CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125164 S089
Priority or Standard	Standard
Submit Date(s)	6/30/2023
Received Date(s)	6/30/2023
PDUFA Goal Date	4/30/2024
Division/Office	DNH
Reviewer Name(s)	Julia Friend
Review Completion Date	Electronic Stamp
Established/Proper Name	methoxy polyethylene glycol-epoetin beta
(Proposed) Trade Name	Mircera
Applicant	Vifor (International) Inc
Dosage Form(s)	Intravenous injection or subcutaneous injection
Applicant Proposed Dosing Regimen(s)	Administer Mircera intravenously once every 4 weeks to pediatric patients (ages 3 months to 17 years) whose hemoglobin level has been stabilized by treatment with an ESA. Administer Mircera as an intravenous or subcutaneous injection at the dose (in micrograms) based on the total weekly ESA dose at the time of conversion.
Applicant Proposed Indication(s)/Population(s)	Pediatric patients with CKD 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.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of anemia associated with CKD in 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.
Recommended Dosing Regimen	In patients less than 6 years of age, maintain the same route of administration as the previous ESA when switching from another ESA to Mircera. Administer Mircera once every 4 weeks as an intravenous or subcutaneous injection to pediatric patients (ages 3 months to 17 years) whose hemoglobin level has been stabilized by treatment with an ESA. The starting dose of Mircera is calculated based on the total weekly ESA dose at the time of conversion.

Table of Contents

Table of Tables

Table of Figures

Glossary

AE	adverse event
AEAB	Anti-EPO antibody
AR	adverse reaction
AUC	area under the curve
BLA	biologics license application
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CF	Conversion Factor
CFR	Code of Federal Regulations
CI	Confidence Interval
CKD	Chronic Kidney Disease
CRF	case report form
CRT	clinical review template
CSR	clinical study report
DBP	diastolic blood pressure
ECG	electrocardiogram
EMA	European Medicines Agency
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
FDA	Food and Drug Administration
GCP	good clinical practice
GFR	glomerular filtration rate
GI	gastrointestinal
Hb	hemoglobin
HD	hemodialysis
ICH	International Council for Harmonization
IMP	Investigational medicinal product
IPDN	International Pediatric Dialysis Network
IPHN	International Pediatric Hemodialysis
IPPN	International Pediatric Peritoneal Network
IRT	Interactive Response Technology
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat
IU	International Units
IV	Intravenous
KDIGO	Kidney Disease: Improving Global Outcomes

MACE	Major Adverse Cardiac Event
MedDRA	Medical Dictionary for Regulatory Activities
NAPRTCS	North American Pediatric Renal Trials and Collaborative Studies
NDA	new drug application
NHANES	National Health and Nutrition Examination Survey
NISSDU	non-interventional study secondary data use
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PASS	post authorization study
PD	peritoneal dialysis
PDP	pediatric development plan
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMARP	per million age related population
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PRCA	pure red cell aplasia
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PTH	parathyroid hormone
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SOC	system organ class
TEAE	treatment emergent adverse event
TSAT	transferrin saturation
USPI	United States Prescribing Information
VAT	vascular access thrombosis
VTE	venous thromboembolism
WHO	World Health Organization

1. Executive Summary

1.1. Product Introduction

Methoxy polyethylene glycol-epoetin beta (Mircera) is an erythropoiesis-stimulating agent (ESA) approved for the treatment of anemia associated with chronic kidney disease (CKD) in adult patients on dialysis and not on dialysis. Mircera is also indicated for pediatric patients 5-17 years of age on hemodialysis (HD) who are converting from another ESA after their hemoglobin (Hb) level was stabilized with an ESA.

In adults, Mircera is administered by subcutaneous (SC) or intravenous (IV) injection. In pediatric patients, Mircera is approved for IV injection only. Patients currently treated with an ESA with stable Hb can switch to Mircera administered once a month (pediatric and adult patients) or once every two weeks (adult patients). Using a conversion factor, the starting dose is based on the calculated total weekly darbepoetin alfa or epoetin alfa dose at the time of substitution. Dosing may be titrated as needed in order to use the lowest dose of Mircera sufficient to reduce the need for red blood cell (RBC) transfusions.

With the original pediatric approval (BLA 125164/S-078) in 2018, the following postmarketing Requirements (PMRs) under the Pediatric Research Equity Act (PREA) were issued, which are the majority of the content of this submission (Supplement 89):

- PMR 3385-1: Conduct a multi-center, single-arm, clinical trial to confirm the dosing of U.S. 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 (Protocol 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 U.S.-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.

In this submission, the Applicant proposes to extend the current pediatric indication down to 3 months of age, expand the pediatric indication to include patients on peritoneal dialysis (PD) and not on dialysis, and to include a SC route of administration for pediatric patients. The proposed indication is as follows; for the treatment of anemia associated with CKD in 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.

1.2. Substantial Evidence of Effectiveness

Study NH19708, was a phase 2, open-label, single-arm, multicenter trial, in which 40 pediatric patients (4 months to 17 years) received Mircera SC for the maintenance treatment of anemia associated with CKD in patients on dialysis (HD or PD) or not yet on dialysis. All patients were switched from other ESAs (epoetin alfa/beta or darbepoetin alfa) to Mircera every 4 weeks (Q4W) SC for 20 weeks (core study period). The majority of patients (25 patients, 62.5%), continued to receive Mircera in the optional safety extension period which included up to 24 weeks of treatment for stable patients. The starting dose was based on the conversion factors obtained from the intravenous dose-finding study. After the first administration of Mircera, dose adjustments were permitted to maintain target Hb levels (10-12 g/dL).

Similar to the previous pediatric study (Study NH19707) to support approval of Mircera IV in pediatric patients ≥5 years of age with anemia and CKD on HD, efficacy for NH19708 was established based on the change in Hb concentration (g/dL) between the baseline and evaluation periods. The study confirmed that the conversion factors were appropriate. For the 38 patients who had Hb concentration data available during the evaluation period (Weeks 17-21), the mean change in Hb concentration between the baseline and the evaluation period was 0.48 g/dL with 95% CI (0.15, 0.82). Supportive efficacy results demonstrated that 50% of patients maintained Hb values within ± 1 g/dL of baseline and 63% maintained Hb values within 10 to 12 g/dL during the evaluation period. Dose adjustments (either a dose decrease, increase or both) were reported in 85% of patients.

To provide further evidence of safety and efficacy of Mircera in the pediatric population with anemia and CKD, the Applicant provided data from a non-interventional registry study, MH40258, in which patient level data on Mircera dosing and Hb values were reported from the International Pediatric Dialysis Network (IPDN), which included two existing registries. Data was collected prospectively, at baseline, and every 6 months. The study included 229 pediatric patients (ages 3 months to <18 years) on dialysis for CKD and received Mircera (either IV or SC). Overall, Hb levels were stable over time and did not differ substantially by age group. Mean Hb levels were maintained within the treatment target of 10-12 g/dL in nearly 50% of patients.

Substantial evidence of effectiveness was demonstrated based on results from Study NH19708, an adequate and well controlled trial, as patients with anemia associated with CKD would not be expected to maintain Hb levels near baseline or in the target range without medications or blood transfusions. Confirmatory evidence for this supplemental application is provided by the registry study MH40258, along with existing clinical studies that demonstrated the effectiveness of Mircera for the approved indications in adults and pediatric patients (≥5 years of age).

Study NH19708 fulfills PMR 3385-1 and Study MH40258 fulfills PMR 3385-2.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

CKD is a progressive loss of kidney function over time due to irreversible kidney damage due to a variety of underlying causes. Anemia is a common comorbidity in children with CKD. Development of anemia is multifactorial, although common causes include erythropoietin (EPO) deficiency and iron dysregulation. The symptoms associated with anemia include fatigue, decreased exercise tolerance, cardiac dysfunction, and impaired cognitive function. This condition is associated with multiple adverse clinical consequences, including increased morbidity and mortality, increased risk of cardiovascular disease, and decreased quality of life. Treatment for anemia due to CKD includes iron replacement, blood transfusions and ESAs. Epoetin alfa and darbepoetin alfa are ESAs approved for the treatment of anemia due to CKD in pediatric patients one month to 16 years of age and receiving or not receiving dialysis. For correction of anemia, epoetin alfa is recommended for administration three times weekly SC or IV, and darbepoetin alfa is recommended for administration once weekly or once every two weeks SC or IV.

Mircera is an erythropoietin receptor activator which stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. Mircera was initially approved by the FDA in 2007 for adult patients on dialysis and adult patients not on dialysis. In 2018, Mircera was approved for pediatric patients 5 to 17 years of age on HD who are converting from another ESA after their hemoglobin level was stabilized with an ESA. The pediatric indication was primarily based on an open-label, multicenter, dose-finding study in 64 pediatric patients with CKD who were on HD and who had stable Hb levels while previously receiving another ESA. Patients were administered Mircera IV once every 4 weeks for 20 weeks, dosage adjustments were permitted to maintain target Hb levels. The mean change in Hb concentration from baseline between the baseline and the evaluation period was -0.15 g/dL with 95% CI (-0.49, 0.2).

This supplemental application is primarily supported by Study NH19708, an open-label, single-arm, multicenter study performed to ascertain the optimal starting dose of Mircera administered SC for the maintenance treatment of anemia in 40 pediatric patients with CKD on dialysis (HD or PD), or not on dialysis when switching from stable SC treatment with epoetin alfa, epoetin beta or darbepoetin alfa. The starting dose was based on the conversion factors obtained from the intravenous dose-finding study. Mircera was administered SC once every 4 weeks for 20 weeks, followed by an optional extension period. The mean age of patients was 10 years (range; 4 months to 17 years). The patient population was 58% male, 75% White, 8% Black, and 10% Hispanic or Latino. For the 38 patients who had Hb concentration data available

during the evaluation period (Weeks 17-21), the mean change in Hb concentration between the baseline and the evaluation period was 0.48 g/dL with 95% CI (0.15, 0.82), demonstrating that Mircera maintained Hb levels near baseline. Supportive efficacy results demonstrated that 50% of patients maintained Hb values within ± 1 g/dL of baseline and 63% maintained Hb values within 10 to 12 g/dL during the evaluation period. Dose adjustments (either a dose decrease, increase or both) were reported in 85% of patients. Overall, these results are consistent with the results from adult and pediatric clinical studies.

The review of safety was primarily based on Study NH19708, in which 40 patients received at least one dose of Mircera. In the core period, 38 patients received at least 5 administrations of Mircera. Serious adverse events (SAEs) were reported in 32.5% of patients who received Mircera in the core period. Peritonitis (3 patients [7.5%]) was the only SAE experienced by more than one patient. The most common adverse events (>5%) in the core period were upper respiratory tract infection, gastroenteritis, peritonitis, oropharyngeal pain, and pyrexia. One patient had multiple thrombotic events of the dialysis catheter. Overall, the pattern of adverse events reported was similar to the established safety profile of Mircera in adult patients and pediatric patients aged 5 to 17 years from the previous intravenous study.

To further support an expanded indication, the Applicant provided data from a non-interventional study, Study MH40258, in which data (Mircera dosing, Hb values, hospitalizations and deaths) were extracted from all pediatric patients below 18 years of age on dialysis included in the IPPN and IPHN registries with at least one observation while being treated with Mircera. Data was collected prospectively, at baseline, and every 6 months. The study included 229 patients, ages 3 months to <18 years on either PD or HD dialysis for CKD and received Mircera (either IV or SC). Overall, Hb levels were stable over time and did not differ greatly by age group. At last observation, 46.9% of the children on PD and 48.1% of those on HD had a Hb value in the target range of 10-12 g/dl. Mean Hb levels were maintained within the treatment target of 10-12 g/dL in nearly 50% of patients. Approximately 57% of patients were hospitalized, the most frequent reason for hospitalization was due to issues with the dialysis catheter and infections. No thrombotic events were reported. In total, 7 deaths were reported (3%) in the study. While data should be interpreted with caution, given limitations due to study design, the results continue to support efficacy and safety findings from clinical trials.

In summary, anemia is a serious complication of CKD in pediatric patients. Mircera offers a long-acting ESA option to maintain Hb levels in the target range. The benefit/risk profile of Mircera continues to be favorable in pediatric patients, including those down to 3 months of age, patients on dialysis on and not on dialysis and for both the IV and SC route of administration. Of note, 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.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CKD is a progressive loss of kidney function over time due to irreversible kidney damage due to a variety of underlying causes. Patients with CKD may be on dialysis or not on dialysis and patients with advanced CKD are commonly awaiting kidney transplant as a definitive therapy for their disease. • Anemia is a common and progressive consequence of CKD due to insufficient EPO production and iron dysregulation. The prevalence of anemia in children ranges from approximately 30% in stage 1 CKD to 95% in end stage renal disease (ESRD). • Anemia associated with CKD results in an increased risk of morbidity and mortality, along with an increased risk of cardiovascular disease, and decreased quality of life. The symptoms associated with anemia include fatigue, decreased exercise tolerance, cardiac dysfunction, and impaired cognitive function.	Anemia is a common and serious complication in both adult and pediatric patients with CKD. Anemia associated with CKD increases the risk of morbidity and mortality, and reduced quality of life.
Current Treatment Options	• Options for the treatment of anemia of CKD include iron (oral or intravenously), ESAs, and RBC transfusions. The treatment depends on the severity of anemia and iron deficiency. RBC transfusions are used primarily for acute or life-threatening anemia.	ESAs are the current standard therapy for the treatment of anemia in patients with CKD. Mircera, an approved ESA, offers the convenience of every 4-week dosing.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• ESAs approved for pediatric patients with anemia and CKD: - Epogen/Procrit (epoetin alfa), Aranesp (darbepoetin alfa), and Retacrit (epoetin alfa-epbx) are approved in pediatric patients with CKD receiving or not receiving dialysis, one month to 16 years of age. Epoetin alfa is recommended for administration three times weekly SC or IV, and darbepoetin alfa is recommended for administration once weekly or once every two weeks SC or IV. - Mircera (methoxy polyethylene glycol-epoetin beta), is approved in pediatric patients with CKD receiving HD, ages 5 to 17 years of age and converting from another ESA. In pediatric patients, Mircera IV is dosed every 4 weeks. - All ESA labels contain a boxed warning for increased risk of death, myocardial infarction (MI), stroke, venous thromboembolism (VTE), thrombosis of vascular access and tumor progress or recurrence. - The target hemoglobin in pediatric patients with CKD receiving ESAs is typically 11-12g/dL in clinical practice.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Study NH19708, was a phase 2, open-label, single-arm, multicenter trial, in which 40 pediatric patients (4 months to 17 years) received Mircera SC for the maintenance treatment of anemia associated with CKD in patients on dialysis (HD or PD) or not yet on dialysis. ○ In 38 patients, the mean change in Hb concentration between the baseline and the evaluation period was 0.48 g/dL with 95% CI (0.15, 0.82). ○ 50% of patients maintained Hb values within ± 1 g/dL of baseline and 63% maintained Hb values within 10 to 12 g/dL during the evaluation period. ○ Dose adjustments were reported in the majority of patients. • Study MH40258 was a non-interventional study in which data on Mircera dosing and Hb values were reported from two existing international registries. The study included 229 pediatric patients (ages 3 months to <18 years) on dialysis for CKD and received Mircera (either IV or SC). Mean Hb levels were stable and were maintained within the treatment target of 10-12 g/dL in nearly 50% of patients.	Study NH19708 confirmed the starting dose of Mircera which is calculated using a conversion factor and demonstrated that Mircera SC every 4 weeks maintains hemoglobin in the target range with dose titration. Most patients required dose adjustments, including dose reductions for Hb >12g/dL. This was determined to be acceptable given Hb levels generally returned to target range with dose adjustments and there were no significant safety findings associated with Hb excursions. While targeting higher Hb values is associated with increased cardiovascular mortality in adults, this has not been demonstrated in pediatric patients. The totality of data from Study NH19708, along with supportive data from Study MH40258 and previous pediatric and adult studies supports expanding the pediatric indication to pediatric patients down to 3 months of age, on dialysis (PD or HD), not on dialysis and both IV and SC routes of administration.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• In Study NH19708, 40 patients received at least one dose of Mircera. • The most common adverse events (AEs) (>5%) in the core period were upper respiratory tract infection, gastroenteritis, peritonitis, oropharyngeal pain, and pyrexia. • Serious adverse events (SAEs) were reported in 32.5% of patients who received Mircera in the core period. Peritonitis was the only SAE experienced by more than one patient. • One patient had multiple thrombotic events associated with the dialysis catheter. • No events of pure red cell aplasia (PRCA) were reported. No trends in elevated blood pressure were observed. • No deaths or drug discontinuations due to an AE occurred. • In study MH40258 approximately 57% of patients were hospitalized, the most frequent reason for hospitalization was due to issues with the dialysis catheter and infections. No thrombotic events were reported. In total, 7 deaths (3%) were reported in the study.	Overall, the pattern of AEs reported was similar to the established safety profile of Mircera in adult patients and the patients aged 5 to 17 years in the previous intravenous study.

1.4. Patient Experience Data

Patient reported data was not reviewed. Given the open-label, single-arm design of Study NH19708, patient reported outcome data is not interpretable.

