U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA #: **Supplement #:**	125164 S-78
Drug Name:	MIRCERA®
Indication(s):	Chronic kidney disease (CKD)
Applicant:	Vifor (International) Inc.
Stamp Date: **Primary Review Date:** **PDUFA Date:**	14-DEC-2017 21-MAY-2018 14-OCT-2018
Review Priority:	Priority
Biometrics Division:	DB V / CDER
Statistical Reviewer:	Dr. Kallappa M. Koti
Concurring Reviewers:	Dr. Lei Nie, Team Leader Dr. Thomas Gwise, Deputy Division Director Division of Biometrics V
Medical Division:	DHP
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1. Introduction

Mircera was approved in 2007 for use in adult patients with chronic kidney disease on dialysis or not on dialysis to correct and maintain hemoglobin levels. In this submission, the Sponsor submitted study results to fulfill a Pediatric Research Equity Act (PREA) PMR 2471-1.

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 patients ages 5 to 17 years who have chronic kidney disease and are undergoing dialysis (Study NH19707)

The study is NH19707 entitled "An Open-Label, Single-Arm, Multicenter Study to Ascertain the Optimal Dose of Mircera® Given Subcutaneously for the Maintenance Treatment of Anemia in Pediatric Patients with Chronic Kidney Disease on Dialysis or Not Yet on Dialysis". Protocol for NH19707 was reviewed under IND 10158 (SDN 723).

2. Study NH19707

The primary efficacy objective was to find 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 when switching from stable subcutaneous maintenance treatment with epoetin beta or darbepoetin alfa. Study NH19707 was conducted between 28 July 2008 and 29 March 2016. Schedule of Activities are shown below in Table 2.1.

Table 2.1: Schedule of Activities

Study Period	Screening Period (3 weeks)		Dose Titration Period 16 weeks					Evaluation Period 4 weeks		
Visit Number	1	2	3	4	5	6	7	8	9	10
Visit Day	Wk -3	Wk -1	Wk 1	Wk 3	Wk 5	Wk 9	Wk 13	Wk 17	Wk 19	Wk 21
Informed consent	X									
Physical exam	X									
Vital signs / weight	X	X	X		X	X	X	X		
Hematology										
Iron parameters	X	X				X		X		
Anti-EPO and Anti-Mircera antibody			X							X
Injection pain Ques.	X	X	X			X				
Adverse events			Record throughout the dose titration							
ESA* administration	X	X								
Mircera administer			X		X	X	X	X		
Iron supplementation	As needed to maintain iron stores									
PK sampling			X	X		X		X	X	

*erythropoietin-stimulating agent

The starting dose was based on conversion factors obtained from trial NH19797 (see IND 10158 [SDN 723; dated 6-DEC-2017]). Details are provided in Table 2.2 below.

Table 2.2: Mircera Starting Dose

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

The dose conversion of Mircera was aimed to maintain the hemoglobin within a range of ±1 g/dL of baseline hemoglobin level and between 10 – 12 g/dL. Table 2.3 below shows some guidelines to Mircera dose adjustments in Study NH19707.

Table 2.3: Mircera Dose Adjustments

Hemoglobin Assessment	Compared with the Previous Mircera Dose
Hb decreases by more than 1.0 g/dL compared with baseline Hb	Increase dose by approximately 25%
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%
Hb is less than 9 g/dL (Hb < 9.0 g/dL)	Increase dose by approximately 50%
Hb increases by more than 1.0 g/dL compared with the baseline Hb or Hb is approximately 12 g/dL	Decrease dose by approximately 25%
Hb continues to increase (i.e., Hb exceeds 12 g/dL following dose reduction	Stop doses until Hb is less than 12.0 g/dL. Resume dose at approximately 25% below previous dose

Two groups were considered:
Dose Group 1: Patients who started with an intermediate-conversion factor dose
Dose Group 2: Higher conversion factor dose, double that of Group 1.

Patients received Mircera once every four weeks in sequential dosing groups; no randomization was performed. This was an exploratory study without a powered statistical group comparison. No formal sample size estimation was performed. Descriptive statistics of the primary endpoint were calculated.

The ITT and Completers populations. The intent-to-treat (ITT) population includes all patients enrolled in the study. Efficacy evaluation was not based on ITT population. The patients completing at least 18 weeks of treatment with at least 3 Hb assessments during the evaluation period were characterized as completers. A total of 64 were enrolled (16 in Group 1 and 48 in Group 2). Of the 48 of Group 2, 9 patients withdrew from the study due to renal transplant. Two patients withdrew due to administrative reasons. One patient died and 1 refused treatment. One of these patients who withdrew entered the evaluation period. Four patients from Group 1 withdrew from the study due to renal transplant. Thus, there were 12 completers in Group 1 and 36 in Group 2. Efficacy evaluation was based on completers population.

Table 2.4 below shows the numbers of patients by previous ESA agent and dose group. There were no patients in Group 1 who previously had epoetin alfa.

