22 June 2023
EMA/321300/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mircera

International non-proprietary name: methoxy polyethylene glycol-epoetin beta

Procedure No. EMEA/H/C/000739/II/0092

Note

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

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List of abbreviations

ADA Anti-Drug-Antibody
CFs conversion factor
CKD chronic kidney disease
CL Clearance
CSR clinical study report
CV coefficient of variation
eCTD electronic Common Technical Document
EMA European Medicines Agency
EPO erythropoietins
ESA erythropoiesis-stimulating agents
ESRD end-stage renal disease
Hb Hemoglobin
HD Hemodialysis
IPHN International Pediatric Hemodialysis Network
IPPN International Pediatric Peritoneal Dialysis Network
IPDN International Pediatric Dialysis Network
IV intravenous
Ka absorption rate constant
KRT kidney replacement therapy
MAH marketing authorization holder
NAPRTCS North American Pediatric Renal Trials and Collaborative Studies
NI-PASS non-interventional voluntary post-authorization safety study
PD peritoneal dialysis
PDCO Paediatric Committee
PIP pediatric investigation plan
PK/PD pharmacokinectic/pharmacodynamics
SC subcutaneous
SC50 concentration of Mircera at which 50% of the maximum increase is achieved
SCP Summary of Clinical Pharmacology
Smax maximum increase in Hb production rate after switch to Mircera, relative to production rate in the absence of any ESA treatment
USRDS United States Renal Data System
V volume of distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 1 June 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include treatment of paediatric patients from 3 months to less than 18 years of age requiring dialysis or not yet on dialysis and switching from another ESA to Mircera, based on final results from study NH19708; this is a single-arm, open-label, Phase II study of Mircera in patients aged 3 months to <18 years with CKD on dialysis or not yet on dialysis to generate PK, efficacy, and safety data for subcutaneous (SC) administration of Mircera. In addition, supportive data from studies NH19707, Modeling & Simulation study (Study 3) and MH40258 were included. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to update the Instruction for Use in the Package Leaflet.

The variation requested amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0317/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0317/2017 was completed.

The PDCO issued an opinion on compliance for the PIP P/0317/2017.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Maria Concepcion Prieto Yerro Co-Rapporteur: <N/A>

Timetable	Actual dates
Submission date	1 June 2022
Start of procedure:	18 June 2022
CHMP Rapporteur Assessment Report	17 August 2022
CHMP members comments	5 September 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	9 September 2022
Request for supplementary information (RSI)	15 September 2022
CHMP Rapporteur Assessment Report	31 January 2023
CHMP members comments	13 February 2023
Updated CHMP Rapporteur Assessment Report	17 February 2023
Request for supplementary information (RSI)	23 February 2023
CHMP Rapporteur Assessment Report	30 May 2023
CHMP members comments	12 June 2023
Updated CHMP Rapporteur Assessment Report	16 June 2023
Opinion	22 June 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Kidney disease is defined as an abnormality of kidney structure or function with implications for the health of an individual, which can occur abruptly, and either resolve or become chronic. Chronic kidney disease (CKD) is a general term for heterogeneous disorders affecting kidney structure and function with variable clinical presentation, in part related to cause, severity and the rate of progression (Kidney International Supplements, 2012).

Several paediatric nephrology societies from European countries have provided data on the incidence of CKD in children, as summarized by Harambat et al, 2012. Based on this data, even though age categories and the definition of CKD differed among countries, the incidence in Europe was broadly consistent, around 11-12 per million age-related populations for CKD stages 3-5, and 8 per million age-related population for CKD stages 4-5. Children in CKD represent a very small percentage of the total of CKD population (NAPRTCS 2014 Annual Report and USRDS 2016 Annual Report).

Anaemia is a common comorbidity in patients with CKD, including children. This condition is associated with multiple adverse clinical consequences and its management is a core component of nephrology care. Increased morbidity and mortality, increased risk of cardiovascular disease and decreased quality of life have been associated with anaemia of CKD, also in children. Although numerous complex factors interact in the development of this anaemia, erythropoietin deficiency and iron dysregulation (including iron deficiency and iron-restricted erythropoiesis) are the primary causes. The symptoms associated with anaemia include fatigue, decreased exercise tolerance, cardiac dysfunction and impaired cognitive function. The mechanism of anaemia due to CKD in children is identical to that in adults.

The principal aims of anaemia management are to alleviate signs and symptoms arising from anaemia, improve quality of life, and to reduce the need for blood or red blood cell transfusions. Exogenous replacement of erythropoietin is an established method for treatment of symptomatic anaemia in CKD. This therapy can be divided into two phases: the initial correction phase, during which haemoglobin (Hb) levels rise and reach plateau levels, and the subsequent maintenance phase during which plateau levels are maintained by regular erythropoietin administration.

Currently available treatment options for the management of symptomatic anaemia associated with CKD include short-acting human recombinant erythropoietins and longer-acting erythropoiesis stimulating agents (ESAs). In Europe, epoetin alfa, epoetin beta, epoetin zeta and darbepoetin alfa are approved for the treatment of anaemia due to CKD in paediatric patients. Epoetin alfa and zeta are approved for patients aged 1 to 18 years on haemodialysis (HD), and epoetin beta is approved for treating symptomatic anaemia caused by CKD in paediatric patients on dialysis and not yet on dialysis. Darbepoetin was approved by EMA for paediatric patients on and not yet on dialysis in 2015. Darbepoetin and epoetin beta are approved for IV as well as SC use in paediatric patients. Epoetin alfa and epoetin zeta are approved for paediatric patients on HD, and dosing recommendations are given for IV use only.

2.1.2. About the product

Mircera (methoxy polyethylene glycol-epoetin beta) is an erythropoiesis stimulating agent currently approved for the treatment of symptomatic anaemia associated with CKD in adult patients. It has an increased half-life compared to erythropoietin. Mircera was first approved in Europe on 20 July 2007 for the treatment of symptomatic anaemia associated with CKD in adult patients.

In Europe, pursuant to Article 16(1) of Regulation (EC) No 1901/2006, as amended the marketing authorization holder (MAH) submitted on 08 February 2008 an application for a paediatric investigation plan (PIP) for Mircera (EMEA-000172-PIPO-07) to the European Medicines Agency (EMA), which was initially agreed on 23 February 2009. A subsequent modification to the PIP was approved in 2012 (EMEA-000172-PIP-07-M01). In September 2016, the MAH submitted another PIP modification, EMEA 000172-PIP-01-07-M02 for which a negative opinion was received. Therefore, in 2017, an additional modification of this agreed PIP, a waiver for a paediatric subset and a proposed deferral were submitted. The modification proposed was the replacement of a Phase III study with a single-arm Phase II study (NH19707 and NH19708) of Mircera in patients aged 3 months to <18 years with CKD on dialysis or not yet on dialysis to generate PK, efficacy, and safety data for subcutaneous (SC) administration of Mircera. In addition, an extrapolation and simulation study ("Study 3") was added with the aim to pool study

NH19708 data with the PK/PD model developed on adult Phase II/III data and later updated after including NH19707 data. The EMA approved the modification of the agreed PIP for Mircera (EMEA-000172-PIP01-07-M03) in accordance with Regulation (EC) No 1901/2006 on 31 October 2017. The general approach was also considered acceptable by the FDA following the submission of an updated Paediatric Development Plan in February 2017.

The purpose of this submission is to seek approval for the extension of indication to include treatment of symptomatic anaemia associated with CKD in paediatric patients from 3 months to less than 18 years of age on ESA maintenance treatment.

The clinical summary documents supporting this submission comprises 2 clinical phase II studies and an analysis of extrapolation and pooling data from adults and paediatric patients for a PK/PD model-based evaluation. Supportive data from a non-interventional study has also been provided.

2.1.3. General comments on compliance with GCP

According to the MAH, study NH19707 and NH19708 were conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

2.2. Non-clinical aspects

2.2.1. Introduction

The MAH has submitted information for environmental risk assessment (ERA) of methoxy polyethylene glycol-epoetin beta in accordance with EMEA/CHMP/SWP/4447/00 corr 2 guidance, to propose an extension of the indication to the paediatric population.

No additional non-clinical information (pharmacology, pharmacokinetics or toxicology) was submitted.

2.2.2. Toxicology

No toxicology information has been submitted.

In the 13-week repeat dose toxicity studies performed with Mircera, rats and dogs were administered higher amount of PEG (1.86-fold in rats and 6.2-fold in dogs) than that the children will be dosed, and no vacuolation in any of the examined organs and tissues were reported in these studies.

2.2.3. Ecotoxicity/environmental risk assessment

The MAH has presented an ERA based on the Guidance on "Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00 corr 2) for methoxy polyethylene glycol-epoetin beta, also named Continuous Erythropoietin Receptor Activator (C.E.R.A.).

C.E.R.A. is a chemically modified protein and it is not known to be an endocrine disrupter, and it is also not suspected to be a carcinogenic, mutagenic or reprotoxic substance.

Phase I: Estimation of exposure

- *Screening for persistence, bioaccumulation and toxicity.*

The n-octanol/water partition coefficient (logKow) for C.E.R.A has been estimated to be < 3, taking into the high water solubility of >17.5 g/l.

As the estimated log K_{OW} value is below the cu-off of 4.5, a PBT assessment is not required.

- *Calculation of the Predicted Environmental Concentration (PEC)*

The PEC has been calculated, according to the formula established in the guideline EMEA/CHMP/SWP/4447/00 corr 2:

$PEC_{SURFACEWATER}$ = (DOSEai * F_{PEN}) / (default WASTEWinhab * default DILUTION)

The maximum daily dose for C.E.R.A. used as a worst-case for the environmental risk assessment, is 0.8 mg/d. Then,
= (0.8 mg/inhabitant/day * 0.01) / (200 L/inhabitant/day * 10)
= 0.000004 mg/L = 0.004 µg/L

Therefore, the action limit of 0.01 µg/L is not exceeded, and risk assessment could be stopped.

The applicant, in accordance with the ERA draft guidance (EMEA/CHMP/SWP/4447/00 Rev. 1, EMA 2018), calculates a new PEC, using a refined F_{PEN}. For the purpose of the F_{PEN} derivation a prevalence 10 per 100,000 people was used. Using the duration of one treatment period ($t_{TREATMENT}$) of 1 day, assuming the number of treatments per year ($n_{TREATMENT}$) as 26 (every two weeks) and applying the default number of days per year (Nd) of 365, the refined fraction of a population receiving C.E.R.A. during a given time ($F_{PEN-REFINED}$) can be calculated as follows:

$F_{PEN-REFINED} = (F_{PEN-DEFAULT} \times t_{TREATMENT} \times n_{TREATMENT}) \div Nd$

$= (0.01 \times 1 \times 26) \div 365 = 0.00071$

The refined $PEC_{SURFACEWATER}$ is calculated as follows:

$PEC_{SURFACEWATER}$ = (DOSEai * $F_{PEN-REFINED}$ / default WASTEWinhab * default DILUTION

= 800 µg/d × 0.00071 ÷ (200 l/d × 10) = 0.0003 µg/l

The applicant concludes that the $PEC_{SURFACEWATER}$ is below the EMA (2006) guidance action limit of 0,01 µg/l. Since the $PEC_{SURFACEWATER}$ for C.E.R.A. is below 0.01 µg/l, and no other environmental concerns are noted, it is assumed that C.E.R.A. is unlikely to pose a risk to the environment following prescribed use in patients. A Tier A Phase 2 ERA is not required.

However, a limited set of biodegradability and acute ecotoxicity tests were performed for the purpose of classification and labelling. Specifically, a ready biodegradability test as well as acute tests for algal growth inhibition, daphnid immobilisation and fish mortality were performed according to OECD guidelines and in compliance with the OECD Principles on Good Laboratory Practice (GLP).

Phase II-Tier A: Environmental fate and effects analysis

- *Physico-chemical properties and fate*

Biodegradation

A *ready biodegradability test* according to OECD 301 F in compliance with GLP showed 46% mineralisation by BOD/ThOD after 28 days. However, complete primary degradation was observed within 4 days of incubation (figure 1).

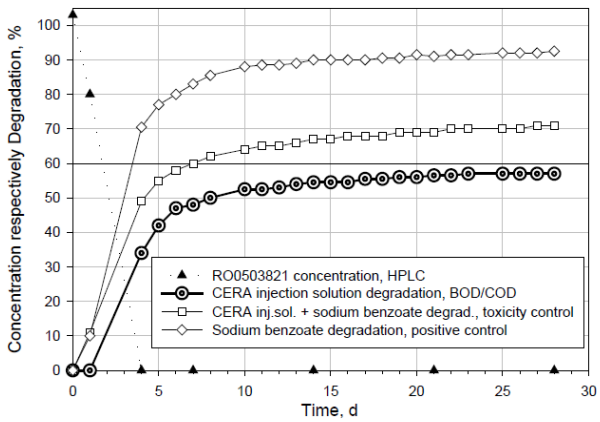


Figure 1. OECD 301F, test performed using regular RO0503821 injection solution; initial concentration adjusted to 100 mg RO0503821/l; RO0503821 analysed by HPLC; NO2/NO3 determined at end of test.

The applicant concludes that C.E.R.A. is not readily biodegradable. However, complete primary degradation with mineralisation presumably of the protein part of the molecule occurs.

- *Aquatic effects studies*

Toxicity data on algae, daphnia and fish were performed for C.E.R.A. The main information of the conducted studies and the study results are summarised in the table below:

Table 1. Data on aquatic effects studies for C.E.R.A

Substance	Study / Report	Species	Results	Conclusions
C.E.R.A.	Toxicity to *Scenedesmus subspicatus* in a 72-hour algal growth inhibition test (OECD 201) / RO0503821	*Scenedesmus subspicatus*	EC_{50} growth rate >200 mg/l nominal concentration (NC) EC_{50} yield were >200 mg/l NC. NOEC = 200 mg/l NC (highest tested concentration).	No toxic effects were observed.
	Acute toxicity to *Daphnia magna* in a 48-hour immobilization test (OECD 202) / RO0503821	*Daphnia magna*	EC_{50} >200 mg/l nominal concentration (NC) NOEC = 200 mg/l NC (highest tested concentration).	No toxic effects were observed.
	Acute toxicity to zebrafish (*Brachydanio rerio*) in a 96-hour static test (OECD 203) / RO0503821	*Danio rerio*	LC_{50} >200 mg/l nominal concentration (NC) NOEC = 200 mg/l NC (highest tested concentration).	No toxic effects were observed.

- *Calculation of Predicted No-Effect Concentration (PNEC)*

The acute-based surface water PNEC is estimated as the lowest of the three acute surface water ecotoxicity EC_{50}/LC_{50} values divided by an assessment factor of 1000. In the case of C.E.R.A., with EC_{50}/LC_{50} values of >200 mg/l for algae, daphnids and fish the following surface water PNEC ($PNEC_{SURFACEWATER}$) was derived:

$$PNEC_{SURFACEWATER} = 200 \text{ mg/l} \div 1000 = 0.2 \text{ mg/l} = 200 \text{ µg/l}.$$

- *Calculation of the groundwater PNEC ($PNEC_{GROUNDWATER}$)*

The groundwater PNEC ($PNEC_{GROUNDWATER}$) is approximated as the acute EC_{50} for daphnids of >200 mg/l divided by an assessment factor of 1000:

$PNEC_{GROUNDWATER}$ = 200 mg/l ÷ 1000 = 0.2 mg/l = 200 µg/l

- *Calculation of the groundwater PEC ($PEC_{GROUNDWATER}$)*

According to the guideline, the $PEC_{GROUNDWATER}$ can be assumed to be typically 0.25 times the $PEC_{SURFACEWATER}$. For C.E.R.A., $PEC_{GROUNDWATER}$ of 0.0003 µg/L* 0,25 = 0.000075 µg/L

- *Calculation of the sewage treatment PEC (PEC_{STP})*

The PEC_{STP} is approximated as the surface water PEC multiplied by 10 (the default surface water dilution factor used in the $PEC_{SURFACEWATER}$ calculation):

PEC_{STP} = 0.0003 µg/l × 10 = 0.003 µg/l

- *Calculation of the sewage treatment PNEC ($PNEC_{STP}$)*

An activated sludge respiration inhibition test according to OECD 209 over 3 hours was not performed. However, the toxicity control in the OECD 301 F ready biodegradability test resulted in a NOEC over 14 days of 100 mg/l nominal concentration (NC)

Based on this substitute data the bacterial PNEC for sewage treatment is calculated as the inhibition control NOEC divided by an assessment factor of 10 according to REACH:

$PNEC_{STP}$ = 100 mg/l ÷ 10 = 10 mg/l = 10000 µg/l

Outcome of Tier A fate and effects analysis

The surface water PEC/PNEC risk characterisation ratio based on acute toxicity data with algae, daphnids and fish is:

0.0003 µg/l ÷ 200 µg/l = 0.000001

The groundwater PEC÷PNEC risk characterisation ratio based on acute daphnid data is:

0.00007 µg/l ÷ 200 µg/l = 0.0000004

The sewage treatment PEC÷PNEC risk characterisation ratio is:

0.0003 µg/l ÷ 10000 µg/l = 0.0000003

It is concluded by the applicant that, since the risk characterisation ratios are 0.000001, 0.0000004 and 0.0000003, C.E.R.A is not expected to cause a risk to surface waters, groundwaters and sewage treatment, respectively.

2.2.4. Discussion on non-clinical aspects

No non-clinical toxicology information has been submitted. PEG has shown to lead to accumulation and vacuolation within specific cells of the CNS (choroid plexus epithelia), liver and kidney in nonclinical species treated with other PEGylated medicinal product. In the 13-week repeat dose toxicity studies performed with Mircera, rats and dogs were administered higher amount of PEG (1.86-fold in rats and 6.2-fold in dogs) than that the children will be dosed, and no vacuolation in any of the examined organs and tissues were reported in these studies. The relevance of these data is limited by the lack of exposure data to PEG in animals and humans following Mircera treatment. However, the amount of PEG administered to humans as part of Mircera (0.000186 µmol/kg/month) is significantly lower (~2000 fold) than the exposure threshold value of 0.4 µmol/kg/month proposed in the Safety Working Party's response to the PDCO regarding the use of PEGylated drug products in the paediatric population and thus, it seems unlikely that PEG levels in humans can reach this threshold value. In addition, *in vivo* distribution data indicated that Mircera can reach brain, but at low levels, and it should be considered that PEG-induced cell vacuolation observed in toxicity studies performed with other PEGylated medicinal products were not associated to functional consequences.

Clinical experience with Mircera in adults and paediatric patients also did not raise any safety concerns pertaining to the PEG-induced vacuolation.

In conclusion, all data together support that Mircera is not expected to cause any safety concern as a consequence of PEG accumulation and its possible vacuolisation to the CNS and other tissues.

No new studies have been carried out to assess the environmental risk.

An estimation of exposure of methoxy polyethylene glycol-epoetin beta in the environment, taking into account the prevalence of the disease, has been provided. In this way, the applicant has calculated a PEC using a refined Fpen, which, as mentioned, follows the postulates of the ERA draft guidance (EMEA/CHMP/SWP/4447/00 Rev. 1, EMA 2018). Although the use of this refined Fpen is considered acceptable, the CHMP pointed that the approaches discussed in this ERA draft guidance are currently in draft format and their guidance are not in force at this present time. Although the principles of the draft guideline, EMEA/CHMP/SWP/4447/00 Rev. 1, EMA 2018, can be acknowledged by the CHMP, current authoritative guidance is EMEA/CHMP/SWP/4447/00 corr 2, EMA 2006.