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		
		☒	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

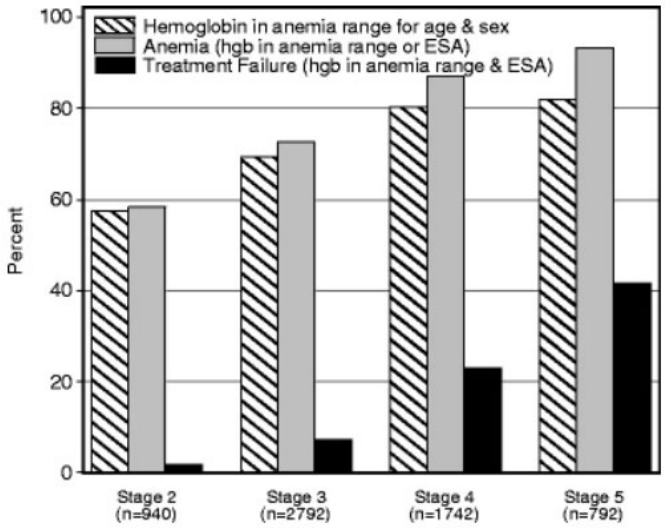
2.1. Analysis of Condition

CKD is a progressive loss of kidney function over time due to irreversible kidney damage due to a variety of underlying causes. While glomerular filtration rate (GFR) varies according to age, sex, race, ethnicity, and size, it is generally understood to represent CKD in children ≥2 years when GFR <60 mL/min per 1.73 m^2 persists for more than 3 months [2]. For children under 2 years, the Kidney Disease Improving Global Outcomes (KDIGO) guideline suggests considering age specific GFR values. The global prevalence of pediatric CKD is estimated to be approximately 15–74.7 cases /million children [3]. The incidence and prevalence of pediatric CKD in the United States is difficult to measure as population-based epidemiologic data on CKD in children in the US are not available. Data is primarily derived from pediatric registries of kidney transplant, when CKD is already far advanced, thereby likely underestimating actual disease prevalence. Based on data from a single US health insurance company including almost 2 million individuals from the pediatric age group (< 21 years), the prevalence of children and adolescents with a CKD diagnosis code (ICD-9 and ICD-10) was 27 per 10,000 (0.27%) in 2016 [4]. While there is a wide variation of CKD prevalence in children based on race and environment, there is a higher prevalence and disproportionate impact on children from minority groups and of lower socioeconomic status.

Anemia of CKD is classified as a normochromic, normocytic anemia and has multifactorial causes including a decrease in endogenous EPO production, absolute and/or functional iron deficiency, inflammation with increased hepcidin levels with resulting ineffective use of iron stores, a reduced bone marrow response to EPO due to uremic toxins and reduced red cell life span. Anemia due to reduced EPO production generally develops when the GFR is below 40 mL/min per 1.73 m^2. The prevalence and severity of anemia of CKD is typically progressive as the stage of CKD progresses. [5] The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) cohort has consistently shown that the risk for anemia increases as CKD stage advances, with a prevalence of 73% at stage 3, 87% at stage 4, and >93% at stage 5 [6].

A diagnosis of anemia Is made when the observed Hb result is at or below the 2.5th percentile of normal, adjusted for age and sex. In a child with CKD and anemia further assessment of hematologic parameters such as iron stores and EPO levels would be obtained [7]. Anemia associated with CKD is more prevalent and severe in Black children than in White children at each stage of CKD. Black children with CKD are more likely to progress to ESRD [8, 9]. The prevalence of pediatric anemia and CKD, by CKD stage in North America is shown in Figure 1 from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) CKD Registry. NAPRTCS includes more than 100 pediatric centers in Canada, Mexico, and the USA that collects data on children who have CKD, are on dialysis, and have undergone kidney transplantation. Approximately 73% of children at CKD stage 3, 87% at CKD stage 4, and over 93% at CKD stage 5 were anemic using the NAPRTCS CKD definition [10, 11]].

Figure 1 Anemia Prevalence at Baseline in the North American Pediatric Renal Trials and Collaborative Study (CKD) Registry



Anemia prevalence at baseline in the North American Pediatric Renal Trials and Collaborative Study (NAPRTCS) chronic kidney disease (CKD) Registry (n = 6242). *ESA* Erythropoiesis-stimulating agent, *hgb* hemoglobin

The adverse effects of chronic anemia related to CKD in children contributes to growth impairment, decreased neurocognitive development, declines in school attendance, and exercise tolerance. Anemia can also have cardiovascular adverse effects including left ventricular hypertrophy, heart failure and cardiomyopathy [12]. Cardiovascular disease is the leading cause of death in pediatric patients with ESRD [13]. Additionally, children with CKD anemia have increased morbidity and mortality, and increased risk for hospitalization [14].

2.2. Analysis of Current Treatment Options

Treatment of anemia due to CKD includes iron supplementation (when indicated) and blood transfusions when patients have acute anemia or anemia-related symptoms. ESAs are considered standard of care therapy for anemia associated with CKD. Multiple ESA are FDA approved for pediatric patients with CKD on dialysis or not on dialysis, this includes Epogen/Procrit (epoetin alfa) and Aranesp (darbepoetin alfa). Epoetin alfa-epbx is a biosimilar to Epogen, with the same indications. Mircera (methoxy polyethylene glycol-epoetin beta) is indicated for pediatric patients ages 5 to 17 years with CKD and receiving HD dialysis and switching from another ESA. Consensus guidelines (KDIGO 2012 Guidelines for CKD and anemia) suggests that the selection of Hb concentration at which ESA therapy is initiated in the

individual patient includes consideration of potential benefits (e.g., improvement in quality of life, school attendance/performance, and avoidance of transfusion) and potential harms. All ESAs contain a box warning for risk of death, myocardial infarction, stroke, VTE, thrombosis of vascular access. Other important risks include hypertension, seizures, PRCA, severe allergic reactions and severe cutaneous reactions. For maintenance ESA therapy, guidelines recommend that the target Hb concentration be in the range of 11.0 to 12.0 g/dl [15]. It is notable, that recently two oral hypoxia-inducible factor–prolyl hydroxylase domain inhibitors (HIF-PHIs) were approved by the FDA for anemia associated with CKD, however these agents are only indicated for adults. Current treatment options for anemia related to CKD in pediatric patients is listed in the table below.

Table 1: Current Treatment Options for Anemia Related to CKD

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Erythropoietin stimulating agents (ESAs)						
Mircera (Methoxy polyethylene glycol-epoetin beta)	Treatment of CKD-anemia in patients on dialysis and not on dialysis. Pediatric patients 5 to 17 years of age on HD who are converting from another ESA after their Hb level was stabilized with an ESA.	2007	IV every 4 weeks	Efficacy was based on an open-label, multiple dose, multicenter, dose-finding study in 36 patients (efficacy population) with CKD on HD who received IV Mircera after converting from `treatment with another ESA. The mean change in Hb concentration from baseline between the baseline and the evaluation period was -0.15 g/dL with 95% CI (-0.49, 0.2).	Boxed warning for risk of death, myocardial infarction, stroke, VTE, thrombosis of vascular access and tumor progression. Warnings for hypertension, seizures, PRCA, severe allergic reactions and severe cutaneous reactions. Most common TEAEs in pediatric patients were headache, nasopharyngitis, hypertension, vomiting, bronchitis, abdominal pain, AV fistula thrombosis, cough, device related infection, hyperkalemia, pharyngitis, pyrexia, thrombocytopenia, and thrombosis in device.	
Epogen/ Procrit (epoetin	Treatment of CKD-anemia in patients on dialysis and not on	1989	Injection either IV or SC three times a week	Efficacy was studied in a placebo-controlled, randomized study of 113 pediatric patients with anemia (Hb≤ 9 g/dL)	Boxed warning for risk of death, myocardial infarction, stroke, VTE, thrombosis of vascular access.	

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
alfa)	dialysis. Pediatric patients, ages 1 month to 16 years of age, for the treatment of anemia associated with CKD requiring dialysis and not requiring dialysis.			undergoing PD or HD. At the end of the initial 12 weeks, a statistically significant rise in mean Hb (3.1 g/dL vs. 0.3 g/dL) was observed only in the epoetin alfa arm. A higher proportion of patients in the epoetin alfa arm achieved Hb of 10g/dL and transfusion independence. Use of Epogen in pediatric patients with CKD not requiring dialysis is supported by efficacy in pediatric patients requiring dialysis.	Warnings for hypertension, seizures, PRCA, severe allergic reactions and severe cutaneous reactions. In pediatric patients with CKD on dialysis, the pattern of adverse reactions was similar to that found in adults.	
Aranesp (darbepoetin alfa)	Treatment of anemia due to CKD in patients on dialysis and not on dialysis. Pediatric patients, ages 1 month to 16 years of age, for the treatment of anemia associated with CKD requiring dialysis and not requiring dialysis.	2001	SQ or IV every 1 or 2 weeks	A double-blind, randomized, controlled study in 114 pediatric patients from 1 to 18 years of age receiving or not receiving dialysis who were anemic ([Hb] < 10.0 g/dL) and not being treated with ESA received darbepoetin alfa weekly or once every 2 weeks for the correction of anemia. For pediatric patients receiving QW dosing, 98% (95% CI: 91%-100%), had Hb concentrations corrected to ≥ 10 g/dL. For those receiving Q2W dosing, 84% (95% CI: 72%-92%), had Hb concentrations corrected to ≥ 10 g/dL.	Boxed warning for risk of death, myocardial infarction, stroke, VTE, thrombosis of vascular access and tumor progression. Warnings for hypertension, seizures, PRCA, severe allergic reactions and severe cutaneous reactions. The most common AEs in the pediatric population were hypertension, injection site pain, rash, and convulsions	
Retacrit (epoetin alfa-epbx)	Treatment of anemia due to CKD in patients on dialysis & not on dialysis.	2018	Injection	Biosimilarity and no clinically meaningful differences between Retacrit and Epogen/Procrit.	Biosimilarity and no clinically meaningful differences between Retacrit and Epogen/Procrit.	

*The above information was obtained from the FDA approved product labels.
Abbreviations: AE-adverse event, AV- arterio-venous, CKD-chronic kidney disease, ESA-erythropoietin stimulating agent, GI-gastrointestinal, Hb-hemoglobin, HD-hemodialysis, IV- intravenous, MACE-major adverse cardiac events, MI- myocardial

infarction, PD- peritoneal dialysis, PRCA- pure red cell aplasia, SC-subcutaneous, TEAE- treatment-emergent adverse event, VTE-venous thromboembolism, URI – upper respiratory infection.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Mircera is an ESA initially approved on November 14, 2007, for adult patients on dialysis and not on dialysis. The PREA PMRs associated with the BLA approval were:

- PMR 2471-1: To conduct a multi-center, dose-finding study to determine the optimum starting dose of intravenously administered methoxy polyethylene glycol-epoetin beta when used for the maintenance treatment of anemia in pediatric patients ages 5 to 17 years who have CKD and are undergoing dialysis.

- PMR 2471-2: To conduct a multi-center, randomized, controlled, parallel-group study to confirm the optimal methoxy polyethylene glycol-epoetin beta dosage when used for the maintenance treatment of anemia in pediatric patients ages 5 to 17 years who have CKD, inclusive of patients undergoing dialysis as well as patients who are not undergoing dialysis.

An efficacy supplement was approved in June 2018 for use in pediatric patients 5 to 17 years of age on HD who are converting from another ESA after their Hb level was stabilized with an ESA. Approval was based on an open-label, multiple dose, multicenter, dose-finding study (Study NH19707) to determine the dose of IV Mircera when converting from treatment with another ESA (epoetin alfa/beta or darbepoetin alfa). The study was conducted in 64 pediatric patients (ages 5 to 17 years) with CKD who were on HD and who had stable Hb levels while previously receiving another ESA. Eligible patients were administered Mircera IV once every 4 weeks for 20 weeks. Efficacy was established based on the change in Hb concentration (g/dL) between the baseline and evaluation periods. For the 36 patients who entered the evaluation period and received the dose of Mircera calculated using the recommended conversion factor, the mean change in Hb concentration between the baseline and the evaluation period was -0.15 g/dL with 95% CI (-0.49, 0.2). Supportive efficacy results in the group treated with Mircera using the recommended conversion factor demonstrated that 75% of patients maintained Hb values within ± 1 g/dL of baseline and 81% maintained Hb values within 10 to 12 g/dL during the evaluation period.

With approval of the pediatric supplement, the following PREA PMRs were issued:

- PMR 3885-1: Conduct a multi-center, single-arm, clinical trial to confirm the dosing of U.S. 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 (Protocol NH19708).

- PMR 3885-2: 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 U.S.-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.

3.2. Summary of Presubmission/Submission Regulatory Activity

Study NH19708 was designed to address PREA PMR 2471-2 (see Section 3.1 U.S. Regulatory Actions and Marketing History). The study was originally planned to be initiated once the Phase II dose-ranging study NH19707 (PMR 2471-1) had been completed. The Applicant reported that recruitment difficulties and a higher than anticipated rate of withdrawal of patients due to kidney transplantation caused delays in the completion of Study NH19707 and the final study report was submitted in August 2016. In September 2016, in view of the positive results from the Phase II study and the findings of population pharmacokinetics (PK) and PK/pharmacodynamic analyses, the Applicant requested a Type C meeting (December 8, 2016) to discuss the proposal to replace the previously agreed upon phase Ill, randomized, controlled study with a phase 2, single-arm, open-label study of SC Mircera treatment in pediatric patients with CKD on dialysis or not on dialysis. The FDA recommended that the Applicant submit revised PMR proposals for the new phase 2 study and patient registry to substitute for the agreed upon PMR 2471-2 randomized phase 3 trial.

On February 17, 2017, the Applicant submitted an updated pediatric development plan (PDP) containing the newly proposed phase 2 study to demonstrate an optimal Mircera maintenance dose for pediatric patients with CKD associated anemia, as well as a real-world registry study to supplement safety information from at least 100 pediatric patients with CKD including patients on dialysis and not on dialysis to substitute for the previously agreed upon randomized phase 3 trial.

On April 27, 2017, a General Advice letter was sent to the Applicant providing review comments and recommendations on the updated PDP. The following recommendations were advised:

1. Increase the sample size of the proposed phase 2 trial to 40 evaluable patients.
2. Add an extension study to provide longer term safety information.
3. Commented on the registry information being supportive of dosing information only.
4. Recommended to include pediatric patients down to 3 months of age.
5. To submit a revised phase 2 protocol to the Agency review.
6. Include a PK and pharmacodynamic sampling plan.

The protocol for the new Phase 2 study and responses to each of the Agency's comments and recommendations were submitted by the Applicant to IND 10158 on July 20, 2017.

June 2, 2018, a letter of notification of approval was sent from the Agency to the Applicant for the original pediatric supplement (Supplement 78). In the approval letter, it was stated that the Agency agreed with the updated PDP submitted on February 17, 2017, to conduct a single-arm multicenter trial and a registry study in pediatric patients with CKD treated with US-licensed Mircera and was released from PMR 2471-2. PMR 3885-1 and 3885-2 were issued.

On October 19, 2022, preliminary responses to a Type B Pre-sBLA Meeting were provided. The Agency agreed that the Applicant may submit the final reports for the PREA PMR studies. In addition, the Agency requested an Integrated Summary of Safety (ISS) that includes an analysis of pooled pediatric safety data from studies NH19708 and NH19707.

February 10, 2023, The Applicant requested a Type D Meeting to obtain feedback and gain agreement with the Agency on the safety analysis strategy for the ISS based on the FDA's input received in the Type B Pre-sBLA Meeting Preliminary Comments dated October 19, 2022.

On March 27, 2023, Written responses for a Type D Meeting were provided by the Agency to the Applicant regarding the plan to pool pediatric safety data for all patients who received at least one dose of study drug on study NH19708 or study NH19707, along with the proposed outputs for the ISS to be submitted as part of the planned sBLA submission. The proposal was determined to be acceptable.

3.3. Foreign Regulatory Actions and Marketing History

Mircera is currently approved for the treatment of anemia associated with CKD in patients, including those on dialysis and those not on dialysis, in 117 countries worldwide.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Applicant (F. Hoffmann-La Roche AG) site was inspected. It was determined that the oversight and monitoring of clinical study (NH19708) was acceptable. See finalized review in DARRTS by Anthony Orencia on February 23, 2024.

The inspection reviewed monitoring reports for six high enrolling sites and found no issues. The process of safety and adverse event reporting was reviewed, and no issues were identified.

One issue of concern was that two subjects received an overdose as the result of a coding error in the Interactive Response Technology Platform. No negative safety sequelae or harms were reported from these events. The overdose was immediately identified and upon investigation it was determined that Interactive Response Technology Platform was the cause of the overdosing. The system had not been programed to account for dosing holds. As part of the corrective action, an immediate alert was sent to clinical investigators for Study NH19708, with active subjects to be made aware of the issue. (b) (4) the vendor for the Interactive Response Technology (IRT) Platform, IxRS system, was notified of the issue and the coding was corrected.

4.2. Product Quality

The CMC team recommended approval of this supplement from an immunogenicity assay and product quality perspective.

