15 December 2016
EMA/67470/2017
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Mircera

methoxy polyethylene glycol-epoetin beta

Procedure no: EMEA/H/C/000739/P46/038

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Introduction

On 17th October 2016, the MAH submitted a completed paediatric study for Mircera, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

1. Scientific discussion

1.1. Information on the development program

MIRCERA was first approved in the European Economic Area in 2007 for the treatment of anemia associated with CKD including adult patients on dialysis and those not on dialysis. Since then, the drug has been approved in 112 countries worldwide, and anextensive body of post-marketing experience in adults is available.

In January 2009 the PDCO and the marketing authorization holder (MAH) agreed to a pediatric investigation plan (PIP) which consisted of the following two studies:

Phase II study NH19707 with primary objectives:

- To determine the starting dose of MIRCERA in pediatric patients with CKD on hemodialysis when switching from stable maintenance treatment with epoetin alfa, epoetin beta or darbepoetin alfa,
- To demonstrate changes in hemoglobin (Hb) over time in response to different intravenous (iv) doses of MIRCERA.

Phase III study NH19708 with primary objective:

- To confirm the optimal dose of MIRCERA selected in the previous exploratory dose-finding study, in a larger group of pediatric patients with CKD on dialysis and not yet on dialysis.

In July 2012, the MAH submitted a PIP modification to increase the number of patients in the phase II study in the group having a stable Hb response and to extend the completion timelines for both studies. Patient numbers were increased due to concerns that the variability in Hb was considerably higher than assumed in the original protocol sample size calculations. The decision was also made to replace all patients who withdrew early from the study (mainly due to the high transplantation rate in paediatric patients), leading to even higher requirements in patient numbers. Timelines were extended due to the difficulty of recruiting paediatric patients with CKD on hemodialysis despite international recruitment. As such, it took 7 years with 28 sites to complete the phase II study of 64 patients; safety extension phase was also shortened because the last two patients were transplanted. Thus, the fulfilment of this PIP, as it was originally agreed in January 2009 has been difficult. In support of the current PIP modification, a systematic literature review to identify data for estimating the size of patient population eligible for participation in the planned phase III trial has been prepared. Data has been sought from different countries and age groups on the administration of erythropoiesis stimulating agents. The calculations show that the number of CKD paediatric patients on peritoneal dialysis is limited, (approximately 1400 patients aged 5-19 years are estimated to be on peritoneal dialysis at a given time in Europe and the US).

The new proposed Phase II study NH19708 would be conducted in order to confirm the extrapolation of results for the subcutaneous administration of MIRCERA in pediatric patients on peritoneal dialysis and pre-dialysis.

The above suggested study would shorten study time lines and supports the submission of a solid data set to CHMP, to support a paediatric indication for MIRCERA in the near future.

The two phase II studies, along with PK/PD modelling and simulation will be used to support a paediatric indication.

Given that study NH19707 has already generated data in paediatric patients on haemodialysis, such patients will not be included in the proposed phase II study, which will therefore enrol patients on peritoneal dialysis and patients not yet on dialysis.

1.2. Information on the pharmaceutical formulation used in the study<ies>

MIRCERA is available in pre-filled syringes

CHMP comments:
A specific paediatric presentation has not been developed. Pending on the finally approved dose, the riskfor dosing errors with the pre-filled syringes in children should be discussed.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted final report(s) for:

- Phase II study NH19707 "An Open-Label, Multi-Center, Multiple Dose Study to Determine the

Optimum Starting Dose of Intravenous MIRCERA for Maintenance Treatment of Anaemia in Paediatric Patients with Chronic Kidney Disease on Hemodialysis";

- Population PKPD modelling and simulation analysis

1.3.2. Clinical study<ies>

STUDY NH19707

Title: An Open-Label, Multi-Centre, Multiple Dose Study to Determine the Optimum Starting Dose of Intravenous MIRCERA for Maintenance Treatment of Anaemia in Paediatric Patients with Chronic Kidney Disease on Haemodialysis.

Description

This phase II, dose-finding study was an open-label, multicentre, multiple dose study of MIRCERA administered once every 4 weeks iv for 20 weeks in paediatric CKD patients aged 5-17 years old receiving haemodialysis who switched from other ESAs (epoetinalfa/beta or darbepoetin alfa). In the core study period, after the first administration of MIRCERA, dose adjustments were permitted to maintain target Hb levels, which were measured once per week.

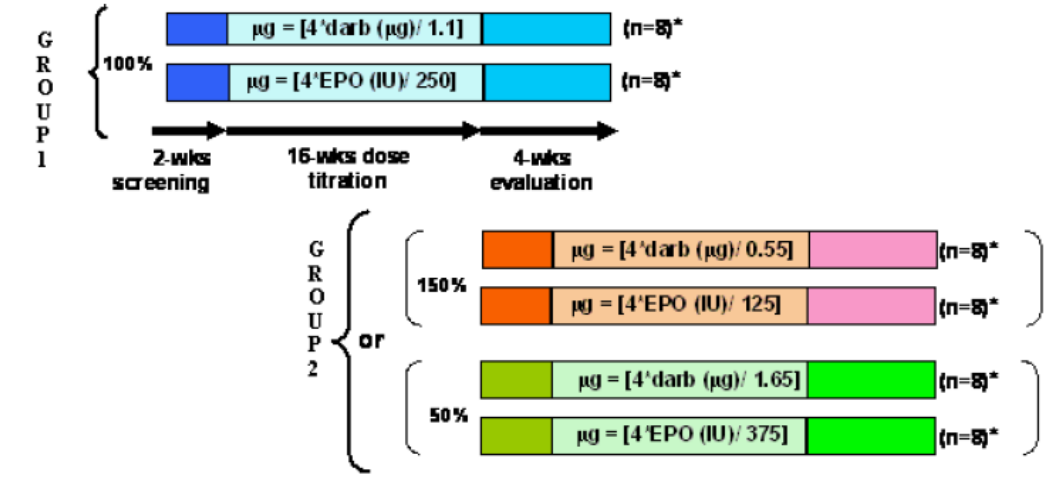
To find the optimum MIRCERA starting dose, the study tested two groups with different conversion factors related to their previous ESA dose.

The first 16 patients (intermediate-conversion-factor group, described as Group 1 in the protocol and clinical study report [CSR]) were enrolled and treated with MIRCERA at a starting dose based on their previous ESA dose (4 x previous weekly epoetin dose [IU] / 250 or 4 x previous weekly darbepoetinalfa dose [µg] / 1.1). After 16 patients had completed at least 16 weeks of treatment, a preliminary assessment of the safety and efficacy of MIRCERA was made.

For the preliminary efficacy assessment, the uncorrected 90% confidence interval (CI)for the average Hb change from baseline to weeks 14-16 was calculated. If Hb levels had been adequately controlled with balanced dose increases and decreases, no other dose group would have been started, and additional patients would have been recruited to receive the same MIRCERA dose (Figure 1). However, a high-conversion-factor group was required (described as Group 2 in the protocol).

Patients in Group 2 received MIRCERA based on a conversion factor from their previous ESA dose, double that of Group 1 (4 x previous weekly epoetin dose [IU] / 125 or4 x previous weekly darbepoetin alfa dose [µg] / 0.55). Similarly, after 16 patients had completed the first 16 weeks of treatment, a preliminary assessment of this group was also made. Based on the same criterion for decision making (Hb change from baseline within ±1g/dL, balanced dose changes and safety considerations), the decision was taken to recruit 20 additional patients into this high conversion factor group (Group 2).

Figure 1 Core Study Design



* The total number of patients was to be at least 36 in the group with optimum dose conversion

Methods

Objective(s)

The primary objectives of the study NH19707 were

• To determine the starting dose of MIRCERA in paediatric patients with CKD on haemodialysis when switching from stable maintenance treatment with epoetin alfa, epoetin beta or darbepoetin alfa

• To demonstrate changes in Hb over time in response to different iv doses of MIRCERA

The secondary objectives of the study NH19707 were:

• To study the pharmacokinetics (PK) of MIRCERA in paediatric patients

• To explore MIRCERA exposure-response relationship

• To assess the safety and tolerability of multiple doses of MIRCERA in paediatric patients

• To document long-term safety and efficacy of MIRCERA administration in paediatric patients with anaemia associated with CKD

Study design

This phase II, dose-finding study was an open-label, multicentre, multiple dose study of MIRCERA administered once every 4 weeks iv for 20 weeks in paediatric patients 5-17years old with CKD receiving haemodialysis who switched from other ESAs (epoetinalfa/beta or darbepoetin alfa). In this core study period, after the first administration of MIRCERA, dose adjustments were permitted to maintain target Hb levels, which were measured once a week.

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 was approximately balanced across the patients, no other dose group would have been started, and additional patients would have been recruited to receive the same MIRCERA dose.

This condition was not met; the upper limit of the CI for average Hb change was below -1 g/dL. Based on this finding and consideration of dose changes and safety information, the Data and Safety Monitoring Board (DSMB) approved the initiation of a high conversion-factor group as per the study design (denominated Group 2 in the protocol). If the lower limit of the CI had been above 1 g/dL, a lower-dose group could have been initiated (figure 1).

Patients in Group 2 received MIRCERA based on a conversion factor from their previous ESA dose, double that of Group 1 (4 × previous weekly epoetin dose [IU] / 125 or4 × previous weekly darbepoetin alfa dose [µg] / 0.55). Similarly, after 16 patients had completed the first 16 weeks of treatment, a preliminary assessment of this group was also made. Based on the same criterion for decision making (Hb change from baseline within ±1g/dL, balanced dose changes and safety considerations), the decision was taken, with the support of the DSMB, to recruit further patients into this high conversion factor group (Group 2).

Although the protocol provided for the possibility of a third dose group, this was not considered necessary. The preliminary assessment also suggested higher than expected variability in Hb; to account for this, the protocol was amended to increase the minimum size of Group 2 from 25 to 36patients. At the same time, the decision was made to replace all patients who did not complete at least 18 weeks of treatment.

Table 1 Assignment to Dose Groups

	Group 1:	Group 2:	Total
Initial dose	Intermediate conversion factor	High conversion factor	
Initial enrollment	16	16	
Preliminary assessment decision	Start Group 2	Enroll additional patients[a]	
Additional patients	0	20	
Protocol specified minimum number	16	36	52
Replacement for early withdrawal	0	12	12
Total			64

[a]Decision to enroll additional patients taken before initial target enrolment reached.

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 52-weeksafety extension period. During this period, the patients continued to receive MIRCERAonce every 4 weeks and Hb concentration measurements occurred less frequently (every 4 weeks).

Study population /Sample size

The target population comprised paediatric patients 5 - 17 years old with clinically stable chronic renal anaemia on haemodialysis treatment and who were receiving maintenance treatment with an erythropoietic agent.

At least one third of the patients in each dose group were to be in the age group of ≥ 5years to < 12 years. Additionally, the aim was to recruit equal numbers of patients previously treated with darbepoetin alfa and those treated with epoetin alfa or beta.

Inclusion criteria

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

Paediatric patients 5 - 17 years old (in Russia only: 12−17 years old) with clinically stable chronic renal anaemia

• Hemodialysis treatment for at least 8 weeks

• Body weight ≥ 10 kg

• Adequate hemodialysis: urea reduction ratio (URR) of ≥ 65% or Kt/V ≥1.2 for patients on three times weekly hemodialysis. Patients with fewer or with more hemodialysis sessions per week had to have a weekly Kt/V ≥3.6.

• Baseline pre-dialysis Hb concentration 10.0 – 12.0 g/dL determined from the mean of weekly Hb values measured between weeks -2 to -1

• Intravenous maintenance epoetin alfa, epoetin beta, or darbepoetin alfa with same dosing interval for at least 8 weeks before screening. The approved ESA compounds allowed prior to enrolment in the study (if the product had been approved for paediatric use in the country) were darbepoetin alfa (Aranesp®,Nespov®, Aranest®), epoetin alfa (Eprex®, Epogen®, Epopen®, Erypo®), and epoetinbeta (NeoRecormon®, Recormon®).

• Stable maintenance epoetin alfa, epoetin beta, or darbepoetin alfa treatment with no weekly dose change ≥25% (increase or decrease) during the 2-weeks of screening.

Patients who had been previously treated by the sc route could only participate if they had been receiving their ESA by the iv route for at least 8 weeks before screening.

Adequate iron status defined as serum ferritin ≥100 ng/mL or transferrin saturation (TSAT) ≥20% (or percentage of hypochromic red cells < 10%); mean of two values measured during screening weeks -2 and -1.

Exclusion criteria

• Overt gastrointestinal bleeding within 8 weeks before screening or during the screening period

• Red blood cell (RBC) transfusions within 8 weeks before screening or during the screening period

Hemoglobinopathies (e.g., homozygous sickle-cell disease, thalassemia of all types)

• Hemolysis

• Active malignant disease

• Chronic, uncontrolled or symptomatic inflammatory disease (e.g. systemic lupus erythematosus)

• Uncontrolled hypertension as assessed by the investigator

• Epileptic seizures within 3 months prior to screening and during the screening period

• Administration of any investigational drug within 4 weeks prior to screening and planned during the study

• Severe hyperparathyroidism (intact parathyroid hormone [PTH] ≥ 1000 pg/mL or whole PTH ≥ 500 pg/mL) or biopsy-proven bone marrow fibrosis

• Known hypersensitivity to recombinant human erythropoietin, polyethylene glycol, or to any constituent of the investigational medicinal product formulation

• Pure red cell aplasia (PRCA) or history of PRCA

• High likelihood of early withdrawal or interruption of the study (e.g. a planned living donor kidney transplant within 16 weeks after study drug initiation)

• Planned elective surgery during the entire study period (except hemodialysis access surgery)

• Sexually active females of childbearing potential and sexually active males who were not willing to use reliable contraception during treatment and for 90 days following the end of treatment

• Females who were pregnant, lactating, or intending to become pregnant during study conduct.

Treatments

MIRCERA (available in pre-filled syringes) was administered by iv injection, using the venous injection port of the hemodialysis lines.