Since the $PEC_{SURFACEWATER}$ value for methoxy polyethylene glycol-epoetin beta is less than 0.01 µg/L, and no other environmental concerns have been reported, it is assumed that the medicinal product is unlikely to pose a risk for the environment following prescribed use in patients.

In addition, a biodegradability and three aquatic effect studies, that were performed for the purpose of classification and labelling, have been provided for this variation.

The biodegradability methoxy polyethylene glycol-epoetin beta was assessed by the MAH following the OECD guideline 301. methoxy polyethylene glycol-epoetin beta is considered not readily biodegradable and, therefore, a Phase II Tier B does not have to be carried out.

In toxicity studies, methoxy polyethylene glycol-epoetin beta does not show toxicity to aquatic organisms (algae, daphnids and fish).

No further assessment is needed to characterize the risk of methoxy polyethylene glycol-epoetin beta to the environment.

2.2.5. Conclusion on the non-clinical aspects

The MAH provided a weight of evidence approach regarding the risk of PEG-induced cell vacuolation following Mircera treatment to paediatric population. Available non-clinical and clinical data with Mircera did not raise any safety concerns pertaining to the PEG-induced vacuolation.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of methoxy polyethylene glycol-epoetin beta. Considering the above data, methoxy polyethylene glycol-epoetin beta is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

- Tabular overview of clinical studies

Study No (Phase)	**Population**	**Study Design**	**Number of patients**	**Dose, Route and Regimen**
NH19707 (Phase II)	Paediatric patients 5-17 years old who had clinically stable chronic renal anaemia on haemodialysis and who were receiving maintenance IV treatment with an ESA	A Phase II, open-label, single-arm, multicenter, sequential dose-finding study with Mircera administered once every 4 weeks IV in paediatric patients with CKD receiving haemodialysis who had switched from other ESAs (epoetin alfa/beta or darbepoetin alfa). The core study was of 22 weeks and consisted of 3 periods: Screening (2 weeks), dose titration (16 weeks), and evaluation or core period (4 weeks). Patients who completed the 20 weeks of core treatment, who adequately maintained Hb levels were eligible to enter an optional 52-week	64 patients: Group 1: 16 patients Group 2: 48 patients	Mircera was administered IV once every 4 weeks for the duration of the study. <u>For patients previously on epoetin alfa or beta:</u> Intermediate dose (Group 1): Mircera starting dose: 4 × weekly EPO dose (IU)/250, 1×/4 weeks IV High dose (Group 2): Mircera starting dose: 4 × weekly EPO dose (IU)/125, 1×/4 weeks IV <u>For patients previously on darbepoetin alfa:</u> Intermediate dose (Group 1): Mircera starting dose: 4 × weekly darbepoetin alfa dose (µg)/1.1, 1×/4 weeks IV High dose (Group 2): Mircera starting dose: 4 × weekly darbepoetin alfa dose (µg)/0.55, 1×/4 weeks IV.

		safety extension period with the same dosing frequency.		Dose adjustments could be performed during the entire study (core study period and safety extension period). 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.
NH19708 (Phase II)	Paediatric patients 3 months-17 years old who had clinically stable chronic renal anaemia on dialysis or not yet on dialysis, and who were receiving maintenance SC treatment with an ESA	A Phase II, open-label, single-arm, multicenter study to ascertain the optimal starting dose of Mircera administered SC for the maintenance treatment of anaemia in paediatric patients with CKD on dialysis or not yet on dialysis. The core study was for 23 weeks and consisted of three periods: Screening (3 weeks), dose titration (16 weeks), and evaluation or core period (4 weeks). Patients who completed the 20 weeks of core treatment, who adequately maintained Hb levels were eligible to enter an optional 24-week safety extension period with the same dosing frequency.	40 patients	Mircera was administered SC once every 4 weeks for the duration of the study. <u>For patients previously on epoetin alfa or beta:</u> Mircera starting dose: 4 × weekly EPO dose (IU)/125, 1×/4 weeks SC <u>For patients previously on darbepoetin alfa</u>:Mircera starting dose: 4 × weekly darbepoetin alfa dose (µg)/0.55, 1x/4 weeks SC Dose adjustments could be performed during the entire study (core study period and safety extension period). 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.
MH40258 (Supportive study)	All paediatric patients below 18 years of age on PD or HD who were included in the IPPN and IPHN registries with at least one observation while being	A non-interventional study secondary data use (NIS SDU) and voluntary post-authorization safety study (PASS) that selected data elements included in the IPPN and IPHN registries among patients who received Mircera.	N=229 patients (PD: 177 patients; HD: 52 patients)	Data was extracted from all paediatric patients below 18 years of age on PD or HD included in the IPPN and IPHN registries with at least one observation while being treated with Mircera

	treated with Mircera			

2.3.2. Pharmacokinetics

Analytical methods

Method validation

REPORT NO. 1046298: Validation of an Immunoassay Method for the Determination of Anti-EPO Antibodies in Human Serum YBS Study YCM/010

A bioanalytical procedure was developed to determine the presence of anti-EPO antibodies (ADA) in human serum (Screening Assay). A test was also established to confirm the specificity of the anti-EPO antibodies (Confirmatory Assay).

The presence of anti-EPO antibodies is determined using a bridging ELISA format. Briefly, biotin labelled EPO is added to the streptavidin coated microtitre plate. After a wash step, aliquots of pre-mixed serum samples and digoxigenylated EPO are then added to the microtitre plate and incubated. After a wash step, anti-digoxigenin Fab fragments conjugated to HRP are added to the microtitre plate and incubated. After a final wash step, a colorimetric HRP substrate (TMB) is incubated, stop solution (0.25 M sulphuric acid) is added then the optical density at 450 nm (Ref 630 nm) is measured.

Samples are initially analysed using the screening assay. Samples identified as positive are tested in the confirmatory assay in the presence of excess unlabelled drug. Finally, if required, the samples confirmed positive may be assayed at different dilutions to determine anti-EPO antibody titer.

- Cut point and Normalization Factor Determination:
  To determine cut point (CP), 40 individual blank matrix samples were assayed in duplicate on three separate occasions resulting in 120 mean assay values. The global mean optical density of NC for the six batches was equal to 0.0805. The normalization factor (NF) was determined as CP minus the global mean optical density of NC, and this NF is to be used for plate specific CP calculation in subsequent analytical runs.
  The summary of CP determination is presented below:
  CP = 0.09875
  Global mean NC = 0.0805
  NF = 0.01825
  Plate specific CP (floating CP) = mean assay NC + 0.01825
  CP of each subsequent plate is to be calculated as the mean of 8 replicates of NC run on that plate + 0.01825.
- Low and High Positive Control: The antibody concentration corresponding to the assay response at LPC was back-calculated and was 14.6 ng/mL. The LPC was prepared in bulk by spiking the positive control antibody into NC serum at 14.6 ng/mL and stored frozen as single use aliquots. The concentration of the HPC was selected at 369 ng/mL. The HPC was prepared in bulk by

spiking the positive control antibody into NC serum at 369 ng/mL and stored frozen as single use aliquots.

The intra-assay precision of NC ranged from 2.2 to 27.3 %*. The intra-assay precision of LPC ranged from 1.1 to 7.0 %. The intra-assay precision of HPC ranged from 0.9 to 5.2 %. The inter-assay precision of NC was 23.7 %*. The inter-assay precision of LPC was 13.8 %. The inter-assay precision of HPC was 11.5 %.

- Assay sensitivity: Assay sensitivity, calculated as the average of the antibody concentration at CP obtained from the nine curves, was 8.87 ng/mL.
- Drug tolerance: The highest drug concentration still providing a positive result (mean assay response above CP) was considered as the assay drug tolerance for the specific antibody concentration.
- Stabilities:
    - The stability of the positive control antibody at room temperature in NC serum up to 4 hours: LQC: %CV=4.8%. HQC: CV=1.5%.
    - Freeze/thaw: Six cycles: LQC: %CV=1.8%. HQC: CV=3.0%.
    - Freezer stability: The freezer stability of the positive control antibody in NC serum was investigated at -80 and -20ºC for 3 weeks. LQC: %CV=1.9%. HQC: CV=4.7% at -80 ºC. LQC: %CV=1.8%. HQC: CV=3.5% at -20 ºC.
- Determination of confirmatory cut-point (CCP): A sample with ratio of assay response in the presence of 10 µg/mL EPO to assay response in the absence of added EPO less than 0.848 is confirmed positive for the presence of specific antibodies.

<u>REPORT NO. 1046299. Validation of an Immunoassay Method for the Determination of Anti-RO0503821 (Anti-Mircera) Antibodies in Human Serum from Study YCM/009.</u>

A bioanalytical procedure was developed to determine the presence of anti-RO0503821 antibodies (ADA) in human serum (Screening Assay). A test was also established to confirm the specificity of the anti-RO0503821 antibodies (Confirmatory Assay). The presence of anti-RO0503821 antibodies is determined using a bridging ELISA format similar to the one described above.

- Cut point and Normalization Factor Determination:

    To determine cut point (CP), 40 individual blank matrix samples were assayed in duplicate on three separate occasions resulting in 120 mean assay values. The global mean optical density of NC for the six batches was equal to 0.0215. The normalization factor (NF) was determined as CP minus the global mean optical density of NC, and this NF is to be used for plate specific CP calculation in subsequent analytical runs.

    The summary of CP determination is presented below:

    CP = 0.03861

    Global mean NC = 0.0215

    NF = 1.8

    Plate specific CP (floating CP) = mean assay x 1.8

    CP of each subsequent plate is to be calculated as the mean of 8 replicates of NC run on that plate multiplied by 1.8.

- Low and High Positive Control: The antibody concentration corresponding to the assay response at LPC was back-calculated and was 0.208 μg/mL. The LPC was prepared in bulk by spiking the positive control antibody into NC serum at 0.208 μg/mL and stored frozen as single use aliquots. The concentration of the HPC was selected at 5.54 μg/mL. The HPC was prepared in bulk by spiking the positive control antibody into NC serum at 5.54μg/mL and stored frozen as single use aliquots.

  The intra-assay precision of NC ranged from 7.7 to 31.8 %*. The intra-assay precision of LPC ranged from 1.8 to 13.2 %. The intra-assay precision of HPC ranged from 1.1 to 6.7%. The inter-assay precision of NC was 21.7 %*. The inter-assay precision of LPC was 20.3 %*. The inter-assay precision of HPC was 21.0 %*.
- Assay sensitivity: Assay sensitivity, calculated as the average of the antibody concentration at CP obtained from the nine curves, was 0.0575 μg/mL.
- Drug tolerance: The highest drug concentration still providing a positive result (mean assay response above CP) was considered as the assay drug tolerance for the specific antibody concentration.

- Stabilities:
  - The stability of the positive control antibody at room temperature in NC serum up to 4 hours: LQC: %CV=1.7%. HQC: CV=2.3%.
  - Freeze/thaw: Six cycles: LQC: %CV=7.8%. HQC: CV=8.2%.
  - Freezer stability: The freezer stability of the positive control antibody in NC serum was investigated at -80 and -20ºC for 2 weeks. LQC: %CV=6.4%. HQC: CV=2.7% at -80 ºC. LQC: %CV=7.3%. HQC: CV=2.9% at -20 ºC.
- Determination of confirmatory cut-point (CCP): A sample with ratio of assay response in the presence of 10 μg/mL RO0503821 to assay response in the absence of added RO0503821 less than 0.519 is confirmed positive for the presence of specific antibodies.

<u>REPORT NO. 1054621. Validation of an ELISA Method for the Determination of RO0503821 (Mircera) in Human Serum from Study YCM/013 (including Add I).</u>

The objective of this study was to validate an analytical method for the determination of RO0503821 in human serum, over a concentration range of 150 to 4000 pg/mL, using a sample volume of 50 μL.

<u>Calibration Curve Standards</u>

Each run contained a calibration set of 8 calibration standards in duplicate.

Two calibration standards were rejected but only in one of the duplicates.

The between-run precision (%CV) and accuracy (%Nominal) ranged from 6.2% to 13.5% and from 99.3% to 103.3%, respectively.

<u>Quality control samples</u>

Each run contained two sets of 4 QC levels.

No QC was out of the acceptance range.

The between-run precision (%CV) and accuracy (%Nominal) ranged from 7.8% to 27.7%* and 91.7% to 112.5%, respectively.

The target LLOQ in this study was 150 pg/mL. CV: 7.8% and bias 2.7%.

One sample of *lipaemic serum and one sample of haemolysed serum* were each be spiked with RO0503821 to the concentration level of the Low QC sample. The mean bias in lipaemic and haemolysed serum were -0.5% and -6.0%, respectively. And the CV was 1.5% and 2.9 %, respectively, therefore there is no effect of lipaemia or haemolysis on the assay.

Stabilities:

- Room temperature 24 hours: LQC: CV (%): 0.8%. Difference from nominal (%): 5.5%. HQC: CV (%): 17.0%. Difference from nominal (%): -0.9%.
- Five cycles of freeze-thaw: LQC: CV (%): 5.1%. Difference from nominal (%): 9.3%. HQC: CV (%): 18.5%. Difference from nominal (%): 1.6%.
- Long term in matrix at -20ºC for one month: LQC: CV (%): 189.3%. Difference from nominal (%): -20%. HQC: CV (%): 5.3%. Difference from nominal (%): -16.3%
- Long term in solution at -20ºC for one month:

Addendum I: The Study objective to assess the long term stability of RO0503821 when spiked into human serum and stored at -20°C was achieved. Stability was established for 16 months. Difference from nominal (%) LQC: -12.8% and HQC: -1.3%.

REPORT NO. 1062976. Validation of a cell-based assay for the determination and confirmation of neutralizing antibodies against Mircera in human serum samples

The anti- Mircera NAb assay is a quasi-quantitative cell assay based on stimulation of ASE2 cells. This direct NAb assay is based on growth stimulation of AS-E2 cells induced by Mircera followed by the measurement of ATP using the CeiiTiter Glo® ATP luminescence assay. In the presence of neutralizing anti- Mircera antibodies, growth stimulation is diminished or stopped, depending on the antibody concentration.

Table 2. Summary of test results

Item	Result
Screening assay	
Assay Sensitivity	630 ng/mL in pool matrix
Cut point determination	Plate specific cut point: Mean NC (% proliferation)*0.66
Titer precision	4-25 %
Definition of low and high positive control concentration	LPC: 700 ng/mL; HPC: 1200 ng/mL
Robustness (CV %)	Cell passage (2, 10 and 20): 0 - 8 % Assay time 94 - 98h: 0 – 6 %
Drug tolerance	6.25 ng/mL
Selectivity and Specificity	9 out of 20 HD samples false negative after 700 ng/mL spike -> 9 out of 9 HD samples positive after 1200 ng/mL spike 1 out of 19 CKD samples false negative after 700 ng/ml spike 5 out of 5 hemolytic samples false positive when unspiked 1 out of 5 lipemic samples false positive when unspiked 2 out of 5 lipemic samples false negative after 700 ng/mL spike -> 2 out of 2 lipemic samples positive at 1200 ng/mL spike
Intra-assay precision	NC: 1 %; LPC: 5 %; HPC: 3 %
Inter-assay precision	NC: 7 %; LPC: 7 %; HPC: 17 %
Plate homogeneity	CV of columns: 2 - 8 % CV of rows: 1 - 7 %
Positional effects	None (CV: 2 – 6 %)
Stability of analyte in matrix	Stable for up to 4 freeze/ thaw cycles, up to 24h at RT, up to 24h at 4°C
Confirmatory assay (see validation report 13ROC005)	
Cut point determination	Plate specific cut point: Mean NC (% proliferation)*0.31
Intra-assay precision	NC: 2 %
Inter-assay precision	12 %
Robustness (CV %)	Cell passage (2, 10 and 20): 9 – 19 % Assay time 94 - 98h: 1 – 3 %

REPORT NO. 1062977. Validation of a cell-based assay for the determination and confirmation of neutralizing antibodies against EPO in human serum samples

Table 3. Summary of test results

Item	Result
Screening assay	
Assay Sensitivity	121 ng/mL
Cut point determination	Plate specific cut point: Mean NC (% proliferation)*0.77
Titer precision	2-19 %
Definition of low and high positive control concentration	LPC: 200 ng/mL; HPC: 400 ng/mL
Robustness (CV %)	Cell passage (2, 10 and 20): 6 - 18 % Assay time 94 - 98h: 0.2 – 12 %
Drug tolerance	6.25 ng/mL
Selectivity and Specificity at 200 ng/mL	0 false positive out of 20 healthy donor samples 7 false positive out of 20 CKD samples 1 false positive out of 5 lipemic samples 5 false positive out of 5 hemolytic samples
Intra-assay precision	NC: 1 %; LPC: 7 %; HPC: 9 %
Inter-assay precision	NC: 10 %; LPC: 15 %; HPC: 19 %
Plate homogeneity	CV of columns: 1 – 18 % CV of rows: 1 – 14 %
Positional effects	None (CV: 2 – 5 %)
Stability of analyte in matrix	Stable for up to 4 freeze/ thaw cycles, up to 24h at RT, up to 24h at 4°C
Confirmatory assay	
Cut point determination	Plate specific cut point: Mean NC (% proliferation)*0.31
Intra-assay precision	NC: 2 %
Inter-assay precision	12 %
Robustness (CV %)	Cell passage (2, 10 and 20): 9 – 19 % Assay time 94 - 98h: 1 – 3 %

Pharmacokinetics in the target population

Study NH19707

Study NH19707 was designed to determine the starting dose of IV Mircera in paediatric patients (aged 5-17 years) with anaemia associated with CKD on HD when switching from stable maintenance treatment with epoetin alfa, epoetin beta or darbepoetin alfa and to demonstrate changes in Hb over time in response to different doses of Mircera. The study also aimed to evaluate the PK of Mircera in paediatric patients.