Per the CMC review (finalized on April 3, 2024), the Applicant's proposed categorical exclusion from the environmental assessment requirement for Mircera based on 21 CFR 21.35(c) is acceptable. Immunogenicity samples from clinical study NH19708 were tested for anti-Mircera (RO0503821) and anti-EPO antibodies using validated screening, confirmatory, and titer assays at (b) (4) The validated screening, confirmatory, and titer cut points were used in the clinical study and the false positive rate (FPR) of 2.5% for both anti-Mircera and anti-EPO antibodies at baseline are within the accepted FPR of range 2 – 11 %. Thus, the validated cut points are adequate to assess immunogenicity of the clinical samples. No approvability issues were identified with respect to the performance of the validated immunogenicity assays used during the clinical studies. As an additional comment, the Applicant will be requested to establish system suitability criteria for the positive and negative controls to support ADA assay consistency during future clinical studies.

4.3. Nonclinical Pharmacology/Toxicology

Not applicable to this application, no new nonclinical was submitted.

4.4. Clinical Pharmacology

The clinical pharmacology review team evaluated the starting doses of Mircera and noted the data from Study NH19708 showed patients developed Hb >12 g/dL at Weeks 3, 5, or 9 (timepoints following the transition to Mircera). In discussions with the clinical review team, the team determined this is acceptable given the risk of cardiovascular mortality is likely lower in the pediatric population, along with the transient nature of elevated Hb levels, see Section 6 for further details.

(b) (4) , the Applicant did not submit data to support dosing and safety

for the IV route of administration in pediatric patients younger than 6 years old. The exposures following IV administration will be greater compared to SC administration, and there is no clinical experience for IV dosing in pediatric patients younger than 6 years of age. Safety could not be extrapolated, so it was 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 SC to the IV route of administration while transitioning from another ESA to Mircera. The Applicant agreed and updated the label accordingly.

The final recommendation by the clinical pharmacology team; *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 and has determined PMR 3385-1 is fulfilled*. See finalized review in DARRTS dated April 15, 2024.

4.5. Devices and Companion Diagnostic Issues

There were no device issues for this application.

4.6. Consumer Study Reviews

There was no consumer study review for this application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2 Listing of Clinical Trials Relevant to this NDA/BLA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. patients enrolled	Eligible Study Population	Centers and Countries
NH19708 (NCT03552393)	Open-label, single-arm, multicenter study	SC injection every 4 weeks	Primary Endpoint: change in Hb concentration (g/dL) between Baseline and the Evaluation Period Secondary endpoints: # 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	20 weeks, plus optional 24-week safety extension period	40	Children ages 3 months to 17.9 years	20 centers U.S. (6) Poland (5) France, Hungary, Italy, Spain (2 each), Lithuania (1)
MH40258	Non-interventional study secondary data use (NIS SDU) and voluntary PASS, selected data elements among patients who received Mircera were extracted from two existing registries within the IPDN (IPPN and IPHN).	IV and SC	Primary objectives: -describe the safety profile of Mircera by aggregate assessment of safety data (number and causes of hospitalizations and deaths) -assess the relationship between Mircera dosing and Hb concentrations using patient level data. Secondary objectives: -confirm dose conversions from previous ESA treatment to Mircera that were determined and tested in study NH19707 (IV) & NH19708 (SC) -validate the previous dose simulation models, especially for the subset of very young patients (0 mo. to <6 years of age).	N/A	229	177 patients, 0.3-17.9 years, on chronic PD, with at least one visit under Mircera 52 patients, aged 2.4 to 17.9 years, on chronic HD, with at least one visit under Mircera.	18 centers Argentina Belgium Chile Colombia Czech Republic France Germany Malaysia Poland Singapore Republic of Korea USA

5.2. Review Strategy

The is a joint review by the clinical and statistical teams. The primary clinical reviewer was Julia Friend, and the clinical team leader was Carrie Diamond. The primary statistical reviewer was Huan Wang, and the team leader was Yeh-Fong Chen.

This review will also serve as the Cross-Discipline Team Leader (CDTL) review.

Trial NH19708 served as the primary trial for both safety and efficacy. For this trial, the clinical study report and datasets were reviewed. Unless otherwise stated, calculations were done by the Agency reviewers. Tools used to reproduce analysis included use of JMP and SAS 9.4; R 4.2.2 was used to produce the forest plot for subgroup analyses of the primary endpoint in NH19708.

Study MH40258, was a non-interventional registry study, used to support efficacy and safety of pediatric use. For this study, a clinical study report (CSR) was submitted and reviewed by the clinical review team.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. NH19708

6.1.1. Study Design

Overview and Objective

Trial name: 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

Study Dates:
First Patient Enrolled: 03 August 2018
Last Patient Last Visit: (b) (4)

Study NH19708 was a single-arm, multicenter study. The primary objective was to ascertain the starting dose of Mircera given SC 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.

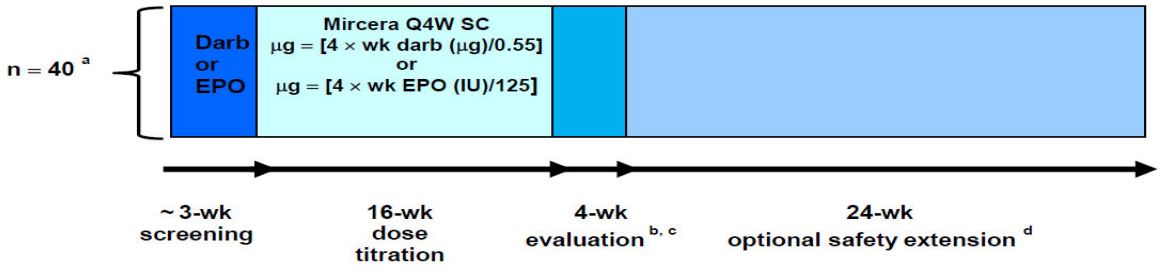
Trial Design

Study NH19708 was an open-label, single-arm, multicenter study 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 was screened for eligibility during a screening period of approximately 3 weeks. During this period, patients continued to receive epoetin alfa, epoetin beta, or darbepoetin alfa at the same weekly dose, route, and interval as before screening. All enrolled patients received Mircera administered SC by study personnel once every 4 weeks for the duration of the study. Dose adjustments could be performed every 4 weeks according to dose adjustment rules defined in below in the dose titration section of this review.

The core study period lasted for 23 weeks and consisted of three periods: screening (3 weeks), dose titration (16 weeks), and evaluation (4 weeks) (see Figure below). 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, were eligible to enter an optional 24-week safety extension period. Visit 10 served 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. The schedule of events can be found in the Appendix of this review.

Figure 2 Study Schema for Study NH19708



Abbreviation: Darb=darbepoetin alfa; EPO=epoetin alfa or epoetin beta; Q4W=once every 4 weeks; Wk=week.
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 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.
Source: Applicant CSR

Clinical reviewer comment: A single-arm study is reasonable in light of the rarity of the disease in the pediatric population. The mechanism of anemia in adults is similar to that in children, allowing for extrapolation from adult to pediatric disease. Further, safety and efficacy were previously established in pediatric patients ages 5 to 17 years with CKD and receiving HD. The study design was discussed and agreed upon prior to the sBLA submission.

Trial Location

The study was conducted in 20 centers in 7 countries, including France, Hungary, Italy, Lithuania, Poland, Spain and the United States.

Patient Population

The patient population included pediatric patients, receiving an ESA for anemia due to CKD, on dialysis or not yet on dialysis and with a stable Hb between 10-12g/dL.

Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

- 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.
- Baseline Hb concentration 10-12 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%; mean of two values measured during screening.

Exclusion Criteria:

- 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).
- 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 EPO, polyethylene glycol, or any constituent of the study drug formulation.
- Anti-EPO antibody (AEAB)-mediated 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).

Dose Selection

The starting dose was based on conversion factors (CFs) obtained from the dose-finding study (Study NH19707). The initial dose of Mircera was one of nine starting doses corresponding to the prefilled syringe strengths based on the total weekly ESA dose during the screening period. See Clinical Pharmacology review for further details. The starting dose is described in the Table below.

Table 3 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

Source: Applicant's CSR

Dose Modification and Discontinuation

The dose of Mircera could be adjusted to maintain the individual patient's Hb within a target range of ±1 g/dL of their baseline Hb and between 10-12 g/dL. Dose adjustments were performed at the scheduled dosing days and the dose was based on the Hb value measured on that day. The dose adjustments were not to be performed more often than once every 4 weeks. Dose adjustment rules for Mircera in response to Hb changes, including those required for safety reasons, are summarized in the table below.

Table 4 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.

Source: Applicant CSR

In case of an RBC transfusion due to worsening anemia secondary to inadequate doses or to poor response to Mircera, the dose (administered at the next scheduled dosing day, if possible) was to be adjusted according to protocol guidelines. In case of an RBC transfusion to replace acute blood loss, the dose was not to be changed, and the next dose was administered as scheduled.

Administrative structure:

This trial was sponsored by F. Hoffmann-La Roche Ltd. The Applicant was responsible for the overall study management (monitoring), drug supply, data management, statistical analysis, PK and pharmacodynamic analysis presented separately from this report, drug safety process, and medical writing for the CSR. A list of roles and responsibilities given to external organizations and details on the site of manufacture and site of drug release in the European Union can be found in the CSR Appendix.

Concurrent medications:

Prohibited concomitant therapies included other investigational medicinal products (IMPs), non-FDA and non-European Medicines Agency (EMA) approved biosimilar ESAs within 12 weeks of screening, RBC transfusions within 8 weeks before screening, or immunosuppressive therapies administered in the last 12 weeks before the first screening visit. In addition, immunosuppressive therapies known to exacerbate anemia, such as cyclophosphamide, sirolimus, tacrolimus, azathioprine, and mycophenolate mofetil, administered the last 12 weeks

before the first screening visit are also prohibited. Whenever possible, intermittent treatment or dose change of medications known to influence Hb concentration should have been avoided. These medications include androgens, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and immunosuppressive therapies, except for corticosteroids for a chronic condition, cyclosporine, and monoclonal/polyclonal antibodies.

Subject completion, discontinuation, or withdrawal:
Completion was defined as completion of 20 weeks of treatment (dose titration and evaluation periods).

Patients were discontinued if any of the following occurred:

- Any medical condition that the investigator or Sponsor determined might jeopardize the patient's safety if they continued to receive study treatment.
- Investigator or Sponsor determined it is in the best interest of the patient.
- Pregnancy.
- Kidney transplantation.
- AEAB-mediated PRCA.

Reasons for withdrawal could include the following:

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

Study Endpoints:
The primary efficacy endpoint was the change in Hb concentration (g/dL) between the baseline and the evaluation period for each patient. This was 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 secondary efficacy endpoint was the number of patients with an average Hb concentration during the evaluation period within $\pm$1 g/dL of their baseline Hb or above, within, or below the range of 10-12 g/dL.

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

Statistical Analysis Plan

Determination of Sample Size
This was an exploratory study without a powered statistical group comparison. Therefore, no formal sample size estimation was 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 intent-to-treat (ITT) and safety analysis, more than 26 patients would have data for the evaluation period. Twenty-six patients would 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 would 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, would not be on dialysis. Available HD patients receiving their ESA subcutaneously were eligible for enrollment. No more than 10 patients on HD were to be enrolled.

To achieve the recruitment of the intended number of patients and in case of excessive dropout rate, additional patients could be enrolled to replace patients not treated for a minimum duration of 18 weeks. Of note, no patients were replaced.

Analysis Populations

- Intent to Treat (ITT) Population: The ITT population consisted of all patients enrolled in the study.
- Per Protocol (PP) Population: The PP population was defined as all patients included in the safety population and who had no major protocol deviations as defined below.
  1. Patients with less than 3 Hb values during the evaluation period.
  2. Patients who missed 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 did 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 fulfilled any of the exclusion criteria:
     - Hemolytic anemia.
     - Use of prohibited therapy.
- Safety Population: The safety analysis population consisted of all patients who received at least one dose of study drug regardless of whether they withdrew prematurely or not.

Analysis of the Primary Efficacy Endpoint

The individual change from baseline was reported using summary statistics (including mean, standard deviation and 90% CI of mean change). No formal statistical testing was performed.

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

The Hb change from baseline was 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 was then averaged over all patients and the CI calculated.

If numbers allow, additional analyses would 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).

Protocol Amendments

Protocol Version 2 approved on January 19, 2018
Protocol Version 1 NH19708 was amended primarily to address comments received from the FDA. The resulting changes are summarized below:

- An additional time point for immunogenicity sampling was added at Week 9 (Visit 6).
- An assessment was added of anti-PEG antibodies in those patients where loss of efficacy was observed.
- Age range categories for additional statistical analyses of the primary efficacy endpoint were amended to align with the study goal of including as many patients under 5 years old as possible.

Protocol Version 3 approved on July 11, 2018
Protocol Version 2 NH19708 was amended to address feedback received from the European health authorities. The resulting changes are summarized below:

- The rationale for Mircera dose and schedule was updated with results from real world data from the International Pediatric Dialysis Network registries.
- Added adverse events of special interest (AESIs); Hy's Law and suspected transmission of an infectious agent by the study drug.
- The grading scale for assessment of severity of adverse events was revised to use the current World Health Organization (WHO) toxicity scale.
- Requirements for the reporting of injection reactions were added.

Protocol Version 4, approved on December 7, 2018
Protocol Version 3 NH19708 was amended to add an exclusion criterion and provide additional clarification of procedures. The changes made were as follows:

- Exclusion criteria were amended to exclude patients who have undergone a kidney transplant with use of immunosuppressive therapies known to exacerbate anemia.
- Mircera Dose Adjustments table was amended to clarify the dose adjustment rules for Mircera.

6.1.2. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP).

Protocol amendments were prepared by the Applicant and were submitted to the Institutional Review Boards (IRB)/ independent ethics committees (IEC) and to Regulatory Authorities in accordance with local regulatory requirements. Approval was obtained from the IRB/IEC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

Financial Disclosure

The Applicant provided adequate information regarding financial interests/arrangements with clinical investigators. No investigator was a direct employee of the Applicant, and no investigator had a disclosable financial interest or arrangement.

Data Quality and Integrity

Overall, the quality and integrity of the clinical data appeared acceptable.

Patient Disposition

A total of 62 patients were screened, 34 patients were enrolled after initial screening and 28 patients failed the screening. Among the 28 screen failure patients, 7 patients were re-screened, 6 patients were enrolled, and 1 patient failed the re-screening. The reasons for screen failure were not fulfilling the inclusion criteria (24 patients) or met the exclusion criteria (4 patients). Most of the patients (20/24 patients) did not fulfill inclusion criteria related to adequate HD (8 patients), stable dose of epoetin alfa/beta, or darbepoetin alfa, (7 patients), or baseline Hb concentration within 10 -12 g/dL (5 patients). Two of 4 patients met exclusion criterion of having severe hyperparathyroidism. One patient met exclusion criterion of peritonitis within the past 30 days, and another met AEAB-mediated PRCA or history of AEAB-mediated PRCA or positive AEAB test result.

A total of 40 patients (100%) were enrolled in the core period. The majority of patients (38 patients [95%]) completed the core period. Two patients (5%) discontinued during the core period. The reasons for discontinuation from the core period were kidney transplant (1 patient [2.5%]) and use of prohibited medication (1 patient [2.5%]). In the per protocol population, 33 patients were included, and seven patients were excluded. The main reasons for exclusion of patients from the per protocol population were overdose of Mircera at Week 17 (2 patients) and treatment with prohibited concomitant medication (2 patients).

In total, 25 eligible patients entered the safety extension period. The only reason for discontinuation from the safety extension period was kidney transplant (4 patients). A summary of patient disposition is shown in the table below.

Table 5. Patient Disposition in Study NH19708 (Safety Population)

Disposition	**Mircera SC (N=40) n (%)**
Patients entered core period	40 (100%)
Patients completed core period	38 (95%)
Patients discontinued core period	2 (5%)
Kidney transplant	1 (2.5%)
Prohibited medication	1 (2.5%)
Patients entered extension period	25 (62.5%)
Patients completed extension period	21 (52.5%)
Patients discontinued extension period	4 (10%)
Kidney transplant	4 (10%)

Source: CSR Study NH19708

Clinical reviewer comment: Few patients discontinued the study drug, supporting the tolerability of Mircera.

Protocol Violations/Deviations

Seven patients (17.5%) reported a total of 8 protocol deviations categorized as major. These deviations were related to inclusion criteria in 2 patients (Hb value outside range, 1 (2.5%), change in dose >25% of previous ESA 1 (2.5%). Five patients reported deviations related to medications. One patient took tacrolimus, and mycophenolate mofetil which were prohibited medications. The patient was withdrawn from the study because of this major deviation.

Demographic Characteristics

In Study NH19708, the mean age of patients was 10.3 years (SD 5.69) and the median age was 11 years (range: 0.4-17.7 years). There were 17 patients (42.5%) in the age group of ≥12 years,

11 patients (27.5%) in the group 5-11 years and 12 patients (30%) in the group of <5 years. In total, 4 patients (10%) were under the age of 2.