Table 3 Dose Conversion from Epoetin Alfa or Beta to MIRCERA

	MIRCERA dose (µg)	Injection frequency
Low conversion factor[a]	4 x previous weekly epoetin dose (IU) /375	Once every 4 weeks
Intermediate conversion factor (Group 1)	4 x previous weekly epoetin dose (IU) /250	Once every 4 weeks
High conversion factor[a] (Group 2)	4 x previous weekly epoetin dose (IU) /125	Once every 4 weeks

Table 4 Dose Conversion from Darbepoetin Alfa to MIRCERA

	MIRCERA dose (µg)	Injection frequency
Low conversion factor[a]	4 x previous weekly darbepoetin alfa dose (µg) /1.65	Once every 4 weeks
Intermediate conversion factor (Group 1)	4 x previous weekly darbepoetin alfa dose (µg) /1.1	Once every 4 weeks
High conversion factor[a] (Group 2)	4 x previous weekly darbepoetin alfa dose (µg) /0.55	Once every 4 weeks

The low or the high conversion-factor doses were to be considered only if the intermediate conversion-factor dose (Group 1) did not result in an adequate Hb response. After review of the data from the intermediate-conversion factor group, the DSMB recommended initiation of Group 2

The dose of MIRCERA was adjusted to maintain the individual patient's Hb within a target range of ± 1 g/dL of their baseline Hb and between 10.0 to 12.0 g/dL. Baseline Hb was calculated as the mean of Hb values between week -2 and week -1.

Table 5 MIRCERA Dose Adjustments during Core Study, Optional Safety Extension and for Safety

Hb Assessment	Compared to the Previous MIRCERA Dose
Hb decreases by more than 1.0 g/dL compared to baseline Hb	Increase dose by 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 25%
Hb is less than 9 g/dL (Hb <9.0 g/dL)	Increase dose by 50%
Hb increases by more than 1.0 g/dL compared to the baseline Hb OR Hb is approaching 12 g/dL	Decrease dose by 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 25% below previous dose

Outcomes/endpoints

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

The baseline period was defined as all assessments between the day of first study dose and the previous 20 days. The Hb value on the day of the first dose was included in the baseline calculation as this assessment was performed before the first dose was given.

The average Hb value for each individual during the evaluation period was based on all values recorded on study days 111 to 138.

The following were assessed as secondary endpoints:

1. The number of patients with an average Hb concentration during the evaluation period within ±1 g/dL of their baseline Hb

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

3. The incidence of RBC transfusions

4. Change in reticulocyte count (x10000 /µL) between the baseline and evaluation periods

The following exploratory efficacy endpoints were assessed:

1. Change in dose over time

2. Change in dose between study start and evaluation period

3. The rate of rise in Hb concentration during the titration period

MIRCERA PK parameters were derived from serum concentration versus time data obtained from blood sampling from seven time points following the third iv administration of MIRCERA at week 9. PK parameters were read directly from the serum concentration versus time profiles or were estimated from the serum concentrations by non-compartmental methods.

Statistical Methods

Due to the nature of the study, no formal testing was planned and all tests and p-values were descriptive.

This was an exploratory study without a powered statistical group comparison. Therefore no formal sample size estimation was performed. However, to determine the optimum starting dose of iv MIRCERA, the following sample-size calculations were made as an indication.

Providing the optimum dose maintains the Hb at the baseline level and the true change from baseline was equal to zero, the number of patients sufficient to provide80% power that the 90% CI for Hb change from baseline was between -1 and +1 g/dL is:

• 16 evaluable patients - provided that the standard deviation was <1.3 g/dL

• 36 evaluable patients - provided that the standard deviation was <2.0 g/dL

Additional patients were enrolled to replace patients who did not complete at least 18 weeks of treatment, to ensure a sufficient number of evaluable patients.

At least one third of the patients in each dose group were to be in the age group of ≥5 to<12 years.

Analysis Populations

The following analysis populations were defined in the SAP.

Intention-to-treat Population

The intention-to-treat (ITT) population included all patients enrolled in the study.

Safety Population

All patients who received at least one dose of the trial medication and had a safety follow-up were included in the safety population.

Completers Population

All patients in the safety population who completed at least 18 weeks of treatment (and returned for an assessment in week 19), signifying that they had at least 3 Hb assessments during the evaluation period, were included in the completers population.

Per Protocol Population

The Per-Protocol (PP) population includes all patients included in the safety population and who had no major protocol violations as defined below.

1. Patients with less than 3 Hb values during the evaluation period

2. Patients who missed any administration of study medication at week 13 or week 17

3. Patients who did not fulfill the inclusion criteria for

    – Hb

– iron levels

4. Patients who fulfilled any of the following exclusion criteria:

– Hemoglobinopathies

– Haemolysis

– Overt gastrointestinal bleeding within 8 weeks before screening or during the screening period

– RBC transfusion within 8 weeks before screening or during the screening period

Extension Patients Population

The Extension Patients Population is defined as all patients having signed the informed consent for the optional safety extension period.

Primary Efficacy Endpoint

For patients with no recorded Hb during the evaluation period, the primary endpoint was missing. For all outputs concerning Hb, no imputation was made for missing values and analysis performed on observed cases only; if an RBC transfusion occurred, Hb values measured in the following 3 weeks were excluded (to correct for any Hb increase caused by the transfusion); any Hb values recorded after a renal transplantation were censored.

Descriptive statistics of the primary endpoint were calculated. In addition, baseline covariate adjusted estimates of Hb change from baseline, by dose group, and the corresponding 95% CI were calculated from an Analysis of Covariance (ANCOVA) model. The model contains the patient's baseline Hb as covariate and dependent effects for dose group, age group and previous ESA group.

The primary analysis of the study was based on the ITT population, defined as all patients enrolled.

Results

Recruitment / Number analysed

Between July 2008 and June 2015, a total of 112 patients were screened at 28 sites in Belgium (2), France (6), Germany (5), Hungary (1), Italy (1), Poland (5), Romania (1), Spain (3), Thailand (2) and Ukraine (2).

Of the 112 screened patients, 64 were enrolled (16 initially in Group 1 and then 48 in Group 2, following a preliminary analysis of Group 1.

The reasons for 48 screening failures were as follows (information derived from IxRS and not validated in the study database): 30 patients with pre-dialysis Hb levels outside10-12 g/dL, 4 patients with poorly controlled hypertension, 4 patients with unstable epoetin or darbepoetin alfa doses prior to screening, 3 patients with no signed ICF, 2 patients with inadequate haemodialysis, 2 patients with severe hyperparathyroidism, 1 patient with inadequate iron status, 1 patient with gastrointestinal bleeding during screening, and 1 patient with a high likelihood of withdrawal (kidney transplantation planned).

Replacement of patients not completing at least 18 weeks of treatment lead to a total of48 patients in Group 2, 12 more than the protocol specified minimum of 36.12 patients in Group 1 and 35 in Group 2 completed the evaluation period.

Thirty-seven of these completers went on to participate in the optional 1-year safety extension, and this optional safety extension was completed by 17 patients.

Figure 2.patients disposition

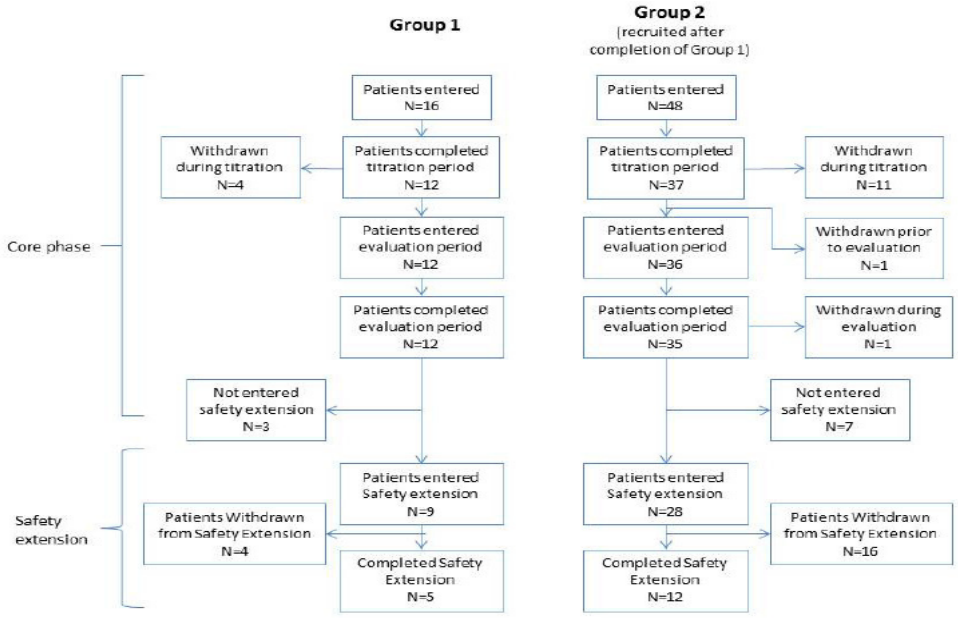


Table. Summary of withdrawals (core period): ITT population

ex11d_core_i Summary of Withdrawals
Protocol(s): NH19707
Analysis: AS SELECTED Center: ALL CENTERS
Intent to Treat Population

Reason for Withdrawal	Group 1 N = 16 No. (%)	Group 2 N = 48 No. (%)
RENAL TRANSPLANT	4 (25.0)	9 (18.8)
ADMIN/OTHER	-	2 (4.2)
DEATH	-	1 (2.1)
REFUSED TREAT/DID NOT COOPERATE	-	1 (2.1)
Total	4 (25.0)	13 (27.1)

Percentages are based on N.
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During the extension period, 20 patients withdrew (16 due to renal transplant, two withdrew consent and a further two, at the same centre, due to 'repair of the dialysis station').

ITT and Safety Populations

As all enrolled patients received at least one dose of study drug and had a safety follow-up visit, the ITT population and safety population were the same. These populations comprised 16 patients in Group 1 and 48 in Group 2 (64 patients overall).

Completers Population

The (core study period) completers population (patients completing at least 18 weeks of treatment with at least three Hb assessments during the evaluation period) comprised 12patients in Group 1 and 36 in Group 2. Note that one patient dropped out at week 19 and so is included in the completers population but did not complete the evaluation period.

The PP population comprised the patients in the completers population with the exclusion of 2 additional patients in Group 2 who were protocol violators of the inclusion criterion regarding iron levels. The PP population thus comprised 12 patients in Group 1 and 34 in Group 2.

Baseline data

Patient Demographics

Overall, there were 34 male patients (53%), with a higher representation in Group 1 compared with Group 2 (Table 11).

The majority of patients were Caucasian, and the mean ± SD age was 11 ± 3.2 years in Group 1 and 13 ± 3.1 years in Group 2. Younger patients (aged 5-11 years) were more strongly represented in Group 1 (56%) compared with Group 2 (33%)The mean baseline body surface area (according to the Mosteller formula) was 1.14 and 1.24 in Group 1 and Group 2, respectively.

Table 11 Summary of Demographic Data: ITT Population

	Group 1 N = 16	Group 2 N = 48	Total N = 64
Sex			
MALE	11 (68.8%)	23 (47.9%)	34 (53.1%)
FEMALE	5 (31.3%)	25 (52.1%)	30 (46.9%)
n	16	48	64
Race			
CAUCASIAN	11 (68.8%)	35 (72.9%)	46 (71.9%)
BLACK	1 (6.3%)	1 (2.1%)	2 (3.1%)
ORIENTAL	2 (12.5%)	5 (10.4%)	7 (10.9%)
OTHER	2 (12.5%)	7 (14.6%)	9 (14.1%)
n	16	48	64
Age in years			
Mean	11.3	13.0	12.6
SD	3.24	3.06	3.17
SEM	0.81	0.44	0.40
Median	11.0	14.0	13.0
Min-Max	7 - 16	6 - 17	6 - 17
n	16	48	64
Weight in kg			
Mean	33.18	39.01	37.55
SD	12.244	14.389	14.022
SEM	3.061	2.077	1.753
Median	29.15	39.10	34.80
Min-Max	20.4 - 62.6	17.7 - 85.4	17.7 - 85.4
n	16	48	64
Height in cm			
Mean	138.7	144.1	142.8
SD	17.91	16.52	16.88
SEM	4.63	2.41	2.14
Median	139.0	148.0	144.0
Min-Max	115 - 185	106 - 175	106 - 185
n	15	47	62
Age Category			
5 - 11 Years	9 (56.3%)	16 (33.3%)	25 (39.1%)
12 - 17 Years	7 (43.8%)	32 (66.7%)	39 (60.9%)
n	16	48	64
Smoker			
NO	16 (100%)	47 (97.9%)	63 (98.4%)
YES	-	1 (2.1%)	1 (1.6%)
n	16	48	64
Z-Score for Height*			
Mean	-1.547	-1.776	-1.721
SD	1.8361	1.4060	1.5080
SEM	0.4741	0.2051	0.1915
Median	-1.065	-1.670	-1.574
Min-Max	-6.16 - 1.87	-6.54 - 0.23	-6.54 - 1.87
n	15	47	62
Z-Score Pre-dialysis Weight*			
Mean	-1.270	-1.301	-1.293
SD	1.7921	1.6524	1.6739
SEM	0.4480	0.2385	0.2092
Median	-0.873	-1.315	-1.290
Min-Max	-6.61 - 1.14	-6.38 - 1.81	-6.61 - 1.81
n	16	48	64

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values).
* The Z-score provides a normalized score standardised by age and sex using the US CDC Growth Charts as reference.
A Z-score of 0 is average, a score outside of plus/minus 1, 2 or 3 is respectively more extreme then 68, 95 or 99 percent of values for the reference sex and age category.
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Table 13 Summary of Previous ESA Therapy: ITT Population

sum1_tr11pep_t_I Summary of Erythropoietic Agent History

Protocol(s): NH19707
Analysis: Intent to Treat Population
Filter Applied: where p_itt='YES'