Population PK model

Table 4. Summary of the studies included in the analysis

Study	Phase	Route	Treatment setting	Total number of patients	Number of Patients with PK data	Target population	Number of patients on Peritoneal dialysis
BA16260	2	sc	Correction	61	59	On dialysis	21, 19 with PK data
BA16528	2	sc	Correction	65	65	Not on dialysis	0
BA16736	3	iv	Correction	165	135	On dialysis	3 with PK data
BA16739	3	iv	Maintenance	223	122	On dialysis	0
BA16740	3	sc	Maintenance	190	143	On dialysis	28, 11 with PK data
NH19707	2	iv	Maintenance	64	63	On dialysis	0

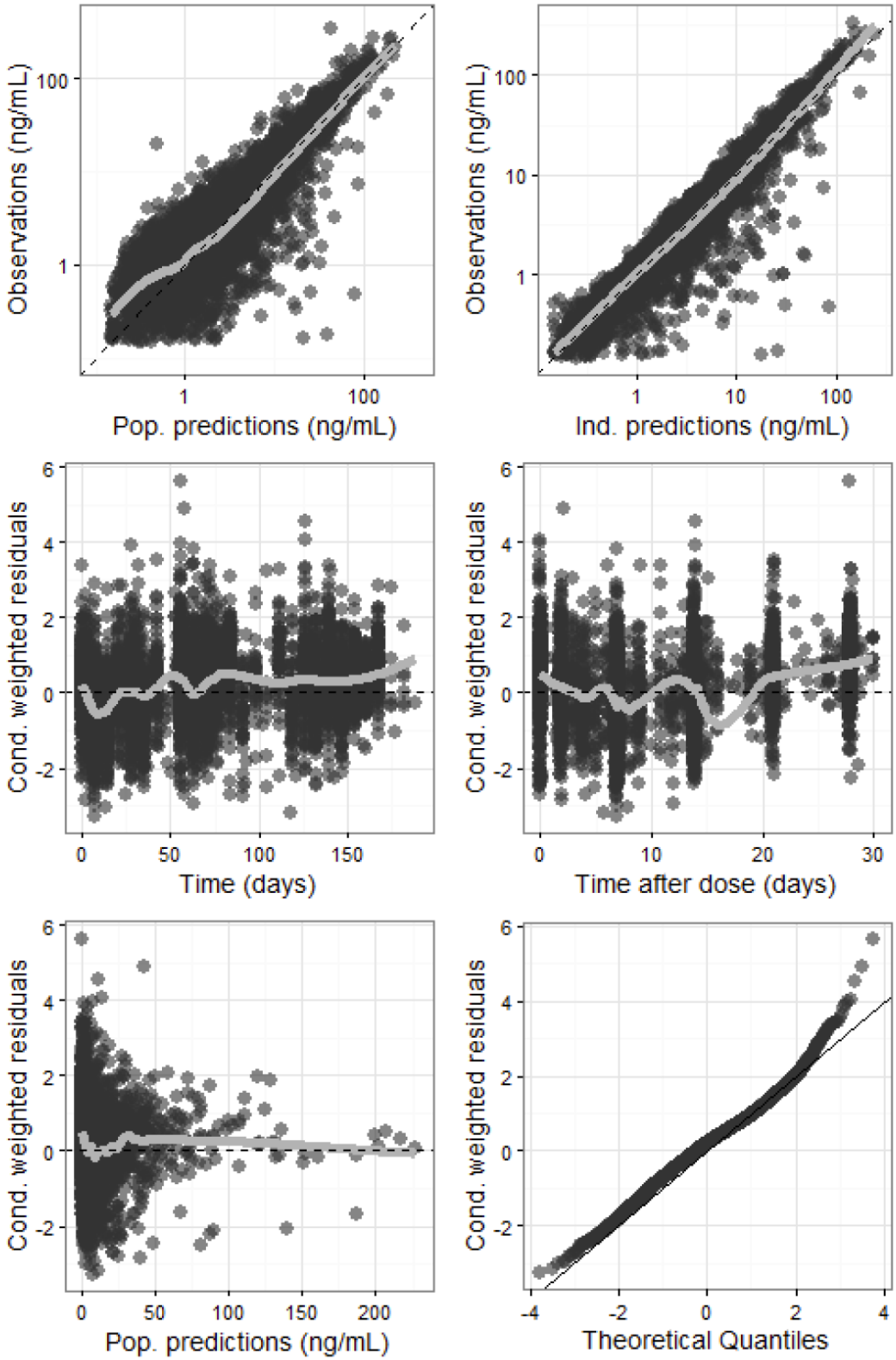
iv: intravenous; sc: subcutaneous.

A full model (ROCH1061b31) included effects of body weight and age on both CL and V. The effect of age on CL was removed during the backward deletion step, the resulting model (ROCH1061b34) was the final model. Its parameter estimates are recorded in Table 5. Parameters estimates were consistent to those found during the Phase 3 analysis, especially CL estimated at 0.74 L/day versus 0.75 L/day. V and F were lower 3.5 L and 0.33 respectively compared to Phase 3 estimates (4.7 L and 0.39). The estimates of body weight effects on CL and V were higher compared to previous estimates: 0.76 versus 0.57 and 0.61 versus 0.44. The derived ka value was 0.41 /day, lower by two-fold than the Phase 3 estimates. This may be explained by the alternative parameterization used here. Diagnostic plots presented in Figure 2 were good without major trend in residuals versus time or population predictions.

Table 5. Parameter estimates of the final PK model ROCH1061b34

Parameter	Unit	Estimate	SE	RSE (%)	Variability (%)	Shrinkage (%)
Fixed Effects						
CL	L/day	0.738	0.0231	3		
V	L	3.46	0.143	4		
Ka-Ke	/day	0.198	0.0616	31		
F		0.326	0.0200	6		
Random Effects (variance)						
CL		0.202	0.0317	16	45	7
V		0.135	0.0242	18	37	16
Covariance CL-V		0.111	0.0274	25	correlation 0.68	
Inter occasion variability (variance)						
CL		0.0160	0.00344	22	13	
Covariate effects						
Body weight on CL		0.761	0.0665	9		
Body weight on V		0.612	0.0686	11		
Age on V		0.232	0.0383	17		
Residual variability (variance)						
Proportional		0.147	0.00726	5	38	
Additive		1.02	0.119	12		

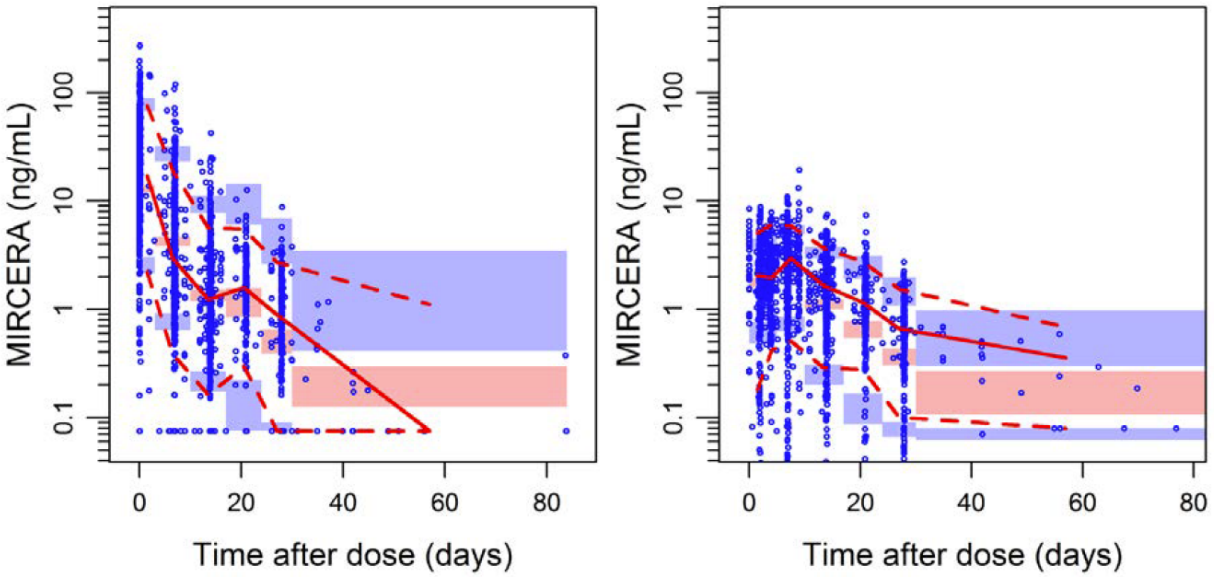
SE: standard error; RSE%: relative standard error.



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

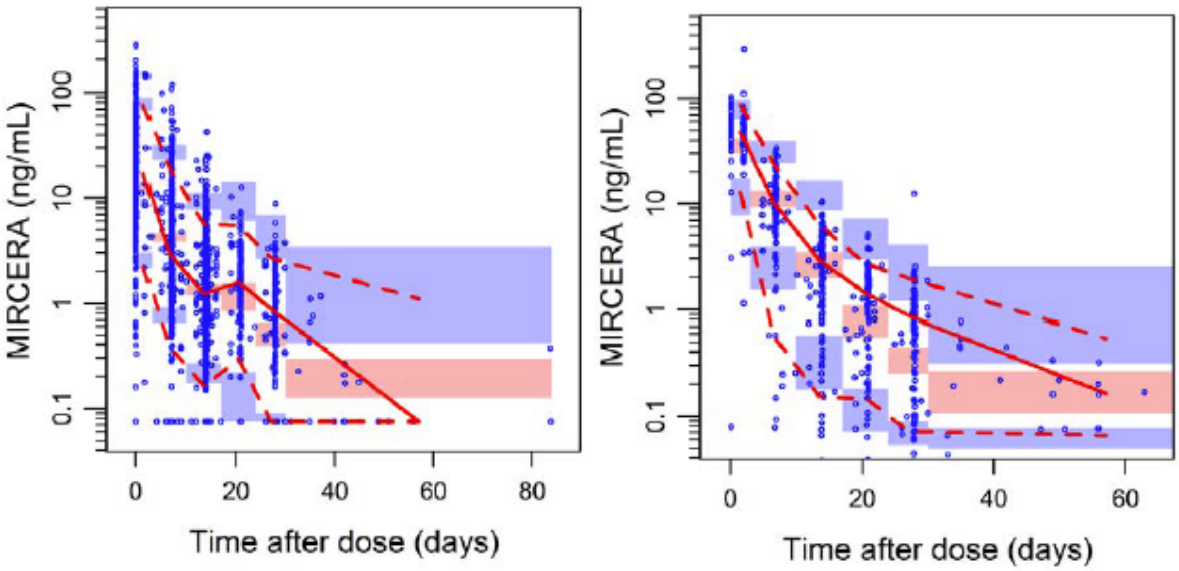
Figure 2. Diagnostic plots of the final PK model

Model qualification was performed using pcVPC in adult patients receiving Mircera iv, adult patients receiving Mircera sc (Figure 3) and paediatric patients receiving Mircera iv (Figure 4). The central tendency and the variability were well captured by the model. There was a slight tendency towards under prediction with the sc route of administration. In adults, the observed and the simulated data reflect the variety of dosing intervals: every 1, 2, 3 or 4 weeks. This assessment of the model predictive performance qualified its use to perform the PK/PD analysis and exploratory simulations e.g. investigating sc administration of Mircera.



Blue dots: observed data, dashed red lines: 5th and 95th percentiles of observed data, red line: median of observed data, red area: 90% prediction interval of the simulated medians (1000 replicates), blue areas: 90% prediction interval over 1000 replicates of the 5th and 95th percentiles of simulated data.

Figure 3. Model qualification (pcVPC) of final PK model in adult patients receiving Mircera iv (left panel) and Mircera sc (right panel)



Blue dots: observed data, dashed red lines: 5th and 95th percentiles of observed data, red line: median of observed data, red area: 90% prediction interval of the simulated median (1000 replicates), blue areas: 90% prediction interval over 1000 replicates of the 5th and 95th percentiles of simulated data.

Figure 4. Model qualification (pcVPC) of final PK model in adult (left panel) and paediatric (right panel) patients receiving Mircera iv

Study NH19708

Study NH19708 was designed to determine the optimal starting dose of SC Mircera for paediatric patients (aged 3 months-17 years) on the maintenance treatment of anemia with CKD on dialysis or not yet on dialysis. The study also aimed to evaluate the PK and the PD of Mircera in paediatric patients.

Population PK model

Table 6. Summary of the adult studies and number of patients contributing PK and Hb data into the analysis

Study	Phase	Route	Treatment setting	Number of Patients with PK and Hb data	Number of patients not on dialysis	Number of patients on Peritoneal dialysis	Number of patients on hemodialysis
BA16260	II	SC	Correction	59	-	19	40
BA16528	II	SC	Correction	65	65	-	-
BA16736	III	IV	Correction	135	-	3	132
BA16739	III	IV	Maintenance	122	-	-	122
BA16740	III	SC	Maintenance	143	-	11	132

IV: intravenous; SC: subcutaneous.

Table 7. Summary of the paediatric patients studies and number of patients contributing PK and Hb data into the analysis

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

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

Table 8. Summary of the real world data and number of patients contributing haemoglobin data into the analysis

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

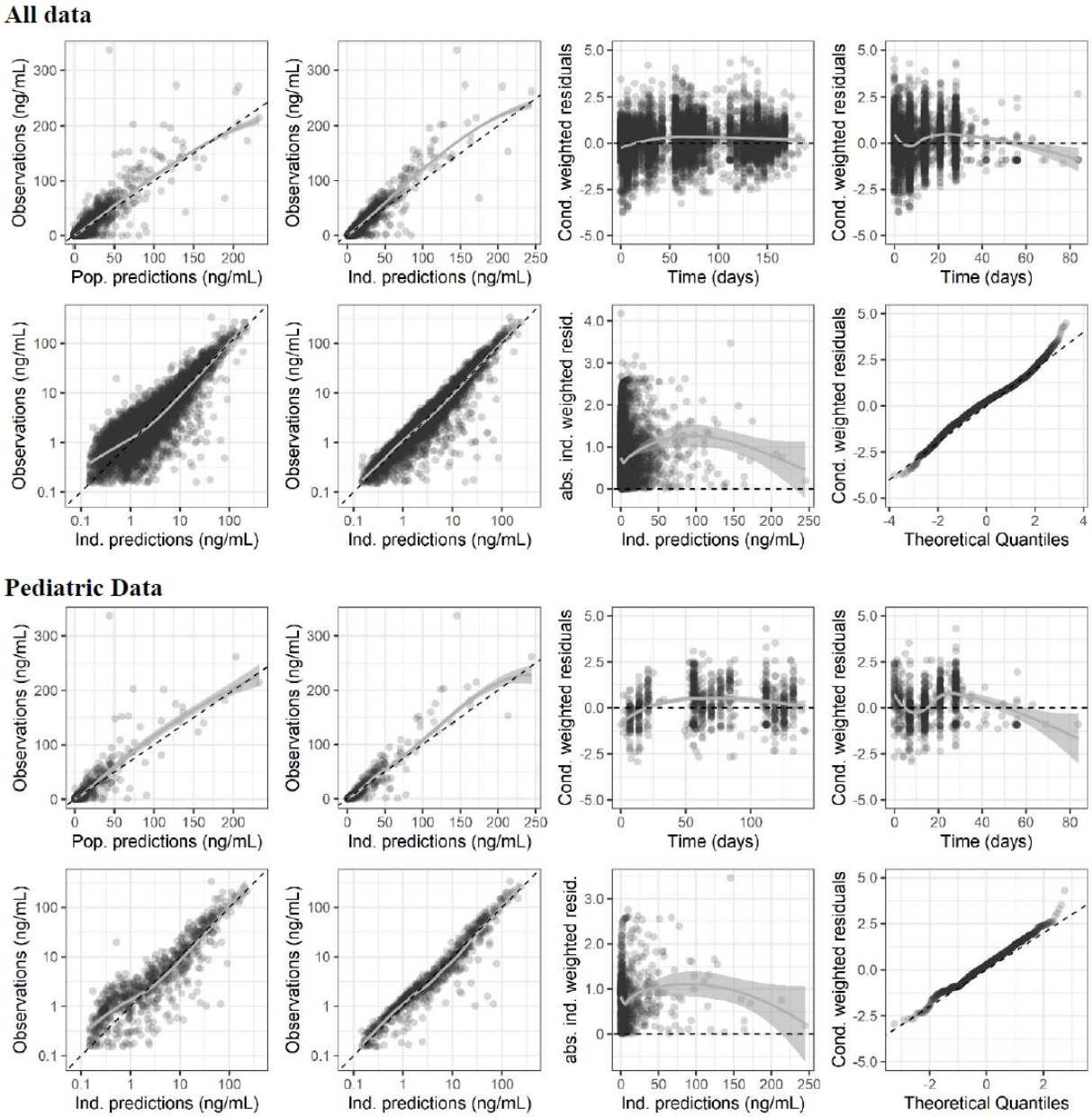
IV: intravenous; SC: subcutaneous. Patients with more than one Route of administration or with missing Route of administration were excluded.

The previous final model ROCH1061b34 was used as a starting point. It was first fitted as is allowing the re-estimation of all fixed and random effects. Then, the paediatric effect on the SC bioavailability was tested as a flag being paediatric yes/no or by testing an age effect on it. The model having paediatric flag (Ped Frel) was selected as it resulted in a larger drop in objective function value. Table 9 present the population PK parameters estimates of the re-fitted historical final model after adding paediatric effect on the SC bioavailability. All parameters were very well estimated with parameters consistent with the previous analysis.

Table 9. Parameter estimates of the final PK model Ped Frel

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

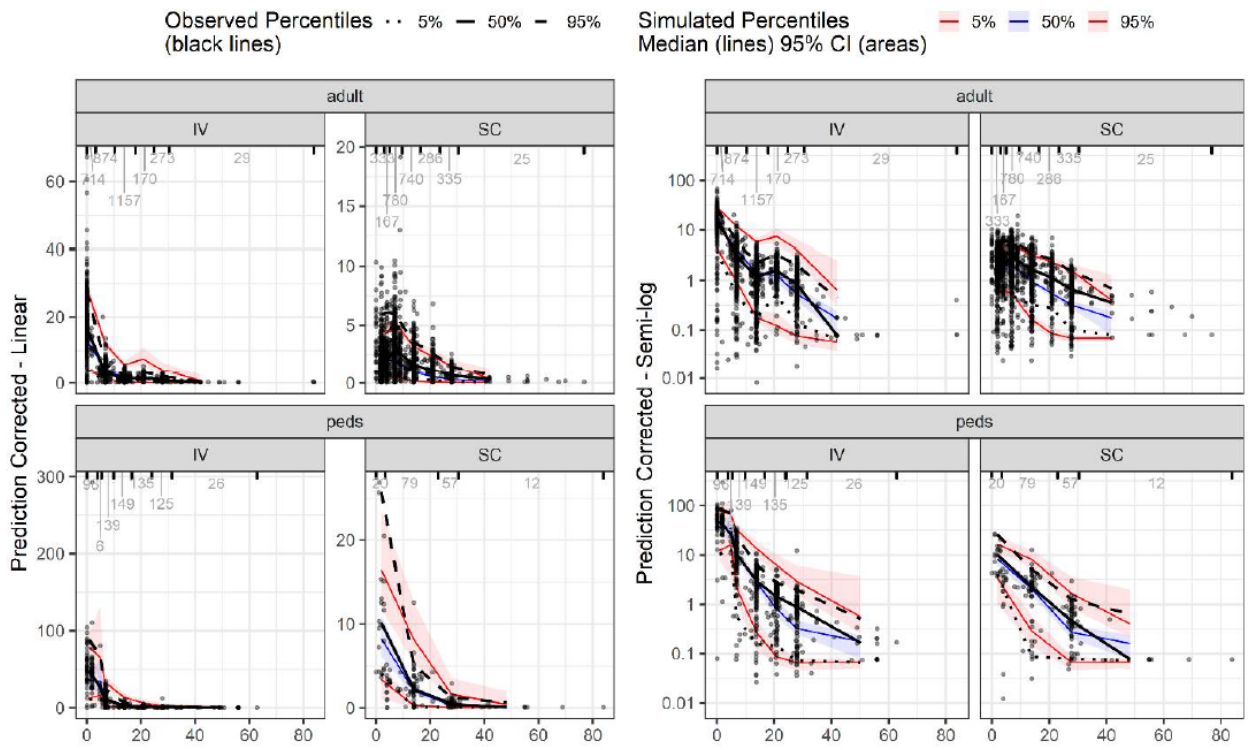
RSE%: relative standard error. nParm =14, Nobs 6727, NSub 627, EpsShrinkage 0.14842, Condition 13.24



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

Figure 5. Diagnostic plots of the final PK model overall and in paediatrics

Model qualification was performed using pcVPC stratified by adult and study and it is presented in Figure 6. The central tendency and the variability in paediatric patients were overall well captured by the model for both routes of administration with some tendency towards under prediction at low concentrations. This assessment of the model predictive performance qualified its use to perform the sequential PK/PD analysis in paediatric patients.



