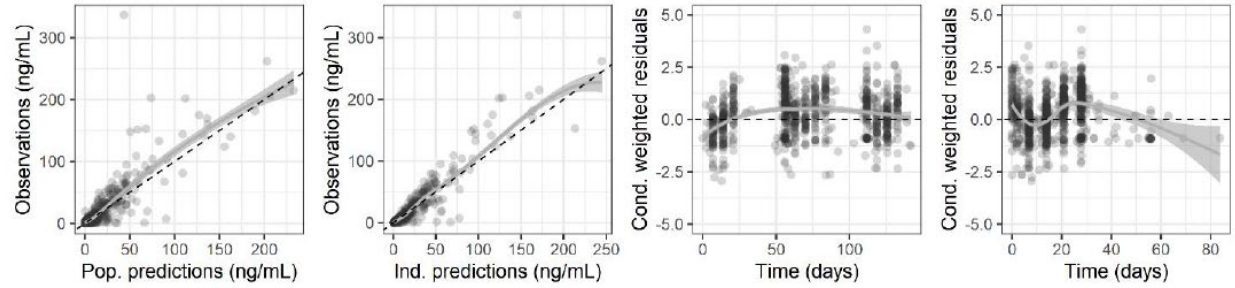
Figure 1. Goodness-of-Fit Plots for final PopPK model

[1] DARRTS, BLA 125164, Li, Liang, 5/21/2018, Rev-CLINPHARM-21 (Primary Review), Supplement-13

All pooled data



Pediatric Data

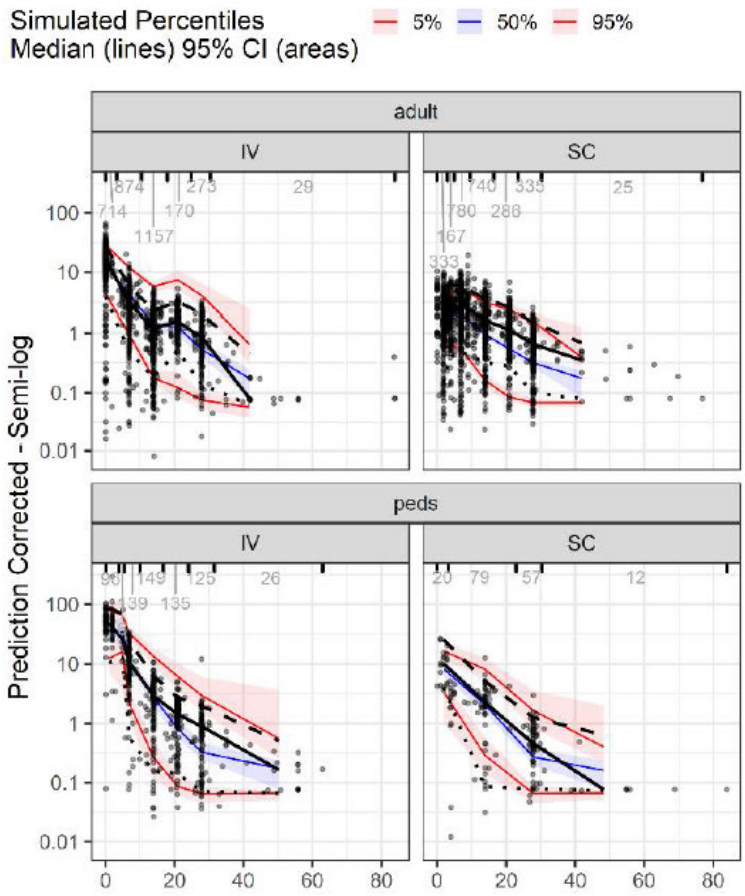


Pop. predictions: population predictions; Ind. Predictions: individual predictions; Cond. weighted residuals: conditional weighted residuals; Grey line: LOESS (locally weighted scatterplot smoothing) and Grey areas: loess associated confidence intervals;
Dashed line: identity line or y=0 line.
Source: Figure 4-2, Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis of MIRCERA in Pediatric Patients (Study No. NH19708 (Skipper) and MH40258, No. ROCH-PMX-MIRCERA-2969

Based on PopPK result, the SC route bioavailability in pediatric patients was estimated to be 2.18-fold (coming from exp 0.780 which is pediatric effect estimate on F in PopPK estimates) higher than in adults. The other estimates such as CL, V, and body weight effects on CL and V were similar as previous PopPK model. There was no impact of dialysis modality.