Parameter Statistics/Catogory	Group 1 (N=16)	Group 2 (N=48)	Total (N=64)
Time [months] from first ESA Administration			
n	16	47	63
Mean	30.82	26.27	27.42
Std Dev	23.253	30.928	29.060
Median	21.86	14.23	16.16
Q1-Q3	14.9:44.1	5.7:36.8	6.2:37.0
Min-Max	5.4:77.6	2.4:141.5	2.4:141.5
Last Weekly Darbepoetin Alfa Dose before Screening [ug/week]			
n	8	26	34
Mean	17.31	19.97	19.34
Std Dev	9.445	12.703	11.936
Median	17.50	20.00	20.00
Q1-Q3	9.3:25.0	10.0:20.0	10.0:20.0
Min-Max	5.0:30.0	2.5:50.0	2.5:50.0
Last Weekly Epoetin Alfa/Beta Dose before Screening [IU/week]			
n	8	22	30
Mean	4937.50	5965.91	5691.67
Std Dev	3342.769	3258.958	3256.084
Median	4500.00	6000.00	6000.00
Q1-Q3	2250.0:7500.0	4000.0:6000.0	3000.0:6000.0
Min-Max	1000.0:10000.0	2000.0:15000.0	1000.0:15000.0
Schedule of Darbepoetin Alfa Administration			
n	8	26	34
Once a Week	6 (75.0%)	18 (69.2%)	24 (70.6%)
Every two Weeks	2 (25.0%)	7 (26.9%)	9 (26.5%)
Every three Weeks	0 (0.0%)	1 (3.8%)	1 (2.9%)
Schedule of Epoetin Alfa/Beta Administration			
n	8	22	30
Three Times a Week	4 (50.0%)	11 (50.0%)	15 (50.0%)
Twice a Week	1 (12.5%)	10 (45.5%)	11 (36.7%)
Once a Week	3 (37.5%)	1 (4.5%)	4 (13.3%)

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Output : $PROD/cdp10524/nh19707/reports/sum1_tr11pep_t_I.out
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PREVIOUS AND CONCURRENT DISEASES AND TREATMENTS

Table 15 Summary of Risk Factors for Vascular Events and Hemo ITT Population

dg11rf_t_i Summary of Risk Factors
Protocol(s): NH19707
Analysis: AS SELECTED Center: ALL CENTERS
Intent to Treat Population

Body System/ Disease	Group 1 N = 16 No. (%)	Group 2 N = 48 No. (%)	Total N = 64 No. (%)
ALL BODY SYSTEMS			
Total Pts with at Least one Disease	6 (37.5)	28 (58.3)	34 (53.1)
Total Number of Diseases	11	45	56
ARTERIAL HYPERTENSION			
Total Pts With at Least one Disease	6 (37.5)	26 (54.2)	32 (50.0)
ARTERIAL HYPERTENSION	6 (37.5)	26 (54.2)	32 (50.0)
Total Number of Diseases	6	26	32
VENOUS THROMBOSIS			
Total Pts With at Least one Disease	1 (6.3)	5 (10.4)	6 (9.4)
VASCULAR ACCESS THROMBOSIS	1 (6.3)	5 (10.4)	6 (9.4)
DEEP VENOUS THROMBOSIS	1 (6.3)	-	1 (1.6)
Total Number of Diseases	2	5	7
HEMORRHAGE			
Total Pts With at Least one Disease	1 (6.3)	4 (8.3)	5 (7.8)
VASCULAR ACCESS HEMORRHAGE	1 (6.3)	3 (6.3)	4 (6.3)
CEREBRAL VASCULAR HEMORRHAGE	-	1 (2.1)	1 (1.6)
GASTROINTESTINAL HEMORRHAGE	1 (6.3)	-	1 (1.6)
OTHER HEMORRHAGE	-	1 (2.1)	1 (1.6)
Total Number of Diseases	2	5	7
MYCOPHENOLATE TREATMENT			
Total Pts With at Least one Disease	1 (6.3)	4 (8.3)	5 (7.8)
MYCOPHENOLATE TREATMENT	1 (6.3)	4 (8.3)	5 (7.8)
Total Number of Diseases	1	4	5
HEMODIALYSIS CATHETER INFECTION			
Total Pts With at Least one Disease	-	3 (6.3)	3 (4.7)
HEMODIALYSIS CATHETER INFECTION	-	3 (6.3)	3 (4.7)
Total Number of Diseases	-	3	3
CYCLOPHOSPHAMIDE TREATMENT			
Total Pts With at Least one Disease	-	2 (4.2)	2 (3.1)
CYCLOPHOSPHAMIDE TREATMENT	-	2 (4.2)	2 (3.1)
Total Number of Diseases	-	2	2

Percentages are based on N.
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Table 17 Dialysis Treatment at Baseline: ITT Population

sum1_tr11td_t_I Summary of Dialysis Treatment at Baseline

Protocol(s): NH19707
Analysis: Intent to Treat Population
Filter Applied: where p_itt='YES'

Parameter Statistics/Category	Group 1 (N=16)	Group 2 (N=48)	Total (N=64)
Years Since First Dialysis			
n	16	48	64
Mean	3.079	2.841	2.900
Std Dev	3.7611	3.5711	3.5906
Median	1.537	1.199	1.258
Q1-Q3	1.09:3.39	0.48:4.08	0.54:3.65
Min-Max	0.48:15.52	0.22:13.37	0.22:15.52
Years Since First Hemodialysis			
n	16	48	64
Mean	1.659	1.820	1.780
Std Dev	1.1815	2.3477	2.1093
Median	1.310	0.984	1.131
Q1-Q3	0.93:2.17	0.44:2.21	0.48:2.17
Min-Max	0.21:4.71	0.22:11.91	0.21:11.91
Current Hemodialysis Vascular Acces Type			
n	16	48	64
Arteriovenous fistula	13 (81.3%)	31 (64.6%)	44 (68.8%)
Arteriovenous graft	0 (0.0%)	1 (2.1%)	1 (1.6%)
Indwelling (tunneled) catheter	3 (18.8%)	14 (29.2%)	17 (26.6%)
Temporary (untunneled) catheter	0 (0.0%)	2 (4.2%)	2 (3.1%)
Number of Hemodialysis Sessions per Week			
n	16	48	64
2	0 (0.0%)	5 (10.4%)	5 (7.8%)
3	13 (81.3%)	35 (72.9%)	48 (75.0%)
4	0 (0.0%)	1 (2.1%)	1 (1.6%)
5	0 (0.0%)	3 (6.3%)	3 (4.7%)
6	3 (18.8%)	4 (8.3%)	7 (10.9%)
Kt/V			
n	10	35	45
Mean	1.573	1.604	1.597
Std Dev	0.3767	0.4084	0.3976
Median	1.495	1.580	1.560
Q1-Q3	1.22:1.89	1.28:1.87	1.28:1.87
Min-Max	1.03:2.17	0.98:2.53	0.98:2.53
Weekly Kt/V			
n	0	4	4
Mean		7.478	7.478
Std Dev		4.2993	4.2993
Median		5.980	5.980
Q1-Q3		4.43:10.53	4.43:10.53
Min-Max		4.40:13.55	4.40:13.55

Program : $PROD/cdp10524/nh19707/sum1.sas
Output : $PROD/cdp10524/nh19707/reports/sum1_tr11td_t_I.out
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Other Treatments

Apart from surgical and medical procedures (all patients were on haemodialysis), anticoagulants and antianemic agents the most frequently used concomitant treatments were vitamins and minerals (15 [94%] in Group 1 and 44 [92%] in Group 2), of which vitamin D supplements were the top 3 treatments; calcium compounds and regulators (9 [56%] in Group 1 and 37 [77%] in Group 2) and supplements (11 [69%] in Group 1 and 30 [63%]in Group 2), of which the most frequently used were sodium bicarbonate and carnitine.

Efficacy results

PRIMARY EFFICACY ENDPOINT

In the ANCOVA model of this data, with adjustment for dose group (Group 1/Group 2),age (5-11/12-18 years), previous ESA treatment (darbepoetin alfa/epoetin alfa or beta)and baseline Hb AUC, the adjusted mean change in Hb AUC from baseline to evaluation period was -0.74 (95% CI: -1.32 to -

0.16) for Group 1 and -0.09 (95% CI: -0.45 to 0.26)for Group 2 (Table 18). Terms from the model show no indication of a strong effect on change in Hb due to previous ESA treatment or age.

In Group 2, 19 patients had Hb 1 g/dL or more above their baseline value at week 3, 17at week 4, and 11 at week 5. The corresponding tabulations to the graphs indicate that based on the third quartile, 75% of patients were under 12.5 g/dL at week 4, and less than 1.75 g/dL from their baseline value. The maximum Hb value seen at this time was 14.7 g/dL.

Table 18 Summary of Change in Average Haemoglobin between Baseline and the Evaluation Period: ITT Population

sum3_ahgbbtr_ac_I Summary of Change in Average Hemoglobin Between Baseline and Evaluation Period

Protocol(s): NH19707
Analysis: Intent to Treat Population
Filter Applied: where p_itt='YES'

Treatment Study Period	Hemoglobin [g/dL] n	Mean	Std Dev	Min	Q1	Median	Q3	Max
Group 1 (N=16)								
Baseline	16	11.26	0.496	10.2	11.05	11.23	11.67	12.1
Evaluation Period	12	10.37	1.063	8.9	9.53	10.37	11.14	12.0
Change from Baseline (per patient)	12	-0.78	1.237	-2.7	-1.65	-0.73	0.12	1.0
Group 2 (N=48)								
Baseline	48	11.08	0.493	10.1	10.69	11.09	11.38	12.1
Evaluation Period	36	10.94	0.947	7.9	10.40	11.04	11.65	12.3
Change from Baseline (per patient)	36	-0.15	1.014	-3.1	-0.58	-0.11	0.50	1.7

For calculation of average Hb, AUC approach with following settings is applied:
Values within 21 days after blood transfusion(s) are dropped.

Program : $PROD/cdp10524/nh19707/sum3.sas
Output : $PROD/cdp10524/nh19707/reports/sum3_ahgbbtr_ac_I.out
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anc3_ahgbbtr_ac_I Summary of Change in Average Hemoglobin Between Baseline and Evaluation Period

Protocol(s): NH19707
Analysis: Intent to Treat Population
Filter Applied: where p_itt='YES'

Adjusted Mean Estimates from ANCOVA Model for Average Change from Baseline (per patient)

Treatment	n	Adjusted Mean Change from Baseline	Standard Error	Lower 95% CI	Upper 95% CI
Group 1 (N=16)	12	-0.74	0.2876	-1.32	-0.16
Group 2 (N=48)	36	-0.09	0.1767	-0.45	0.26

For calculation of average Hb, AUC approach with following settings is applied:
Values within 21 days after blood transfusion(s) are dropped.

Figure 4 Mean Haemoglobin Values during the Core Study Period: ITT Population

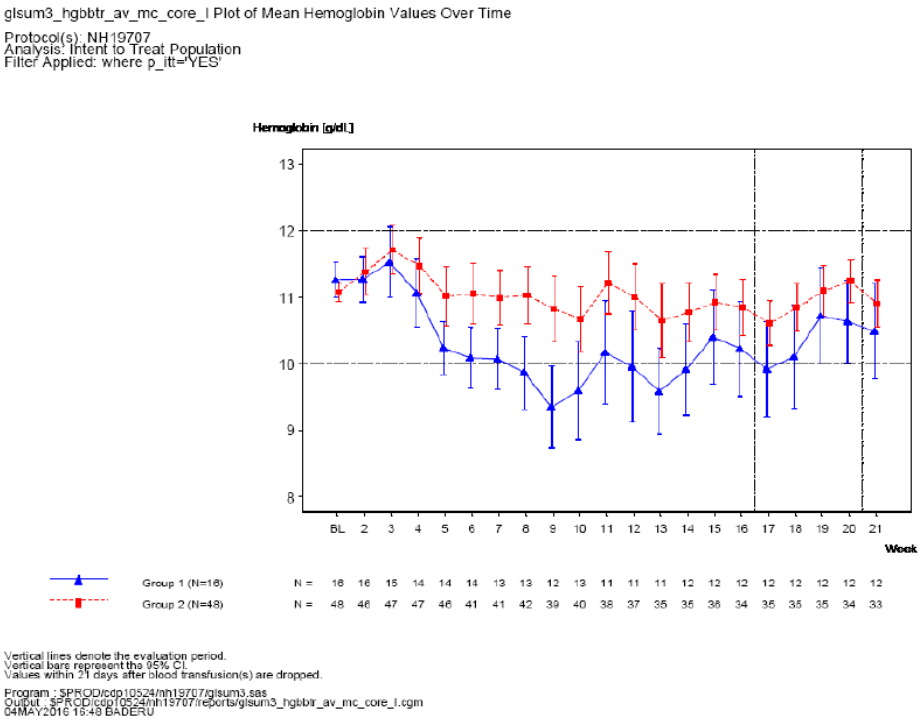
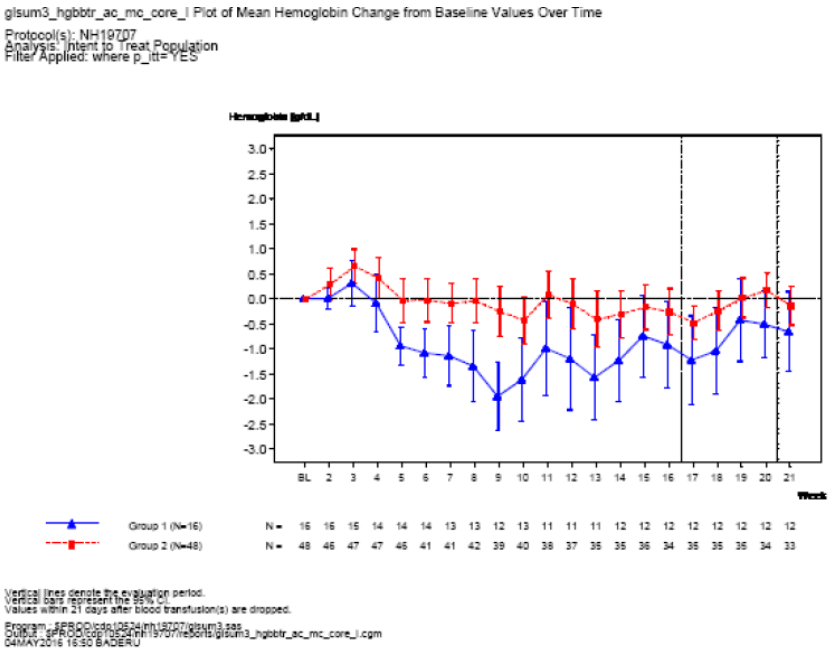


Figure 5 Mean Haemoglobin Change from Baseline Values during the Core Study Period: ITT Population



SECONDARY EFFICACY ENDPOINTS

- Patients With Haemoglobin 10-12 g/dL during Evaluation and With Change from Baseline ± 1 g/dL
  During the evaluation period, in Group 2, 75% of patients maintained Hb values within ± 1 g/dL of baseline and 81% maintained Hb values within 10-12 g/dL (in Group 1,these figures were 58% and 75%, respectively) (Table 20). The proportions of patients with Hb values within ± 1 g/dL and within 10-12 g/dL were 69% in Group 2 and 58% in Group 1.