The gray numbers on the top of each panel are the N of observed data in each bin.
The vpc is shown with a linear axes on the left and a semi-log (log y, linear x) on the right.
Source: GOF_PK.R

Figure 6. Model qualification (pcVPC) of final PK model stratified route for adult and paediatric patients

Immunogenicity

Study NH19707

In Study NH19707, blood samples to measure anti-Mircera and anti-EPO antibodies were collected on Day 1 (before the first drug administration), at Week 13 and at final visit of the core period (Week 21), and at final visit (Week 73) of the safety extension period.

No patients tested positive for anti-Mircera and anti-EPO antibodies at any time during the study, including the safety extension period. For this reason, the present summary of clinical pharmacology studies does not include any information about correlation between immunogenicity and PK, PD, safety, or efficacy.

Study NH19708

In Study NH19708, blood samples to measure anti-EPO and anti-Mircera antibodies were collected on Day 1 (before the first drug administration), at Week 9 and at final visit of the Core period (Week 21), and at final visit (Week 45) of the safety extension period.

A total of 131 samples were tested for anti-Mircera and anti-EPO antibodies. Two samples tested positive for anti-Mircera antibodies and four samples tested positive for anti-EPO antibodies in 2 patients.

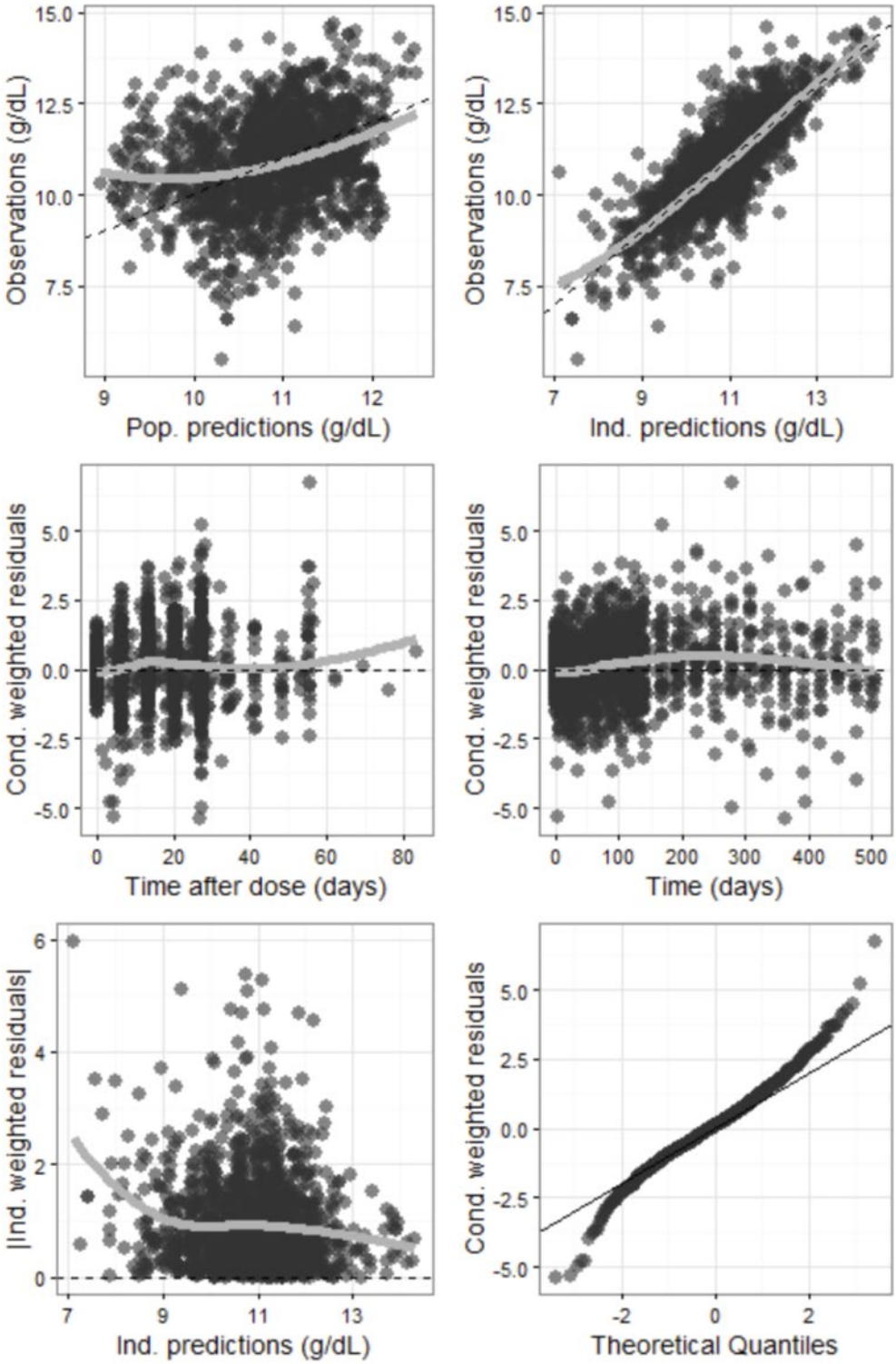
However, in both of these patients, there was no evidence of PRCA or other safety concerns. Both patients continued to show good Hb response to Mircera treatment. Hb and Mircera doses were stable. The PK parameters in these 2 patients were not different from the rest of the patients in Study NH19708.

2.3.3. PK/PD modelling

Study NH19707

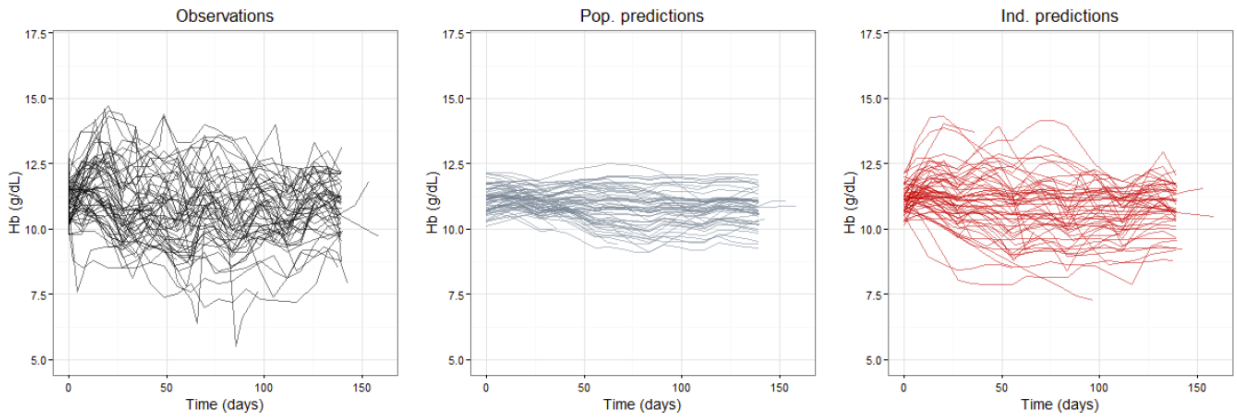
The PK/PD dataset included EBEs of PK parameters obtained with the final PK model. It consisted of the same patient population as the PK dataset and comprised 14366 data points: 12786 from adults and 1580 from paediatrics.

Parameters estimates of the final PK/PD model are recorded in Table 10. Fixed effects were fixed to Phase 3 estimates. There was a full matrix of random effects with strong correlation particularly between Smax and SC50 i.e., 0.92, all covariance terms were well estimated. Interindividual variability in PK/PD parameters was found consistent with Phase 3 estimates, with low shrinkage. The estimate of the previous ESA dose effect on SC50 i.e., 0.389 was consistent with the Phase 3 estimate i.e., 0.303. Diagnostic plots in paediatric and adult patients presented in Figure 7 and Figure 8 showed minor trends in population predictions.



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

Figure 7. Diagnostic plots of the final PK/PD model in paediatric patients



Pop. predictions: population predictions; Ind. Predictions: individual predictions.

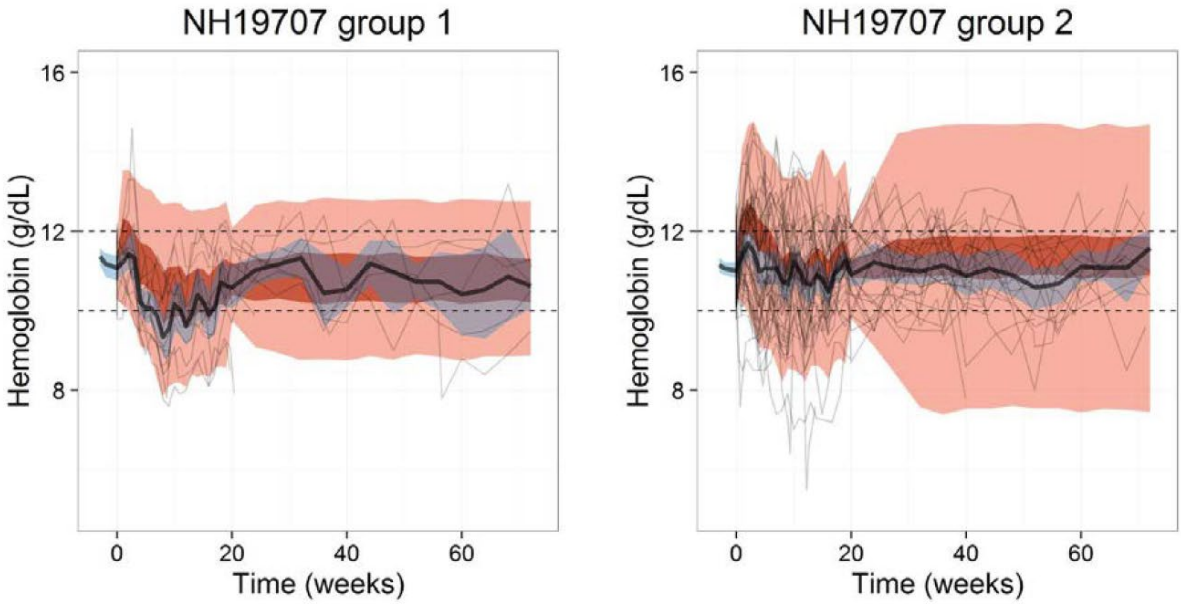
Figure 8. Observations, population and individual predictions obtained with model ROCH1061c56 in paediatric patients

Table 10. Parameter estimates of the final PK/PD model ROCH1061c56

Parameter	Unit	Estimate	SE	RSE (%)	Variability (%)	Shrinkage (%)
Fixed Effects						
Smax		0.425 fixed				
SC_{50}	ng/mL	0.898 fixed				
LS	day	61.3 fixed				
Hb_0	g/dL	9.3 fixed				
Random Effects (variance)						
Smax		2.03	0.130	6.4	142	15
SC_{50}		4.95	0.343	6.9	222	16
LS		0.283	0.0200	7.1	53	16
Hb_0		0.0596	0.00425	7.1	24	25
Covariate effects						
ESA dose on SC_{50}		0.389	0.0234	6.0		
Body weight on Hb_0		0.144	0.0102	7.1		
Residual variability (standard deviation)						
Additive	g/dL	0.583	0.00116	0.2		

SE: standard error; RSE%: relative standard error.

Model qualification in paediatric patients was performed using VPC stratified by dose group. Results are presented in Figure 9. In both panels, model-based simulations well captured the variability in the data; the observed mean Hb time course (and its confidence interval) was also fairly well captured by the prediction interval of the simulated mean in both treatment groups. During the first 8 weeks the prediction interval was on some occasions slightly above the confidence interval, however the overall shape of the observed mean and especially the fluctuations during the evaluation period were well captured by the model in both groups. Further model qualification was performed using PPC stratified by dose group. Table 11 demonstrates the qualification of the simulation framework on three endpoints: mean change from baseline in Hb, occurrence of Hb>12g/dL during the evaluation period and doses at the end of the evaluation period. All prediction intervals included the corresponding observed value in NH19707 for each treatment group and each endpoint of interest. This assessment of the model predictive performance qualified its use to perform exploratory simulations e.g. investigating sc administration of Mircera.



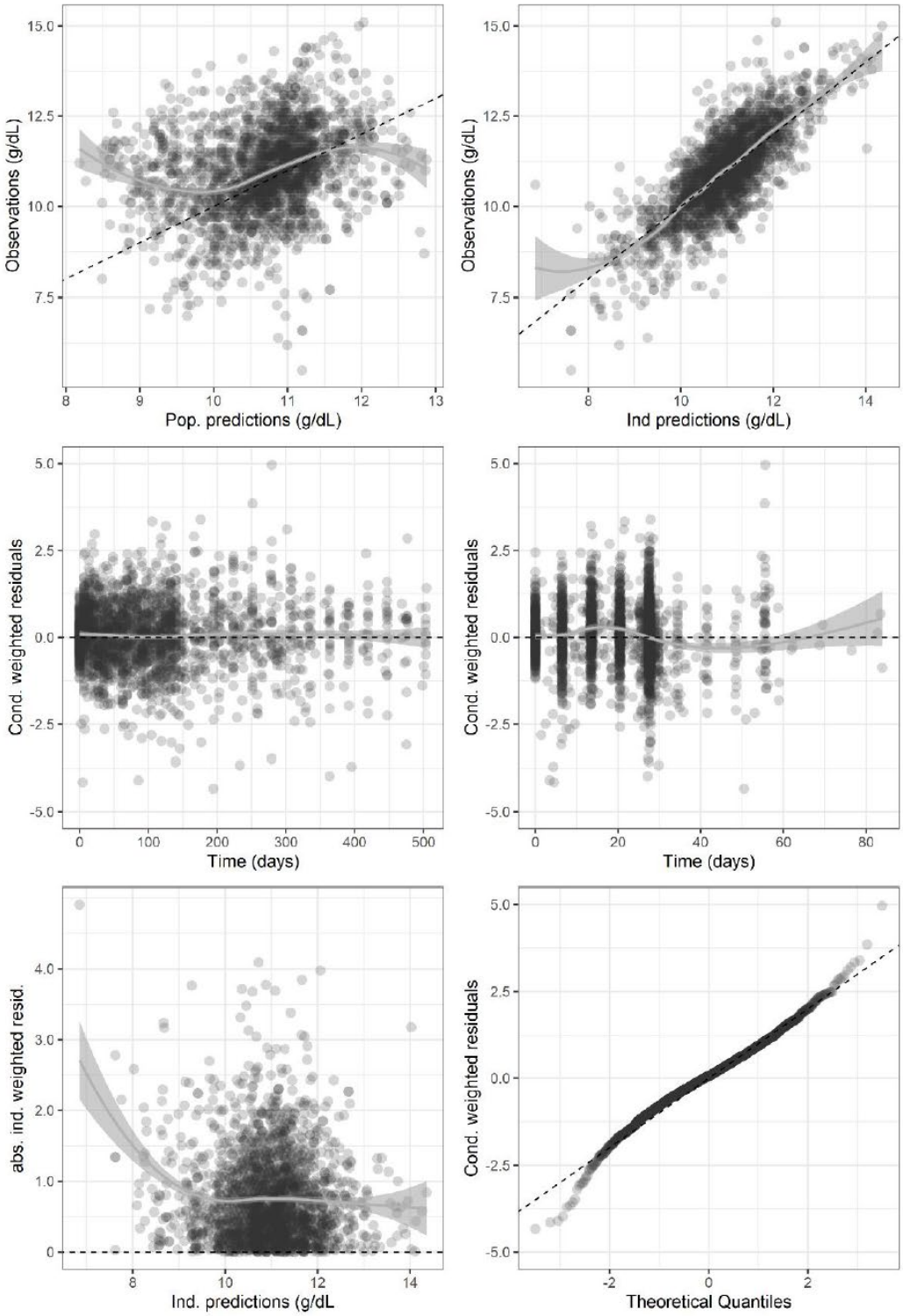
Thin black line: observed data; Black thick line: mean of observed data; Blue area: 95% confidence interval of the mean of observed data; Dark red area: 95% prediction interval of the simulated mean (200 replicates); Light red area: overall 95% prediction interval of simulated data (200 replicates); Dashed lines: target range of Hb [10;12] g/dL.

Figure 9. Model qualification (VPC) of final PK/PD model in paediatric patients from study NH19707 receiving Mircera iv

Table 11. Model qualification (PPC) of final PK/PD model in paediatric patients from study NH19707 receiving Mircera iv

Dose group	Simulations (metric, 95% prediction interval)	Observations
	Primary endpoint: mean change in Hb between baseline and evaluation periods (g/dL)	
1	-0.66 [-1.21;-0.11]	-0.74, 95%CI[-1.32;-0.16]
2	0.07 [-0.22;0.43]	-0.09, 95%CI[-0.45;0.26]
	Patients experiencing at least once Hb>12 g/dL during the evaluation period (%)	
1	21 [5;45]	16.7
2	49 [36;66]	36.1
	Median dose at end of evaluation period (µg)	
1	68 [36;127]	64
2	84 [60;123]	120

Study NH19708



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

Figure 10. Diagnostic plots of PK/PD model in paediatric patients

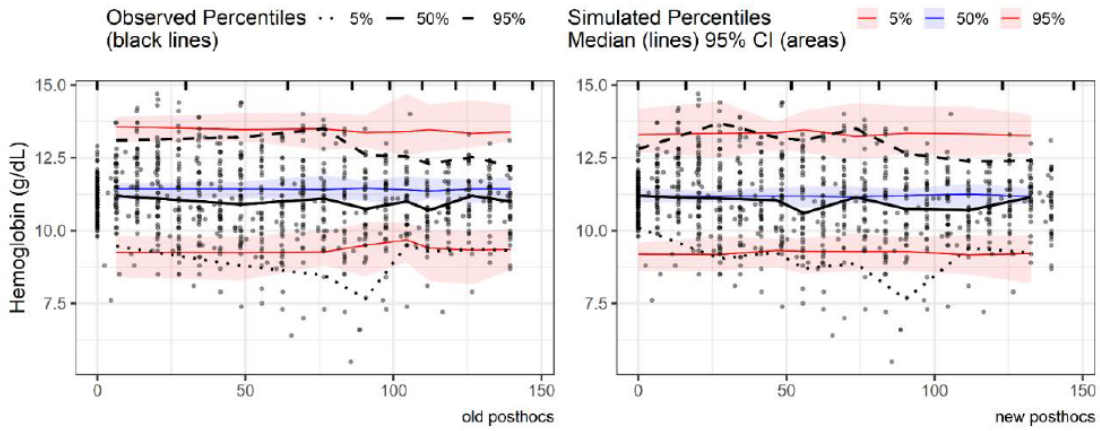
The estimate of the previous ESA dose effect on SC50, i.e. 0.295, was slightly lower than the previous estimate of 0.389. Hb0 was 7% and 14% lower in peritoneal dialysis and hemodialysis paediatric patients, respectively. While LS was 18% and 38% shorter in peritoneal dialysis and hemodialysis patients, respectively.