Table 6 Demographic Characteristics, Study NH19708

Demographic Parameters	Mircera SC (N=40)
Sex	
Male	23 (57.5%)
Female	17 (42.5%)
Age	
Mean years (SD)	10.2 (5.69)
Median age, range	11.35, (0.4-17.7)
Age Group	
< 5 years	12 (30%)
5-11 years	11 (27.5%)
Greater/equal to 12 years	17 (42.5%)
Race	
White	30 (75%)
Black or African American	3 (7.5%)
Unknown	7 (17.5%)
Ethnicity	
Hispanic or Latino	4 (10%)
Not Hispanic or Latino	27 (67.5%)
Not reported	2 (5%)
Unknown	7 (17.5%)
Region	
North America	9 (22.5%)
Latin America	0
Europe	31 (77.5%)
Asia/Arabia	0

Source: Applicant's CSR

Other Baseline Characteristics

There were 18 patients (45%) who were on PD, 5 patients (12.5%) who were on HD and 17 patients (42.5%) who were not on dialysis. Of note, the number of patients on HD that could be enrolled in this study was capped at 10. A similar proportion of enrolled patients were previously treated with darbepoetin alfa or epoetin alfa/beta (20 patients [50%] each from previous ESAs). For a detailed description of baseline characteristics please see the table below.

Table 7 Baseline Characteristics, Study NH19708

Characteristic	Mircera SC N=40
Dialysis type, n (%)	
Not on dialysis	17 (42.5%)
HD	5 (12.5%)
PD	18 (45%)
Time on dialysis	
PD mean years (SD)	1.42 (1.01)
PD median years since 1st dialysis (range)	1.06 (0.5-3.6)
HD mean years (SD)	1.62 (2.56)
HD median years since 1st dialysis (range)	0.52 (0.1-6.2)
Previous ESA therapy, n (%)	
Darbepoetin alfa	20 (50%)
Epoetin alfa or epoetin beta or biosimilars	20 (50%)
No prior ESA	0
Days on ESA prior to start of Mircera	
Mean (SD)	342.1 (345.5)
Median, range	196.5 (42-1344)
Baseline Hb, g/dL	
Mean (SD)	11.02 (0.53)
Median (range)	11.08 (10.1-12.2)

ESA erythropoietin stimulating agent, Hb hemoglobin, HD hemodialysis, PD peritoneal dialysis, SD standard deviation
Source: CSR NH19708

Clinical Reviewer comment: In the prior pediatric trial, Study NH19707, which supported approval of Mircera down to the age of 5 years, all 64 patients enrolled were on HD and received Mircera IV. Study NH19708 provides additional pediatric information in patients on other types of dialysis (i.e., PD), not on dialysis and in patients who received Mircera SC.

Concomitant Medications

All enrolled patients (N=40) continued receiving at least one concomitant treatment during the study including the extension period. The concomitant treatment classes taken by ≥ 30% of patients were vitamin D and analogues (29 patients [72.5%]), calcium (22 patients [55%]), folic acid and derivatives (19 patients [47.5%]), ACE inhibitors (18 patients [45%]), iron bivalent, oral preparations and iron trivalent, oral preparations (17 patients [42.5%] in each class), drugs for treatment of hyperkalemia and hyperphosphatemia (16 patients [40%] in each class), dihydropyridine derivatives (13 patients [32.5%]), antibiotics and antacids with sodium bicarbonate, anti-psoriatic topical agents (14 patients [35%] in each class), somatropin and

somatropin agonists and sulfonamides (12 patients [30%] in each class). Key concomitant medications are listed in the table below.

Table 8 Concomitant Medications, Study NH19708

Medication	Mircera N=40 n (%)
Anticoagulant	
enoxaparin sodium	1 (2.5%)
nadroparin calcium	1 (2.5%)
Iron Supplementation (taken by ≥10% of patients)	
ferrous sulfate	12 (30%)
saccharate iron oxide	7 (17.5%)
ferric pyrophosphate	5 (12.5%)
Folic acid	4 (10%)
Antihypertensive Agents	
ACE inhibitor	18 (45%)
angiotensin II receptor blockers	4 (10%)
alpha-adrenoreceptor antagonists	4 (10%)
dihydropyridine derivatives	13 (32.5%)
beta blocking agent non-selective selective	 2 (5%) 1 (2.5%)
alpha and beta blocking agents	1 (2.5%)

Source: CSR Study NH19708

Efficacy Results – Primary Endpoint

Core Period

The primary endpoint was the change in Hb concentration (g/dL) between baseline and evaluation period. The Hb concentration data was available for 38 patients during the evaluation period (Weeks 17-21). The mean change in Hb concentration between the baseline and the evaluation period was 0.48 g/dL (SD 1.03) with 95% CI (0.15, 0.82).

Statistical reviewer's comments: The analysis of the primary endpoint was based on the 38 patients who completed the core period. According to the CSR, the reasons for discontinuation from the core period were kidney transplant (1 patient [2.5%]) and use of prohibited medication (tacrolimus and mycophenolate mofetil) (1 patient [2.5%]).

The statistical review team performed following the sensitivity analyses to evaluate the

robustness of the efficacy result only based on the completed patient population:

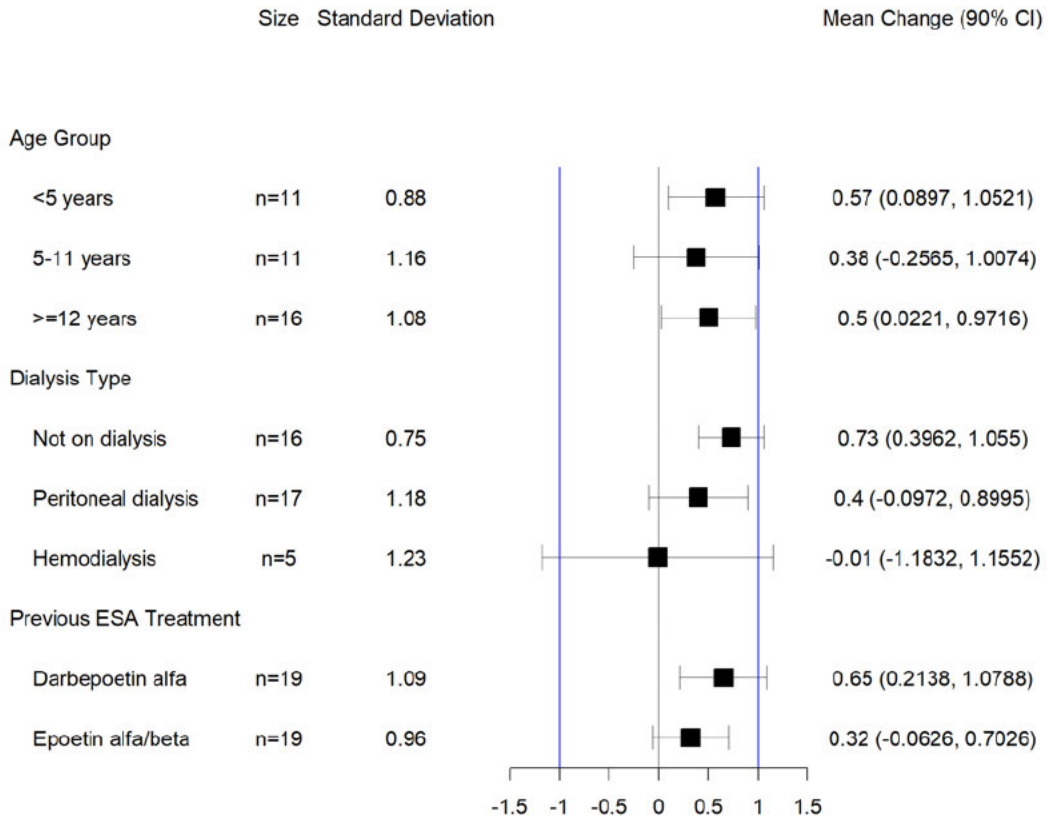
1) *Impute two missing values using the largest change in mean Hb concentration levels from baseline.*
2) *Impute two missing values using the smallest change in mean Hb concentration levels from baseline.*

The 90% CIs of the change in mean Hb concentration levels were (0.2921, 0.8739) and (0.0709, 0.6671) for sensitivity analyses 1) and 2), respectively. The SDs are 1.09 and 1.12 for sensitivity analyses 1) and 2), respectively.

The robustness of the statistical significance of the primary endpoint is evident as the results from the above sensitivity analyses also satisfy the success criteria for the primary endpoint.

In addition, the Applicant conducted subgroup analyses for the primary endpoint based on age group (<5, 5-11, ≥12 years), dialysis status at the start of the study (no dialysis, PD or HD), and previous ESA treatment (epoetin [alfa or beta] or darbepoetin), but they did not provide results of 90% CIs for the change in mean Hb concentration levels. The statistical review team conducted the subgroup analyses including the 90% CIs for the primary endpoint, as shown in figure below.

Figure 3 Subgroup Analyses of the Primary Endpoint



Source: FDA analysis

According to Figure 4, not all of the 90% CIs fall within the specified range of -1 to 1 g/dL , potentially attributed to the limited sample sizes within some subgroups, although they appear to be just slightly outside the -1 to 1 range.

A summary table of change in mean Hb is shown below.

Table 9 Change in Mean Hb concentration by Age Group, Dialysis Type, and Previous ESA Treatment

	Mircera SC Mean Hb (g/dL) baseline	**Mircera SC Mean Hb (g/dL) evaluation period**	**Mircera SC Hb (g/dL) change from baseline**
Primary Efficacy Population (N=38)	11.05 (0.51)	11.54 (0.96)	0.48 (1.03)
Age Group Subgroup			
<5 years (N=11)	11.02 (0.33)	11.63 (0.90)	0.57 (0.88)

	Mircera SC Mean Hb (g/dL) baseline	Mircera SC Mean Hb (g/dL) evaluation period	Mircera SC Hb (g/dL) change from baseline
5-11 years (N=11)	10.85 (0.50)	11.23 (1.07)	0.38 (1.16)
≥12 years (N=16)	11.12 (0.64)	11.68 (0.92)	0.50 (1.08)
Dialysis Type Subgroup			
Not on Dialysis (N=16)	10.89 (0.45)	11.66 (0.95)	0.73 (0.75)
PD (N=17)	11.14 (0.53)	11.57 (0.98)	0.40 (1.18)
HD (N=5)	11.02 (0.74)	11.01 (0.90)	-0.01 (1.23)
Prior ESA Treatment Subgroup			
Epoetin alfa or beta (N=19)	11.03 (0.54)	11.40 (0.78)	0.32 (0.96)
Darbepoetin (N=19)	11.01 (0.52)	11.67 (1.11)	0.65 (1.09)

Source: CSR NH19708
Abbreviations: ESA erythropoietin stimulating agent, Hb hemoglobin, HD hemodialysis, ITT intention to treat, PD peritoneal dialysis, SD standard deviation

Efficacy Results – Secondary and other relevant endpoints

The results of secondary endpoints were supportive of the primary endpoint:
Patients with mean Hb within 10-12 g/dL and change from baseline within ±1 g/dL during Evaluation Period.

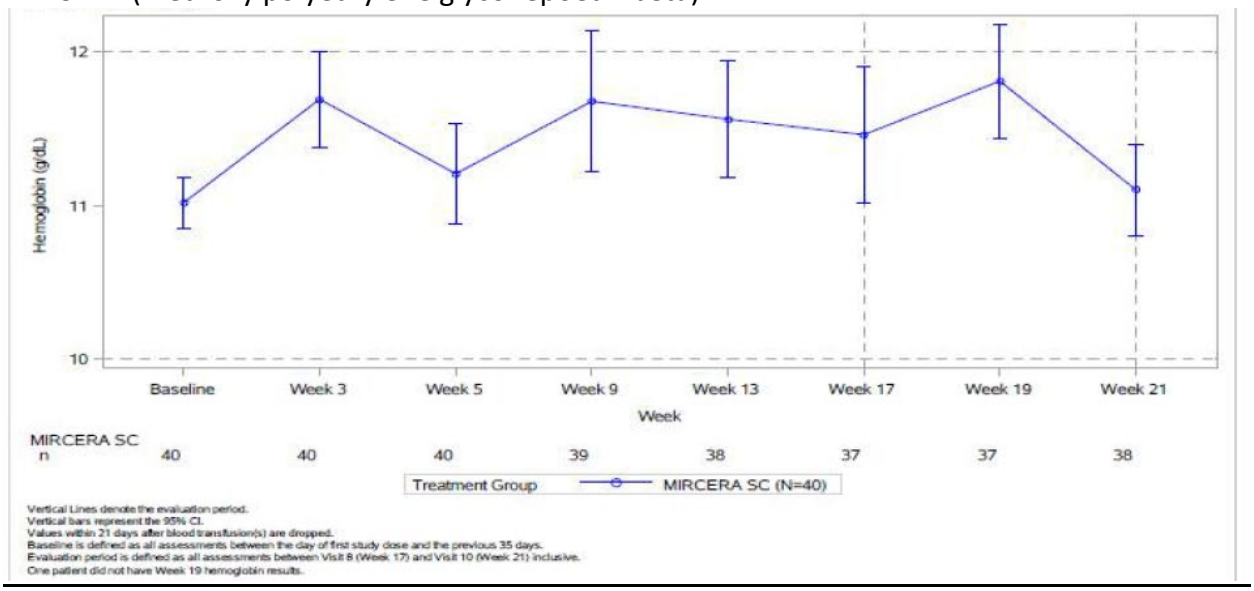
The mean Hb concentration levels during the evaluation period were maintained in:

- 24 patients (63.2%) within the range of 10-12 g/dL,
- 19 patients (50%) within the range of ±1 g/dL of the baseline, and
- 18 patients (47.4%) within both the ranges of 10-12 g/dL and ±1 g/dL of the baseline Hb concentration levels.

During the evaluation period, few patients had mean Hb concentration levels below 10 g/dL (2 patients [5.3%]) or more than 1 g/dL below the baseline mean Hb level (4 patients [10.5%]). There were 15 patients (39.5%) who had mean Hb concentration levels more than 1 g/dL above the baseline level and 12 patients (31.6%) had mean Hb level above 12 g/dL.

Throughout the entire core period, the mean Hb concentration levels remained within 10-12g/dL. See figure below.

Figure 4 Mean Hb Values During Core Study Period



Source: Applicant CSR

Clinical reviewer comment: The data from Study NH19708 showed that the mean change in Hb concentration was within the equivalence bounds of -1,1 g/dL (i.e., 0.48g/dL) however, approximately 1/3 of patients had a hemoglobin above 12g/dL. In the Mircera USPI it is stated in a boxed warning that in controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin level of greater than 11 g/dL, however this is based on adult data. Comorbidities, including cardiovascular disease are very different between adult and pediatric patients with CKD. In fact, prevalence of cardiovascular disease is very low in children.[16] The KDIGO Guidelines from 2012, recommends that ESAs target a Hb level between 11-12g/dL in pediatric patients. Whether a Hb level above 12g/dL increases the risk of adverse outcomes, including cardiovascular disease and death in pediatric patients is not known. Rheault et al performed a large population-based study using data from the Centers for Medicare and Medicaid Services ESRD Clinical Performance Measure project and United States Renal Data System. The investigators collected data from 1569 children receiving HD for CKD and measured outcomes including mortality, hospitalization, and cardiovascular events over 1 year follow-up. They found the hazard ratio of all-cause mortality and the adjusted relative rate of all-cause hospitalization were significantly lower in the hemoglobin 12 g/dl or greater group, and cardiovascular hospitalizations were significantly higher in the hemoglobin under 10 g/dl group. While a randomized controlled trial needs to be conducted to verify these findings, the risk of mortality and cardiovascular outcomes in pediatric patients with elevated Hb levels is likely not as great. In fact, a lower Hb concentration may be associated with increased risk.[2] In addition, given consideration of the close follow up, elevated Hb levels are likely transient. Therefore, while Hb excursions occurred in clinical trials, it likely does not pose a significant risk.

Dose/Dose Response

Overall, the median ratio of starting Mircera dose at Week 1 to the dose at the Week 17 was 1.44 (range: 0.2 -3.8) (N=33 patients), indicating a decrease in Mircera dose. The median ratio (Week 1:Week 17) of Mircera dose indicated a greater decrease in dose among patients in the 5-11 and <5 (1.50 in each group) years age groups as compared with ≥12 years age group (1.23). The median Mircera dose at Week 1 was 75 µg (range: 15-360 µg, and 50 µg (range: 0-250 µg) at Week 17. This was a median decrease by 20 µg (range: 250.0–- 120 µg) compared to the starting dose at Week 1. The median Mircera starting doses were 40, 75, and 120 µg in the age groups of <5, 5-11, and 12-17, respectively. During the evaluation period, the median Mircera dose decreased to 30, 50, and 75 µg in the age groups of <5, 5-11, and 12-17, respectively.

Mircera dose adjustments (increase, decrease, or both) were made for the majority of the patients (34 patients [85%]) during the core period. For most of the patients, Mircera dose was decreased (25 patients [62.5%]). The Mircera dose was increased in 7 patients (17.5%). The predominant reason for these dose modifications was to maintain the individual patient's Hb concentration levels within a target range of 10-12 g/dL or within +/-1 g/dL of baseline Hb levels. In terms of absolute number of dose changes, the mean number of dose increases was 0.4 (SD 0.8) and the mean number of dose decrease was 1.1 (SD 0.9).