Table 20 Patients Maintaining Stable Hemoglobin During the Evaluation Period: ITT Population

sum3_hgb18_I Summary of Patients Maintaining Stable Hemoglobin During the Evaluation Period within Baseline +/- 1g/dL and/or within 10-12 g/dL

Protocol(s): NH19707
Analysis: Intent to Treat Population
Filter Applied: where p_itt='YES'

	Group 1 (N=16)	Group 2 (N=48)
Hb within +/-1 g/dL of Baseline		
n	12	36
Above +1 g/dL	1 (8.3%)	4 (11.1%)
Maintained	7 (58.3%)	27 (75.0%)
Below -1 g/dL	4 (33.3%)	5 (13.9%)
Hb within 10-12 g/dL		
n	12	36
Above 12 g/dL	0 (0.0%)	3 (8.3%)
Maintained	9 (75.0%)	29 (80.6%)
Below 10 g/dL	3 (25.0%)	4 (11.1%)
Hb within +/-1 g/dL of Baseline and within 10-12 g/dL		
n	12	36
Yes	7 (58.3%)	25 (69.4%)
No	5 (41.7%)	11 (30.6%)

For calculation of average Hb, AUC approach with following settings is applied:
Values within 21 days after blood transfusion(s) are dropped.

Program : $PROD/cdp10524/nh19707/sum3.sas
Output : $PROD/cdp10524/nh19707/reports/sum3_hgb18_I.out
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- Three patients required blood transfusions during the core study period, one in Group 1 and two in Group 2.
- The reasons for transfusion were Hb decreased, procedural haemorrhage, and intracranial hematoma. The patient with intracranial hematoma died as a result of the event

- Reticulocyte Counts during the Core Study Period

In both groups, mean reticulocytes showed a cyclic variation over time, with peaks at week 2, subsequently every 4 weeks and with troughs at week 4 to 5 and subsequently every 4 weeks throughout the study but otherwise showed no overall tendency to increase or decrease

EXPLORATORY ANALYSES

- MIRCERA Dose during the Core Study Period

A summary of the equivalent 4-weekly MIRCERA dose over time during the core study period is provided in Table 22 and these data are presented graphically in Figure 7

Table 22 Summary of Equivalent 4-Weekly MIRCERA Dose over Time during the Core Study Period: Safety Population

sum2_ed16_core_S Summary of Equivalent 4-Weekly Mircera Dose Over Time

Protocol(s): NH19707
Analysis: Safety Population
Filter Applied: where p_saf='YES'

Treatment Week of Treatment	n	Equivalent 4-Weekly Dose [ug/4-weeks] Mean	Std Dev	Minimum	Q1	Median	Q3	Maximum
Group 1 (N=16)								
Week 1 - 4	16	66.64	47.348	16.0	24.5	58.3	104.5	160.0
Week 5 - 8	14	48.82	39.640	0.0	22.8	38.8	66.3	160.0
Week 9 -12	13	66.95	43.820	22.8	28.4	48.6	90.0	160.0
Week 13-16	12	71.54	44.189	22.8	36.8	55.3	100.1	160.0
Week 17-20	12	82.06	49.404	21.9	47.2	69.7	115.7	197.0
Last 4-weeks Interval	16	90.45	47.232	22.8	50.0	79.2	124.0	197.0
Group 2 (N=48)								
Week 1 - 4	48	163.33	99.517	18.2	75.0	147.8	196.9	480.0
Week 5 - 8	45	134.72	96.740	0.0	75.0	112.5	185.1	360.0
Week 9 -12	41	135.10	106.835	0.0	72.7	100.0	170.0	450.0
Week 13-16	37	146.93	124.089	0.0	71.1	93.8	225.0	450.0
Week 17-20	36	166.87	127.870	36.0	80.0	120.0	220.0	560.0
Last 4-weeks Interval	48	161.42	123.065	0.0	78.2	117.1	220.0	560.0

Equivalent 4-weekly dose is derived to estimate the total dose received in each strict 28 day time window.

Program : $PROD/cdp10524/nh19707/sum2.sas
Output : $PROD/cdp10524/nh19707/reports/sum2_ed16_core_S.out
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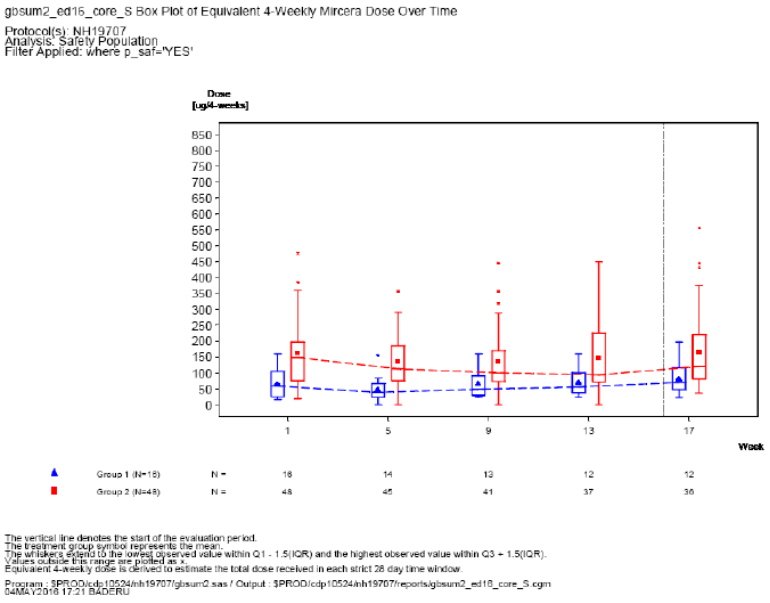
Figure 7 Box Plot of Equivalent 4-Weekly MIRCERA Dose over Time during the Core Study Period: Safety Population



In Group 2, the within-patient change in the 4-weekly MIRCERA dose during the evaluation period compared to their first dose was in general small, as indicated by a median ratio of 1.0 and a mean ratio of 1.1. In the case of Group 1, this ratio was larger (median ratio, 1.6; mean ratio, 1.9).

Conversion Factors for Previous Weekly ESA Dose during the Evaluation Period

The conversion factors for previously weekly ESA dose to equivalent weekly MIRCERA dose during the evaluation period are shown in Table 25. In Group 2, the median [IQR] conversion factors were 1.8 [1.4, 2.8] for darbepoetin alfa and 0.008 [0.005, 0.01] for epoetin alfa/beta. These are both very close to the conversion factors used to calculate the first dose (1/0.55=1.8 and 1/125=0.008 for darbepoetin and epoetins respectively).

The graphs show an even distribution either side of the line of these initial dose conversion factors (Figure 8 and Figure 9).

Table 25 Summary of the Conversion from Previous Weekly ESA Dose to Equivalent Weekly MIRCERA Dose during Evaluation: Safety Population

sum2_ed16cf_prevesa_core_S Summary of the Conversion from Previous Weekly ESA Dose to Equivalent Weekly Mircera Dose during Evaluation

Protocol(s): NH19707
Analysis: Safety Population
Filter Applied: where p_saf='YES'

Treatment Previous ESA Week of Treatment	Ratio: Equivalent Weekly Dose / Previous Weekly ESA Dose							
	n	Mean	Std Dev	Minimum	Q1	Median	Q3	Maximum
Group 1 (N=16)								
Darbepoetin Alfa (N=8)								
Week 17-20	6	1.4443	0.77056	0.183	1.067	1.487	2.220	2.222
Epoetin Alfa/Beta (N=8)								
Week 17-20	6	0.0076	0.00494	0.003	0.005	0.006	0.010	0.016
Group 2 (N=48)								
Darbepoetin Alfa (N=26)								
Week 17-20	19	2.2516	1.33918	0.600	1.375	1.819	2.812	6.284
Epoetin Alfa/Beta (N=22)								
Week 17-20	17	0.0077	0.00376	0.002	0.005	0.008	0.010	0.016

Previous weekly ESA dose is the last weekly dose before screening in ug/week for Darbepoetin Alfa or IU/week for Epoetin Alfa/Beta treated patients.
Equivalent weekly Mircera dose in ug/weeks is the equivalent 4-weekly Mircera dose for the weeks 17-20 in ug/4-weeks divided by 4.

Program : $PROD/cdp10524/nh19707/sum2.sas
Output : $PROD/cdp10524/nh19707/reports/sum2_ed16cf_prevesa_core_S.out
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Figure 8 Plot of Previous Darbepoetin Alfa Dose Vs Equivalent Weekly MIRCERA Dose during the Evaluation Period

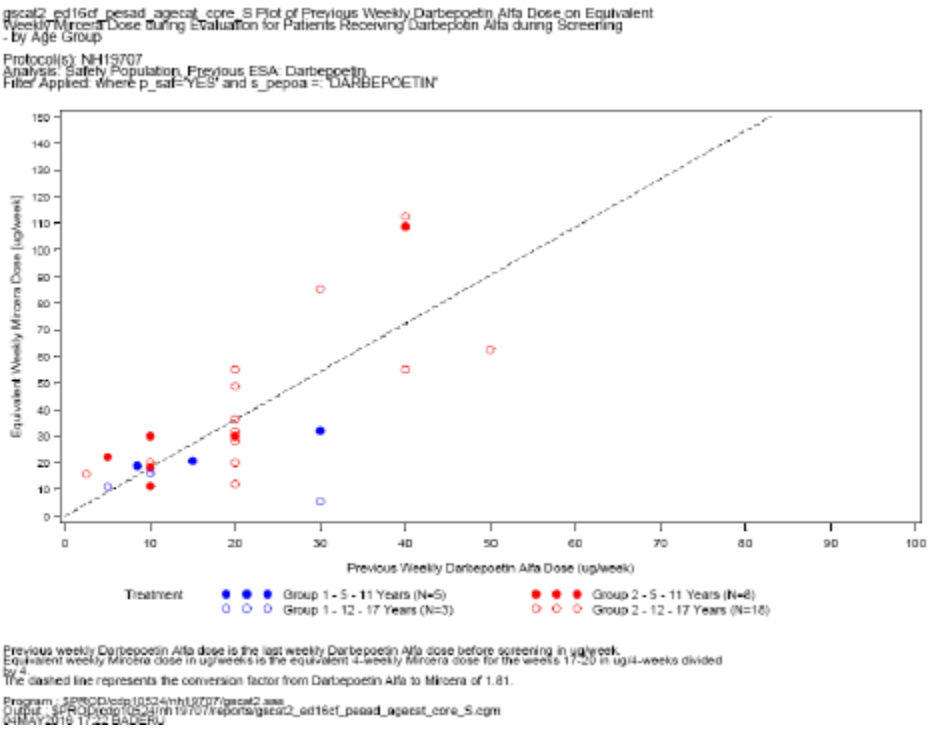
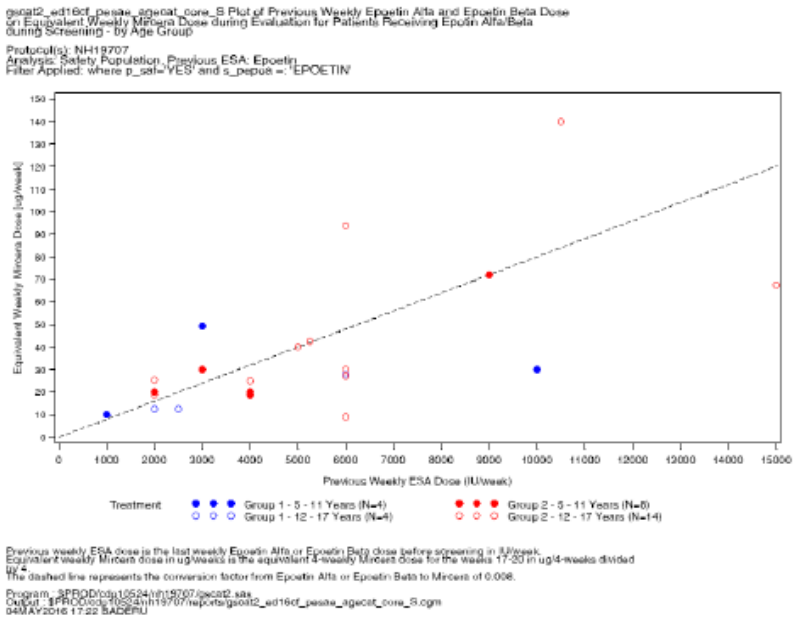


Figure 9. Previous Epoetin Alfa/Beta Dose Vs Equivalent Weekly MIRCERA Dose during the Evaluation Period



Dose Adjustments during the Core Study Period

During the core study period, dose changes occurred frequently in both conversion factor groups (77% of patients in Group 2 and 81% in Group 1 required a dose change)(Table 26). A lower proportion of patients in Group 2 compared to Group 1 required a dose increase only during the core study period (29% compared to 56%). A greater proportion of patients in Group 2 required no dose change (23%) compared with Group1 (19%). A greater proportion of patients in Group 2 had both dose decreases and increases (38%) compared with Group 1 (13%).