Table 12. Parameter estimates of the final PK/PD model

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

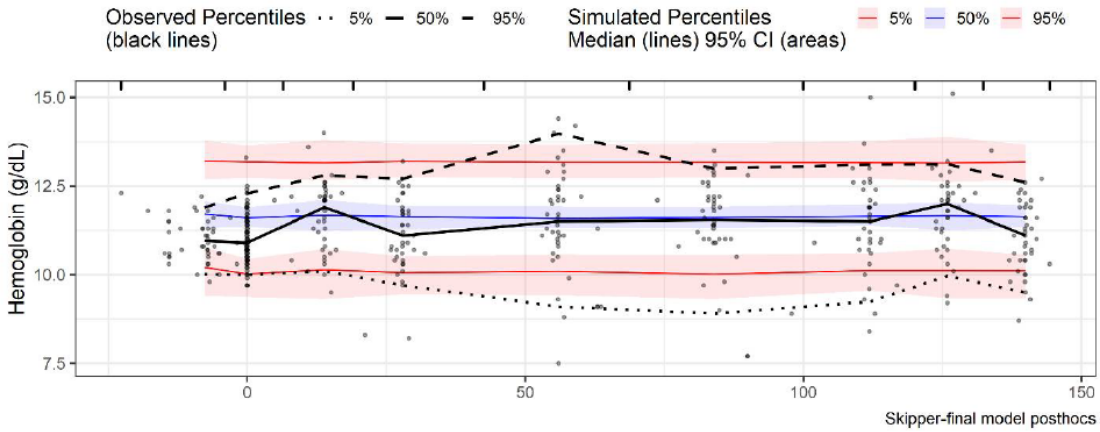
SE: standard error; RSE%: relative standard error. nParm = 18, nObs = 2128, nSub = 103, -2LL = 5593.817 (QRPEM)
EpsShrinkage = 0.01843, Condition number = 298.0486
Source: Phoenix model peds_estim_hb0_LS_dialysishb0_LS

Model qualification in paediatric patients was performed using EBEs' based visual predictive checks (VPC) including dose titration and are presented in Figure 11 for NH19707, and Figure 12 for NH19708.



Source: ts_read_data_vpc_ebe_dolphin.r

Figure 11. Model qualification (VPC) of final PK/PD model in paediatric patients from study NH19707 receiving Mircera iv (comparison of the previous posthocs – left and the new posthocs – right)



Source: ts_read_data_vpc_ebe_skipper.r

Figure 12. Model qualification (VPC) of final PK/PD model in paediatric patients from study NH19708 receiving Mircera SC

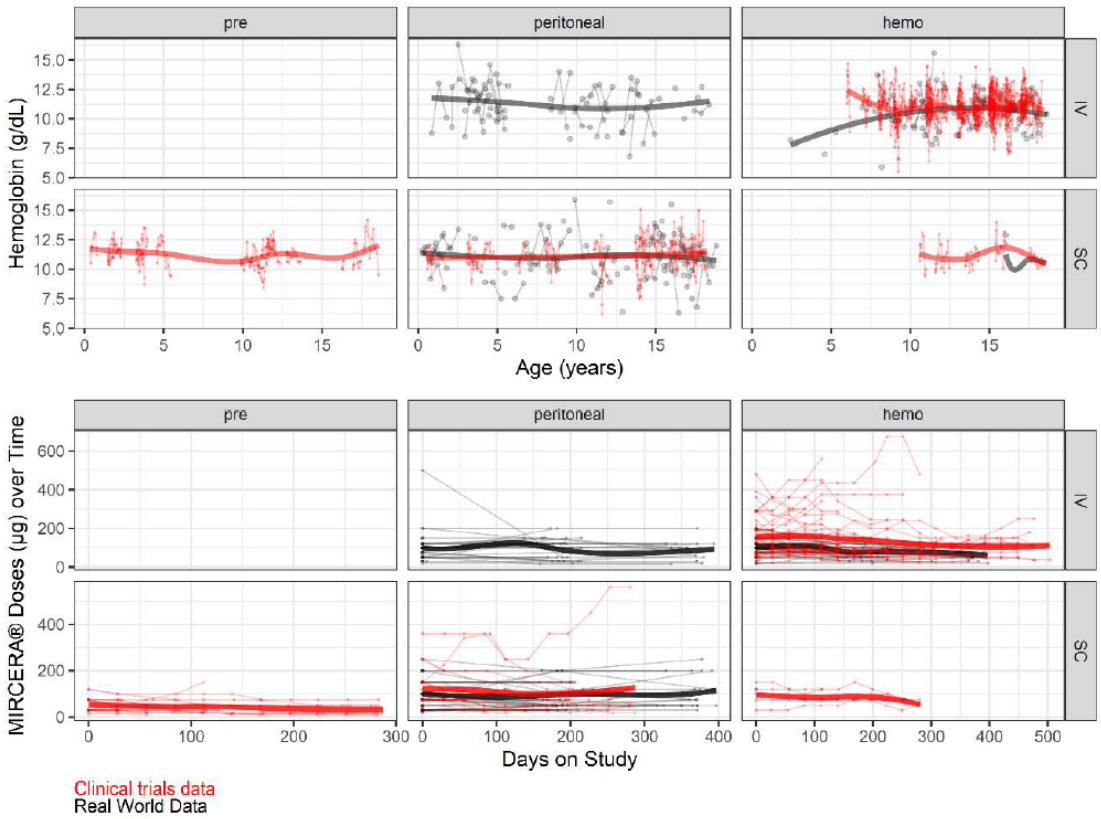
Study MH40258

Study MH40258 was a non-interventional study secondary data use (NIS SDU) and voluntary post-authorization safety study (PASS) that collected data elements of patients who received Mircera. The data were extracted from two existing registries within the IPDN (International Paediatric Peritoneal Network [IPPN] and International Paediatric Haemodialysis Network [IPHN]). The data was collected for a period from 1 January 2007 to 30 June 2021 for IPPN and from 1 January 2013 to 30 June 2021 for IPHN. Study MH40258 did not provide PK data for the model-based analyses but contributed real world data from the IPDN registry. The data from Study MH40258 (i.e., Hb levels and Mircera dose time courses) was used to perform visual comparison with the clinical trials data and PK/PD model predictions.

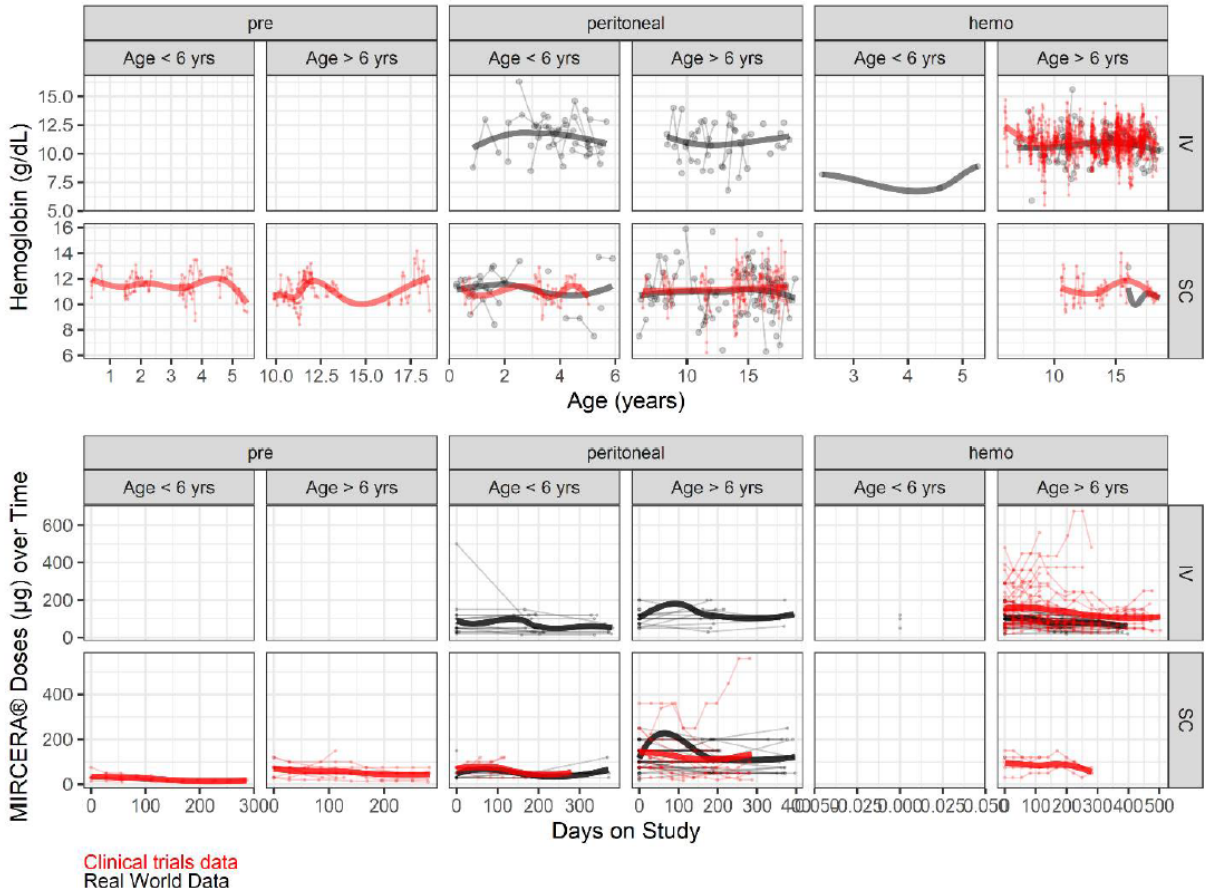
Data was extracted from all paediatric patients below 18 years of age on PD or HD included in the IPPN and IPHN registries with at least one observation while being treated with Mircera.

As shown in Figure 13, the clinical trial data spanned the same ranges and were similar to those collected from the IPDN registry, which provided additional evidence that the clinical trial data could be reproduced in clinical practice.

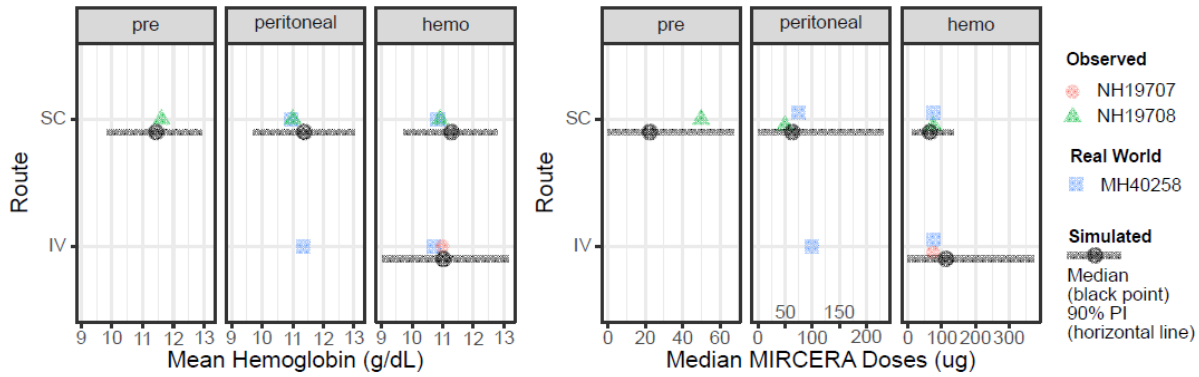
(Overall-Longitudinal)



(Split by Age group-Longitudinal)



(Focus on Endpoints of interest)



Source: rwd.r

Figure 13. Real world data compared to clinical data (longitudinal, by age and focused on endpoints) and to clinical data and PK/PD model predictions (endpoints of interest)

2.3.4. Discussion on clinical pharmacology

The characterization of the clinical pharmacology properties of Mircera in paediatric patients after IV and SC administration has been conducted in the current analysis based on the experimental evidence collected in studies NH19707, NH19708 and MH40258.

The modelling strategy used by the MAH is endorsed, since it re-uses the structural PK and PK/PD model definition established in the adult population and the clinical evidence collected in paediatric patients is pooled together with the adult data to re-evaluate its predictive performance. In addition, the Applicant conducted a staggered approach, since first IV data was analysed and secondly, PK evidence after SC administration was incorporated. A similar approach was applied to characterize the time course of haemoglobin over time after IV and SC in paediatric patients.

The final population PK model developed with data from studies NH19707 and NH19708 and adult data may overall capture the observed data. However, the provided pcVPC for adult data following SC administration, shows that the model excessively underpredicts the median of the data, which indicates that the estimated bioavailability of 31% may be biased and the true SC bioavailability for adults is higher than this estimate. Furthermore, the SmPC states that the SC bioavailability for adult CKD patients was 54% and 62% for non-dialysis and dialysis patients, respectively, which is almost 2-fold higher than the estimate from the popPK model. An updated version of the population PK model has been developed, which includes a specific volume of distribution for adult patients treated with Mircera SC. However, the effect of the route of administration in pediatric patients was not significant, possibly due to the lack of sufficient experimental evidence. The updated version improves the model performance based on the VPC. However, no differences in the volume of distribution could be attributed to the type of dialysis. Despite the SmPC reports different SC bioavailability based on the type of dialysis, the population PK model did not identify such effect as significant. In addition, a relevant aspect required clarification since a 2.18-fold increase on SC bioavailability was estimated in paediatric patients compared to adult patients, considering that a higher exposure in paediatric subjects may be relevant in terms of safety concerns. Since no definitive and clear exposure-safety relationship has been established, dose selection in pediatric patients is based under the assumption that similar exposure should be achieved between pediatric and adult patients. In this regard, the MAH has provided the observed concentrations data for pediatric and adult patients, showing similar trend among both populations. Therefore, no need for a model-based evaluation of the exposure is required.

The PK/PD framework previously developed in the adult population has been applied to characterize paediatric observations. Final PK/PD parameter estimates were consistent with the estimated values in adult patients and therefore, no relevant differences in terms of system-related parameters (LS and Hb0) were observed. The use of fixed drug-related parameters may be justified based on the large evidence from adult data and to reduce the likely confounding effect on the estimation of the covariate effects. The join PK/PD model with adult and paediatric data was able to characterize the median tendency and the overall variability. The external evaluation of the PK/PD relationship using real world data (MH40258) demonstrated the adequacy of the modelling structure to satisfy the observed behaviour.

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology properties of Mircera in paediatric patients after IV and SC administration have been characterized. Some aspects have not been fully clarified, however, since no definitive and clear exposure-safety relationship has been established, and dose selection in pediatric patients is based under the assumption that similar exposure should be achieved between pediatric and adult patients, a model-based evaluation of the exposure is no longer being required.

The overall strategy and the results provided are overall acceptable.

2.4. Clinical efficacy

The efficacy is based on the extrapolation from adult data, two dose finding studies (NH19707 and NH19708) and a popPK model. Results from paediatric registry study MH40258 are considered supportive for the claimed indication.

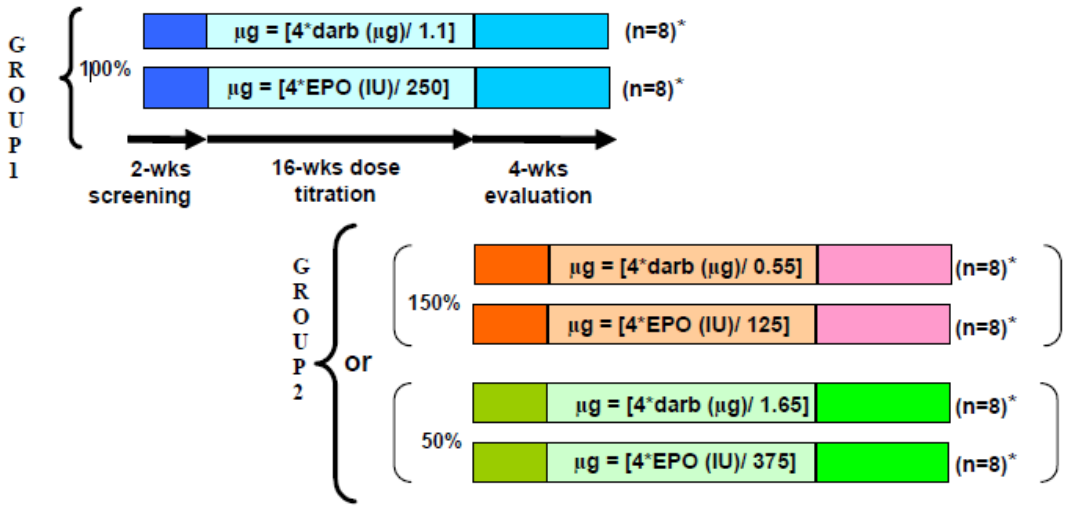
2.4.1. Main studies

Study NH19707: a phase II, dose-finding study, open-label, multicenter, multiple dose study of Mircera administered once every 4 weeks intravenously (IV) for 20 weeks in paediatric patients with CKD receiving haemodialysis who switched from other erythropoiesis-stimulating agent (ESAs) (epoetin alfa/beta or darbepoetin alfa).

Methods

After the first administration of methoxy polyethylene glycol-epoetin beta (Mircera), dose adjustments were permitted to maintain target Hb levels, which were measured once a week during the core study period. The evaluation period for Hb levels was Week 17-21. Patients who completed the 20 weeks of treatment and who adequately maintained Hb levels were eligible to enter an optional 52-week safety extension period with the same dosing frequency.

In this study, the protocol foresaw different groups with different conversion factors related to their previous ESA dose to find the optimum Mircera starting dose. The first group comprised patients who started with an intermediate conversion factor dose (Group 1 hereinafter). If this intermediate conversion factor proved inadequate, a second group (Group 2) was enrolled for treatment with a higher or lower conversion factor dose. The first 16 patients were enrolled in Group 1. After 16 patients had completed at least 16 weeks of treatment, a preliminary assessment of the safety and efficacy of Mircera was made.



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

Figure 14. Core study design

Study participants

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 8 weeks before enrolment).

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

Key inclusion criteria:

- Paediatric patients 5 - 17 years old (in Russia only: 12−17 years old) with clinically stable chronic renal anaemia
- Haemodialysis treatment for at least 8 weeks
- Body weight ≥10 kg
- Adequate haemodialysis: urea reduction ratio (URR) of ≥ 65% or Kt/V ≥ 1.2 for patients on three-times weekly haemodialysis. Patients with fewer or with more haemodialysis 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.
- 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.

Key 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)
- Haemolysis
- 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 haemodialysis 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 was injected iv by trained healthcare professional once every four weeks during the study (4 doses during the titration period and one dose during the evaluation period).