A prediction-corrected visual predictive check (pcVPC) was performed to ensure that the model maintained fidelity with the observed Mircera PK data. Model based simulations of 1000 replicates of the original data sets were performed. Simulated and observed distributions were compared by calculating the median, 5th, and 95th percentiles for each time interval (**Figure 2**). Overall, the central tendency and the variability in pediatric patients were well captured by the PopPK model for both IV and SC routes of administration.

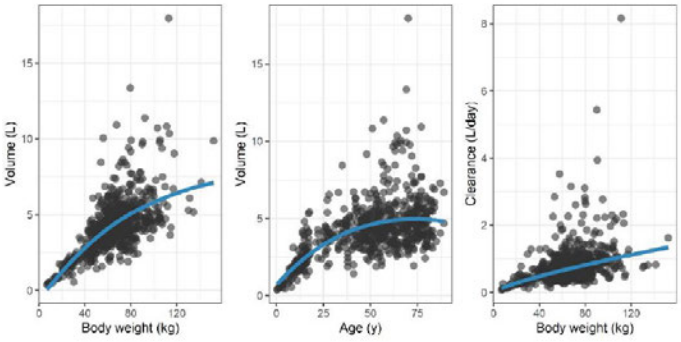
Figure 2. pcVPC plots for final PopPK model



The gray numbers on the top of each panel are the N of observed data in each bin. The vpc is shown with a linear axes on the left and a semi-log (log y, linear x) on the right.
Source: Figure 4-5, Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis of MIRCERA in Pediatric Patients (Study No. NH19708 (Skipper) and MH40258, No. ROCH-PMX-MIRCERA-2969

The impact of the covariates of interest on MIRCERA PK was assessed by graphical evaluation (**Figure 3**). There is trend for positive body weight effect on clearance (CL) and volume of distribution (V), and a positive age effect on V.

Figure 3. Parameter-Covariate Relationship predicted by final PopPK model



The blue line is the model predicted parameter as per the final model parameter equation. Parameter = function of covariates as per the final model equation, the points are the empirical bayes estimates (EBE)'s.
Source: Figure 4-4, Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis of MIRCERA in Pediatric Patients (Study No. NH19708 (Skipper) and MH40258, No. ROCH-PMX-MIRCERA-2969