In terms of absolute numbers of dose changes, the mean number of dose increases and decreases was 1.69 and 0.25, respectively, in Group 1 and 1.19 and 0.73, respectively, in Group 2

Table 26 Summary of Patients with Dose Adjustments of the Equivalent 4- Weekly Dose during the Core Study Period: Safety Population

sum2_edc14_core_S Summary of Patients with Dose Adjustments of the Equivalent 4-Weekly Dose

Protocol(s): NH19707
Analysis: Safety Population
Filter Applied: where p_saf='YES'

	Group 1 (N=16)	Group 2 (N=48)
No Dose Change	3 (18.8%)	11 (22.9%)
Any Dose Change	13 (81.3%)	37 (77.1%)
Dose Increase(s) only	9 (56.3%)	14 (29.2%)
Dose Decrease(s) only	2 (12.5%)	5 (10.4%)
Dose Decrease(s) and Increase(s)	2 (12.5%)	18 (37.5%)

Criterion for dose adjustment: Current 4-weekly dose differs more than +- 20% from previous dose.
Equivalent 4-weekly dose is derived to estimate the total dose received in each strict 28 day time window.

Program : $PROD/cdp10524/nh19707/sum2_edc14.sas
Output : $PROD/cdp10524/nh19707/reports/sum2_edc14_core_S.out
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Subgroup Analyses

In Group 1, 9/16 patients (56%) were aged 5-11 years and 7/16 (44%) were aged 12-17years. In Group 2, 16/48 patients (33%) were aged 5-11 years and 32/48 (67%) were aged 12-17 years

Age Group (5-11 or 12-17 Years)

Table 29 Summary of Change in Average Hemoglobin between Baseline and Evaluation Periods by Age Group: ITT Population

sum3_ahgbbtr_ac_agecat_I Summary of Change in Average Hemoglobin Between Baseline and Evaluation Period - by Age Group

Protocol(s): NH19707
Analysis: Intent to Treat Population
Filter Applied: where p_itt='YES'

Treatment / Age Group / Study Period	Hemoglobin [g/dL] n	Mean	SD	Min	Q1	Med.	Q3	Max
Group 1 (N=16)								
5 - 11 Years (N=9)								
Baseline	9	11.26	0.603	10.2	11.15	11.18	11.69	12.1
Evaluation Period	6	10.53	0.970	9.0	10.20	10.48	11.20	11.8
Change from Baseline (per patient)	6	-0.58	1.340	-2.7	-0.98	-0.73	0.68	1.0
12 - 17 Years (N=7)								
Baseline	7	11.26	0.360	10.7	11.00	11.28	11.65	11.8
Evaluation Period	6	10.20	1.217	8.9	8.90	10.18	11.08	12.0
Change from Baseline (per patient)	6	-0.98	1.214	-2.4	-2.10	-0.88	-0.44	0.9
Group 2 (N=48)								
5 - 11 Years (N=16)								
Baseline	16	11.05	0.498	10.1	10.75	10.95	11.24	12.0
Evaluation Period	11	11.18	0.721	10.1	10.43	11.22	11.85	12.3
Change from Baseline (per patient)	11	0.16	0.750	-1.1	-0.53	0.08	0.86	1.1
12 - 17 Years (N=32)								
Baseline	32	11.09	0.497	10.3	10.65	11.13	11.45	12.1
Evaluation Period	25	10.84	1.027	7.9	10.25	11.03	11.50	12.3
Change from Baseline (per patient)	25	-0.28	1.098	-3.1	-0.63	-0.19	0.47	1.7

For calculation of average Hb, AUC approach with following settings is applied:
Values within 21 days after blood transfusion(s) are dropped.

Program : $PROD/cdp10524/nh19707/sum3.sas
Output : $PROD/cdp10524/nh19707/reports/sum3_ahgbbtr_ac_agecat_I.out
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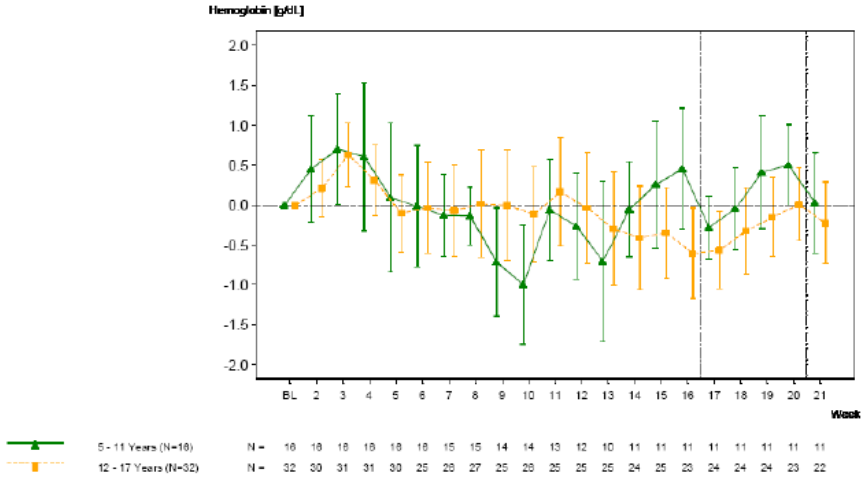
Figure 10 Mean Hemoglobin Change from Baseline over Time by Age Group during the Core Study Period (Group2 Only): ITT Population

glsum3_hgbbtr_ac_agecat_mc_2_core_l Plot of Mean Hemoglobin Change from Baseline Values Over Time - by Age Group for Mircera Group 2 Only

Protocol(s): NH19707
Analysis: Intent to Treat Population
Filter Applied: where p_itt='YES'



Vertical lines denote the evaluation period.
Vertical bars represent the 95% CI.
Values within 21 days after blood transfusion(s) are dropped.

Program : $PROD/cdp10524/nh19707/glsum3.sas
Output : $PROD/cdp10524/nh19707/reports/glsum3_hgbbtr_ac_agecat_mc_2_core_l.opm
04MAY2016 16:51 BADERU

Table 31 Summary of Equivalent 4-Weekly MIRCERA Dose per Kg over Time by Age Group during the Core Study Period: Safety Population

sum2_ed16kg_agecat_core_S Summary of Equivalent 4-Weekly Mircera Dose by Body Weight Over Time - by Age Group

Protocol(s): NH19707
Analysis: Safety Population
Filter Applied: where p_saf='YES'

Treatment Age Group Week of Treatment	Equivalent 4-Weekly Dose by Body Weight [ug/4-weeks/kg] n	Mean	Std Dev	Minimum	Q1	Median	Q3	Maximum
Group 1 (N=16)								
5 - 11 Years (N=9)								
Week 1 - 4	9	3.350	2.2986	0.76	1.67	2.81	3.74	7.30
Week 5 - 8	8	2.328	1.9993	0.00	1.16	1.79	3.09	6.52
Week 9 -12	7	3.119	1.8177	1.17	1.77	2.73	4.29	6.55
Week 13-16	6	3.372	1.8913	1.44	2.16	2.68	4.76	6.50
Week 17-20	6	3.716	1.8795	1.83	2.68	3.02	4.74	7.00
Last 4-weeks Interval	9	4.152	1.9087	1.83	2.70	3.46	4.74	7.30
12 - 17 Years (N=7)								
Week 1 - 4	7	1.078	0.7130	0.29	0.38	1.05	1.85	2.02
Week 5 - 8	6	0.990	0.6385	0.28	0.48	0.89	1.44	1.95
Week 9 -12	6	1.198	0.8742	0.35	0.60	1.01	1.44	2.79
Week 13-16	6	1.354	0.8625	0.35	0.89	1.20	1.64	2.84
Week 17-20	6	1.603	0.9588	0.33	1.21	1.49	1.86	3.24
Last 4-weeks Interval	7	1.675	0.9548	0.35	1.21	1.64	1.86	3.49
Group 2 (N=48)								
5 - 11 Years (N=16)								
Week 1 - 4	16	5.813	4.6020	1.48	2.49	3.15	9.44	16.25
Week 5 - 8	16	4.258	4.1186	0.00	1.81	3.11	5.86	13.47
Week 9 -12	14	5.588	5.0562	1.79	2.29	3.25	8.92	17.85
Week 13-16	12	5.608	5.4324	0.00	2.73	3.19	7.63	16.00
Week 17-20	11	4.848	4.2309	1.43	2.70	2.82	4.54	13.66
Last 4-weeks Interval	16	5.849	5.2393	0.00	2.73	3.58	9.40	17.89
12 - 17 Years (N=32)								
Week 1 - 4	32	4.035	2.2603	0.44	2.29	3.64	5.69	10.69
Week 5 - 8	29	3.534	2.1188	0.00	2.19	3.32	5.15	7.95
Week 9 -12	27	3.078	2.3896	0.00	1.23	2.65	4.35	8.99
Week 13-16	25	3.486	2.7848	0.00	1.51	3.33	4.52	9.28
Week 17-20	25	4.201	2.9198	0.63	2.21	3.25	5.22	11.43
Last 4-weeks Interval	32	3.810	2.8322	0.00	1.89	2.86	5.12	11.43

Equivalent 4-weekly dose is derived to estimate the total dose received in each strict 28 day time window.

Program : $PROD/cdp10524/nh19707/sum2.sas
Output : $PROD/cdp10524/nh19707/reports/sum2_ed16kg_agecat_core_S.out
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Table 32 Dose Ratio between the First and Evaluation Period Equivalent 4-Weekly MIRCERA Dose, By Age Group: Safety Population

sum2_ed16cf2_agecat_core_S Summary of the Dose Ratio between the First Equivalent 4-Weekly Mircera Dose and the Equivalent 4-Weekly Mircera Dose during Evaluation - by Age Group

Protocol(s): NH19707
Analysis: Safety Population
Filter Applied: where p_saf='YES'

Treatment Age Group Week of Treatment	Ratio: Equiv. 4-Weekly Dose / First Equiv. 4-Weekly Dose							
	n	Mean	Std Dev	Minimum	Q1	Median	Q3	Maximum
Group 1 (N=16)								
5 - 11 Years (N=9)								
Week 17-20	6	1.9545	1.31544	0.750	0.756	1.808	2.500	4.104
12 - 17 Years (N=7)								
Week 17-20	6	1.9335	0.89379	1.205	1.250	1.594	2.442	3.516
Group 2 (N=48)								
5 - 11 Years (N=16)								
Week 17-20	11	1.2664	0.53022	0.586	1.000	1.250	1.600	2.442
12 - 17 Years (N=32)								
Week 17-20	25	1.0877	0.68290	0.187	0.615	0.976	1.479	3.453

Equivalent 4-weekly Mircera dose during evaluation in ug/weeks is the equivalent 4-weekly Mircera dose for the weeks 17-20 in ug/4-weeks.

Program : $PROD/cdp10524/nh19707/sum2.sas
Output : $PROD/cdp10524/nh19707/reports/sum2_ed16cf2_agecat_core_S.out
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Table 32 Dose Ratio between the First and Evaluation Period Equivalent 4-Weekly MIRCERA Dose, By Age Group: Safety Population

sum2_ed16cf2_agecat_core_S Summary of the Dose Ratio between the First Equivalent 4-Weekly Mircera Dose and the Equivalent 4-Weekly Mircera Dose during Evaluation - by Age Group

Protocol(s): NH19707
Analysis: Safety Population
Filter Applied: where p_saf='YES'

Treatment Age Group Week of Treatment	Ratio: Equiv. 4-Weekly Dose / First Equiv. 4-Weekly Dose							
	n	Mean	Std Dev	Minimum	Q1	Median	Q3	Maximum
Group 1 (N=16)								
5 - 11 Years (N=9)								
Week 17-20	6	1.9545	1.31544	0.750	0.756	1.808	2.500	4.104
12 - 17 Years (N=7)								
Week 17-20	6	1.9335	0.89379	1.205	1.250	1.594	2.442	3.516
Group 2 (N=48)								
5 - 11 Years (N=16)								
Week 17-20	11	1.2664	0.53022	0.586	1.000	1.250	1.600	2.442
12 - 17 Years (N=32)								
Week 17-20	25	1.0877	0.68290	0.187	0.615	0.976	1.479	3.453

Equivalent 4-weekly Mircera dose during evaluation in ug/weeks is the equivalent 4-weekly Mircera dose for the weeks 17-20 in ug/4-weeks.

Program : $PROD/cdp10524/nh19707/sum2.sas
Output : $PROD/cdp10524/nh19707/reports/sum2_ed16cf2_agecat_core_S.out
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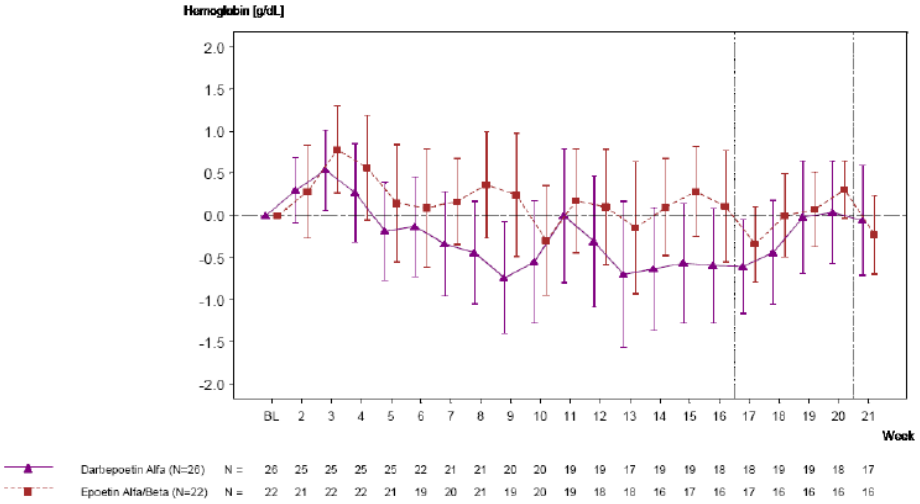
Previous ESA Treatment

Figure 11 Mean Hemoglobin Change from Baseline over Time by Previous ESA Treatment during the Core Study Period (Group 2 Only): ITT Population

glsum3_hgbbtr_ac_prevesa_mc_2_core_I Plot of Mean Hemoglobin Change from Baseline Values Over Time - by Previous ESA Treatment Group for Mircera Group 2 Only

Protocol(s): NH19707
Analysis: Intent to Treat Population
Filter Applied: where p_itt='YES'



Vertical lines denote the evaluation period.
Vertical bars represent the 95% CI.
Values within 21 days after blood transfusion(s) are dropped.