The conversion factors tested in Group 1 were directly derived from experience in adults receiving Mircera intravenously and from the results of a published study of darbepoetin alfa conducted in paediatric patients (Warady et al 2006). As the patients included in this study were already on stable maintenance doses of an ESA prior to conversion to Mircera, and assuming a linear relationship across dose ranges, the use of a conversion factor resulted in a Mircera dose that was proportional to the previous ESA dose, thus correcting for the higher weight-adjusted dose requirements in paediatric patients.

Table 13. 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 14. 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

[a] 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 (see Section 3.4.2)

Dose adjustments could be performed during the entire study (core study period and safety extension period) (Table 15). 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.

Table 15. Mircera Dose adjustments

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

Mircera was provided in sterile injectable solution in single-use pre-filled syringes. The pre-filled syringes were available in the following strengths:

30	50	75	120	200	µg/0.3 mL

360	µg/0.6 mL

All treatments (medications and medical procedures) were permitted before screening, during the screening period and throughout the 20-weeks treatment period except for: investigational medicinal product, other ESAs, red blood cell (RBC) transfusions (except for medical need), immunosupressive therapies known to exacerbate anaemia or intermittent treatment or dose change of medications known to influence Hb concentration. Supplemental iron was administered to prevent iron deficiency during the screening period and during study, and to maintain adequate iron parameters.

Objectives

The primary objectives 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 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

Outcomes/endpoints

Efficacy:

Primary Efficacy Endpoint

- Change in Hb concentration (g/dL) between the baseline period and the evaluation period (weeks 17-21)

Secondary Efficacy Endpoints

- Number of patients with an average Hb concentration during the evaluation period within ±1 g/dL of their baseline Hb
- Number of patients with an average Hb concentration during the evaluation period above, within or below the range of 10-12 g/dL
- Incidence of red blood cell (RBC) transfusions
- Change in reticulocyte count (x10000 /µL) between the baseline and evaluation periods

Exploratory Efficacy Endpoints

- Change in dose over time
- Change in dose between study start and evaluation period
- The rate of rise in Hb concentration during the titration

Pharmacokinetics:

Primary PK Parameters

- AUC0-tau and Cmax

Secondary PK Parameters

- Tmax and t1/2

Safety:

- Adverse events
- Laboratory parameters (iron parameters, hematology, blood chemistry, anti-erythropoietin antibody determination, dialysis adequacy)

- Growth parameters
- Vital signs (weight, blood pressure, heart rate)

Sample size

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 provide 80% 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

As per Protocol, 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.

Randomisation

Patients were enrolled to receive Mircera once every four weeks in sequential dosing groups; no randomization was performed. An Interactive Voice/Web Response System (IV/WRS) system was used to track the enrolment and to monitor the disposition of patients into four strata with respect to type of previous ESA treatment and age category. Enrolment of 12- to 17-year-old patients was closed earlier to ensure that a sufficient number of younger patients were included in the study.

Blinding (masking)

Not applicable, this was an open-label study.

Statistical methods

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

The following analysis populations were defined in the SAP:

- The intention-to-treat (ITT) population included all patients enrolled in the study.
- All patients who received at least one dose of the trial medication and had a safety follow-up were included in the safety 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.

- The Per-Protocol (PP) population includes all patients included in the safety population and who had no major protocol violations (patients with less than 3 Hb values during the evaluation period, patients who missed any administration of study medication at week 13 or week 17, patients who did not fulfill the inclusion criteria for Hb or iron levels, patients who fulfilled any of the exclusion criteria: hemoglobinopathies, hemolysis, overt gastrointestinal bleeding or RBC transfusion within 8 weeks before screening/during screening period)
- The Extension Patients Population is defined as all patients having signed the informed consent for the optional safety extension period.

Efficacy Analysis

The different Mircera conversion factor groups were summarized descriptively in an exploratory manner using summary statistics based on means, standard deviations and percentiles. Analyses were presented by dose group. The main subgroups of interest in this paediatric study were the age groups (based on age at study start, 5-11; 12-17 years) and previous ESA (epoetin alfa/beta; darbepoetin alfa), both of which were used for stratification.

The primary endpoint (change in Hb concentration between the baseline and evaluation periods), and one secondary endpoint (change in reticulocyte count) were 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. For patients with no recorded Hb during the evaluation period, the primary endpoint was missing. No imputation was made for missing values. If an RBC transfusion occurred, Hb values measured in the following 3 weeks were excluded; any Hb values recorded after a renal transplantation were censored.

The average Hb for the baseline and evaluation periods were used to classify each patient for the Hb-based secondary efficacy endpoints.

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.

PK and PD Analysis

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 noncompartmental methods using WinNonlin software (Phoenix 64, Pharsight Corporation, Mountain View, CA, USA). Actual sampling times were used for the calculation of PK parameters, except for all pre-dose time points, which were set to zero.

Results

Participant flow

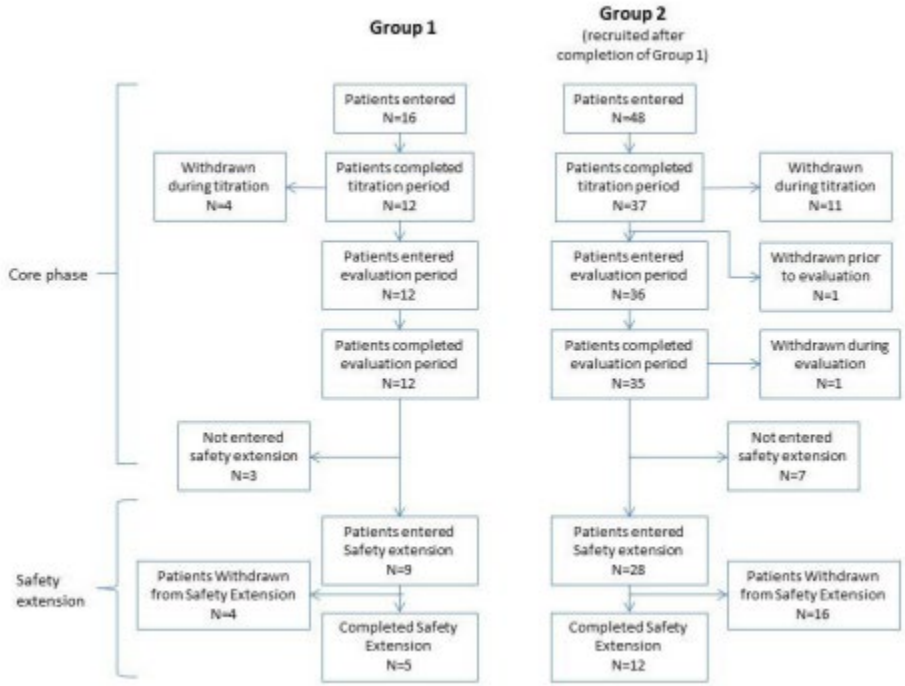


Figure 15. Patient disposition of study NH19707

A total of 112 patients were screened; of these 64 were enrolled (16 initially in Group 1 and then 48 in Group 2, following a preliminary analysis of Group 1). Among the 48 screening failures, 44 patients did not meet inclusion criteria, 3 patients did not sign ICF and 1 patient had a high likelihood of withdrawal (kidney transplantation planned).

Replacement of patients not completing at least 18 weeks of treatment lead to a total of 48 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.

During the core study period, 4 patients in Group 1 (25%) and 13 in the Group 2 (27%) withdrew from treatment. The most frequently reported reason for withdrawal was renal transplant (4 patients in Group 1 and 9 patients in Group 2). Of the two 'other' reasons one was due to liver transplant, the other because the department moved to another hospital. One patient in Group 2 died during the core study period of intracranial hematoma, considered not related to study drug (Table 16).

Table 16. Summary of Withdrawals (Core Period): ITT 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)

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

Baseline data

Patient Demographics

Overall, there were 34 male patients (53%), with a higher representation in Group 1 compared with Group 2 (Table 17).

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 youngest patient was 6 years old (see age distribution in Figure 16). The mean baseline body surface area (according to the Mosteller formula) was 1.14 and 1.24 in Group 1 and Group 2, respectively.

Median Z scores for height and pre-dialysis weight were negative in both groups (height: -1.07 and -1.67, respectively, for Group 1 and Group 2; weight -0.87 and -1.32, respectively), indicating, as expected in this patient population, under-developed, underweight patients compared with children of the same sex and age.

Table 17. Summary of Demographic Data NH19707: 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.

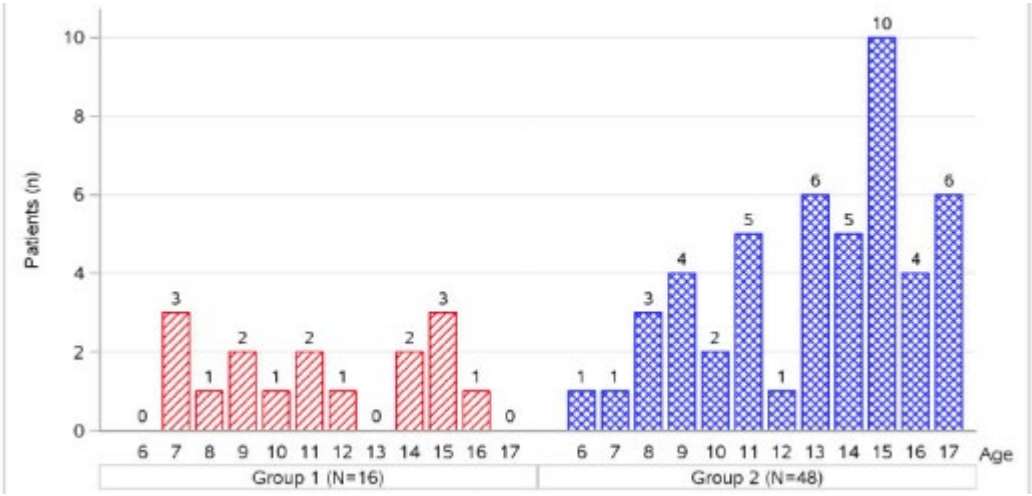


Figure 16. Age distribution at Baseline: ITT population

Baseline Laboratory Parameters

Median baseline haemoglobin levels were 11.2 g/dL in Group 1 and 11.1 g/dL in Group 2 (Table 18). Ferritin and calculated transferrin saturation levels were generally higher in Group 1 than in Group 2. Of note, overall, 12 patients (19%) had C reactive protein levels above 5 mg/L.

Table 18. Baseline Haemoglobin and Iron Parameters

Parameter Statistics	Group 1 (N=16)	Group 2 (N=48)	Total (N=64)
Hemoglobin [g/dL]			
n	16	48	64
Mean	11.26	11.08	11.12
Std Dev	0.496	0.493	0.496
Median	11.23	11.09	11.15
Q1-Q3	11.1:11.7	10.7:11.4	10.7:11.4
Min-Max	10.2:12.1	10.1:12.1	10.1:12.1
Ferritin [ug/L]			
n	16	47	63
Mean	702.97	405.41	480.98
Std Dev	392.285	352.789	382.907
Median	746.25	328.00	373.45
Q1-Q3	371.5:915.3	139.0:588.5	172.8:762.0
Min-Max	173.0:1570.0	34.0:1525.8	34.0:1570.0
Transferrin Saturation Calculated [%]			
n	16	48	64
Mean	39.50	32.69	34.39
Std Dev	15.853	26.136	24.048
Median	37.19	26.82	28.10
Q1-Q3	27.6:48.5	20.3:34.2	21.7:41.3
Min-Max	13.2:69.1	12.4:165.3	12.4:165.3
RO0503821 1*/4 weeks Start Dose [ug]			
n	16	48	64
Mean	66.35	163.19	138.98
Std Dev	47.349	99.551	98.557
Median	56.00	147.75	125.00
Q1-Q3	24.6:104.5	75.0:193.5	72.7:192.0
Min-Max	16.0:160.0	18.2:480.0	16.0:480.0

Previous ESA Therapy

The median time since first ESA administration was 22 months in Group 1 and 14 months in Group 2 (Table 19). In Group 1, the last ESA administered prior to screening was darbepoetin in 8 patients

(median weekly dose, 17.5 µg) and epoetin alfa/beta in 8 patients (median weekly dose, 4500 IU). In Group 2, the last ESA administered prior to screening was darbepoetin in 26 patients (median weekly dose, 20 µg) and epoetin alfa/beta in 22 patients (median weekly dose, 6000 IU). For the patients receiving darbepoetin, most patients were receiving once-weekly administrations. For those patients receiving epoetin alfa/beta, most were dosed 2-3 times a week, which is in accordance with the posology authorized.

Table 19. Summary of Previous ESA Therapy: ITT population

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%)

Previous and Concurrent Diseases

Aetiology of Chronic Kidney Disease

The most frequently reported aetiology of CKD was hereditary nephropathy (16 patients overall), followed by hypoplastic/dysplastic kidneys (14 patients overall).

Risk Factors for Vascular Events and Haemorrhage

A total of 32 patients (50%) had reported experiencing arterial hypertension at any time before enrolment, 6 patients (9%) had experienced venous thrombosis and 5 (8%) had experienced at least one haemorrhage event.

Previous and Concomitant Treatments

Anticoagulation Treatment

All patients had anticoagulation treatment prior to study start, with the most frequently used agents being heparin sodium (3 [19%] in Group 1 and 25 [52%] in Group 2) and enoxaparin sodium (11 [69%] in Group 1 and 16 [33%] in Group 2).

Iron Supplementation

Most patients recorded receiving iron supplementation prior to study start (58 patients [91%]); during the study, including the safety extension period, iron supplementation was recorded by 15 patients (94%) in Group 1 and 47 (98%) in Group 2. The most frequently used agents were iron sucrose, ferrous gluconate, and ferric hydroxide.

Antihypertensive Agents

Using a classification based on selected coded medication classes, at study start, 37 (58%) patients were taking or had taken 'antihypertensive and/or diuretic agents', the most common categories being angiotensin-converting enzyme inhibitors, calcium channel blocking agents and 'beta-adrenoceptor blocking agents. There were 38 patients recorded as taking at least one of these agents during the study.

Other Treatments

Apart from surgical and medical procedures (all patients were on haemodialysis), anticoagulants and anti-anaemic 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.

Haemodialysis at Baseline

The median duration of haemodialysis at baseline was 1.3 years in Group 1 and just under 1 year in Group 2. Approximately 75% of patients had been on haemodialysis for under 2.2 years, and had dialysis treatment (i.e., possible previous peritoneal dialysis) for less than 4 years. The majority of patients in both groups had three haemodialysis sessions per week. Mean ± SD Kt/V, a measure of dialysis adequacy, was 1.57 ± 0.377 in Group 1 and 1.60 ± 0.408 in Group 2 (a higher score indicates better dialysis adequacy, with 1.20 considered adequate). Mean ± SD urea reduction ratio, another measure of dialysis adequacy, was 79% ± 8.5% in Group 1 and 72% ± 9.0% in Group 2 (a higher percentage indicates better dialysis adequacy, with 65% considered adequate).

Recruitment/Numbers analysed

All ITT patients (16 patients in Group 1 and 48 in Group 2, 64 patients overall) received at least one dose of the treatment and were included in the safety population. Therefore, the ITT and safety population were the same.

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 12 patients in Group 1 and 36 in Group 2. One patient dropped out at week 19, therefore was included in 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.

In total, 37 patients signed the informed consent to enter the safety extension (9 from Group 1 and 28 from Group 2). In Group 1, one patient withdrew consent without receiving any study drug or performing any study procedures during the extension period.

Table 20. Summary of Populations

	Group 1 (N = 16)	Group 2 (N = 48)	Total (N = 64)
No. Included in Intent-To-Treat	16 (100.0%)	48 (100.0%)	64 (100.0%)
No. Included in Safety	16 (100.0%)	48 (100.0%)	64 (100.0%)
No. Included in Completers	12 (75.0%)	36 (75.0%)	48 (75.0%)
No. Excluded from Completers	4 (25.0%)	12 (25.0%)	16 (25.0%)
Less than 3 hemoglobin assessments during evaluation period	4 (25.0%)	12 (25.0%)	16 (25.0%)
No. Included in Per Protocol	12 (75.0%)	34 (70.8%)	46 (71.9%)
No. Excluded from Per Protocol	4 (25.0%)	14 (29.2%)	18 (28.1%)
Inclusion criterion regarding iron levels not fulfilled		2 (4.2%)	2 (3.1%)
Less than 3 hemoglobin assessments during evaluation period	4 (25.0%)	12 (25.0%)	16 (25.0%)
Missed application of study treatment at week 13 or week 17	4 (25.0%)	12 (25.0%)	16 (25.0%)
No. Included in Safety Extension	9 (56.3%)	28 (58.3%)	37 (57.8%)
No. Excluded from Safety Extension	7 (43.8%)	20 (41.7%)	27 (42.2%)

In the core study period, 21 protocol deviations were reported in 15 patients; all these violations were related to the inclusion/exclusion criteria (Table 21). The two patients with inadequate iron status at baseline were excluded from the PP population.

Table 21. Overview of protocol deviations

Category of Protocol Deviation	Number of Deviations
Adequate hemodialysis	6
Intravenous maintenance of ESA with same dosing interval for at least 8 weeks before screening (inclusion criterion)	3
Weekly dose change ≥25% during the 2-weeks of screening (inclusion criterion)	6
Inadequate iron status (inclusion criterion)	2
Use of ESA biosimiliars, prior to inclusion	2
Others[a]	2

[a]Missing pregnancy test and use of prohibited medication (mycophenolate mofetil) before screening

Conduct of Study

Five protocol amendments were issued. Of note, in the original protocol, the standard deviation of the Hb change from baseline used for the sample size calculation was assumed to be 1.5 g/dL. However, following the preliminary assessment of Group 2, the variability (standard deviation) of the data ranged from 1.9 to 2.1 g/dL. The assumed standard deviation was therefore increased to 2.0 g/dL and the

sample size revised in Protocol Amendment D. The sample size, for the optimum dose group only, for the group to enrol additional patients, was increased to 36 patients (an additional 20 patients instead of 9 after the assessment of the initial 16 patients). It was also recommended at this time that patients that did not complete the core study period were to be replaced, as allowed per-protocol.

The protocol stated that for the primary analysis the last observation carried forward method (LOCF) was to be used to impute missing Hb values. However, since the protocol was developed, LOCF was no longer considered an appropriate method for dealing with missing values, partly because of concerns of underestimation of the variability. This, along with justification based on the specific case of this study (notably that the majority of missing values were due to early withdrawals for renal transplantation, which was not expected to be directly linked to a systematic decline [or increase] in Hb), led to the decision to change this method. No imputation was made for missing values in the primary analysis, and values after a RBC transfusion were excluded and not imputed. The analysis as specified in the protocol was performed as a sensitivity analysis.