Table 2.4: Number of patients by previous ESA and dose group

Previous ESA Agents	Group 1	Group 2	Total
Darbepoetin alfa	6	19	25
Epoetin alfa	0	4	4
Epoetin beta	6	13	19
Total	12	36	48

Table 2.5 below shows the numbers of patients by age-group and dose group.

Table 2.5: Number of patients by age-group and dose group

Age Group	Group 1	Group 2	Total
5 - 11	6	11	17
≥12	6	25	31
Total	12	36	48

The baseline period was defined as all assessments between the day of first dose and the previous 20 days. Baseline Hb was calculated as the area under the curve (BAUC). Descriptive statistics of baseline Hb are shown below in Table 2.6.

Table 2.6: Descriptive statistics of BAUC g/dL

Statistics	Group 1 (N = 12)	Group 2 (N = 36)
Mean	11.14	11.09
Standard Deviation	0.4	0.46
First Quartile	11.05	10.72
Median	11.16	11.09
Third Quartile	11.3	11.31
Minimum, Maximum	10.18, 11.69	10.28, 12.1

3. The primary and secondary endpoints

The primary endpoint was the change in Hb concentration (g/dL) between the baseline period and the evaluation period (weeks 17-21), where Change = Evaluation Period Hb – Baseline Hb. Evaluation period was defined as all assessments between Visit 8 (Week 17) and Visit 10 (Week 21) inclusive. The average Hb value during the evaluation period was based on study days 111 to 138.

The Sponsor used an analysis of covariance model for the change in Hb with independent variables, age group (5-11 vs 12-17), baseline hemoglobin, previous treatment (epoetin alfa or epoetin beta), and Mircera dose group. The SAS names of these independent variables are BAUC, S_PEPOA2, S_AGEGRPS and S_RNDRUG, respectively.

The following secondary endpoints were proposed. Only the first two secondary endpoints are reviewed in this report.

1) Percentage of patients with average Hb within ±1 g/dL of baseline Hb
2) Percentage of patients with average Hb within or below the range of 10-12 g/dL
3) Incidence of red blood cell (RBC) transfusions
4) Change in reticulocyte count (×10000/μ) between baseline and evaluation

4. Efficacy results

The results of the Sponsor proposed ANCOVA of change in Hb are as follows.

Table 4.1: Sponsor's ANCOVA model based results

Source	DF	TYPE III SS	Mean Sq	F	Pr > F
Baseline Hb (BAUC)	1	8.252	8.252	8.33	0.0061
Previous Treatment (S_PEPOA2)	1	0.003	0.003	0.00	0.9575
Age Group (S_AGEGRPS)	1	1.217	1.217	1.23	0.2737
Mircera Dose Group (S_RNDRUG)	1	3.594	3.594	3.63	0.0634
Error	43	42.5752	0.99		

Sponsor's model based adjusted means for Group 1 and Group 2 were -0.7367 and -0.0927, respectively. The corresponding 95% confidence intervals are (-1.32, -0.16) and (-0.45, 0.26) for Group 1 and Group 2, respectively. As the confidence interval for Group 2 includes 0, the Sponsor claims that Group 2 did maintain Hb levels close to the target range. However, it is noted that there was no significant difference in change in Hb between the groups. Conventional pooled t-test approach resulted in a p-value of 0.084, and 95% confidence intervals on mean change for Group 1 and Group 2 are (-1.4, -0.15) and (-0.5, 0.21), respectively.

As stated by the Sponsor, Study NH19707 was an exploratory study without a powered statistical group comparison. Therefore, this reviewer calculated 95% confidence intervals on means

separately for each group assuming the samples are from normal populations with unknown variances. Results are shown below.

Table 4.2: Reviewer's results:

Descriptive statistics	Group 1 (N = 12)	Group 2 (N = 36)
Mean	-0.7764	-0.1452
Median	-0.7292	-0.1083
Standard deviation	1.2366	1.0143
95% confidence interval on mean	(-1.56, 001)	(-0.49, 0.2)

Secondary endpoint results in Group 2 showed that 75% of patients maintained Hb values within ±1 g/dL of baseline and 81% maintained Hb values within 10 -12 g/dL during the evaluation period. Further details are shown below in Table 4.3.

Table 4.3: Secondary endpoints

Endpoint	Group 1	Group 2
Stable Hb with in ±1 g/dL	7/12 = 58%	27/36 = 75%
Hb within 10 – 12 g/dL	9/12 = 75%	29/36 = 81%
Hb within 10 – 12 g/dL and ±1 g/dL of BL	7/12 = 58%	25/36 = 69%

5. Conclusion

- Both conversion factors tested in Group 1 and Group 2 did maintain Hb levels close to the target range. Results of the secondary endpoints support the conversion factor tested in Group 2. Conversion factor tested in Group 2 is recommended.

- The labeling claim should be based on the data from the recommended conversion factor only. Therefore, in the labeling, Sponsor's statement: "(b) (4) [redacted]" should be replaced by: "The mean change in Hb from baseline to the evaluation period with the recommended conversion factor was -0.15 g/dL and a 95% confidence interval: (-0.49 to 0.2)."

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