Program : $PROD/cdp10524/nh19707/glsum3.sas
Output : $PROD/cdp10524/nh19707/reports/glsum3_hgbbtr_ac_prevesa_mc_2_core_I.cgm
04MAY2016 16:52 BADERU

Table 33 Summary of Equivalent 4-Weekly MIRCERA Dose over Time by Previous ESA Treatment: Safety Population

sum2_ed16_prevesa_core_S Summary of Equivalent 4-Weekly Mircera Dose Over Time - by Previous ESA Treatment Group

Protocol(s): NH19707
Analysis: Safety Population
Filter Applied: where p_saf='YES'

Treatment Previous ESA Week of Treatment	Equivalent 4-Weekly Dose [ug/4-weeks]							
	n	Mean	Std Dev	Minimum	Q1	Median	Q3	Maximum
Group 1 (N=16)								
Darbepoetin Alfa (N=8)								
Week 1 - 4	8	56.45	39.988	18.2	18.2	52.0	92.0	109.1
Week 5 - 8	8	37.80	28.187	0.0	20.5	30.2	59.3	82.5
Week 9 -12	7	60.31	39.425	22.8	28.4	48.6	82.5	129.5
Week 13-16	6	57.41	30.537	22.8	33.6	51.6	82.5	102.5
Week 17-20	6	69.39	36.186	21.9	44.4	69.7	82.5	128.0
Last 4-weeks Interval	8	77.52	36.976	22.8	54.2	74.5	105.2	129.5
Epoetin Alfa/Beta (N=8)								
Week 1 - 4	8	76.82	54.476	16.0	36.0	58.3	125.0	160.0
Week 5 - 8	6	63.52	50.194	20.0	34.9	50.0	66.3	160.0
Week 9 -12	6	74.69	51.085	25.0	37.1	65.0	96.0	160.0
Week 13-16	6	85.66	53.709	31.2	40.0	73.9	135.0	160.0
Week 17-20	6	94.74	60.619	40.0	50.0	80.7	120.0	197.0
Last 4-weeks Interval	8	103.38	55.056	40.0	50.0	110.0	135.0	197.0
Group 2 (N=48)								
Darbepoetin Alfa (N=26)								
Week 1 - 4	26	143.15	92.588	18.2	75.0	142.8	150.0	360.0
Week 5 - 8	23	123.70	105.678	0.0	45.5	109.1	150.0	360.0
Week 9 -12	21	131.01	112.127	0.0	72.7	91.0	162.5	450.0
Week 13-16	19	146.34	120.117	0.0	61.3	91.0	225.0	450.0
Week 17-20	19	169.16	123.555	45.0	80.0	120.0	220.0	450.0
Last 4-weeks Interval	26	151.89	117.101	0.0	76.5	106.3	220.0	450.0
Epoetin Alfa/Beta (N=22)								
Week 1 - 4	22	187.18	104.211	64.0	125.0	192.0	198.9	480.0
Week 5 - 8	22	146.25	87.389	0.0	80.0	142.5	192.0	360.0
Week 9 -12	20	139.38	103.715	0.0	68.6	132.0	194.7	360.0
Week 13-16	18	147.55	131.644	0.0	75.0	96.9	270.0	450.0
Week 17-20	17	164.32	136.308	36.0	80.0	108.0	170.0	560.0
Last 4-weeks Interval	22	172.69	131.627	0.0	80.0	120.0	270.0	560.0

Equivalent 4-weekly dose is derived to estimate the total dose received in each strict 28 day time window.

Program : $PROD/cdp10524/nh19707/sum2.sas
Output : $PROD/cdp10524/nh19707/reports/sum2_ed16_prevesa_core_S.out
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Table 34 Dose Ratio between the First and Evaluation Period Equivalent 4- Weekly MIRCERA Dose by Previous ESA Treatment during the Core Study Period: Safety Population

sum2_ed16cf2_prevesa_core_S Summary of the Dose Ratio between the First Equivalent 4-Weekly Mircera Dose and the Equivalent 4-Weekly Mircera Dose during Evaluation - by Previous ESA Treatment Group

Protocol(s): NH19707
Analysis: Safety Population
Filter Applied: where p_saf='YES'

Treatment / Previous ESA / Week of Treatment	Ratio: Equiv. 4-Weekly Dose / First Equiv. 4-Weekly Dose							
	n	Mean	Std Dev	Minimum	Q1	Median	Q3	Maximum
Group 1 (N=16)								
Darbepoetin Alfa (N=8)								
Week 17-20	6	1.9227	1.05023	0.756	1.174	1.824	2.442	3.516
Epoetin Alfa/Beta (N=8)								
Week 17-20	6	1.9653	1.19393	0.750	1.250	1.594	2.500	4.104
Group 2 (N=48)								
Darbepoetin Alfa (N=26)								
Week 17-20	19	1.2691	0.73953	0.330	0.750	1.000	1.571	3.453
Epoetin Alfa/Beta (N=22)								
Week 17-20	17	1.0007	0.48457	0.187	0.600	1.000	1.250	1.953

Equivalent 4-weekly Mircera dose during evaluation in ug/weeks is the equivalent 4-weekly Mircera dose for the weeks 17-20 in ug/4-weeks.

Program : $PROD/cdp10524/nh19707/sum2.sas
Output : $PROD/cdp10524/nh19707/reports/sum2_ed16cf2_prevesa_core_S.out
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Sensitivity Analysis

The changes in average Hb between baseline and evaluation period in the population were similar to those reported in the ITT population.

As no imputation was made for missing values in the primary analysis, in effect, this population includes data for two less patients.

In the analysis imputing missing Hb values using the LOCF method, as originally specified in the protocol, results were also very similar to the ITT change from baseline values without imputation. Thus, in Group 1, the mean change from baseline (per patient)was -0.86 g/dL and in Group 2 -0.22 g/dL compared to -0.78 g/dL and -0.15g/dL, respectively, without imputation.

EFFICACY EVALUATIONS DURING THE SAFETY EXTENSIONPERIOD

In Group 2, during the safety extension period, all mean Hb values remained within the10-12 g/dL range (Figure 12). In Group 1, although mean values were below this range at some time points during the core study period, in the safety extension period, mean values in this group also remained within the 10-12 g/dL.

Figure 12 Mean Hemoglobin Values over Whole Study Duration (Including Safety Extension)

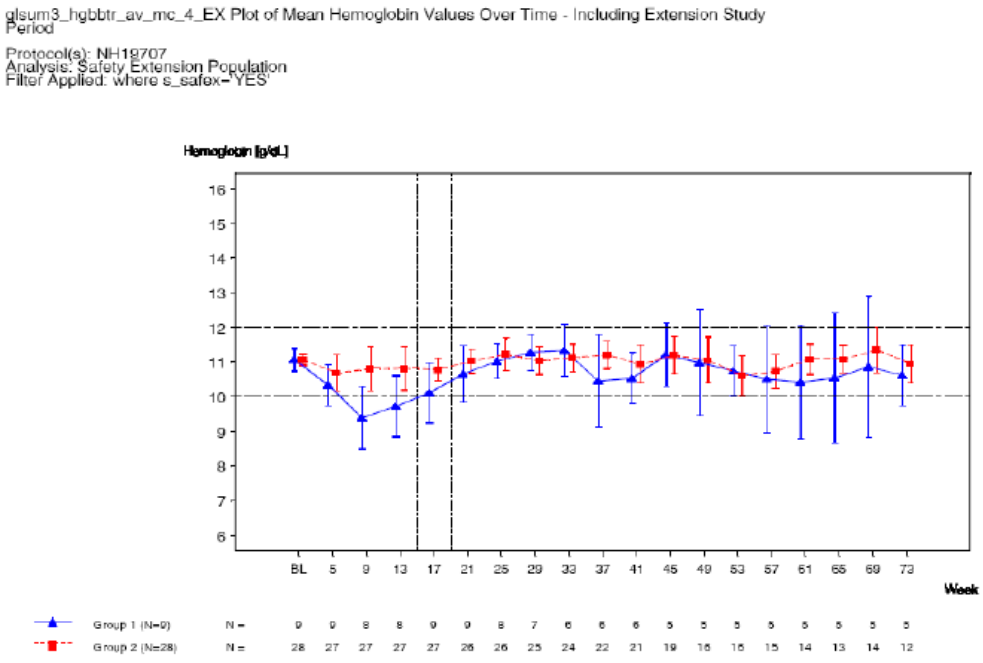

Figure 14 Box Plot of Equivalent 4-Weekly MIRCERA Dose over Whole Study Duration (Including Extension Study)

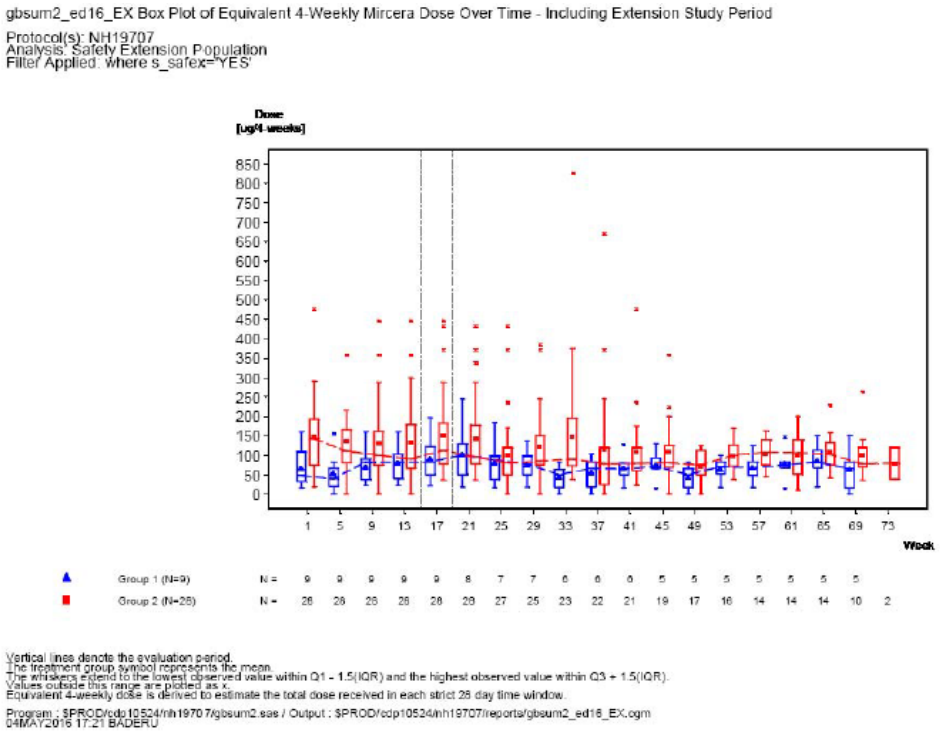

Table 36 Summary of Number of Dose Adjustments in the Equivalent 4-Weekly Dose during the Safety Extension

sum2_edc15_ext_EX Summary of the Number of Dose Adjustments in the Equivalent 4-Weekly Dose per Patient - Extension Period Only

Protocol(s): NH19707
Analysis: Safety Extension Population
Filter Applied: where s_safex='YES'

	Dose Adjustments							
Treatment	n	Mean	Std Dev	Minimum	Q1	Median	Q3	Maximum
Group 1 (N=9)								
N of Any Dose Changes	8	2.38	3.378	0	0.0	1.0	4.0	9
N of Dose Decreases	8	1.25	1.753	0	0.0	0.5	2.0	5
N of Dose Increases	8	1.13	1.808	0	0.0	0.0	2.5	4
N of Constant Doses	8	6.00	4.751	0	2.5	4.5	11.0	12
N of Monthly Doses	8	9.38	5.181	1	4.5	13.0	13.0	13
Group 2 (N=28)								
N of Any Dose Changes	28	3.32	2.625	0	1.0	3.5	6.0	7
N of Dose Decreases	28	1.54	1.598	0	0.0	1.0	3.0	5
N of Dose Increases	28	1.79	1.397	0	1.0	2.0	3.0	4
N of Constant Doses	28	4.68	3.662	0	2.0	4.0	6.5	12
N of Monthly Doses	28	9.00	4.372	1	5.5	10.5	13.0	14

Criterion for dose adjustment: Current 4-weekly dose differs more than +- 20% from previous dose.
Equivalent 4-weekly dose is derived to estimate the total dose received in each strict 28 day time window.
Including the core study period final visit dose.

Program : $PROD/cdp10524/nh19707/sum2.sas
Output : $PROD/cdp10524/nh19707/reports/sum2_edc15_ext_EX.out
04MAY2016 17:07 BADERU Page 1 of 1

RESULTS: PHARMACOKINETICS

PK parameters were calculated using non-compartmental analysis

Table 38 Summary of Pharmacokinetic Parameters of MIRCERA in Serum Following the Third Dose at Week 9

Group	n	Dose (µg)	T_{max} (hr)	C_{max} (pg/mL)	$AUC_{0\text{-}tau}$ (pg . hr/mL)	$t_{1/2}$ (hr)
1	12[a]	44.5 (22.8 – 160)	2.00 (1.98 – 2.17)	37700 (74.5)	3630000 (91.8)	147 (30.1)
2	34[b]	132 (34.0 – 450)	2.00 (1.83 – 164)	66100 (149.5)	7170000 (140.0)	121 (43.5)

Median (range) for Dose, Median (range) for T_{max}, geometric mean (CV%) for all other parameters

[a] n=11 for $AUC_{0\text{-}tau}$ and $t_{1/2}$

[b] n= 32 for $AUC_{0\text{-}tau}$ and $t_{1/2}$

T_{max} = time of maximum concentration; C_{max} = maximum concentration; AUC = area under the curve (concentration-time); $t_{1/2}$ = apparent terminal phase half-life; hr = hour.

Source: Supporting Data Presentations

Safety results

The majority of patients (77%) reported at least one AE in the core study period.

• During the core-study period, serious adverse events (SAEs) were reported in 16patients overall (25%). Two of these SAEs were considered related to MIRCERA. A further two were considered life-threatening (intracranial hematoma leading to death and procedural hemorrhage).