1.5 PK simulation based on PopPK model

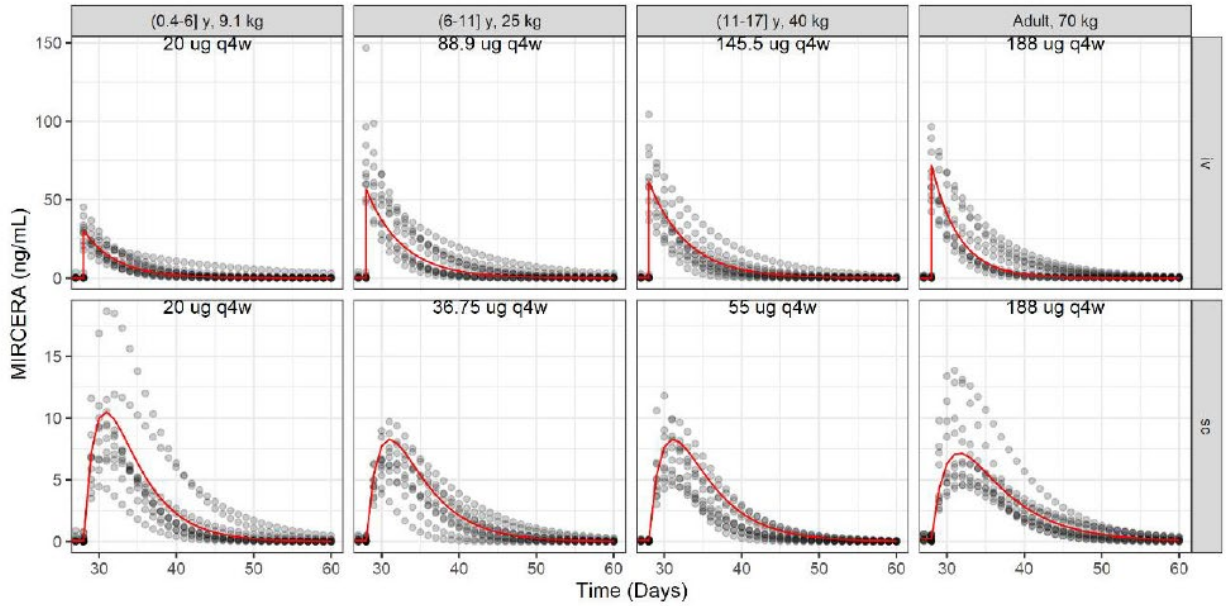
Typical simulations based on the final PK model were performed to compare the expected MIRCERA concentration-time profile at steady state (second dosing interval) in adult and pediatric patients in clinical practice. Simulations were performed for MIRCERA administered IV or SC in the following scenarios:

1. A typical child below the age of 6 years category: 3.1 years old, 9.1 kg, median SC or IV maintenance dose of 20 µg (data from NH19708).
2. A typical child representing the 6-11 years age category: 9 years old, 25 kg, median IV maintenance dose of 88.9 µg (data from NH19707) and SC maintenance dose of 36.75 µg (data from NH19708).
3. A typical adolescent representing the 12-17 years age category: 15 years old, 40 kg, median IV maintenance dose of 145.5 µg (data from NH19707) and SC maintenance dose of 55 µg (data from NH19708).
4. A typical adult: 55 years old, 70 kg, median maintenance dose of 188 µg every 4 weeks (data from BA16739).

The results are shown in **Figure 4**. Based on the results, the range of MIRCERA concentrations are similar between pediatric and adult patients following IV administration. The maximum MIRCERA concentration in pediatric patients was similar to a typical adult patient following SC administration, which is potentially due to the higher SC bioavailability in pediatric patients than adult could lead to lower maintenance doses after SC administration comparing to IV route. Based on the simulation, the MIRCERA concentration ratio between IV and SC is higher in adult than pediatric for individual simulated patient between 0.4-17 years old range. Per approved MIRCERA label[2], adult and pediatric (5 to 17 years old) use the same conversation factor for IV and SC route starting dose for patients whose hemoglobin has been stabilized by treatment with an ESA. In current supplement, the applicant proposed to use the same conversation factor for starting dose of adult and pediatric patients (3 months to 17 years old) who are converting from another ESA after their hemoglobin level was stabilized with an ESA. The reviewer deems it is acceptable to use the same conversation factor for IV and SC routes starting dose for current proposed pediatric age range (3 months to 17 years old) as the MIRCERA concentration is more similar in IV and SC route in pediatric than adult patient based on simulation result and the clinical dose will be adjusted based on response. However, there is no patient enrolled with the age ranging from 3 months to 2 years old and receiving the MIRCERA via IV route, which may limit the PopPK model accuracy when describes this specific patient population. Considering there is potential difference in bioavailability between pediatric and adult (2.18 fold higher in pediatric for SC route), it is better to switch with the same route of administration for patients whose hemoglobin have been stabilized by treatment with an ESA.