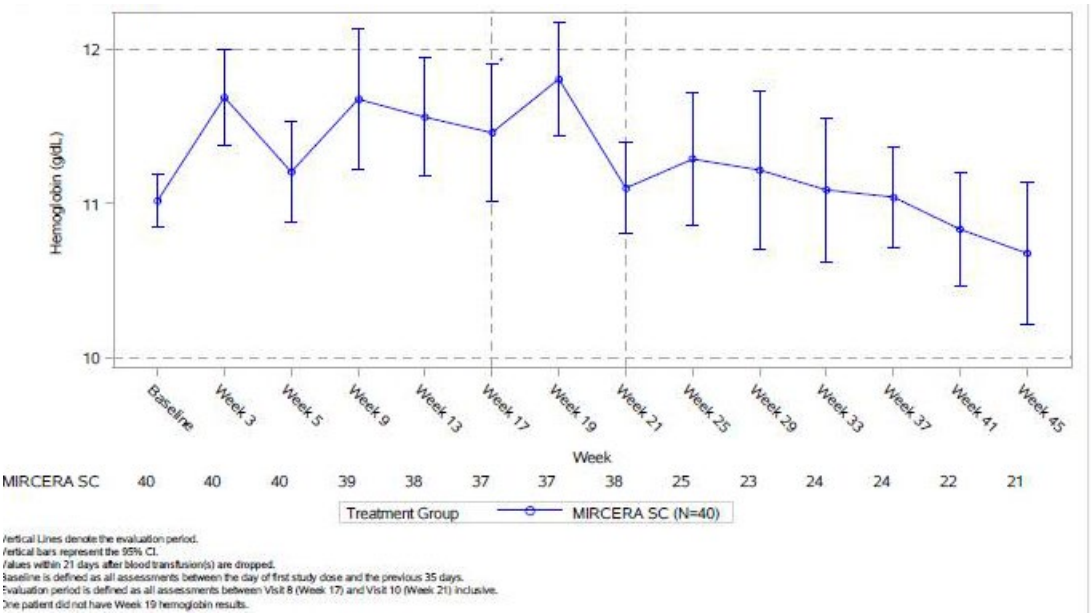
Clinical reviewer comment: Most patients required a dose increase or decrease to maintain in the target hemoglobin range. However, the majority of patients only required one dose adjustment. Of note, the majority of patients (77%) in Study NH19707, which was used to support a pediatric indication for patients >5 years old on HD for CKD, had dose adjustments to maintain Hb in the target range. As patients will be closely monitored in clinical practice, there is little risk with transient increases or decreases in hemoglobin level in pediatric patients that can be effectively managed with dose titration per the USPI. Further, while most patients required a dose reduction due to elevated hemoglobin levels, the risk of major adverse cardiovascular event (MACE) is not as prominent in the pediatric population. The clinical reviewer reviewed the patients who had a hemoglobin >12g/dL and did not find a trend in adverse events, including hypertension.

Durability of Response

A total of 25 patients who were eligible entered the safety extension period. The results in the safety extension period were generally consistent with the core period.

- Throughout the entire safety extension period, the mean Hb concentration levels remained within 10-12 g/dL (see figure below).
- The Hb concentration levels were maintained within 10-12 g/dL by 13/21 patients (61.9%) and within ±1 g/dL of the baseline Hb concentration level by 12/21 patients (57.1%) at Week 45.

Figure 5 Mean Hb Values Including Safety Extension Period, Study NH19708



Source: Applicant CSR NH 19708

During the safety extension period, a decrease in the median Mircera dose was observed compared to Week 1. The median (range) Mircera dose at Week 1 was 75 µg (range: 15-360 µg) and it was 50 µg (range: 10.0-560.0 µg) at Week 41. This was a median decrease by 25 µg at Week 41 compared to Week 1.

Mircera dose adjustments (increase, decrease, or both) were made in majority of the patients (18 patients [72%]). Seven patients (28%) did not require any dose change. Mircera dose increase as well as decrease were made in 10 patients (40%). Six patients (24%) had dose decrease only, and 2 patients (8%) had dose increase only. In terms of absolute number of Mircera dose changes, the mean (±SD) number of dose increases were 0.8 (1.1) doses, and the mean (±SD) number of dose decrease was 1.7 (1.4) doses.

Persistence of Effect

Persistence of effect after treatment was not evaluated.

6.2. Study MH40258

6.2.1 Study Design

Overview and Objective

Study Name: "Real World Evidence of Safety and Dosing of Mircera in Children with Chronic Kidney Disease"

The rationale for this study was to provide data on the efficacy and safety of Mircera in pediatric patients on dialysis to supplement results obtained from two clinical trials of Mircera in pediatric patients, Studies NH19707 and NH19708. This independent pediatric registry provided real world experience as well additional aggregated safety data and patient level data on Mircera dosing and Hb values from an independent pediatric registry.

The primary objectives for the study were to:

- Describe the safety profile of Mircera by aggregate assessment of safety data (number and causes of hospitalizations and deaths).
- Assess the relationship between Mircera dosing and Hb concentrations using patient level data.

The secondary objectives for the study were to:

- Confirm dose conversions from previous ESA treatment to Mircera that were determined and tested in study NH19707 (IV) and NH19708 (SC).
- Validate the previous dose simulation models, especially for the subset of very young patients (i.e., 0 months to <6 years of age).

Trial Design

In this non-interventional study, selected data elements among patients who received Mircera were extracted from two existing registries within the IPDN. The IPDN is a global consortium of pediatric nephrology centers dedicated to the care of children on chronic dialysis. IPDN is comprised of two registries, IPPN and IPHN. As of June 2021, 135 centers in 43 countries contributed to the IPPN registry, and 92 centers in 37 countries contributed to the IPHN registry.

Data was extracted from the 229 pediatric patients below 18 years of age on PD or HD included in the IPPN and IPHN registries during the study period with at least one observation while being treated with Mircera. Descriptive analyses were performed to describe the relationship between Mircera dosing and Hb concentrations.

Patient Population

Inclusion criteria:

- Aged 0 months to <18 years at initial Mircera visit.
- On chronic PD or HD .
- At least one observation while treated with Mircera.

Variables and Data Sources

Data were obtained from the IPPN and IPHN registries, collecting prospective observational data at 6-month intervals from pediatric dialysis centers worldwide (Asia, Europe, Latin America, and the USA). The participating centers were asked to enroll all incident and prevalent patients and enter data longitudinally until chronic PD or HD was discontinued.

The patient characteristics collected at entry to the registry were age, sex, cause of end-stage renal disease, age at initiation of dialysis, and presence of comorbidities, including a defined syndrome, cognitive impairment, motor impairment, cardiac abnormalities, pulmonary abnormalities, ocular abnormalities, and hearing impairment.

Variables analyzed: Demographics, clinical characteristics, dialysis information, treatment, laboratory parameters, number and causes of hospitalization events and deaths.

Missing data of non-key data elements are documented in the results and were taken into account in the results interpretation. The key data elements (i.e., age, hospitalizations, deaths and Hb level) were mandatory information provided to the registry.

Statistical Analysis Plan (SAP):

The primary objectives were addressed by conducting descriptive analyses of safety data, Mircera dose and Hb concentration and selected patient characteristics. Summary results (aggregate level) were provided for the safety data and patient characteristics. Patient level results were provided to describe the relationship between Mircera dosing and Hb concentrations. No amendments were made to the SAP.

6.2.2 Study Results

Data Quality and Integrity

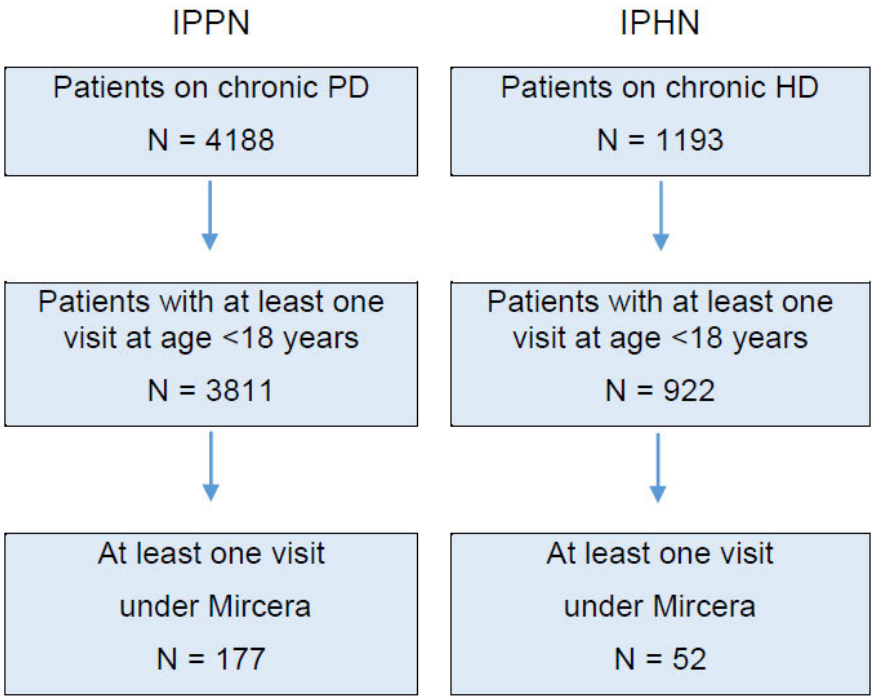
Overall, the quality and integrity of the clinical data appear acceptable.

Patient Disposition

Between 2007 and 2015, a total of 2453 infants, children, and adolescents aged 11 days to 18.8 years (median, 10.5 years; interquartile range, 3.4-14.2 years) were enrolled from 105 pediatric dialysis centers in 38 countries. As of June, 4188 patients had been enrolled in the IPPN registry, and 1193 patients had been enrolled in the IPHN registry.

Between January 1, 2007, and June 30, 2021, a total of 229 pediatric dialysis patients were analyzed in Study MH40258. A total of 177 patients on chronic PD, with at least one visit while treated with Mircera were observed in the IPPN. Between January 1, 2013, and June 30, 2021, 52 patients on chronic HD, with at least one visit while treated with Mircera were observed in the IPHN registry. See Figure 6 below for an overview of patient disposition.

Figure 6 Patient Disposition, Study MH40258



HD = hemodialysis; IPHN = International Pediatric Hemodialysis Network; IPPN = International Pediatric Peritoneal Network; PD = peritoneal dialysis

Source: Applicant CSR MH40258

Patient Demographics and Characteristics

There were 177 patients who received PD and 52 patients on HD.

The median age at first visit was 10.6 (range 0.3-17.9) years for the PD and 14.1 (2.4-17.9) years for the HD cohort, respectively. No patients under the age of 2 were included in the HD cohort. Approximately, 94% of the HD cohort received Mircera IV, only 26% of children in the PD cohort received the drug via the IV route. A summary of baseline characteristics as summarized in Table 10 in the PD population and Table 11 in the HD population. The median observation time under Mircera exposure was 6.1 (0-12.5) months and 11.9 (0-17.9) months for the PD and HD patients, respectively.

Table 10 Baseline Characteristics and Demographics of PD Population

Characteristic	Mircera Age 0-<2yr N=19	Mircera Age 2-<5yr N=31	Mircera Age 5-<12yr N=55	Mircera Age 12-<18yr N=72	Mircera All ages N=177
Age at first visit, yrs					
Mean (SD)	0.9 (0.5)	3.5 (0.7)	8.9 (2.1)	15.2 (1.6)	9.6 (5.5)
Median (range)	0.8 (0.3-1.7)	3.6 (2.1-4.9)	9.0 (5.1-12.0)	15.3 (12.1-17.9)	10.6 (0.3-17.9)
Gender					
Male, n (%)	12, (63.2%)	22 (71.0%)	37(67.3%)	39(54.2%)	110 (62.1%)
Female, n (%)	7 (36.8%)	9 (29%)	18(32.7%)	33(45.8%)	67 (37.9%)
Region of origin					
Latin American, n (%)	8(42.1%)	7(22.6%)	13(23.6%)	8 (11.1%)	36 (20.3%)
Asia/Arabia, n (%)	0 (0.0%)	1 (3.2%)	17(30.9%)	29(40.3%)	47 (26.6%)
Europe, n (%)	11(57.9%)	23(74.2%)	25(45.5%)	35(48.6%)	94 (53.1%)
Time on dialysis, months					
Mean (SD)	4 (2.7)	19.2 (18.2)	15.9 (16)	23.6 (24.1)	18.3 (20.1)
Median (range)	3.6 (1.6, 5.8)	17.4 (1.7, 32.5)	11.1 (3.4, 24.6)	14.2 (6, 34.3)	11 (3.1, 27.5)
Mircera dosing route					
IV, n (%)	1 (5%)	15 (48.4%)	18 (32.7%)	12 (16.7%)	46 (26%)
SC, n (%)	12 (63.2%)	6 (19.4%)	18 (32.7%)	29 (40.2%)	75 (42.4%)
Missing, n (%)	6 (31.5%)	10 (32.3%)	19 (34.5%)	21 (29.2%)	56 (31.6%)

Abbreviations: SD, standard deviation, IV, intravenous, SC, subcutaneous, yr, year
Source: Applicant's CSR

Table 11 Baseline Characteristics and Demographics of HD Population

Characteristic	Mircera Age 2-<5yr N=2	Mircera Age 5-<12yr N=17	Mircera Age 12-<18yr N=33	Mircera All ages N=52
Age at first visit, yrs				
Mean (SD)	3.5 (1.5)	9.4 (1.7)	15.5 (1.6)	13.0 (3.8)
Median (range)	3.5 (2.4-4.6)	9.6 (5.3-11.6)	15.9 (12.2-17.9)	14.1 (2.4-17.9)
Gender				
Male, n (%)	2 (100%)	9 (52.9%)	21(63.6%)	32(61.5%)
Female, n (%)	0	8 (47.1%)	12 (36.4%)	20 (38.5%)
Region of Origin				
Asia/Arabia, n (%)	0	1 (5.9%)	0 (0%)	1 (1.9%)
North America, n (%)	0	0	1 (3%)	1 (1.9%)

Characteristic	Mircera Age 2-<5yr N=2	Mircera Age 5-<12yr N=17	Mircera Age 12-<18yr N=33	Mircera All ages N=52
Europe, n (%)	2 (100%)	16 (94.1%)	32 (97%)	50 (96.2%)
Time on dialysis, months				
mean (SD)	23.4(31.5)	6.1 (9)	10.1 (13.8)	9.3 (13.3)
median (range)	23.1(1.1-45.7)	2.7 (0.9- 37.4)	2.5 (0.1-53)	2.6 (0.1- 53)
Mircera Dosing route				
IV	2 (100%)	17(100%)	30 (90.9%)	49 (94.2%)
SC	0	0	3 (9.1%)	3 3 (5.8%)

Abbreviations: HD hemodialysis, IV intravenous, SC subcutaneous, SD standard deviation, yr year
Source: Applicant's CSR

Concomitant Medications

A description of concomitant medications in the PD population is provided in Table 12 and in the HD population in Table 13. The majority of patients in the PD population received antihypertensive agents (67.8%) and iron therapy (78.5%). Common antihypertensives included calcium channel blocker (50.9%), ACE inhibitor/ARB (40.1%), and beta-blocker (25.7%). The majority of patients in the HD population received antihypertensive agents (51.9%) and iron therapy (84.6%). Common antihypertensives included calcium channel blocker (34.6%), ACE inhibitor/ARB (26.9%), diuretic (23.1%), and beta-blocker (9.6%).

Table 12 Concomitant Medications in PD Population

Medication	Mircera Age 0-<2yr N=19	Mircera 2-<5yr N=31	Mircera 5-<12yr N=55	Mircera 12-<18yr N=72	Mircera All ages N=177
Antihypertensive Prescribed					
Yes, n (%)	10 (52.6%)	8 (25.8%)	40 (72.7%)	62 (86.1%)	120 (67.8%)
Iron Therapy					
Yes, n (%)	11 (57.9%)	26 (83.9%)	48 (87.3%)	54 (75%)	139 (78.5%)
Oral, n (%)	11 (57.9%)	16 (51.6%)	28 (50.9%)	34 (47.2%)	89 (50.3%)
IV, n (%)	0 (0%)	7 (22.6%)	18 (32.7%)	16 (22.2%)	41 (23.2%)
Oral + IV, n (%)	0 (0%)	3 (9.7%)	2 (3.6%)	4 (5.6%)	9 (5.1%)
None, n (%)	8 (42.1%)	5 (16.1%)	7 (12.7%)	18 (25.0%)	39 (21.5%)

Abbreviations: ACE/ARB Angiotensin-converting-enzyme, ARB Angiotensin-converting-enzyme, IV intravenous, PD Peritoneal dialysis
Source: Clinical Study Report Study MH40258

Table 13 Concomitant Medications in HD Population

Medication	Mircera Age 2-<5yr N=2	Mircera Age 5-<12yr N=17	Mircera Age 12-<18yr N=33	Mircera All ages N=52
Antihypertensive prescribed				
Yes, n (%)	0 (0%)	7 (41.2%)	20 (60.6%)	27 (51.9%)
Iron Therapy				
Yes, n (%)	1 (50%)	14 (82.4%)	29 (87.9%)	44 (84.6%)
Oral, n (%)	0	1 (5.9%)	3 (9.1%)	4 (7.7%)
IV, n (%)	1 (50%)	13 (76.5%)	26 (78.8%)	40 (76.9%)
None, n (%)	1 (50%)	3 (17.6%)	4 (12.1%)	8 (15.4%)

ACE/ARB Angiotensin-converting-enzyme, ARB Angiotensin-converting-enzyme, IV intravenous, PD Peritoneal dialysis
Source: Clinical Study Report Study MH40258

Relationship Between Mircera Dosing and Hb Concentrations

In both of the cohorts, mean Hb levels were stable over time and did not differ by age group. At the last observation, 46.9% of the children on PD (Table 14) and 48.1% of those on HD (Table 15) had a Hb value within the target range of 10-12 g/dL. In general, the absolute monthly Mircera dose increased with age. Patients on HD received a lower dose of Mircera.