Table 22. Overview of protocol amendments

Version	Date	Summary of Main Changes
B	25.04.2008	• Changes in reporting guidelines for SAEs and clarification of roles within the DSMB
C	21.11.2008	• Use of prefilled syringes adopted instead of vials • Medical judgment rather than numerical values used to assess hypertension as an exclusion criterion
D	9.11.2012	• The sample size increased from 25 to 36 patients for the optimal conversion-factor group due to high variability seen in the preliminary analysis and clarification of replacement for early drop-outs was made • Updates due to a planned change in the electronic data capture system • Handling of missing Hb values for the analysis changed
E	24.03.2014	• Applicable to Russia only. To fulfill a requirement of the Russian Ministry of Health, only patients aged 12-17 years recruited
F	24.07.2014	• Clarifications regarding informed consent, prior medications, exclusion of pregnant patients • Addition of guidance in case of suspected anti-erythropoietin antibody-mediated pure red cell aplasia

DSMB: Data and Safety Monitoring Board; SAE: serious adverse events

Outcomes and estimation

Primary efficacy endpoint

Change in Hb concentration (g/dL) between the baseline period and the evaluation period (weeks 17-21)

The changes from baseline to the evaluation period are summarized in the Table 23.

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 24). 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, mean Hb values remained above 10 g/dL and below 12 g/dL throughout the study. However, in the Group 1 there was a clear decrease in Hb levels during the titration period, with mean values dropping below 10 g/dL (Figure 17) and reaching a nadir at week 9 before increasing without returning to baseline levels at the start of the evaluation period. In both groups, there was a small increase in Hb at the beginning of the study from baseline to week 3, although mean levels remained below 12 g/dL with a mean increase from baseline of the order of 0.5 g/dL for Group 1 and less than 0.5 g/dL for Group 2 (see Figure 18). In Group 2, 19 patients had Hb 1 g/dL or more above their baseline value at week 3, 17 at week 4, and 11 at week 5. 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 23. Summary of change in average haemoglobin between baseline and the evaluation period: ITT population

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.

Table 24. Comparison of Average Haemoglobin at Baseline and During Evaluation: ITT Population

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.

Parameter Estimates from all terms included in the ANCOVA Model

Parameter	Estimate	Standard Error	t value	Pr > |t|
Intercept	10.33	3.6691	2.82	0.0073
Treatment: Group 1	-0.64	0.3380	-1.91	0.0634
Treatment: Group 2	0.00			
Age Group: 5 - 11 Years	0.34	0.3067	1.11	0.2737
Age Group: 12 - 17 Years	0.00			
Prev. ESA: Darbepoetin Alfa	0.02	0.2891	0.05	0.9575
Prev. ESA: Epoetin Alfa/Beta	0.00			
Baseline Hemoglobin AUC	-0.95	0.3308	-2.89	0.0061

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

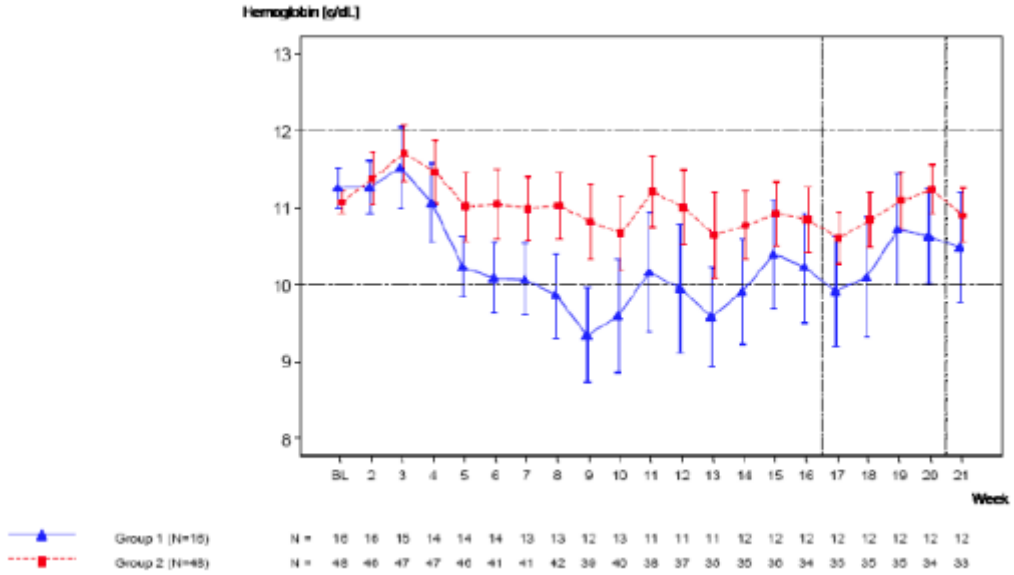


Figure 17. Mean Haemoglobin Values during the Core Study Period: ITT Population

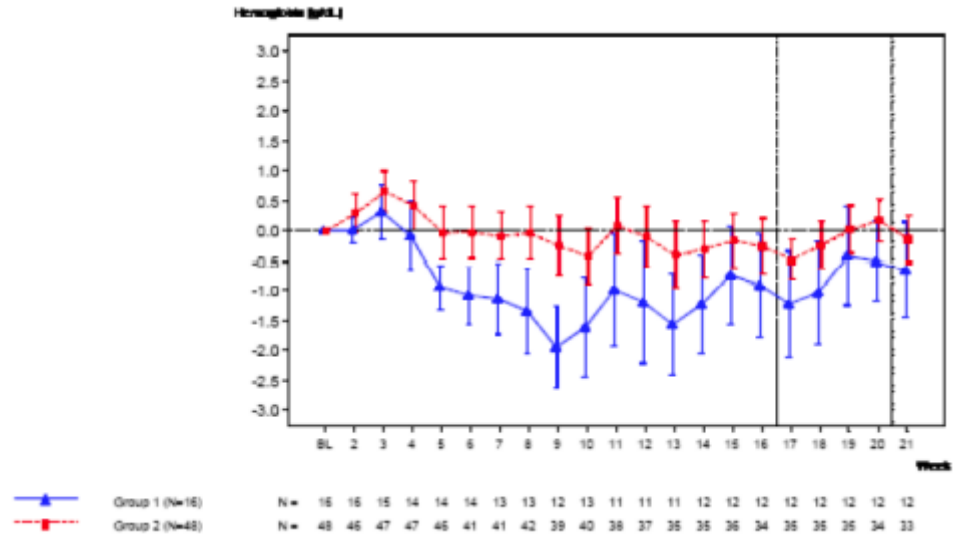


Figure 18. Mean Haemoglobin Change from Baseline Values during the Core Study Period: ITT

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 25). 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 25. Patients maintaining stable haemoglobin during the evaluation period: ITT population

	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.

Blood Transfusions during the Core Study Period

Three patients required blood transfusions during the core study period, one in Group 1 and two in Group 2 (Table 26). The reasons for transfusion were Hb decreased, procedural hemorrhage, and intracranial hematoma. The patient with intracranial hematoma died as a result of the event.

Table 26. Patients with blood transfusions during the core study period: ITT population

Center/ Patient No.	Age [yr]	Sex	Weight [kg]	Study Day	Transfusion Type	Total Volume Transfused [ml]	Triggering Hb Value	Triggering Hb Unit	Treatment for AE	Adverse Event
[redacted]				64	Packed red cells	800	7.80	g/dL	Yes	HAEMOGLOBIN DECREASED
				146	Packed red cells	800	7.90	g/dL	Yes	HAEMOGLOBIN DECREASED
Treatment: Group 2 (N=48, n=2)										
[redacted]				67	Washed packed red cells	590	6.40	g/dL	Yes	PROCEDURAL HAEMORRHAGE
				87	Packed red cells	150	5.50	g/dL	Yes	INTRACRANIAL HAEMATOMA
				90	Packed red cells	150	6.60	g/dL	Yes	INTRACRANIAL HAEMATOMA
				99	Packed red cells	300	7.60	g/dL	Yes	INTRACRANIAL HAEMATOMA

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.

Ancillary analyses

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 27.

Mean (±SD) 4-weekly Mircera dose increased from 66,64 (±47,348) µg (week 1-4) to 90,45 (±47,232) µg (last 4 weeks interval) in Group 1, and decreased from 163,33 (±99,517) µg (week 1-4) to 161,42 (±123,065) µg (last 4 weeks interval) in Group 2.

Median(Q1-Q3) 4-weekly Mircera dose increased from 58,3 (24,5-104,5) µg (week 1-4) to 79,2 (50,0-124,0) µg (last 4 weeks interval) in Group 1, and decreased from 147,8 (75,0-196,9) µg (week 1-4) to 117,1 (78,2-220,0) µg (last 4 weeks interval) in Group 2.

When considering the median values, which are less affected by outliers, in Group 2, the dose decreased slightly through to week 13 and then increased for the fifth and final dose at week 17. In Group 1, the median dose increased slowly throughout the core study, in response to the course of Hb over time.

Table 27. Summary of Equivalent 4-Weekly Mircera dose over time during the core study period: Safety population

	Equivalent 4-Weekly Dose [ug/4-weeks]							
Treatment Week of Treatment	n	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.

Dose ratio between first and evaluation period equivalent 4-weekly Mircera dose

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).

Table 28. Dose Ratio between the First and Evaluation Period Equivalent 4-weekly Mircera Dose: Safety Population

Treatment 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)								
Week 17-20	12	1.9440	1.07228	0.750	1.190	1.594	2.471	4.104
Group 2 (N=48)								
Week 17-20	36	1.1423	0.63802	0.187	0.655	1.000	1.524	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.

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 29.

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 (Figures 19 and 20).

Table 29. Summary of the Conversion from previous weekly ESA dose to equivalent during evaluation: safety population

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.

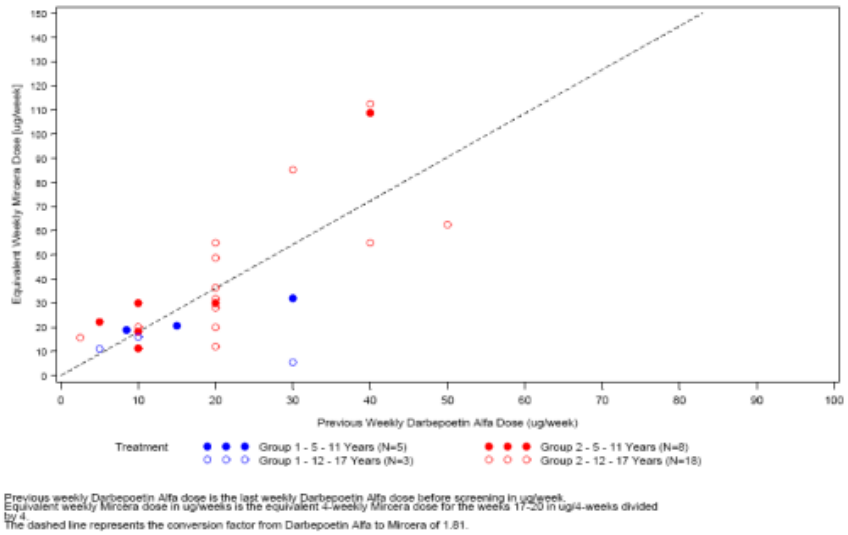


Figure 19. Plot of previous darbepoetin alfa dose vs equivalent Mircera dose during the evaluation period

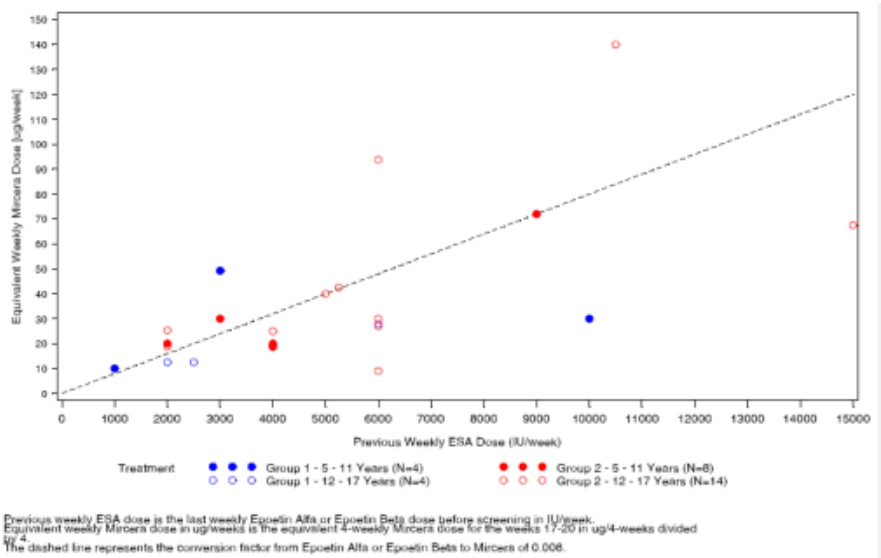


Figure 20. Plot of previous epoetin alfa/beta dose vs equivalent Mircera dose during the evaluation period

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 30). 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 Group 1 (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 30. Summary of Patients with Dose Adjustments of the Equivalent 4-Weekly Dose during the core study period: safety population.

	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.

Subgroup analyses

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

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

Primary Efficacy Endpoint

The difference in change in average Hb between baseline and evaluation periods is presented in Table 31. Change from baseline in group 2 is presented in Figure 21.

Table 31. Summary of change in average haemoglobin between baseline and evaluation periods by age group: ITT population

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.

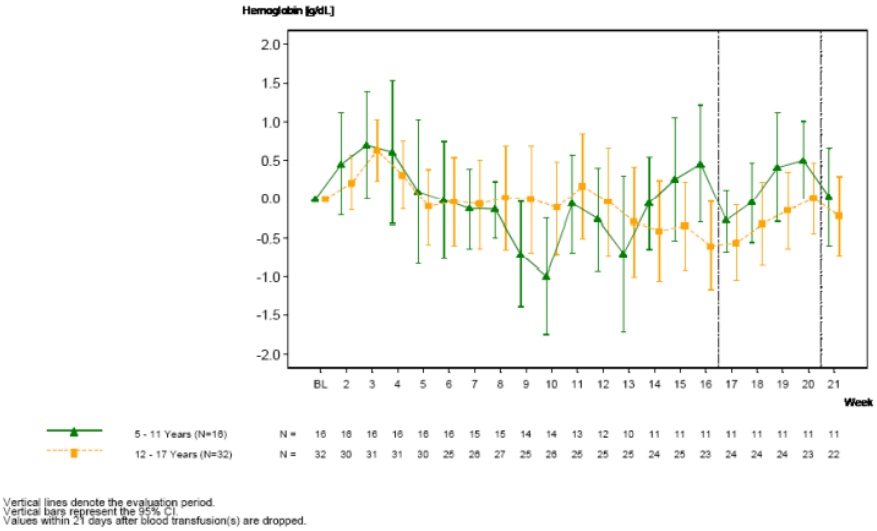


Figure 21. Mean hemoglobin change from baseline over time by age group during the core study period (Group 2 only): ITT population.

Mircera dose during the core study period

In Group 2, the median equivalent 4-weekly dose during the evaluation period (week 17) was 89 and 127 µg/4 weeks in the 5-11 years and 12-17 years age groups respectively, whereas the median starting doses were 86 and 150 µg/4 weeks (Table 32).

Table 32. Summary of equivalent 4-weekly Mircera dose by age group during the core study period: safety population

Treatment Age Group Week of Treatment	Equivalent 4-Weekly Dose [ug/4-weeks]							
	n	Mean	Std Dev	Minimum	Q1	Median	Q3	Maximum
Group 1 (N=16)								
5 - 11 Years (N=9)								
Week 1 - 4	9	85.67	50.378	16.0	48.0	75.0	109.1	160.0
Week 5 - 8	8	59.83	48.676	0.0	28.8	52.8	77.7	160.0
Week 9 -12	7	88.23	45.627	25.0	48.6	82.5	129.5	160.0
Week 13-16	6	95.30	47.511	31.2	60.6	92.5	135.0	160.0
Week 17-20	6	107.16	54.394	40.0	75.5	101.3	128.0	197.0
Last 4-weeks Interval	9	110.66	47.630	40.0	76.0	120.0	129.5	197.0
12 - 17 Years (N=7)								
Week 1 - 4	7	42.17	31.287	18.2	18.2	32.0	68.6	100.0
Week 5 - 8	6	34.15	17.780	18.2	22.8	28.8	40.0	66.3
Week 9 -12	6	42.12	27.140	22.8	28.4	32.8	40.0	96.0
Week 13-16	6	47.77	26.133	22.8	33.6	41.3	50.0	97.7
Week 17-20	6	56.97	29.989	21.9	44.4	50.0	64.0	111.4
Last 4-weeks Interval	7	64.46	33.928	22.8	44.4	50.0	100.0	120.0
Group 2 (N=48)								
5 - 11 Years (N=16)								
Week 1 - 4	16	144.81	104.513	36.4	74.0	85.7	216.0	390.0
Week 5 - 8	16	107.98	97.530	0.0	50.0	85.5	144.5	360.0
Week 9 -12	14	140.18	108.124	56.3	72.7	80.9	219.4	360.0
Week 13-16	12	143.93	119.556	0.0	76.4	92.4	199.3	360.0
Week 17-20	11	138.60	117.345	45.0	75.0	88.9	120.0	435.0
Last 4-weeks Interval	16	150.02	120.242	0.0	77.5	104.5	234.0	435.0
12 - 17 Years (N=32)								
Week 1 - 4	32	172.59	97.285	18.2	112.6	150.0	196.9	480.0
Week 5 - 8	29	149.48	94.744	0.0	90.0	145.5	192.0	360.0
Week 9 -12	27	132.46	108.134	0.0	57.1	144.0	170.0	450.0
Week 13-16	25	148.37	128.605	0.0	60.3	100.0	225.0	450.0
Week 17-20	25	179.31	132.588	36.0	80.4	127.2	220.0	560.0
Last 4-weeks Interval	32	167.12	125.957	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.

When considering the individual patient ratios of initial dose to dose during evaluation (Table 33) in Group 2, there was a small increase (1.25) in the medians in the 5-11 age group whereas the ratio was close to 1 in the 12-17 age group (0.98). In the younger age group, this corresponds to not more than one protocol specified dose change of 25%. In Group 1, the median ratios were both greater than 1 (1.81 for the 5-11 age group and 1.59 for the 12-17 age group). While absolute doses differ, results for changes in dose are generally reflected in the smaller Group 1 age subsets. Overall, for Group 1, dose increases were required and larger increases were seen in the younger patients and smaller increases in the older patients.

Table 33. Dose ratio between the first and evaluation period equivalent 4-weekly Mircera dose, by age group: safety population

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.

Previous ESA treatment

In Group 1, 8 patients were previously on darbepoetin alfa and 8 were previously on epoetin alfa/beta. In Group 2, 26 were previously on darbepoetin alfa and 22 were previously on epoetin alfa/beta.

Primary Efficacy Endpoint

When considering changes in Hb over time in Group 2, the mean Hb change from baseline for patients previously on darbepoetin alfa was generally below baseline whereas the mean for patients previously taking epoetin alfa/beta remained closer to baseline throughout (Figure 22).