Figure 4. Typical PK Simulations in Patients of Different Age Categories Receiving MIRCERA for Maintenance of Hb Levels

[2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125164s087lblcorrection.pdf



The red lines are the population predictions. The individual points are profiles from random simulation with between subject variability N =10.
Source: Figure 4-6, Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis of MIRCERA in Pediatric Patients (Study No. NH19708 (Skipper) and MH40258, No. ROCH-PMX-MIRCERA-2969

2. POPULATION PK/PD ANALYSIS

2.1 Review Summary

In general, the population PK/PD model could be used for simulation purpose to confirm the appropriateness of the proposed general dosing regimen using the conversion factor for the treatment of anemia associated with CKD in pediatric patients (3 months to 17 years old) on dialysis or not on dialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

2.2 Methods

The PK/PD model developed on adult Phase II/III data and later updated after including Study #NH19707 were used as a starting point for analysis. It is a sequential PK/PD model where individual Empirical Bayesian Estimates (EBEs) of PK parameters for MIRCERA were used to derive the concentration of MIRCERA at any time which drove the drug effect (see below). In the latest PK/PD analysis including NH19707's pediatric data, body weight was added as a covariate on Hb_0 to explain the adult to pediatric differences[3].

$$Hb'(t) = S(t) - S(t - LS) + S_{ESA}$$
$$S(t) = Hb_0 / LS * (1 + E(C(t)))$$
$$S_{ESA} = (Hb_0 - Hb_{sw}) / LS \quad if\ 0 \le t \le LS \text{ otherwise } S_{ESA} = 0$$
$$E(C(t)) = S_{max} * C(t) / (SC_{50} + C(t))$$

Hb' [(g/dL)/d]: the change in hemoglobin concentration over time; LS [d]: the apparent lifespan of Red Blood Cells (RBCs); Hb_0 [g/dL]: the hemoglobin concentration at baseline without any ESA treatment; S(t) [(g/dL)/d] and its LS-delayed value S(t-LS) describe the production and elimination of Hb, respectively. Hb_0/LS: the production rate of Hb at baseline which is considered to be constant during one LS before time of Hb_0 assessment. S(t): the relative change in baseline Hb production and is related to C(t) via an Emax type model with parameters Smax and SC_{50}. Smax: the maximum increase in Hb production rate relative to Hb baseline production rate; SC_{50}: the concentration of MIRCERA at which 50% of the maximum increase is achieved. Individual drug concentrations C(t) for the PD model were calculated from individual EBEs of PK parameters based on the final population PK model. S_{ESA}: introduced for the maintenance treatment condition, corresponding to the Hb loss rate due to the interruption of former ESA treatment after switch to MIRCERA, only valid during one LS after the switch. Hbsw [g/dL]: the hemoglobin concentration at switch from previous epoetin treatment to MIRCERA.

Source: Section 3.3.1, Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis of MIRCERA in Pediatric Patients (Study No. NH19708 (Skipper) and MH40258, No. ROCH-PMX-MIRCERA-2969

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

[3] DARRTS, BLA 125164, Li, Liang, 05/21/2018, Rev-ClinPharm-21 (Primary Review), Supplement-13 (CMC)

A visual comparison of the clinical trial data after IV administration (NH19707) and SC administration (NH19708) was planned to assess how they would compare to the real-world data collected in study MH40258, which was a non-interventional study to further characterize the safety and efficacy of MIRCERA in pediatric patients in a real-world-data (RWD) setting.

The PK/PD analysis work was performed using Phoenix NLME (build 8.3.0.4720) with QRPEM (quasi-random parametric expectation maximization) algorithm engine. Exploratory data analyses and post-processing of model and simulation outputs were performed using R® Version 4.1.0. PK/PD model qualifications were simulated using in Pharsight® Trial SimulatorTM version 2.3 (PK/PD with dose titration). The simulations were then post processed using the R package tidyvpc 1.0.