Table 14 Mean Hb and Mircera Dose at First and Last Documented Observation of the Study, PD Population

	Mircera Age 0-<2yr N=19	Mircera Age 2-<5yr N=31	Mircera Age 5-<12yr N=55	Mircera Age 12-<18yr N=72	All Ages N=177
Hemoglobin					
Hb g/dL, Mean (SD)					
First observation	11.4 (1.3)	11.1 (1.8)	10.8 (1.7)	11.1 (2.2)	11.0 (1.9)
Last observation	11.0 (1.3)	11.1 (1.5)	11.0 (1.6)	10.8 (1.9)	10.9 (1.7)
Hb Level at last observation					
<10 g/dL, n (%)	4 (21.1%)	7 (22.5%)	18 (32.7%)	21 (29.2%)	50 (28.2%)
10-12 g/dL, n (%)	10 (52.6%)	15 (48.4%)	24 (43.6%)	34 (47.2%)	83 (46.9%)
>12 g/dL, n (%)	5 (26.3%)	9 (29%)	13 (23.6%)	17 (23.6%)	44 (24.9%)
Mircera Dose					
Mircera Monthly Dose at First Observation (µg)					
Mean (SD)	57 (38)	88 (86)	95 (61)	125 (64)	102 (69)
Median (range)	30 (30-150)	75 (10-500)	80 (20-429)	114 (75-161)	100 (10-500)
Mircera Monthly Dose at last observation (µg)					

	Mircera Age 0-<2yr N=19	Mircera Age 2-<5yr N=31	Mircera Age 5-<12yr N=55	Mircera Age 12-<18yr N=72	All Ages N=177
Mean (SD) Median (range)	62 (42) 50 (15-150)	77 (38) 75 (10-150)	92 (56) 80 (30-400)	138 (67) 146 (21-321)	105 (63) 100 (10-400)
Mode of Mircera administration at last observation					
IV, n (%) SC, n (%) Missing, n (%)	2 (10.5%) 12 (63.2%) 5 (26.3%)	18 (58%) 3 (9.7%) 10 (32.3%)	18 (32.7%) 21 (38.2%) 16 (29.1%)	15 (20.8%) 37 (51.4%) 20 (27.8%)	53 (30%) 73 (41.2%) 51 (28.8%)

dL deciliter, Hb hemoglobin, mcg microgram, HD hemodialysis, PD peritoneal dialysis, SD standard deviation
Source: Clinical Study Report MH42508

Table 15 Mean Hb and Mircera Dose at First and Last Documented Observation of the Study, HD Population

	Mircera Age 2-<5yr N=2	Mircera Age 5-<12yr N=17	Mircera Age 12-<18yr N=33	All Ages N=52
Hemoglobin				
Hb g/dl Mean (SD) First observation Last observation	 7.6 (0.8) 7.6 (0.8)	 9.8 (1.7) 10.0 (2.1)	 10.6 (1.4) 10.8 (1.2)	 10.2 (1.6) 10.4 (1.7)
Hb Level at last observation <10 g/dL, n (%) 10-12 g/dL, n (%) >12 g/dL, n (%)	 2 (100%) 0 0	 10 (58.8) 5 (29.4%) 2 (11.8%)	 8 (24.2%) 20 (60.6%) 5 (15.2%)	 20 (38.5%) 25 (48.1%) 7 (13.5%)
Mircera Dose				
Mircera Monthly Dose at First Observation (µg) Mean (SD) Median (range)	 91 (53) 91 (54-129)	 98 (39) 86 (54-214)	 113 (52) 107 (21-214)	 107.0 (48) 107 (21-214)
Mircera Monthly Dose at last observation (µg) Mean (SD) Median (range)	 91.1 (53) 91.1 (53.6 128.6)	 88.2 (33.7) 85.7 (53.6-160.7)	 117.6 (145.1) 80 (16.1-857.1)	 107.0 (117.6) 80.4 (16.1-857.1)
Mode of Mircera administration at last observation IV, n (%)	 2 (100%)	 17 (100%)	 32 (97%)	 51 (98.1%)

	Mircera Age 2-<5yr N=2	Mircera Age 5-<12yr N=17	Mircera Age 12-<18yr N=33	All Ages N=52
SC, n (%)	0 (0%)	0 (0%)	1 (3.0%)	1 (1.9%)

dL deciliter, Hb hemoglobin, mcg microgram, HD hemodialysis, PD peritoneal dialysis, SD standard deviation
Source: Clinical Study Report MH42508

Clinical reviewer comment: MH40258 is based on a voluntary registry from which data was gathered at follow-up visits scheduled every 6 months; thus, not all data points are available and the precise exposure time to Mircera at the time of a Hb measurement was not described. While the results are descriptive and need to be interpreted with caution, nearly 50% of patients maintained a Hb level between 10-12g/dL at the last observation visit, supporting the efficacy of Mircera in pediatric patients. The registry study also provides additional data for the youngest patients as 19 patients were under the age of 2 years.

Patients on HD received a lower dose of Mircera. It is unclear why the HD cohort received lower doses, the Applicant speculates that it may be due to HD-related blood losses and more conservative, risk-aversive Mircera dosing, which is evident by the lower Hb at last observation visit. This rationale appears reasonable to the clinical reviewer.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This section is not applicable as Studies NH19708 and MH40258 could not be pooled due to major differences in study design.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The use of Mircera in the clinical trial is expected to be similar to use in the postmarket setting. This is supported by real-world evidence data which demonstrated that hemoglobin concentrations can be maintained in the desired clinical range (see section 6.2.2).

7.2.2. Other Relevant Benefits

Shorter-acting ESAs are typically dosed three times a week to once every 1-2 weeks, whereas Mircera is dosed once every 4 weeks, thus providing a more convenient dosing schedule and fewer needle sticks in children.

7.3. Integrated Assessment of Effectiveness

Study NH19708 was a phase 2, open-label, single-arm, multicenter study to ascertain the optimal starting dose of Mircera administered SC for the maintenance treatment of anemia in pediatric patients with CKD on dialysis or not yet on dialysis. A total of 40 patients were included in the study between the age of 4 months to less than 18 years. All patients were switched to SC Mircera from a table SC maintenance treatment with epoetin alfa, epoetin beta, or darbepoetin alfa. The study confirmed the starting dose of Mircera and demonstrated that Mircera could maintain hemoglobin levels near baseline. The majority of patients achieved Hb levels between 10-12g/dL. Maintaining Hb levels in pediatric patients with CKD is clinically meaningful as low Hb levels (<10g/dL) is associated with morbidity and mortality, increased risk of cardiovascular disease, and decreased quality of life.

Study MH40258, supported the efficacy results from Study NH19708. Study MH40258 was a non-interventional registry study in which patient level data was collected from pediatric patients with CKD on dialysis and with at least one observation while being treated with Mircera. The study included 229 pediatric patients from 3 months to <18 years, of which 177 were receiving PD and 52 receiving HD. In both cohorts, Hb levels were stable over time and did not differ substantially by age group. At last observation, almost 50% of patients in both cohorts had a Hb value in the target range of 10-12 g/dl.

8. Review of Safety

8.1. Safety Review Approach

The safety review focused on trial NH19708, an open-label, single-arm, multicenter study in which pediatric patients with CKD on dialysis and not on dialysis on a stable dose of an ESA were switched to Mircera (see Section 6.1.1. for further details on the study design). The safety population was defined as all patients who received at least one dose of Mircera.

Also included in the safety review is registry study, MH42508, which included pediatric patients on dialysis and were receiving Mircera. A descriptive analysis of safety (number and causes of hospitalizations and deaths) was reported. Information on whether the cause of hospitalization and/or death was treatment-related was not captured in the registries. Narratives were not collected. The total number and causes of hospitalizations and deaths, were presented overall and by age group.

A pooled safety analysis was not conducted due to major differences in study design. A detailed description of the study design of both studies can be found in Section 6 of this review.

The review of safety of Study NH19708 was based upon:

- Clinical Study Report (CSR)
- Protocol
- Summary of clinical safety (SCS)
- Integrated Summary of Safety (ISS)
- Patient narratives
- Case Report forms
- Datasets

The review of safety of Study MH40258 was based upon:

- CSR
- Protocol

8.2. Review of the Safety Database

8.2.1. Overall Exposure

NH19708

In total, 40 patients were included in Study NH19708. The core period was 20 weeks long, Mircera was dosed once every four weeks. Overall, the patients received a median of 5 Mircera administrations (range: 1-5 administrations), with the majority of patients (38 patient, [95%]) receiving at least 5 Mircera administrations. Thirty-eight (38) patients were exposed to Mircera for 20 weeks, and 21 patients were exposed to Mircera for 44 weeks. Two patients did not complete the administrations in the core period as they were withdrawn from the study due to kidney transplant (1 patient [2.5%]) and prohibited medication (1 patient [2.5%]).

The majority of patients (25 patients [62.5%]) enrolled in the core period continued the study in the optional safety extension period. More than half of the enrolled patients (22 patients [55%]) received at least 11 Mircera administrations. Exposure for core and safety extension periods are summarized below.

Table 16 Summary of Mircera Exposure Study NH19708, Safety Population

	Mircera SC Core Period (N=40)	**Mircera SC Core + Extension Period (N=40)**
Number of Administrations of Mircera		
Mean (SD)	4.9 (0.7)	8.5 (3.2)
Median	5	11
Range	1-5	1-11
Duration of treatment (weeks)		

Mean (SD)	15 (3.2)	29.77 (13.03)
Median	16.4	39.86
Range	0.1-18.3	0.1-41.1

Source: CSR
Abbreviations: SC subcutaneous, SD= standard deviation
*Note: The first dose of Mircera was given at week 1 of the study

MH40258

Overall, 229 (177 PD and 52 HD) patients were included in the registry. Mircera exposure was <12 months in 66% of patients and 12-96 months in 34% of patients. The median observation time under Mircera exposure was 6.1 (0-12.5) months and 11.9 (0-17.9) months for the PD and HD patients, respectively. An overview of exposure reported in Study MH40258 in the PD population is shown in Table 17 and in Table 18 for the HD population.

Table 17 Mircera Exposure in PD Population, Study MH40258

	Mircera Age 0-<2 yr N=19	**Mircera Age 0-<2 yr N=19**	**Mircera Age 0-<2 yr N=19**	**Mircera Age 0-<2 yr N=19**	**Mircera All ages N=177**
Mircera administration interval (days)					
Mean (SD)	30 (5)	28.7 (4)	26.8 (6.3)	27.7 (7.2)	27.9 (6.3)
Median, (range)	30 (15-45)	30 (15-30)	30 (14-42)	30 (10-60)	30 (10-60)
Duration of exposure (months)					
Mean (SD)	12.5 (12.6)	8.9 (9.1)	10.5 (15.5)	9.0 (14.6)	9.8 (13.8)
Median (range)	10.9 (0.0-19.1)	7 (0-39.7)	6 (0.0-67.8)	5.5 (0-91.3)	6.1 (0-91.3)
<6 months	6 (31.6%)	13 (41.9%)	27 (49.1)	40 (55.6%)	86 (48.6%)
6-12 months	6 (31.6%)	7 (22.6%)	12 (21.8%)	13 (18.1%)	38 (21.5%)
12-18 months	2 (10.5%)	7 (22.6%)	7 (12.7%)	6 (8.3%)	22 (12.4%)
18-24 months	2 (10.5%)	2 (6.5%)	4 (7.3%)	4 (5.6%)	12 (6.8%)
24-36 months	2 (10.5%)	1 (3.2%)	1 (1.8%)	5 (6.9%)	9 (5.1%)
36-48 months	1 (5.3%)	1 (3.2%)	0 (0%)	3 (4.2%)	5 (2.8%)
48-60 months	0 (0%)	0 (0%)	2 (3.6%)	0 (0%)	2 (1.1%)
60-72 months	0 (0%)	0 (0%)	2 (3.6%)	0 (0%)	2 (1.1%)
84-96 months	0 (0%)	0 (0%)	0 (0%)	1 (1.4%)	1 (0.6%)

Source: Applicant CSR
Abbreviations: min=minimum, max=maximum, SD= standard deviation, yr= year

Table 18 Mircera Exposure in HD Population, Study MH40258

	Mircera Age 2-<5 yr N=2	**Mircera Age 5-<12 yr N=17**	**Mircera Age 12-<18 yr N=13**	**Mircera All ages N=52**
Mircera administration interval (days)				
Mean (SD)	28 (0)	28 (4)	29 (4)	28 (4)
Median (range)	28 (28, 28)	28 (14, 35)	28 (14, 35)	28 (14-35)
Duration of exposure (months)				
Mean (SD)	0 (0)	16.0 (16.7)	11.4 (10.6)	12.5 (13.0)
Median (range)	0 (0, 0)	12.4 (0, 54.4)	11.7 (0 33.3)	11.9 (0-54.4)
<=6 months	2 (100.0%)	6 (35.3%)	12 (36.4%)	20 (38.5%)
6-12 months	0	1 (5.9%)	5 (15.2%)	6 (11.5%)
12-18 months	0	5 (29.4%)	8 (24.2%)	13 (25.0%)
18-24 months	0	0 (0.0%)	3 (9.1%)	3 (5.8%)
24-36 months	0	3 (17.6%)	5 (15.2%)	8 (15.4%)
36-48 months	0	1 (5.9%)	0	1 (1.9%)
48-60 months	0	1 (5.9%)	0	1 (1.9%)

Source: Applicant CSR
Abbreviations: HD hemodialysis, SD= standard deviation, yr= year

8.2.2. Relevant characteristics of the safety population

The safety population was the same as the efficacy populations in studies NH19708 and MH40258. See Table 6 in Section 6.1.2 for baseline demographic information for patients in NH19708 and Table 10 and Table 11 in Section 6.2.2 for patients in MH40258.

8.2.3. Adequacy of the safety database

In study NH19708, there were 40 patients exposed to Mircera. In study MH40258, 229 patients (177 on PD and 52 on HD) were exposed to Mircera.

Clinical reviewer comment: While the safety database of NH19708 is small, the population is an adequate representation of pediatric patients with anemia and CKD receiving and not receiving dialysis, in particular when considering safety has previously been established in patients >5 years of age with anemia and CKD on hemodialysis receiving IV Mircera. The safety database allows for an adequate safety evaluation. Study MH40258 is a registry study, which provides further evidence of safety, also in younger patients (<5 years of age) receiving IV Mircera. Safety data from Study MH40258 is limited given the nature of the study design (i.e., data points collected every 6 months, observational, no attribution or patient narratives).

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

NH19708

The safety data submitted was well organized and relevant data was easily identified. Patients enrolled in the both the core and safety extension periods of the study were monitored for safety and tolerability throughout the study. The safety data collected during the study included AEs, vital signs, clinical laboratory assessments, and anti-drug antibody assessments according to the protocol's schedule of assessments (see schedule of events in the Appendix of this review). The Applicant provided all clinical datasets with the submission. The Applicant also provided narratives for all patients resulting in death, SAEs, and AEs of interest.

There are no concerns regarding the quality and integrity of this submission.

MH40258

Overall, there are no major concerns with the quality of the data, however results were subject to bias given the study design (registry). Limitations of assessing safety data from Study MH40258 are that follow-ups were recorded approximately once every six months, and treatment information was only available as 6-month snapshots without an actual starting date. The Applicant had no direct access to the registry data nor to patient level data analyzed for study MH40258. Data processing and analysis was performed by members of the Institute of Medical Biometry and Informatics, University Hospital Heidelberg, which are among others overseeing the IPDN data. The capture of clinical information such as vital signs or laboratory data was not possible. Patient narratives and investigator attribution was not provided. Thus, safety information was limited to noting the number and cause of hospitalizations and deaths.

8.3.1. Categorization of Adverse Events

NH19708

TEAEs were classified by System Organ Class (SOC) and Preferred Term (PT). Events were coded using version 24 of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events were graded according to the WHO Toxicity Grading Scale. TEAEs that occurred during the treatment period from the first treatment dose until 28 days after last dose or until the final visit (whichever was latest) were collected.

The Applicant provided accurate definition of AEs and SAEs. The International Council for Harmonization (ICH) guideline for Good Clinical Practice was used, wherein an adverse event was defined as any untoward medical occurrence in a clinical investigation where a subject is administered a pharmaceutical product, regardless of causal attribution. An adverse event could therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition).
- Recurrence of an intermittent medical condition (e.g., headache) not present at Baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., invasive procedures such as blood sampling, discontinuation of medications).
- In the Protocol, the Applicant noted that procedures or surgery related to CKD, such as kidney transplantation and routine diagnostic procedures/tests were not considered adverse events and not recorded as an Adverse Event.

Adverse events of special interest identified by the Applicant included cases of potential drug-induced liver injury and suspected transmission of an infectious agent by the study drug.

MH40258

Adverse event data were not collected in the IPPN and IPHN registries, with the exception of hospitalizations and deaths and the adverse events resulting in death or hospitalization.