• One patient died during the study from an intracranial hematoma, considered by the investigator as unrelated to the study drug. This patient was the only patient who discontinued MIRCERA dosing for safety reasons.

• During the safety extension period, in which patients were exposed to MIRCERA for up to a further 52 weeks, the overall pattern of reported AEs was consistent with that observed in the core study period. SAEs were reported in 24% of patients (none were reported as related to the study drug by the investigator). No patients discontinued treatment due to an AE.

sum6_sae11hs_core_t_S Summary of Overall Incidence Rates of Adverse Events, Withdrawals, a
Deaths

Protocol(s): NH19707
Analysis: Safety Population
Filter Applied: where p_saf='YES'

	Group 1 (N = 16)	Group 2 (N = 48)	Total (N = 64)
	n (%)	n (%)	n (%)
Adverse Events			
Any AEs	12 (75.0)	37 (77.1)	49 (76.6)
Fatal AEs	0 (0.0)	1 (2.1)	1 (1.6)
Serious AEs	4 (25.0)	12 (25.0)	16 (25.0)
Severe AEs	2 (12.5)	6 (12.5)	8 (12.5)
AEs Leading to Withdrawal	0 (0.0)	1 (2.1)	1 (1.6)
AEs Related to TT	1 (6.3)	4 (8.3)	5 (7.8)
Fatal AEs Related to TT	0 (0.0)	0 (0.0)	0 (0.0)
Serious AEs Related to TT	0 (0.0)	2 (4.2)	2 (3.1)
Severe AEs Related to TT	0 (0.0)	2 (4.2)	2 (3.1)
Withdrawals and Patient Deaths			
Withdrawals Incl. Deaths	4 (25.0)	13 (27.1)	17 (26.6)
Withdrawals due to Renal Transplant	4 (25.0)	9 (18.8)	13 (20.3)
Deaths	0 (0.0)	1 (2.1)	1 (1.6)
Blood Transfusions			
Any Transfusions	1 (6.3)	2 (4.2)	3 (4.7)
Packed red cells	1 (6.3)	1 (2.1)	2 (3.1)
Washed packed red cells	0 (0.0)	1 (2.1)	1 (1.6)

AE onset between time of very first drug intake and date of last contact or 30 days after very last drug intake.
Death at/before date of last contact or 30 days after very last drug intake.
n: Number of patients
Severe AEs include life threatening AEs.
TT = Trial Treatment

Program : $PROD/cdp10524/nh19707/sum6_sae11hs.sas
Output : $PROD/cdp10524/nh19707/reports/sum6_sae11hs_core_t_S.out
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Table 40 Overview of Adverse Events during the Safety Extension Period:

Safety Population

sum6_sae11hs_ext_t_EX Summary of Overall Incidence Rates of Adverse Events, Withdrawals, an
Deaths - Extension Period Only

Protocol(s): NH19707
Analysis: Safety Extension Population
Filter Applied: where s_safex='YES'

	Group 1 (N = 9)	Group 2 (N = 28)	Total (N = 37)
	n (%)	n (%)	n (%)
Adverse Events			
Any AEs	4 (44.4)	23 (82.1)	27 (73.0)
Fatal AEs	0 (0.0)	0 (0.0)	0 (0.0)
Serious AEs	1 (11.1)	8 (28.6)	9 (24.3)
Severe AEs	0 (0.0)	5 (17.9)	5 (13.5)
AEs Leading to Withdrawal	0 (0.0)	0 (0.0)	0 (0.0)
AEs Related to TT	0 (0.0)	2 (7.1)	2 (5.4)
Fatal AEs Related to TT	0 (0.0)	0 (0.0)	0 (0.0)
Serious AEs Related to TT	0 (0.0)	0 (0.0)	0 (0.0)
Severe AEs Related to TT	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawals and Patient Deaths			
Withdrawals Incl. Deaths	4 (44.4)	16 (57.1)	20 (54.1)
Withdrawals due to Renal Transplant	3 (33.3)	13 (46.4)	16 (43.2)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
Blood Transfusions			
Any Transfusions	1 (11.1)	0 (0.0)	1 (2.7)
Packed red cells	1 (11.1)	0 (0.0)	1 (2.7)
Washed packed red cells	0 (0.0)	0 (0.0)	0 (0.0)

AE onset between time of very first drug intake and date of last contact or 30 days after very last drug intake.
Death at/before date of last contact or 30 days after very last drug intake.
n: Number of patients
Severe AEs include life threatening AEs.
TT = Trial Treatment

Program : $PROD/cdp10524/nh19707/sum6_sae11hs.sas
Output : $PROD/cdp10524/nh19707/reports/sum6_sae11hs_ext_t_EX.out
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Discussion on clinical aspects

This study represents the primary source of data for MIRCERA use in children. The first and last patients were enrolled in July 2008 and June 2015. The fact that the study took7 years to enroll 64 patients at 28 sites in 10 countries points to the logistic challenge of recruiting pediatric patients on hemodialysis receiving stable ESA treatment. An additional challenge was the high drop-out rate due to renal transplantation (20% of patients during the core study period and 43% of patients during the safety extension period), even though patients with a high likelihood of withdrawal due to renal transplantation were to be excluded from the study.

EXTENT OF EXPOSURE TO STUDY TREATMENT

Table 41 shows the actual number of injected MIRCERA administrations; 11 patients in Group 1 and 24 patients in Group 2 received at least 5 administrations. For patients who did not receive all doses, either they withdrew from the study or dosing was temporarily suspended because Hb continued to increase (Hb> 12 g/dL) despite a first dose reduction, and not for safety reasons.

Table 41 Number of MIRCERA Administrations in Core Study Period: Safety Population

sum2_ed11exp_core_S Summary of the Number of Mircera Administrations

Protocol(s): NH19707
Analysis: Safety Population
Filter Applied: where p_saf='YES'

	Group 1 (N=16)	Group 2 (N=48)
Exposure:		
At least 1 Administration	16 (100.0%)	48 (100.0%)
At least 2 Administrations	14 (87.5%)	44 (91.7%)
At least 3 Administrations	13 (81.3%)	39 (81.3%)
At least 4 Administrations	12 (75.0%)	34 (70.8%)
At least 5 Administrations	11 (68.8%)	24 (50.0%)
Overall Exposure (Administrations):		
n	16	48
Mean	4.13	3.94
Std Dev	1.500	1.343
Median	5.0	4.5
Q1:Q3	3.5:5.0	3.0:5.0
Min:Max	1:5	1:5

0-dose records are not counted.

Program : $PROD/cdp10524/nh19707/sum2_ed11exp_core.sas
Output : $PROD/cdp10524/nh19707/reports/sum2_ed11exp_core_S.out
04MAY2016 17:19 BADERU

During the core study period, the median cumulative total dose of MIRCERA was 466 µgin the Group 2 and 207 µg in the Group 1. The highest single, individually injected dose was 560 µg received by patient 3504, equivalent to 11.4 µg/kg with a total cumulative dose of 1950 µg. The highest cumulative dose was 2000 µg, from patient 6603, who regularly received 450 µg or 9 µg/kg.

Throughout the entire study (including the safety extension period), the median number of administrations was 5.5 in Group 1 and 7.5 in Group 2. Four patients in Group 1 (25%) and 7 patients in Group 2 (15%) received at least 18administrations and one in Group 2 received 19.

COMMON ADVERSE EVENTS

Overall, 49/64 patients (77%) reported at least one AE during the core study period(12/16 [75%] in Group 1 and 37/48 [77%] in Group 2) , for a full summary of all AEs during the core study period, see. The most commonly affected SOCs (with > 15% of patients overall with AEs) were *Infections and infestations* (30/64patients overall [47%]), *General disorders and administration site conditions* (12/64patients [19%]), *Gastrointestinal disorders* (12/64 patients overall [19%]) and *Nervous system disorders* (12/64 patients [19%]).

The individual AEs reported in more than 5% of patients overall were nasopharyngitis(9/64 patients overall [14%]), headache (9/64 [14%]), vomiting (6/64 patients [9%]),hypertension (8/64 patients overall [13%]), abdominal pain (4/64 patients overall [6%]),and bronchitis (4/64 patients overall [6%]).

Seven AEs in 5/64 patients (8%) overall (1 AE in 1 patient in Group 1 and 6 AEs in 4patients in Group 2) were considered by the investigator to be related to the study drug.

Safety Extension Period

During the safety extension period, 27 patients (73%) experienced at least one AE (4[44%] in Group 1 and 23 [82%] in Group 2).

The most frequently reported events were *Infections and infestations* (17 patients overall [46%] had an AE in this SOC) and *Gastrointestinal disorders* (8 patients [22%]).

The most frequently reported individual AEs overall were headache (6 [16%]), hypertension (5 [14%]) and nasopharyngitis (7 [19%]).

Two patients (both in Group 2) had 2 AEs considered by the investigator to be related to the study drug: anemia and urinary tract infection.

ADVERSE EVENTS BY INTENSITY

Overall, there were 2 life-threatening AEs and 10 severe AEs in 7/64 patients (11%), 4 of which were not classified as SAEs during the core study period. Of the remaining AEs, there were 42 moderate AEs in 26/64 patients (41%) and 81 mild AEs in 35/64 patients(55%).

The two life-threatening AEs, both occurring in patients in Group 2 and reported by the investigator as unrelated to the study medication, were intracranial hematoma and procedural hemorrhage during dialysis caused by a poorly adapted dialysate filter and leading to worsening of anemia.

The only severe AE to be reported more than once was arteriovenous fistula thrombosis(2 patients, 1 in each group). One of these cases was classified as an SAE, and both were considered related to the study drug by the investigator. The only other severe AE considered related to the study drug by the investigator were hyperphosphatemia and hyperkalemia.

Safety Extension Period

Overall, there were no life-threatening AEs and 5 severe AEs reported during the safety extension period (all in patients in Group 2). These events were hypotension, hypertension, arteriovenous fistula thrombosis, arterial injury, and sleep disorder. None of these events were considered by the investigator to be related to the study drug.

DEATHS

One patient died during the study (in the core study period). The cause of death was reported as intracranial hematoma. The patient had experienced head trauma as a result of a domestic accident in which he stumbled over a carpet, hitting his head on a chair, apparently without any immediate symptoms or signs. Two days later he received heparin and underwent dialysis, and subsequently experienced vomiting and seizures. ACT scan revealed intracranial hematoma. A craniotomy was performed and hematoma was evacuated. Although the patient was reported as feeling well the next day, his condition deteriorated and he died 24 days after intracranial hematoma was reported(and 26 days after head trauma). The event was considered by the investigator to be unrelated to the study drug

SERIOUS ADVERSE EVENTS

Overall, 16/64 patients (25%) reported a total of 25 SAEs during the core study period(4/16 [25%] in Group 1 and 12/48 [25%] in Group 2).

The most commonly affected SOCs (with > 5% of patients overall with SAEs) were *Infections and infestations*(8 patients overall [13%]), *General disorders and administration site conditions* (4patients overall [6%]), and *Injury, poisoning and procedural complications* (4 patients overall [6%]).

SAEs reported in more than 1 patient overall included device-related infection (3patients), bronchitis (2), thrombosis in device (2), arteriovenous fistula thrombosis (2), procedural hemorrhage (2), fluid overload (2), and hypertension (2).

Of the AEs classified as serious, two were considered related to study medication: arteriovenous thrombosis and thrombosis in device.

Table 44 Summary of Serious Adverse Events during the Core Study Period: Safety Population

aells_core_t_s Summary of Serious Adverse Events
Serious Adverse Events
Protocol(s): NH19707
Analysis: AS SELECTED Center: ALL CENTERS
Safety Population

Body System/ Adverse Event	Group 1 N = 16 No. (%)	Group 2 N = 48 No. (%)	Total N = 64 No. (%)
ALL BODY SYSTEMS			
Total Pts with at Least one AE	4 (25.0)	12 (25.0)	16 (25.0)
Total Number of AEs	5	20	25
INFECTIONS AND INFESTATIONS			
Total Pts With at Least one AE	2 (12.5)	6 (12.5)	8 (12.5)
DEVICE RELATED INFECTION	-	3 (6.3)	3 (4.7)
BRONCHITIS	1 (6.3)	1 (2.1)	2 (3.1)
NASOPHARYNGITIS	-	1 (2.1)	1 (1.6)
PHARYNGITIS	-	1 (2.1)	1 (1.6)
PNEUMONIA	-	1 (2.1)	1 (1.6)
STAPHYLOCOCCAL SCALDED SKIN SYNDROME	1 (6.3)	-	1 (1.6)
Total Number of AEs	2	7	9
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Total Pts With at Least one AE	1 (6.3)	3 (6.3)	4 (6.3)
THROMBOSIS IN DEVICE	-	2 (4.2)	2 (3.1)
DEVICE DISLOCATION	1 (6.3)	-	1 (1.6)
NON-CARDIAC CHEST PAIN	-	1 (2.1)	1 (1.6)
PAIN	-	1 (2.1)	1 (1.6)
Total Number of AEs	1	4	5
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Total Pts With at Least one AE	1 (6.3)	3 (6.3)	4 (6.3)
ARTERIOVENOUS FISTULA THROMBOSIS	1 (6.3)	1 (2.1)	2 (3.1)
PROCEDURAL HAEMORRHAGE	-	2 (4.2)	2 (3.1)
Total Number of AEs	1	3	4
METABOLISM AND NUTRITION DISORDERS			
Total Pts With at Least one AE	1 (6.3)	1 (2.1)	2 (3.1)
FLUID OVERLOAD	1 (6.3)	1 (2.1)	2 (3.1)
Total Number of AEs	1	1	2
VASCULAR DISORDERS			
Total Pts With at Least one AE	-	2 (4.2)	2 (3.1)
HYPERTENSION	-	2 (4.2)	2 (3.1)
Total Number of AEs	-	2	2
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Total Pts With at Least one AE	-	1 (2.1)	1 (1.6)
BACK PAIN	-	1 (2.1)	1 (1.6)
Total Number of AEs	-	1	1

Investigator text for Adverse Events encoded using MedDRA version 18.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
AE onset between time of very first drug intake and date of last contact or 30 days after very last drug intake
For patients going into the safety extension study period AEs up to study day 152 are taken into account
AE11 29APR2016:17:22:59 (2 of 2)

Body System/ Adverse Event	Group 1 N = 16 No. (%)	Group 2 N = 48 No. (%)	Total N = 64 No. (%)
NERVOUS SYSTEM DISORDERS			
Total Pts With at Least one AE	-	1 (2.1)	1 (1.6)
INTRACRANIAL HAEMATOMA	-	1 (2.1)	1 (1.6)
Total Number of AEs	-	1	1
RENAL AND URINARY DISORDERS			
Total Pts With at Least one AE	-	1 (2.1)	1 (1.6)
LUPUS NEPHRITIS	-	1 (2.1)	1 (1.6)
Total Number of AEs	-	1	1

Safety Extension Period

Overall, 9/37 patients (24%) reported a total of 12 SAEs during the safety extension period (1/9 [11%] in Group 1 and 8/28 [29%] in Group 2)The most commonly affected SOCs (with at least 2 patients overall with SAEs) were *Injury, poisoning and procedural complications* (3 patients overall [8%]), *Vascular disorders* (3 patients overall[8%]), and gastrointestinal disorders (2 patients overall [6%]).