2.3 Results

The parameter estimates of the final PK/PD model are listed in **Table 6**. The goodness fitting plot is shown in **Figure 5**. Random effects of final PK/PD model versus covariates such as dialysis, age and weight are shown in **Figure 6**.

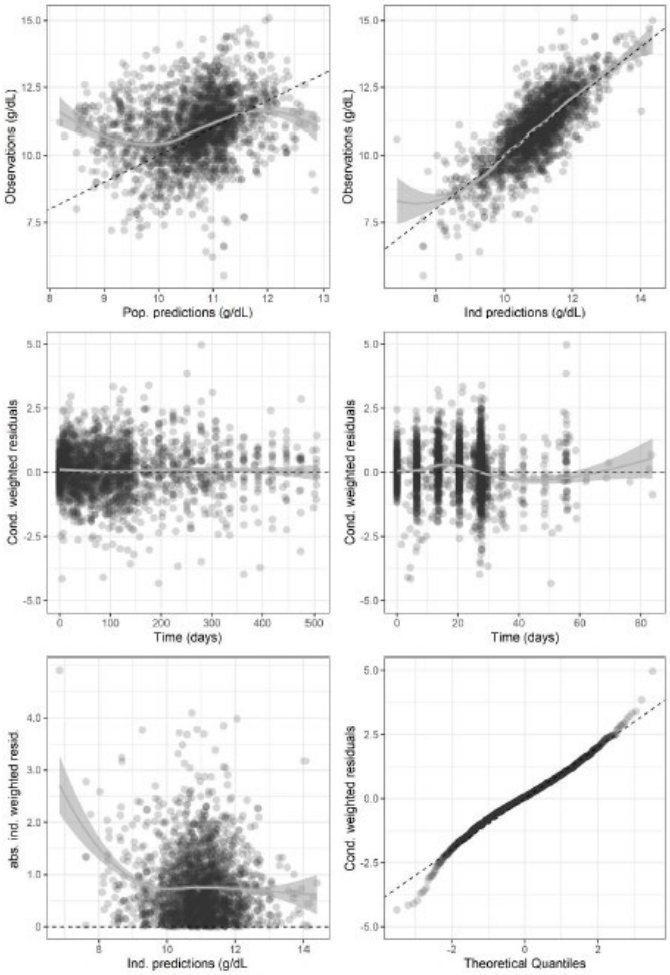
Table 6. Parameter estimates of the final PK/PD model

Parameter	Unit	Estimate	SE	RSE (%)	Variability (%)	Shrinkage (%)
Fixed Effects						
S_{max}		0.425 fixed				
SC_{50}	ng/mL	0.898 fixed				
LS	day	82.33	2.586	3		
Hb_0	g/dL	9.44	0.205	2		
Random Effects (variance)						
S_{max}		1.637	0.130	8	128	20
SC_{50}		4.389	0.343	8	209	24
LS		0.146	0.020	14	38	23
Hb_0		0.041	0.004	10	20	20
Covariate effects					**covariate form**	
ESA dose on SC_{50}		0.295	0.072	24	x(ESA Dose/6000)^ESAdoseeff	
Hemo Dialyis Effect on HB0		0.86	0.018	2	x Effect when Dialysis = peritoneal	
Peritoneal Dialyis Effect on HB0		0.93	0.030	3	x Effect when Dialysis = hemodialysis	
Hemo Dialyis Effect on LS		0.62	0.024	4	x Effect when Dialysis = peritoneal	
Peritoneal Dialyis Effect on LS		0.82	0.061	7	x Effect when Dialysis = hemodialysis	
Residual variability (standard deviation)						
Additive	g/dL	0.76	0.007	1		

SE: standard error; RSE%: relative standard error

Source: Table 4-2, Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis of MIRCERA in Pediatric Patients (Study No. NH19708 (Skipper) and MH40258, No. ROCH-PMX-MIRCERA-2969