8.3.2. Routine Clinical Tests

NH19708

Routine clinical testing and monitoring of vital signs was appropriate. Vital signs and weight were assessed at weeks 1, 5, 6, 7, 8, 9 and 21. CBC and absolute reticulocyte count was done at weeks 3, 4, 5, 6, 8, 9, 13, 17, 19 and 21. Serum creatinine was obtained at week 1 and week 21. Iron parameters were obtained at week 9, 17, and 21. Safety labs were obtained at week 9 and 21, these included leukocytes plus differential, AST, ALT, serum albumin, ALP, C-reactive protein, potassium, phosphorus, calcium, and platelets. Anti-EPO and anti-Mircera antibodies were assessed at week 1,9 and 21. Iron studies, which included serum iron, serum ferritin, serum transferrin or TIBC (total iron binding capacity) were done at week 9, 17 and 21.

During the optional safety extension period, Week 21 to 45, vital signs and weight were obtained at visits for week 25, 29, 33, 27, 41, and the final study visit, week 45. Lab studies were performed for heme (Hb, RBC, absolute reticulocyte count) values at the same intervals as vital signs, serum creatinine at week 45, iron studies at week 45 and safety labs at weeks 33 and 45.

MH40258

Clinical tests were not performed in study MH40258.

8.4. Safety Results for Study NH19708

8.4.1. Deaths

No deaths were reported for study NH19708.

8.4.2. Serious Adverse Events

Core Period
Thirteen patients (32.5%) experienced a total of 23 SAEs. SOCs in which AEs were reported by more than one patient were Infection and infestations (10 patients [25%]) and Gastrointestinal disorders (2 patients [5%]). Peritonitis (3 patients [7.5%]) was the only SAE experienced by more than one patient. All other SAEs were varied across PTs and were experienced by one patient (2.5%) each. No SAE resulted in withdrawal or dose modification/interruption. See tables below for a complete list of SAEs.

Safety Extension Period
In the safety extension period, 3 (12%) patients experienced a total of 4 SAEs. One patient (4%) reported 2 SAEs of device related infection (Grade 2) and postoperative anemia (4%). The remaining 2 patients reported one SAE each; hypotension (Grade 4) and device related thrombosis (Grade 2). All 4 SAEs had resolved by the end of study. See tables below for a complete list of SAEs.

Table 19 Serious Adverse Events, Preferred Term, Study NH19708, Core and Extension Periods

System Organ Class/Preferred Term	Mircera SC Core Period N=40 n (%)	Mircera SC Extension Period N=25 n (%)
Infections and infestations	10 (25%)	1 (4%)
Peritonitis	3 (7.5%)	0
Appendicitis	1 (2.5%)	0
Device related infection	1 (2.5%)	1 (4%)
Enterovirus infection	1 (2.5%)	0
Gastroenteritis	1 (2.5%)	0
Pharyngotonsillitis	1 (2.5%)	0
Pneumonia	1 (2.5%)	0
Pyelonephritis	1 (2.5%)	0
Respiratory syncytial virus bronchiolitis	1 (2.5%)	0
Rhinovirus infection	1 (2.5%)	0
Upper respiratory tract infection	1 (2.5%)	0
Viral infection	1 (2.5%)	0
Gastrointestinal Disorders	2 (5%)	0
Diarrhea	1 (2.5%)	0

System Organ Class/Preferred Term	Mircera SC Core Period N=40 n (%)	Mircera SC Extension Period N=25 n (%)
Vomiting	1 (2.5%)	0
Congenital, familial, and genetic disorders	1 (2.5%)	0
Hydrocele	1 (2.5%)	0
General disorders and administration site conditions	0	1 (4%)
Device related thrombosis	0	1 (4%)
Injury, poisoning and procedural complications	1 (2.5%)	1 (4%)
Anemia postoperative	1 (2.5%)	1 (4%)
Musculoskeletal and connective tissue disorders	1 (2.5%)	0
Back pain	1 (2.5%)	0
Product issue	1 (2.5%)	0
Device malfunction	1 (2.5%)	0
Respiratory, thoracic and mediastinal disorders	1 (2.5%)	0
Hypoxia	1 (2.5%)	0
Vascular disorders	1 (2.5%)	1 (4%)
Hypotension	1 (2.5%)	1 (4%)

Source: Clinical Reviewer
Abbreviations: SC= subcutaneous

Table 20 Serious Adverse Events, FDA Medical Queries, Study NH19708, Core and Extension Periods

FMQ	Mircera SC Core Period N=40 n (%)	Mircera SC Extension Period N=25 n (%)
Peritonitis	3 (7.5 %)	0
Viral infection	2 (5%)	0
Upper Respiratory Infection	2 (5%)	0
Anemia	2 (5%)	0
Hypotension	1 (2.5%)	1 (4%)
Hypoxia	1 (2.5%)	0
Back pain	1 (2.5%)	0
Diarrhea	1 (2.5%)	0
Pneumonia	1 (2.5%)	0
Vomiting	1 (2.5%)	0

Source: Clinical reviewer
Abbreviations: SC= subcutaneous, FMQ= FDA medical query

Clinical reviewer comment: Review of SAEs by the clinical reviewer revealed that the majority of SAEs were unrelated to Mircera and were more likely to be related to the underlying renal disease or comorbidities. Upper respiratory tract infections, pyelonephritis, device related

thrombosis, diarrhea, vomiting, back pain and hypotension are adverse events listed in the current label for Mircera. Therefore, Mircera may have contributed to the SAEs seen in the pediatric population. The patient narrative for the event of device malfunction was reviewed. The catheter was dislodged and needed to be replaced. The facts presented make it unlikely that this event was related to Mircera. This patient later suffered a device thrombosis (PD and HD catheter), this could possibly be related to Mircera as there is a boxed warning of the possibility of thromboembolic events. However, the case is confounded by risk factors of thrombosis including infection (peritonitis), and indwelling catheter.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No patient experienced an AE that led to withdrawal of the study treatment during the core or extension periods.

8.4.4. Significant Adverse Events

Core Period
During the Core treatment period, 6 patients (15%) experienced AEs of WHO grade 3-4. Two patients (5%) experienced Grade 3 AE and 4 patients (10%) experienced a grade 4 AE. See a list of TEAEs that were grade 3 and higher in the core and extension periods. Except for an event of gastroenteritis, all severe AEs had resolved by the end of the Core period.

Safety Extension Period
During the safety extension period, 3 (12%) patients experienced an AE of WHO grade 3-4. All severe AEs resolved by the end of the study.

Table 21 Treatment-Emergent Adverse Events, Grade >3, Study NH19708, Core and Extension Periods

Preferred Term	Mircera SC Core Period N=40 n (%)	Mircera SC Extension Period N=25 n (%)
Anemia postoperative	1 (2.5%)	1 (4%)
Appendicitis	1 (2.5%)	0
Device malfunction	1 (2.5%)	0
Gastroenteritis	1 (2.5%)	0
Hypotension	0	1 (4%)
Peritonitis	1 (2.5%)	0
Pneumonia	1 (2.5%)	0
Pyrexia	0	1 (4%)
Respiratory syncytial virus bronchiolitis	1 (2.5%)	0

Source: Clinical reviewer
Abbreviations: SC= subcutaneous

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Core Period
In the Core Period, a majority of patients (32 patients [80%]) experienced at least one TEAE. The majority of patients (25[62.5%]) had grade 1-2 TEAEs. The most common TEAEs (>5%) by PT were upper respiratory tract infection, accidental overdose, anemia, gastroenteritis, peritonitis, oropharyngeal pain, and pyrexia.

Extension Period
During the Safety Extension Period a total of 16 patients (64%) experienced at least one TEAE. The most common TEAEs (>5%) in the extension period were upper respiratory tract infection, rhinitis, urinary tract infection, pyrexia, hypotension, headache and muscle spasms.

Table 22 Treatment Emergent Adverse Events Occurring in >5% of Patients, Preferred Term, Study NH19708, Core and Extension Periods

System Organ Class/Preferred Term	Mircera SC Core Period N=40 n (%)	Mircera SC Extension Period N=25 n (%)
Infections and infestations	25 (62.5%)	8 (32%)
Upper respiratory tract infection	5 (12.5%)	2 (8%)
Gastroenteritis	3 (7.5%)	0
Peritonitis	3 (7.5%)	0
Bronchitis	2 (5%)	0
Conjunctivitis	2 (5%)	1 (4%)
Nasopharyngitis	2 (5%)	0
Pharyngitis	2 (5%)	0
Rhinitis	0	2 (8%)
Urinary tract infection	0	2 (8%)
Injury, poisoning and procedural complications	7 (17.5%)	2 (8%)
Accidental overdose	4 (10%)	1 (4%)
Respiratory, thoracic and mediastinal disorders	7 (17.5%)	3 (12%)
Oropharyngeal pain	3 (7.5%)	0
Gastrointestinal Disorders	6 (15%)	2 (8%)
Abdominal pain	2 (5%)	1 (4%)
Diarrhea	2 (5%)	1 (4%)
General disorders and administration site conditions	6 (15%)	5 (20%)
Pyrexia	3 (7.5%)	2 (8%)
Blood and lymphatic system disorders	3 (7.5 %)	1 (4%)
Anemia	2 (5%)	0

System Organ Class/Preferred Term	Mircera SC Core Period N=40 n (%)	Mircera SC Extension Period N=25 n (%)
Vascular disorders	3 (7.5%)	2 (8%)
Hypertension	2 (5%)	0
Hypotension	0	2 (8%)
Metabolism and nutrition disorders	2 (5%)	1 (4%)
Hyperphosphatemia	2 (5%)	0
Nervous system disorders	2 (5%)	2 (8%)
Headache	2 (5%)	2 (8%)
Musculoskeletal and connective tissue disorders	0	2 (8%)
Muscle spasms	0	2 (8%)

Source: Clinical reviewer
Abbreviations: SC= subcutaneous

Table 23 Treatment Emergent Adverse Events Occurring in >5% of Patients, FMQ, Study NH19708, Core and Extension Periods

FMQ	Mircera SC Core Period N=40 n (%)	Mircera SC Extension Period N=25 n (%)
Upper respiratory tract infection	14 (35%)	4 (16%)
Nasopharyngitis	5 (12.5%)	3 (12%)
Viral infection	3 (7.5%)	1 (4%)
Peritonitis	3 (7.5%)	0
Abdominal pain	3 (7.5%)	1 (4%)
Anemia	3 (7.5%)	1 (4%)
Hemorrhage	3 (7.5%)	2 (8%)
Pyrexia	3 (7.5%)	2 (85)
Rash	3 (7.5%)	0
Bronchitis	2 (5%)	0
Hyperphosphatemia	2 (5%)	0
Diarrhea	2 (5%)	1 (4%)
Headache	2 (5%)	2 (8%)
Local administration reactions	2 (5%)	1 (4%)
Pruritus	2 (5%)	0
Systemic hypertension	2 (5%)	0
Hypotension	0	2 (8%)

Source: Clinical reviewer
Abbreviations: SC= subcutaneous, FMQ= FDA medical query

Clinical reviewer comment: The AE profile is similar to the established safety profile of Mircera. Accidental overdose AE is discussed in section 8.6.1 of the review.

8.4.6. Laboratory Findings

There were no clinically significant trends identified in any specific hematology or chemistry parameters. Notable laboratory findings are described below. Hemoglobin will not be discussed in this section as this was an efficacy parameter.

Platelets

A decrease in median platelet count was noted in all visits from the baseline value of 262.5 x 10^9/ L to 235 x10^9/L at Week 21 and to 234 x10^9/L at Week 45 but was within the normal range during the entire study period. One patient showed a shift in platelet values from normal to low post baseline and 2 patients shifted from normal to high post baseline value, see table below.

Table 24 Shift Table of Platelet Results from Baseline to Worst Post Baseline Value, Study NH19708

		Worst Post-Baseline Assessment			
Treatment Group	Baseline Assessment	Low	Normal	High	Total
MIRCERA SC (N=40)	Low	3 (7.5%)	0	0	3 (7.5%)
	Normal	1 (2.5%)	33 (82.5%)	2 (5.0%)	36 (90.0%)
	High	0	1 (2.5%)	0	1 (2.5%)
	Total	4 (10.0%)	34 (85.0%)	2 (5.0%)	40 (100%)

Source: Applicant CSR NH19708

Chemistry

A total of 14 patients (35%) and 10 patients (25%) shifted from normal to high during the study for phosphorous and potassium, respectively. However, changes in electrolytes are not uncommon in patients with CKD. No electrolyte abnormality resulted in a SAE or drug discontinuation.

8.4.7. Vital Signs

At study entry, a total of 21 patients (52.5%) had hypertension at baseline. During the core period, after initiating Mircera treatment, 2 patients had 3 nonserious, Grade 2 AEs of hypertension. Of the 2 patients, one patient had medical history of ongoing hypertension and the other patient did not have any history of hypertension at enrollment.

Changes in systolic (SBP) and diastolic blood pressure (DBP) were measured by the Applicant using the change in normalized Z-score from the baseline score. A positive Z-score at any time point indicates that the raw score at that time point was higher than the mean value of raw scores in the reference population. Overall, in all patients, the median Z-score for the SBP and DBP showed small variation across all visits compared to the median score at baseline during core and safety extension period.

In the core period, patients not yet on dialysis or on peritoneal dialysis, the median Z-score for the SBP and DBP showed small variation (within ±1 of baseline) across all visits compared to the median score at baseline. A total of 6 patients (17.1%) had at least three consecutive SBP or DBP values at or above the age, sex, and weight specific 95th percentile. In the safety extension period, patients not yet on dialysis or on peritoneal dialysis, the median Z-score for the SBP and DBP showed small variation (within ±1 of baseline) across all visits compared to the median score at baseline.

In the core period, in hemodialysis patients during the pre-dialysis assessments, the median Z-score for the SBP and DBP showed small variation (within ±1 of baseline) across all visits compared to the median score at baseline. Similarly, during the post-dialysis assessments, the median Z-score change was small (within ±1 of baseline) compared to the median score at baseline. During the pre-dialysis assessments, 2 of 5 patients (40%) had at least three consecutive SBP or DBP values at or above the age, sex, and weight specific 95th percentile. In the safety extension period, during the pre-dialysis assessments, the median Z-score for the SBP and DBP showed greater variation at the later visits compared to the median score at baseline; the greatest change was -2.50 at Week 45 for SBP and -1.22 at Week 45 for DBP. Similarly, during the post-dialysis assessments, the median Z-score change showed greater variation at the later visits compared to the median score at baseline; the greatest change was -1.49 at Week 45 for SBP, and 1.13 at Week 33 for DBP.

Clinical reviewer comment: Overall there were no trends noted in vital signs. Hypertension is a well described AR of Mircera, but no trends in elevated BPs were described in Study NH19708.

8.4.8. Electrocardiograms (ECGs)

Routine ECGs were not conducted during the trial.

8.4.9. QT

Refer to the original Mircera review for formal QT study results. No new QT studies submitted.

8.4.10. Immunogenicity

In Study NH19708, blood samples were collected for anti-drug antibody (ADA) testing at Week 1, 9, 21 and 45. A total of 131 samples were tested for anti-Mircera and anti-EPO antibodies. Two samples (1.5%) tested positive for anti-Mircera antibodies and four samples (3.1%) tested positive for anti-EPO antibodies in two patients. In both of these patients, there was no evidence of PRCA, and both continued to show response to Mircera treatment, with the Hb value of 10.17 and 11.38 g/dl at baseline and 11.73 g/dl and 11.35 g/d during the evaluation period, respectively.

In one patient, the Week 21 sample tested positive for both anti-Mircera and anti-EPO antibodies with titers of 1:1.56 and 1:29.8, respectively. The earlier Week 9 sample from this patient tested negative for both anti-Mircera and anti-EPO antibodies. Since the baseline (Week 1) and end-of-study (Week 45) samples for this patient were unfit for analysis due to incorrect handling there was no way of knowing the initial or final status of this patient. The patient was recalled for an additional ADA sample approximately 7 months after the end of study visit. The patient had continued to be treated with Mircera off-label after participation in the study ended. The samples taken during patient recall tested negative for both anti-Mircera and anti-EPO antibodies. During the period of study participation, Hb and Mircera doses were stable.

In the other patient, the Week 1 sample tested positive for anti-Mircera antibodies with a titer of 1:1.32. and anti-EPO antibodies with a titer of 1:1.56. The patient tested positive for anti-Mircera at Week 1 although he had never been treated with Mircera before study enrollment. The same patient tested positive for anti-EPO antibodies at weeks 9 and 21 with titers of 1:3.20, and 1:8.77, respectively. Anti-Mircera antibodies tested negative at these time points. Subsequent samples taken at Week 45 tested negative for both anti-Mircera and anti-EPO antibodies.

Clinical reviewer comment: The risk of immunogenicity is described in the Mircera UPSI. Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of methoxy polyethylene glycol-epoetin beta products is unknown.

8.5. Safety Results for Registry Study MH42508

The safety of Mircera was assessed by analyzing hospitalization events and deaths during exposure to Mircera.

Hospitalizations
In total, 121/177 (68.4%) PD patients had at least one hospitalization while using Mircera. Approximately, 58% of the patients had a non-elective hospitalization. The most common causes of hospitalization were infections 85/177 (32%) and PD technique complications for 41/177 (23%). There were 18 admissions for hypertensive crisis in 14 patients (8%). A total of 6 hospitalizations in three patients were related to anemia, including two transfusions performed in one patient and two episodes of bleeding in another patient. No thromboembolic events were reported. See table below for the most common causes of hospitalization.