The only individual SAE reported in more than 1 patient overall was hypertension (2patients). Of the AEs classified as serious, none were considered related to the study medication

Table 45 Summary of Serious Adverse Events during the Safety Extension Period: Safety Population

aells_ext_t_ex Summary of Serious Adverse Events - Extension Period Only
Serious Adverse Events
Protocol(s): NH19707
Analysis: AS SELECTED Center: ALL CENTERS
Safety Extension Population

Body System/ Adverse Event	Group 1 N = 9 No. (%)	Group 2 N = 28 No. (%)	Total N = 37 No. (%)
ALL BODY SYSTEMS			
Total Pts with at Least one AE	1 (11.1)	8 (28.6)	9 (24.3)
Total Number of AEs	2	10	12
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Total Pts With at Least one AE	1 (11.1)	2 (7.1)	3 (8.1)
ARTERIAL INJURY	-	1 (3.6)	1 (2.7)
ARTERIOVENOUS FISTULA THROMBOSIS	-	1 (3.6)	1 (2.7)
TRANSPLANT FAILURE	1 (11.1)	-	1 (2.7)
Total Number of AEs	1	2	3
VASCULAR DISORDERS			
Total Pts With at Least one AE	-	3 (10.7)	3 (8.1)
HYPERTENSION	-	2 (7.1)	2 (5.4)
HYPOTENSION	-	1 (3.6)	1 (2.7)
Total Number of AEs	-	3	3
GASTROINTESTINAL DISORDERS			
Total Pts With at Least one AE	1 (11.1)	1 (3.6)	2 (5.4)
ABDOMINAL PAIN	-	1 (3.6)	1 (2.7)
DIARRHOEA	1 (11.1)	-	1 (2.7)
Total Number of AEs	1	1	2
CARDIAC DISORDERS			
Total Pts With at Least one AE	-	1 (3.6)	1 (2.7)
PERICARDITIS	-	1 (3.6)	1 (2.7)
Total Number of AEs	-	1	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Total Pts With at Least one AE	-	1 (3.6)	1 (2.7)
THROMBOSIS IN DEVICE	-	1 (3.6)	1 (2.7)
Total Number of AEs	-	1	1
INFECTIONS AND INFESTATIONS			
Total Pts With at Least one AE	-	1 (3.6)	1 (2.7)
ORCHITIS	-	1 (3.6)	1 (2.7)
Total Number of AEs	-	1	1
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Total Pts With at Least one AE	-	1 (3.6)	1 (2.7)
UTERINE HAEMORRHAGE	-	1 (3.6)	1 (2.7)
Total Number of AEs	-	1	1

Investigator text for Adverse Events encoded using MedDRA version 18.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
AE onset between start of safety extension study period and date of last contact or 30 days after very last drug intake
AE11 29APR2016:17:25:16 (1 of 1)

ADVERSE EVENTS THAT LED TO WITHDRAWAL OF STUDYTREATMENT

One patient died and did not complete study treatment during the core study period. No patients were withdrawn from study treatment due toa non-fatal AE in either study period. No AEs led to dose modification at any time during the study.

SELECTED ADVERSE EVENTS

Hypertension

Core Study Period

Overall, at baseline, 32 patients (50%) had hypertension reported by the investigator as a risk factor and 37 (58%) were already receiving or had received antihypertensive and/or diuretic agents. During the core study period, 8patients (13%) had an increase in antihypertensive treatment.

Of the 8 patients with arterial hypertension reported as an AE during the core study period, 7 had pre-existing hypertension at enrollment or within 12 weeks prior to enrollment, and 1 had previously received antihypertensive therapy although this patient was not reported to have hypertension at enrollment or within 12 weeks of enrollment. In 1 patient, the hypertension was reported as severe in intensity and as an SAE. The event resolved with treatment (doxazosin and carvedilol). One case of moderate hypertension was also reported as an SAE.

Pre- and post-dialysis blood pressure measurements were performed in all patients during the study. Values remained close to baseline level, and no clear trend or difference between groups was apparent during the study.

Safety Extension Period

During the safety extension period, 9 patients (24%) had an increase in antihypertensive treatment

There were 5 adverse events of hypertension reported during this period. One patient with hypertension in the safety extension period had already reported a hypertension event during the core period. In that patient, both events were considered serious and severe; an increase in antihypertensive treatment was reported after the second event.

During the extension period, two patients reported hypertension as an SAE. In both cases, the event was associated with a change in antihypertensive medication.

Vascular Access Thrombosis

Core Study Period

4 patients (3 in Group 2 and 1 in Group 1) reported 5events of vascular access thrombosis.

These events were coded as ‘arteriovenous fistula thrombosis’ in 2 patients and ‘thrombosis in device’ in 2 patients (1 patient experienced 2 such events).

For the patients with ‘thrombosis in device’ the verbatim investigator text was “central venous thrombosis in dialysis catheter” and “thrombosis in extracorporeal system for hemodialysis”.

All cases were classified as SAEs. For 3 of the patients, the events were considered severe, and 2 cases (one case of 'arteriovenous fistula thrombosis' and one case of' thrombosis in device') were considered related to study medication. In all cases, the events resolved without sequelae.

Safety Extension Period

3 patients reported 5 events of vascular access thrombosis (different patients from those with such events during the core period). These were coded as 'arteriovenous fistula thrombosis' in 2 cases and 'thrombosis in device' in 3 cases.

Three of these events (two reports of `thrombosis in device' in 1 patient and 1 report of `arteriovenous fistula thrombosis' in another patient) were classified as SAEs. One of these events (`arteriovenous fistula thrombosis') was also a severe AE. None of these events were considered related to study medication and all resolved without sequelae.

Anti-Erythropoietin Antibody-Induced Pure Red Cell Aplasia

No patients developed anti-drug antibodies or anti-erythropoietin antibodies during the study.

LABORATORY PARAMETERS

Hematology

During the core study period, median Hct remained within 15% of baseline for both groups. Median RBC count remained within 13% and 8% of baseline for Group 1 and Group 2, respectively. Median platelet count remained within 16% and20% of baseline for Group 1 and Group 2, respectively.

Median platelet count at baseline was 221.5 x 109/L (range 182-398) and 208.0 x 109/L(range 80-518) in Group 1 and Group 2, respectively, and decreased slightly during the core study period in both groups. There was substantial within and between-patient variability of platelets in both groups. Shift tables for platelets during the core study period are shown in. In Group 1, 1/16 patients had one or more post-baseline values below the site-specific normal range (typically 150- 400 × 109/L). None had values above normal range. In Group 2, 19/47 patients had one or more post-baseline values below normal range, of whom 6/19 already had low value sat baseline, and 4/47 patients had one or more post-baseline values above normal range, of whom 1/4 already had a high value at baseline. During the extension period, platelet values below the site-specific normal range were reported in 2 patients (29%) in Group 1 and 15 patients (60%) in Group 2. No events of bleeding were reported in any patients in association with low platelet counts. Thrombocytopenia was reported as an AE in two patients; in both cases, the event was classified as mild.

Hematocrit values during the safety extension period were similar to those in the core study period RBC counts were not determined during the safety extension period.

2. Rapporteur's overall conclusion and recommendation

The study NH19707 was designed to provide evidence on the optimal dose of Mircera in the paediatric population with anaemia of CKD, following iv administration of MIRCERA to paediatric patients on haemodialysis. The study is part of the agreed PIP but while the PIP opinion states that children aged 2 to less than 18 years should have been enrolled, this study enrolled only children aged 5 to less than 18 years old. Therefore, the Applicant at the time of the type II variation should address how dosing for these children could be generated. Furthermore, at the time of writing this assessment report, PDCO is discussing modification 02 of the PIP in which changes in the initially planned confirmatory

study (see below) are being dealt with. The MAH does not longer intend to perform such a study but this is something that should be discussed with the PDCO as mentioned above.

Study NH19707 is also a Post-Marketing Requirement agreed in 2007 with the FDA as per the Paediatric Research Equity Act.

The NH19707 Study consists of a phase II, open-label, multicentre, dose finding study to determine the optimum starting dose of Mircera in children aged 5-17 years old receiving haemodialysis who switched from other ESAs (epoetin alfa/beta or darbepoetin alfa). The duration of study were 20 weeks, after 2 weeks of screening period, patients were given Mircera for 16 weeks of dose titration and continued 4 weeks more during the evaluation period.

Two doses have been studied based on two different conversion factors. A total of 16 patients were given MirceraIV with a starting dose based on 4x previous weekly epoetin dose (IU) /250 or 4x previous weekly darbepoetin (µg) /1.1. In the second group a total of 16 patients received a starting Mircera dose double that of group 1, it means 4x previous weekly epoetin dose (IU)/125 or 4x previous weekly darbepoetin alfa µg/0.55.

Of the 112 screened patients, 64 were enrolled (16 initially in Group 1 and then 48 in Group 2, following a preliminary analysis of Group 1).

Considering that the adjusted mean change in Hb from baseline to the evaluation period was smaller in group 2 (-0.09 g/dl (95%IC: -0.45 to 0.26) than in the group 1 (-0.74 g/dl(95% IC -1.32 to -0.16), that the secondary variables also support a more stable Hb level in group 2 than in the group 1 and finally that less dose adjusted were needed in group 2, it is proposed this Group 2 conversion factor to be used as the recommended starting dose of Mircera for the maintenance treatment in children.

However a detailed assessment of the study results is anticipated at the time of the variation application to expand the indication to the paediatric population on haemodialysis. A number of aspects would require clarification before supporting the proposed posology, particularly in the youngest group of patients (5-11 years old), given the limited data available. Furthermore, long-term data with the Group 2 starting dose are limited to 21 patients. There are some methodological issues that should be explained in order to uncertain the potential impact on the validity of study results, i.e. the substitution of patients who withdrew from the study. Finally the high variability in the dose of Mircera administrated throughout the core study period in order to achieve and keep the target of Hb level does not speak in favour of the selected starting dose and further discussion is foreseen on this matter.

Given that a phase III confirmatory study initially planned is not considered feasible any longer in these paediatric populations, it is to be agreed at PDCO whether a different trial is still needed. Whatever the outcome is, the lack of confirmatory data makes it needed a more in depth discussion than the crude data presentation in order to support any changes in the SmPC.

To this aim, the complete assessment of the population PK analysis can be key supportive evidence of the proposed conversion factor and may also help to clarify some of the identified uncertainties.

Overall, the safety profile of Mircera in the paediatric population does not reveal any new signal. The vast majority of adverse events are already described in the SmPC of Mircera. However the frequencies of some adverse events appear to differ in children, which may well be due to the limitations of the safety database. Nevertheless, the need to include any particular information for this population in the SmPC will be decided following a careful review of the totality of the evidence available, without any restrictions based on arbitrary cut-off points (i.e. only AEs >2% or 5% of incidence).

CONCLUSION

The Applicant has submitted the results of Study NH19707, an open-label, multidose study to determine the optimum starting dose of intravenous Mircera for the maintenance treatment of anaemia in paediatric patients with chronic kidney disease on haemodialysis and a population pharmacokinetic analysis of Mircera in the paediatric population.

This submission has been done 6 months after the last patients achieved the last visit in accordance with Article 46 of the Regulation 1901/2006.

The study results do not change the benefit risk balance for Mircera in the currently authorised conditions for use, which is limited to the adult population. Nevertheless, both the phase II study and the population PK analysis are considered of interest to conduct a formal benefit/risk evaluation for the use of Mircerain the paediatric population on haemodialysis. However, some aspects will require a deep evaluation and clarification from the MAH before a conclusion can be drawn.

It is noted that modification M02 of the PIP is currently ongoing at PDCO with regards to the design of the remaining paediatric study in the agreed PIP opinion which is a randomized controlled, open-label, multi-centre, parallel group study to confirm the optimal starting dose of Mircera administered once a month iv or sc for the maintenance treatment of anaemia in paediatric patients with chronic kidney disease not on dialysis or paediatric patients on dialysis (PD and HD) who had been receiving a stable treatment with an approved erythropoiesis stimulating agent (NH19708). The MAH no longer intends to perform such a study. An alternative study design is being discussed with the PDCO for pre-dialysis and peritoneal dialysis patients. The conclusions of this article 46 assessment report have no impact in this and perhaps PDCO can take some advantage of the limitations seen in study NH19707 for their discussion.

Mircera is available in pre-filled syringe with several concentration 167 µg/ml, 250µg/ml, 333µg/ml, 500µg/ml, 667µg/ml, 833µg/ml, 100µg/ml, 133µg/ml, 200 µg/ml, 400µg/ml and 600 µg/ml. It is very likely that these formulations are also valid for children, as proposed by the MAH. However, the final acceptability will depend on the final decision on the recommended starting/maintenance dose for the paediatric population at the time of the variation application assessment. The risk for dosing errors with the current pre-filled syringes in children will need to be discussed.

☒**Fulfilled**

No regulatory action required.

☐**Not fulfilled**

3. Additional clarification requested

None

MAH responses to Request for supplementary information

N/A