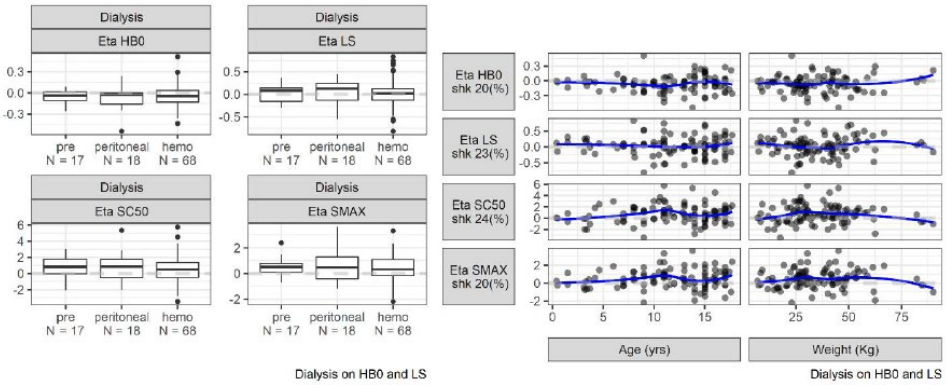
Figure 5. Goodness-of-Fit Plots for final PK/PD model in pediatric patients



Pop. predictions: population predictions; Ind. Predictions: individual predictions; Cond. weighted residuals: conditional weighted residuals; Ind. weighted residuals: individual weighted residuals; Grey line: LOESS (locally weighted scatterplot smoothing) and Grey areas: loess associated confidence intervals; Dashed line: identity line or y=0 line.

Source: Figure 4-13, Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis of MIRCERA in Pediatric Patients (Study No. NH19708 (Skipper) and MH40258, No. ROCH-PMX-MIRCERA-2969

Figure 6. Random effects of the final PK/PD model versus Dialysis, Age and Weight



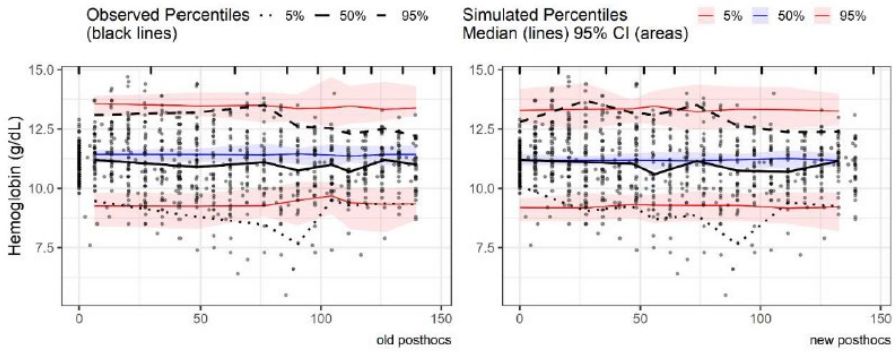
Source: Figure 4-14, Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis of MIRCERA in Pediatric Patients (Study No. NH19708 (Skipper) and MH40258, No. ROCH-PMX-MIRCERA-2969

The results above suggest the PK/PD model can adequately describe the Hb change over time due to MIRCERA effect in pediatric patients. There is no relevant trend for random effects of baseline hemoglobin (Hb_0), apparent lifespan of red blood cells (LS), the concentration of MIRCERA at which 50% of the maximum increase is achieved (SC_{50}) and the maximum increase in Hb production rate relative to Hb baseline production rate (Smax) versus dialysis type, age and body weight. Overall, the current PK/PD model is similar as the pervious one established with adults and pediatric patients from 5-17 years old [4], with the addition of hemo, peritoneal dialysis effect on Hb_0 and LS. Body weight effect on Hb_0 was removed in current PK/PD model which could reduce the underprediction of the low Hb values. Similar as previous PK/PD model, previous ESA dose can impact SC_{50} which is the concentration of MIRCERA at which 50% of the maximum increase is achieved. It supports the use of a conversion factor based on previous ESA dose in each patient to individualize the MIRCERA starting dose.