Table 25 Most Common Causes of Hospitalizations (>5%), PD Population

Hospital admission cause	0 - <2 years N=19 n (%)	2 - <5 years N=31 n (%)	5 - <12 years N=55 n (%)	12 - <18 years N=72 n (%)	All Ages N=177 n (%)
Hospitalization	17 (89.5%)	21 (67.7%)	38 (69.1%)	45 (62.5%)	121 (68.4%)
Elective Hospitalization*	13 (68.4%)	6 (19.4%)	13 (23.6%)	18 (25%)	50 (28.2%)
Non-Elective Hospitalization	14 (73.7%)	19 (61.3%)	32 (58.2%)	37 (51.4%)	102 (57.6%)
PD technique (overall) (non-infectious)	8 (42.1%)	6 (19.4%)	14 (25.5%)	13 (18.1%)	41 (23.2%)
PD initiation*	4 (21.1%)	1 (3.2%)	6 (10.9%)	6 (8.3%)	187 (9.6%)
PD catheter dysfunction	3 (15.8%)	3 (9.7%)	4 (7.3%)	4 (5.6%)	14 (7.9%)
PD catheter exchange	2 (10.5%)	1 (3.2%)	4 (7.3%)	3 (4.2%)	10 (5.6%)
Infection (overall)	10 (52.6%)	11 (35.5%)	18 (32.7%)	17 (23.6%)	56 (31.6%)
Peritonitis	6 (31.6%)	4 (12.9%)	10 (18.2%)	13 (18.1%)	33 (18.6%)
Viral infection	1 (5.3%)	3 (9.7%)	3 (5.5%)	2 (2.8%)	9 (5.1%)
Cardiovascular (overall)	1 (5.3%)	2 (6.5%)	8 (14.5%)	8 (11.1%)	19 (10.7%)
Hypertension	1 (5.3%)	1 (3.2%)	7 (12.7%)	5 (6.9%)	14 (7.9%)
Electrolyte/fluid imbalance (overall)	1 (5.3%)	1 (3.2%)	7 (12.7%)	9 (12.5%)	18 (10.2%)
Fluid overload	1 (5.3%)	0	3 (5.5%)	7 (9.7%)	11 (6.2%)
Gastrointestinal	3 (15.8%)	7 (22.6%)	3 (5.5%)	6 (8.3%)	19 (10.7%)
Surgery (overall)	8 (42.1%)	3 (9.7%)	6 (10.9%)	7 (9.7%)	24 (13.6%)
Nephrectomy*	3 (15.8%)	1 (3.2%)	5 (9.1%)	1 (1.4%)	10 (5.6%)

*Elective hospitalization category
Abbreviations: PD, peritoneal dialysis
Source: Applicant's CSR

In the HD cohort, 36/52 patients (69.2%) had at least one hospitalization while using Mircera. The most common cause for hospitalizations were issues with the HD catheter (38.5%) and infection (26.9%). In total, 10 admissions in seven patients (13.5%) were due to hypertensive crises. No access-unrelated thromboembolic events and no blood transfusions were reported. See table below for the most common causes of hospitalization.

Table 26 Most Common Causes of Hospitalizations (>5%), HD Population

Hospital admission cause	**2-<5 years N=2 n (%)**	**5-<12 years N=17 n (%)**	**12-<18 years N=33 n (%)**	**All N=52 n (%)**
Hospitalization	1 (50%)	14 (82.4%)	21 (63.6%)	36 (69.2%)
Elective Hospitalization*	0	7 (41.2%)	11 (33.3%)	17 (34.6%)
Non-elective hospitalizations	1 (50%)	14 (82.4%)	17 (51.5%)	32 (61.5%)
HD technique (non-infectious)	0	9 (52.9%)	11 (33.3%)	20 (38.5%)
Access dysfunction	0	8 (47.1%)	9 (27.3%)	17 (32.7%)
Infection (overall)	1 (50%)	9 (52.9%)	4 (12.1%)	14 (26.9%)
Viral infection	0	4 (23.5%)	1 (3%)	5 (9.6%)
Bacterial infection	0	4 (23.5%)	0	4 (7.7%)
CVC line infection	0	2 (11.8%)	1 (3%)	3 (5.8%)
UTI/urosepsis	0	2 (11.8%)	1 (3%)	3 (5.8%)
Pneumonia	1 (50%)	1 (5.9%)	1 (3%)	3 (5.8%)
Cardiovascular	0	3 (17.6%)	5 (15.2%)	8 (15.4%)
Hypertension	0	3 (17.6%)	4 (12.1%)	7 (13.5%)
Bone Disease	0	1 (5.9%)	2 (6.1%)	3 (5.8%)
Gastrointestinal	1 (50%)	2 (11.8%)	1 (3.0%)	4 (7.7%)
Surgery	0	5 (29.4%)	4 (12.1%)	9 (17.3%)

*Elective hospitalization category
Abbreviation: HD, hemodialysis, CVC, central venous catheter, UTI, urinary tract infection
Source: Applicant's CSR

Deaths

Five children (2.8%) in the PD cohort and 2 (3.8%) of the children undergoing HD died while receiving Mircera (i.e., 3% of the total population). The cause of death is listed in the table below.

Table 27 Deaths, Study MH42508

Age in years	**Cause of death**	**Dialysis Type**
0-<2	Intracranial bleed	PD
2-<5	Cardiorespiratory decompensation	HD
2-<5	Unexpected sudden death at home	HD
5-<12	Infection	PD
5-<12	CHF	PD

Age in years	Cause of death	Dialysis Type
12-<18	Infection (non-PD-related)	PD
12-<18	Intracranial bleed post cardiac catheterization	PD

Source: CSR Study MH42508
Abbreviations: CHF= congestive heart failure, PD= peritoneal dialysis, HD= hemodialysis

Clinical reviewer comment: As expected, the number of deaths in the pediatric registry were low. Without patient narratives it is not possible to determine if administration of Mircera was related to the event of death. The majority of the hospitalizations appear related to the underlying disease and comorbidities. No new safety signals were identified, but due to lack of details regarding hospitalizations it is difficult to make any conclusions.

8.6. Analysis of Submission-Specific Safety Issues

Elevated Hemoglobin
There were 127 occurrences of hemoglobin level greater than 12 g/dl in 33 patients. Review of AEs for these patients at the time of the elevated Hb did not reveal an association between elevated hemoglobin concentration and a related AE such as thrombosis. Patient (b) (6) had persistently elevated Hb levels (≥12g/dl) between day 85 and 144 and several events of peritoneal catheter thrombosis and hemodialysis catheter thrombosis. It unclear if the elevated Hb contributed to the events of thrombosis, course was confounded by peritonitis and vascular access. Further, the patient's screening Hb was >12g/dL.

Thrombosis
In study NH19708, one patient experienced multiple episodes of thrombosis of the dialysis catheter. Patient (b) (6) aged 13.7 years, experienced a total of 9 AEs of thrombosis of the peritoneal or HD access device, which began on Day 90 of treatment with hospital admission for peritonitis and was followed by recurrent thrombosis of the peritoneal dialysis device. After 37 days of ongoing device access issues, the device modality was changed to hemodialysis. No device related thrombosis was reported from day 127 to day 176. On Study Day 177, the patient was diagnosed with Grade 2 vascular access thrombosis, details not reported) which was considered medically significant. He received treatment with heparin. He experienced another 7 episodes of device related thrombosis, each of which resolved on the same day. It is notable that the patient had Hb levels ≥12g/dL between day 85-144 of the study.

Clinical reviewer comment: There is a boxed warning for thrombosis in the Mircera USPI.

8.7. Safety Analyses by Demographic Subgroups

Age, gender and race subgroups were too small to make meaningful safety comparisons.

8.8. Specific Safety Studies/Clinical Trials

No specific studies were conducted to evaluate any specific safety concern in this submission.

8.9. Additional Safety Explorations

8.9.1. Human Carcinogenicity or Tumor Development

Mircera has a boxed warning for tumor progression or recurrence. No events related to tumor development or cancers occurred in the submitted studies.

8.9.2. Human Reproduction and Pregnancy

No pregnancies occurred during the development program. The trial excluded females who were pregnant or breastfeeding or who intended to become pregnant during the study or within 90 days after the final dose of Mircera. Inclusion criteria allowed for inclusion of post-pubertal female patients of childbearing potential with agreement to remain abstinent or to use acceptable contraceptive methods during the study and for 90 days after the last dose of Mircera.

8.9.3. Pediatrics and Assessment of Effects on Growth

At baseline, 5 patients (12.5%) had a history of growth retardation, and 3 (7.5%) patients had a history of growth failure. The mean height at baseline was 126.74 (32.95) cm and the median Z-score was -1.6, indicating lower height compared to the normal population for the same age and sex. At the end of the Core Period (week 21), the median height Z score was -1.41. The median change from baseline was 0.06. The normalized median Z score for height for participants in the safety extension period (week 21 to week 45) was -1.44. The median change from baseline was 0.17.

Reviewer comment: The median z-score for height showed little variation in both the core and safety extension periods. The results should be taken with caution given the wide range of ages in the cohort and the differing growth velocity in addition to the short study duration.

8.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Drug Abuse
ESAs, including Mircera have the potential for use as blood doping agents in endurance sports. Various methods to detect ESAs including Mircera have been developed [17] [18]. (b) (4)

Drug Overdose
A total of 5 patients (12.5%) were reported with accidental overdoses in study NH19708; four patients during the core period and one patient during the extension period. During the core

period, two accidental overdoses occurred at Week 17 and were because of an issue with the functioning of the Interactive Voice/Web Response System (IXRS) which suggested a wrong dose. Subsequently, the issue in the IXRS was fixed. Both patients were reported with major protocol deviation. The remaining two accidental overdoses were due to medical error and did not exceed 25% of the dose that should have been administered. One patient had accidental overdose during the extension period due to reporting issue in IXRS. In all 5 patients the Mircera dose was corrected at the next visit and the overdosing had no safety impact.

8.10. Safety in the Postmarket Setting

8.10.1. Safety Concerns Identified Through Postmarket Experience

As stated in the Periodic Benefit-Risk Evaluation Report, 172 AEs (111 serious and 61 non-serious) from 81 cases (52 serious and 29 nonserious) were reported from post-marketing sources for pediatric patients. Of these 172 events in 81 cases, 48 cases were reported from non-interventional programs, while the other 33 cases were from spontaneous sources. The most common AEs reported included off label use, no adverse event, intentional product use issue, fetal exposure during pregnancy, death, tachycardia, respiratory distress, systemic lupus erythematosus, and low birth weight baby.

Clinical reviewer comment: No new safety concerns were identified in the postmarket experience.

8.10.2. Expectations on Safety in the Postmarket Setting

There is no expectation of new safety signals in the post market setting.

8.10.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified from other disciplines.

8.11. Integrated Assessment of Safety

The clinical safety of Mircera has been established in adults since approval in 2007 for the treatment of symptomatic anemia associated with CKD in adult patients. With approval in 2018 for use in pediatric patients 5 to 17 years of age (for maintenance treatment of anemia by the intravenous route in patients on HD who are converting from other ESAs after their Hb level was stabilized with an ESA), the safety profile of Mircera has been described in children down to the age of 5. The current study, NH19708, along with the registry information from Study MH40258, demonstrated the safety of subcutaneously administered Mircera in pediatric patients with CKD, including patients <5 years of age and in patients on dialysis and not on dialysis.

Overall, the safety profile for Mircera in the pediatric population studied in NH19708 was

similar to the known safety profile of Mircera.

While the interpretation of safety from Study MH40258 is limited, given the nature of the study (i.e., registry study in which data was collected every 6 months and did not include patient narratives), no new safety concerns were identified.

9. Advisory Committee Meeting and Other External Consultations

This application was not presented at an Advisory Committee meeting or to any other external consultants.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Table 28 Summary of Label Changes

Summary of Significant Label Changes (High Level Changes)		
Section	**Proposed Labeling**	**Approved Labeling**
Indications and Usage	(b) (4)	The Agency revised the indication to include all patients on dialysis, PD and SC. • 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.
Dosage and Administration	Revised labeling to include SC administration for pediatric patients.	The Agency recommended the following additional language for pediatric patients: In patients less than 6 years of age, maintain the same route of administration as

		the previous ESA when switching from another ESA to Mircera. The Agency recommended addition of a table for Mircera dose adjustments in pediatric patients as described in pediatric clinical trials.
Warnings and Precautions	(b) (4)	No revisions proposed by the Applicant. The Agency is in agreement.
Contraindications	Uncontrolled hypertension • Pure red cell aplasia (PRCA) that begins after treatment with Mircera or other erythropoietin protein drugs • History of serious allergic reactions to Mircera, including anaphylaxis	No changes were proposed by the Applicant. The Agency agrees with the Applicant's proposal.

Adverse Reactions	No new safety signal was detected.	The Agency recommended that the Applicant report Mircera exposure.
Clinical Pharmacology	The Applicant updated the immunogenicity section.	The Agency recommended the Applicant also provide Anti-EPO data.
Clinical Studies	The Applicant added study NH19708 data to the label.	The Agency recommended that the Applicant provide demographic and detailed efficacy information.

10.2. Nonprescription Drug Labeling

Not applicable

11. Risk Evaluation and Mitigation Strategies (REMS)

No safety issues were identified during the review of this application that warranted a REMS.

12. Postmarketing Requirements and Commitments

No new PMRs or postmarketing commitments (PMCs) are recommended. Study NH19708 fulfills PMR 3385-1 and Study MH40258 fulfills PMR 3385-2.

13. Appendices

13.1. Schedule of Activities

Table 29 Procedures and Schedule

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Source: Protocol NH19708 v.4 Appendix 1 and Appendix 2

Table 30 Schedule of Activities for Optional Safety Extension Period (Week 21 to Week 45)

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

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

[a] Visit window ± 3 days.

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

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

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

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

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

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

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

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

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

Source: CSR NH19708

Table 31 WHO Toxicity Grading Scale

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

13.2. References

1. Levin A, et.al., *Kidney disease: Improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease* Kidney International Supplements 2013. **3**: p. 1-150.
2. *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.* Kidney International Supplements, 2024. **105**(4S).
3. Amanullah, F., A.A. Malik, and Z. Zaidi, *Chronic kidney disease causes and outcomes in children: Perspective from a LMIC setting.* PLoS One, 2022. **17**(6): p. e0269632.
4. Harambat, J. and I. Madden, *What is the true burden of chronic kidney disease in children worldwide?* Pediatr Nephrol, 2023. **38**(5): p. 1389-1393.
5. Drueke, T.B. and P.S. Parfrey, *Summary of the KDIGO guideline on anemia and comment: reading between the (guide)line(s).* Kidney Int, 2012. **82**(9): p. 952-60.
6. Atkinson, M.A. and B.A. Warady, *Anemia in chronic kidney disease.* Pediatr Nephrol, 2018. **33**(2): p. 227-238.
7. Staffa, S.J., et al., *Pediatric hematology normal ranges derived from pediatric primary care patients.* Am J Hematol, 2020. **95**(10): p. E255-E257.
8. Foundation, N.K. *Social Determinants of Kidney Disease.* . 2021; Available from: https://www.kidney.org/news/newsroom/factsheets/African-Americans-and-CKD.
9. Lea, J.P., K. Norris, and L. Agodoa, *The role of anemia management in improving outcomes for African-Americans with chronic kidney disease.* Am J Nephrol, 2008. **28**(5): p. 732-43.
10. Koshy, S.M. and D.F. Geary, *Anemia in children with chronic kidney disease.* Pediatr Nephrol, 2008. **23**(2): p. 209-19.
11. Atkinson, M.A., et al., *Risk for anemia in pediatric chronic kidney disease patients: a report of NAPRTCS.* Pediatr Nephrol, 2010. **25**(9): p. 1699-706.
12. Bhagat, N., et al., *Impact of anemia on the cardiovascular status in children with chronic kidney disease: A pilot study.* Clin Nutr ESPEN, 2022. **47**: p. 283-287.

13. Mitsnefes, M.M., *Cardiovascular disease in children with chronic kidney disease.* J Am Soc Nephrol, 2012. **23**(4): p. 578-85.
14. VanSickle, J.S. and B.A. Warady, *Chronic Kidney Disease in Children.* Pediatr Clin North Am, 2022. **69**(6): p. 1239-1254.
15. Kliger, A.S., et al., *KDOQI US commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD.* Am J Kidney Dis, 2013. **62**(5): p. 849-59.
16. Hattori, M., *Hemoglobin target in children with chronic kidney disease: valuable new information.* Kidney Int, 2017. **91**(1): p. 16-18.
17. Jelkmann, W. and C. Lundby, *Blood doping and its detection.* Blood, 2011. **118**(9): p. 2395-404.
18. Yasuoka, Y., et al., *Progress in the Detection of Erythropoietin in Blood, Urine, and Tissue.* Molecules, 2023. **28**(11).

13.3. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study NH19708: 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.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 20		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JULIA C FRIEND
04/30/2024 12:58:28 PM

HUAN WANG
04/30/2024 01:00:44 PM

YEH FONG CHEN
04/30/2024 01:07:10 PM

CARRIE E DIAMOND
04/30/2024 01:09:49 PM

ANN T FARRELL
04/30/2024 01:18:33 PM