Model qualification in pediatric patients was performed using EBEs' based VPC including dose titration and are presented in **Figure 7**. Overall, the model-based simulations captured the central tendency of the data for both NH19707 and NH19708 studies. The applicant also conducted posterior predictive checks (PPC) of clinical endpoints including primary endpoint mean change in Hb between baseline and evaluation periods (g/dL), median dose at start of evaluation period week 17 (ug), and percentage of patients with mean Hb >12 g/dL during evaluation period Week 17-21. It is noted that the model predicted a lower percentage of patients Pct[95%CI] = 18.75[7.5-32.5%] (N=200 simulation replicates) that might experience at least once Hb > 12g /dL, however the observed percentage (95% prediction intervals, N=40) was 31.6%. The observed vs simulated ratio is within 1.1-1.2 for the other two evaluated endpoints.

Figure 7. VPC of Final PK/PD Model in Pediatric Patients

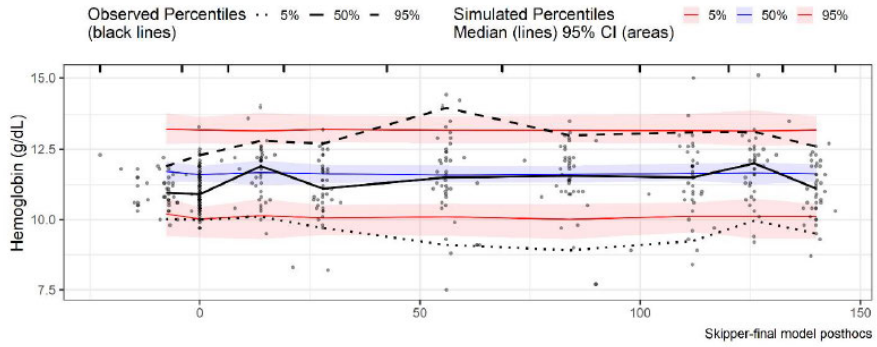
Study NH19707 receiving MIRCERA IV



Left panel is the post-hoc estimates using previous PK/PD model; right panel is the post-hoc estimate using the current PK/PD model

[4] DARRTS, BLA 125164, Li, Liang, 05/21/2018, Rev-ClinPharm-21 (Primary Review), Supplement-13 (CMC)

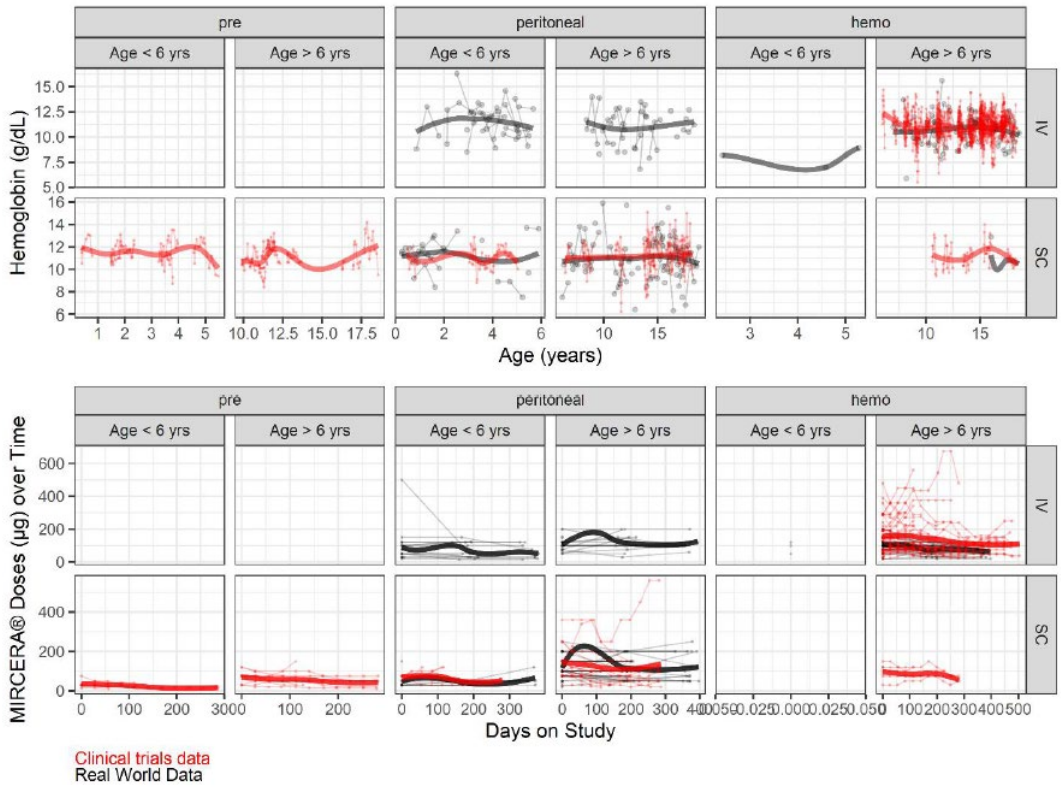
Study NH19708 receiving MIRCERA SC

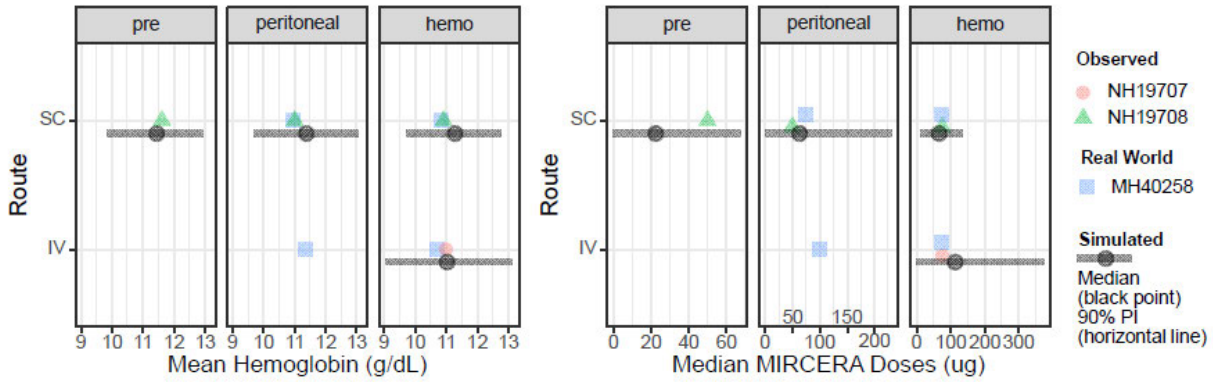


Source: Figure 4-15 and 4-16, Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis of MIRCERA in Pediatric Patients (Study No. NH19708 (Skipper) and MH40258, No. ROCH-PMX-MIRCERA-2969

A visual comparison of the clinical trials data (i.e., hemoglobin and MIRCERA dose time courses) after IV administration (NH19707) and SC administration (NH19708) was conducted to assess how they would compare to the real world data collected in Study #MH40258, and PK/PD model predictions (**Figure 8**).

Figure 8. Real world data compared to clinical data and PK/PD model predictions





Source: Figure 4-18, Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis of MIRCERA in Pediatric Patients (Study No. NH19708 (Skipper) and MH40258, No. ROCH-PMX-MIRCERA-2969

Overall, the clinical trial data spanned the same ranges and were similar to those collected from the real world study, which provided additional evidence that the clinical trial data could be reproduced in clinical practice. The simulation based on PK/PD model can capture the central tendency of key endpoints of interests (Hb concentration).

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