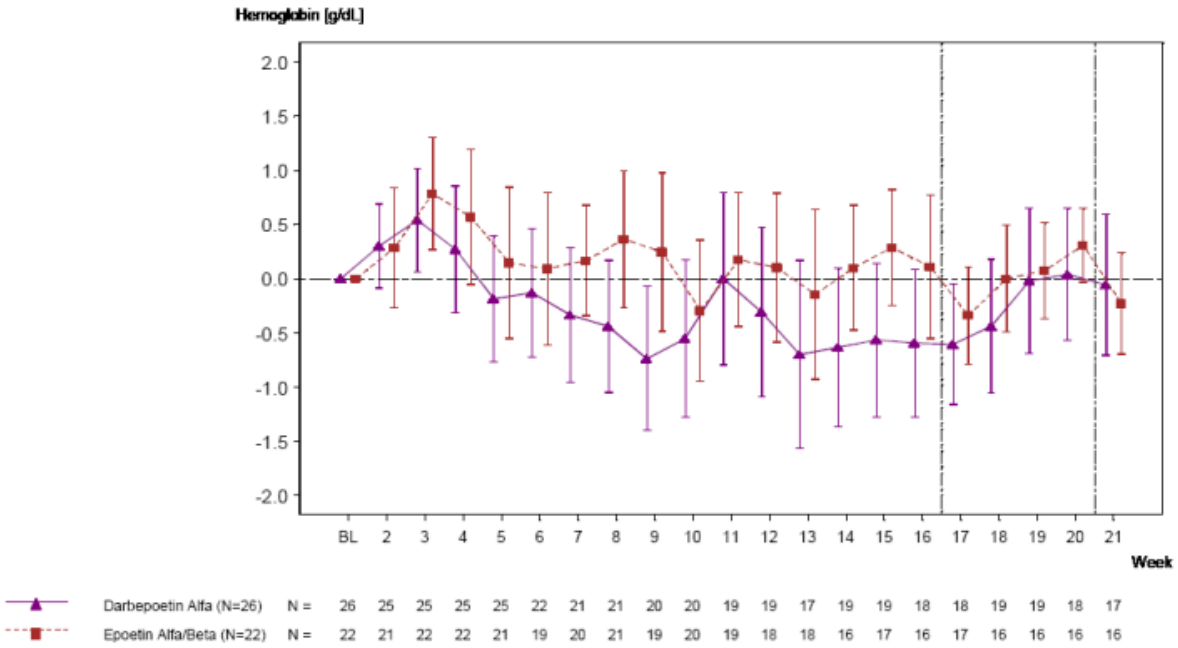


Figure 22. Mean haemoglobin change from baseline over time by age group during the core study period (Group 2 only): ITT population.

In Group 2, the median per-patient ratio in change from first to evaluation dose was 1 for both previous ESA treatments (Table 34).

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

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.

Efficacy evaluations during the safety extension period

Haemoglobin over time

In Group 2, during the safety extension period, all mean Hb values remained within the 10-12 g/dL range (Figure 23). 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. The change from baseline in Group 2 during the safety extension period fluctuated around baseline.

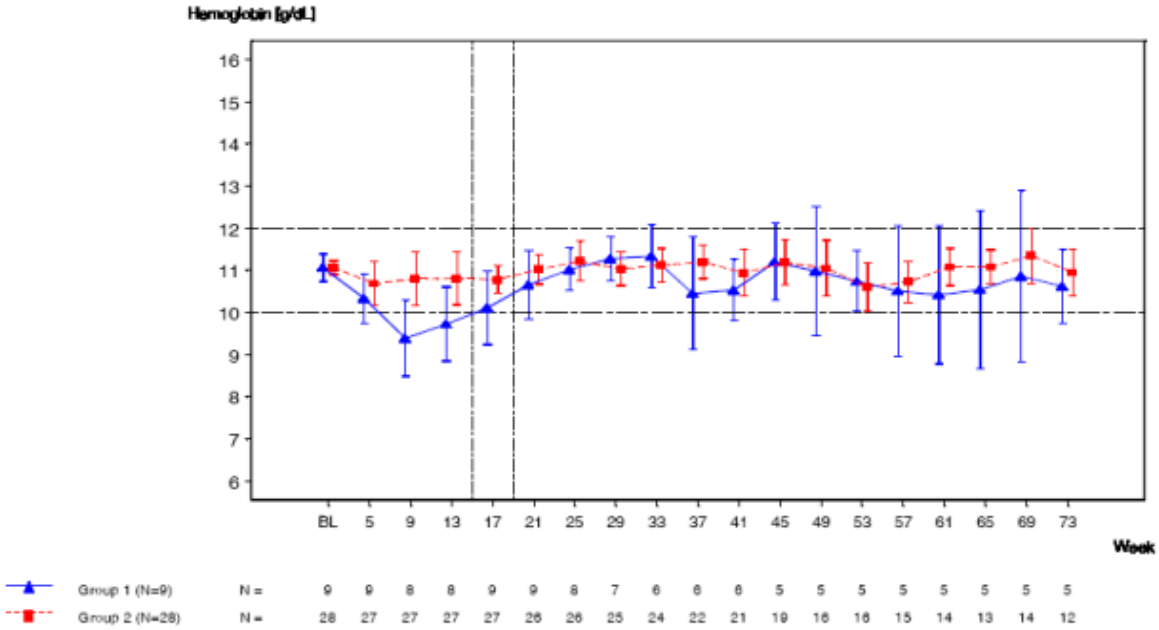


Figure 23. Mean haemoglobin change from baseline values over whole study duration (including safety extension)

During the entire study period, the median dose ratio between the first equivalent 4-weekly Mircera dose and the last 4-weekly Mircera dose was approximately 1 in both groups.

Table 35. Summary of the Dose Ratio between the First Equivalent 4-Weekly Mircera Dose and the Last 4-Weekly Mircera Dose - Including Extension Study Period

Treatment 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=9)								
Last 4-weeks Interval	9	1.5230	1.26228	0.000	0.756	1.005	2.188	3.750
Group 2 (N=28)								
Last 4-weeks Interval	28	1.1197	1.12524	0.000	0.478	1.000	1.396	6.181

Blood Transfusions

During the safety extension period, one patient required blood transfusion after transplant failure.

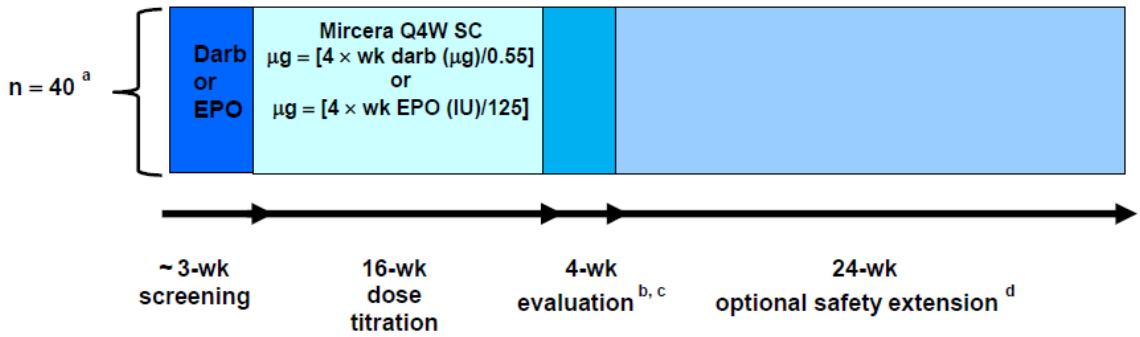
Study NH19708: phase II, open-label, single-arm, multicenter study to ascertain the optimal starting dose of Mircera given subcutaneously for the maintenance treatment of anaemia in paediatric patients with CKD on dialysis or not yet on dialysis.

Methods

The core study was for 23 weeks and consisted of three periods: Screening (3 weeks), dose titration (16 weeks), and evaluation (4 weeks). Patients completing the 20 weeks of treatment with Hb within ±1 g/dL of their baseline Hb and within the target range of 10-12 g/dL, were eligible to enter an optional 24-week safety extension period. Mircera was administered subcutaneously once every 4 weeks for the duration of the study. Dose adjustments were permitted to maintain target Hb levels (according to dose adjustment predefined rules).

Once 12 patients had completed 20 weeks of treatment, an interim analysis to assess efficacy, safety, and pharmacokinetics was performed.

The starting dose was based on conversion factors (CFs) obtained from the dose-finding study (Study NH19707). The initial dose of Mircera was one of nine starting doses corresponding to the prefilled syringe strengths based on the total weekly ESA dose during the screening period.



darb = darbepoetin alfa; EPO = epoetin alfa or epoetin beta; Q4W = once every 4 weeks; wk = week.

[a] Approximately 10–15 of the patients will be < 12 years old, with a goal to include as many patients < 5 years old as possible (with a minimum of 3 patients). Approximately 10–15 patients, irrespective of age, was not on dialysis. Available hemodialysis (HD) patients receiving their Erythropoiesis-stimulating agents (ESA) subcutaneously were eligible for enrollment. No more than 10 patients on HD could be enrolled.

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

[c] All patients completed a follow-up visit (Week 21, Visit 10), regardless of whether they continued in the safety extension period.

[d] Patients completing the 20 weeks of treatment with Hb within ± 1 g/dL of their baseline Hb and within the target range of 10–12 g/dL, would be eligible to enter an optional 24-week safety extension period.

Figure 24. Study Schema

Study participants

The target population comprised paediatric patients 3 months - 17 years old with clinically stable chronic renal anaemia on dialysis or not yet on dialysis.

Approximately 10-15 of the patients were to be <12 years old, with a goal to include as many patients < 5 years old as possible (with a minimum of 3 patients). Approximately 10-15 patients, irrespective of age, were not on dialysis. Available haemodialysis (HD) patients receiving their Erythropoiesis-stimulating agents (ESA) subcutaneously were eligible for enrolment. No more than 10 patients on HD could be enrolled.

Key inclusion criteria:

- Paediatric patients 3 months-17 years of age with clinically stable chronic renal anaemia
- CKD with estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73 m2 (determined by the Bedside Schwartz formula [Appendix 3 of the Protocol v4]) or dialysis treatment for at least 8 weeks before the first dose of Mircera.
- For patients on PD: a weekly Kt/V ≥ 1.8
- For patients on HD: adequate HD, urea reduction ratio (URR) >65% or Kt/V > 1.2 for patients on HD three times per week.
- Patients with fewer than or more than three HD sessions per week should have a weekly Kt/V ≥ 3.6.
- Baseline Hb concentration 10.0-12.0 g/dL determined from the mean of two Hb values measured at Visit 1 (Week -3) and Visit 2 (Week -1).
- Stable SC maintenance treatment with epoetin alfa, epoetin beta, or darbepoetin alfa with the same dosing interval for at least 6 weeks before the first dose of Mircera
- Stable dose of epoetin alfa, epoetin beta, or darbepoetin alfa treatment with no weekly dose change > 25% (increase or decrease) for at least 4 weeks before the first dose of Mircera
- Adequate iron status defined as ferritin ≥100 ng/mL or transferrin saturation (TSAT) ≥ 20% (or percentage of hypochromic red cells <10%); mean of two values measured during screening
- For post-pubertal female patients of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or to use acceptable contraceptive methods during the study and for 90 days after the final dose of Mircera. A female patient is considered to be of childbearing potential if she is postmenarcheal.

Key exclusion criteria:

- Overt gastrointestinal bleeding within 8 weeks before screening or during the screening period
- RBC transfusions within 8 weeks before screening or during the screening period
- Hemoglobinopathies (e.g., homozygous sickle-cell disease, thalassemia of all types)
- Haemolytic anaemia
- Active malignant disease
- PD subjects with an episode of peritonitis within the past 30 days prior to screening and/or during the screening period
- Uncontrolled or symptomatic inflammatory disease (e.g., systemic lupus erythematosus)

- Uncontrolled hypertension as assessed by the investigator.
- Epileptic seizures within 3 months prior to screening and during the screening period
- Administration of any investigational drug within 4 weeks prior to screening or planned during the study
- Kidney transplant with use of immunosuppressive therapies known to exacerbate anemia
- Severe hyperparathyroidism (intact parathyroid hormone [PTH] ≥1000 pg/mL or whole PTH ≥500 pg/mL) or biopsy-proven bone marrow fibrosis
- Known hypersensitivity to recombinant human EPO, polyethylene glycol, or any constituent of the study drug formulation
- Anti-EPO antibody (AEAB)-mediated pure red cell aplasia (PRCA) or history of AEAB-mediated PRCA or positive AEAB test result in the absence of PRCA
- High likelihood of early withdrawal or interruption of the study (e.g., planned living donor kidney transplant within 5 months of study start)
- Planned elective surgery during the entire study period
- Females who are pregnant or breastfeeding or who intend to become pregnant during the study or within 90 days after the final dose of Mircera

Treatments

Mircera was administered SC once every 4 weeks for the duration of the study. The starting dose was based on CFs obtained from the dose-finding study (Study NH19707).

The initial dose of Mircera was to be one of nine starting doses corresponding to the PFS strengths based on the total weekly ESA dose during the screening period, as described below (Table 36):

Table 36. Mircera Starting Dose NH19708

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 of Mircera could be adjusted to maintain the individual patient's Hb within a target range of ±1 g/dL of his or her baseline Hb and between 10.0–12.0 g/dL. Dose adjustments were performed at the

scheduled dosing days and was based on the Hb value measured on that day as shown in Table 37. The dose adjustments were not to be performed more often than once every 4 weeks.

Table 37. Mircera Dose adjustments NH19708

Hemoglobin Assessment	Compared with the Previous Mircera Dose
Hb decreases by more than 1.0 g/dL compared with baseline Hb.	Increase dose by approximately 25% *(or closest higher PFS strength).*
Hb is less than 10 g/dL and greater than or equal to 9 g/dL (Hb < 10.0 and ≥ 9.0 g/dL).	Increase dose by approximately 25% *(or closest higher PFS strength).*
Hb is less than 9 g/dL (Hb < 9.0 g/dL).	Increase dose by approximately 50% *(or closest to 50% increase PFS strength).*
Hb increases by more than 1.0 g/dL compared with the baseline Hb.	Decrease dose by approximately 25% *(or closest lower PFS strength).*
Hb is increasing and is approaching 12 g/dL or Hb is greater than or equal to 12 g/dL (Hb ≥12 g/dL).	*Decrease dose by approximately 25% (or closest lower PFS strength).*
If Hb exceeds 12 g/dL *and continues to increase* following a dose reduction.	Stop doses until Hb is less than 12.0 g/dL. Resume dose at approximately 25% below previous dose *(or closest lower PFS strength) at next scheduled dosing day.*

Hb = hemoglobin; *PFS =prefilled syringe..*

Mircera was provided in sterile injectable solution in single-use pre-filled syringes. The pre-filled syringes were available in the following strengths:

30	50	75	100	120	150	200	250	µg/0.3 mL

360	µg/0.6 mL

All treatments (medications and medical procedures) were permitted before screening, during the screening period and throughout the 20-weeks treatment period except for: investigational medicinal product, non-FDA and non-EMA approved biosimilar ESAs within 12 weeks of screening, red blood cell (RBC) transfusions within 8 weeks before screening, or immunosuppressive therapies administered in the last 12 weeks before the first screening visit. Supplemental iron was administered to prevent iron deficiency during the screening period and during study, and to maintain adequate iron parameters.

Objectives

Efficacy Objective: To ascertain the starting dose of Mircera given subcutaneously in paediatric patients with CKD on dialysis or not yet on dialysis when switching from stable SC maintenance treatment with epoetin alfa, epoetin beta, or darbepoetin alfa.

Safety Objective: To assess the safety and tolerability of multiple doses of Mircera given subcutaneously in paediatric patients.

Pharmacokinetic and Pharmacodynamic Objective: To evaluate the pharmacokinetics and the pharmacodynamics of Mircera in patients on dialysis or not yet on dialysis who receive the study medication by the SC route of administration.

Outcomes/endpoints

Efficacy:

Primary Efficacy Endpoint:

- Change in Hb concentration (g/dL) between the baseline and the evaluation period for each patient.

Secondary Efficacy Endpoints:

- Number of patients with an average Hb concentration during the evaluation period within ± 1 g/dL of their baseline Hb or above, within or below the range of 10-12 g/dL.
- Change in Mircera dose over time, including the change between the starting dose and the evaluation period.

Pharmacokinetics and Pharmacodynamics:

- Serum concentrations of Mircera and Hb were used to evaluate the pharmacokinetics (PK) and the pharmacodynamics (PD) of Mircera through PK and PK/PD models.

Safety:

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

Sample size

This study was designed to include 40 paediatric patients. It was planned to include approximately 10-15 of the patients <12 years old, with the objective to include as many patients as possible <5 years old (with a minimum of 3 patients).

It was also planned to include approximately 10-15 patients, irrespective of age, who were not on dialysis, and no more than 10 patients on HD.

This was an exploratory study without a powered statistical group comparison. Therefore, no formal sample size estimation was performed. However, the calculations below mentioned indicate the approximate precision that could be achieved:

Assuming a 30% withdrawal rate (based on the withdrawal rate for the NH19707 study), of the 40 patients evaluable for ITT and safety analysis, more than 26 patients would have data for the evaluation period. Twenty-six patients would be sufficient to provide approximately 90% power that the 90% CI for the Hb change from baseline to the evaluation period is between -1 and +1 g/dL, provided the standard deviation is smaller than 1.5 and the optimum dose conversion is able to maintain the Hb at

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

To achieve the recruitment of the intended number of patients and in case of excessive dropout rate, additional patients were planned to be enrolled to replace patients not treated for a minimum duration of 18 weeks.

Randomisation

No randomization was performed.

Blinding (masking)

Not applicable, this was an open-label study.

Statistical methods

All efficacy variables (original values and change from baseline) over time are presented in summary tables and graphically. The estimates are summarized descriptively using means, standard deviations, and percentiles.

The analysis population for the primary and secondary efficacy analyses is the ITT population consisting of all enrolled patients.

An additional analysis would be performed based on the per-protocol population, which would be precisely defined in the statistical analysis plan, before database closure, as the subset of the ITT population without major protocol deviations.

Safety data for the whole study including the safety extension period is presented. The safety analysis population consisted of all patients who received at least one dose of study drug regardless of whether they withdrew prematurely or not.

Mircera serum concentration-time data would be described using non-linear mixed effect modelling. The previously developed model was a one-compartment model with first order absorption and elimination processes. It will be updated with Study NH19708 data.

Analysis Populations

The following analysis populations were defined in the SAP:

- Intent to Treat (ITT) Population. The ITT population consisted of all patients enrolled in the study.
- Per-Protocol (PP) Population. The PP population was defined as all patients included in the safety population and who have no major protocol deviations as defined below:

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

  2. Patients who miss any application of study medication at week 13 or week 17.

3. Patients with an overdose of Mircera at week 17 captured as a protocol deviation

4. Patient with wrong Mircera starting dose

5. Patients who do not fulfil the inclusion criteria for: haemoglobin, iron levels, stable dose and dosing interval of SC treatment with epoetin alfa, epoetin beta or biosimilars, or darbepoetin alfa.

6. Patients who fulfil any of the exclusion criteria: Haemolytic anaemia or use of prohibited therapy.

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

Results

Participant flow

Table 38. Patient Disposition Study NH19708- Including Safety Extension Period: ITT population

Protocol: NH19708

Status	MIRCERA SC (N=40)
Patients entered core period	40 (100%)
Patients completed core period	38 (95.0%)
Patients entered extension period	25 (62.5%)
Patients completed extension period	21 (52.5%)
Patients discontinued core study period	2 (5.0%)
Adverse events	0
Pregnancy	0
Death	0
Lack of Efficacy	0
Lost to Follow-up	0
Protocol Deviation	0
Withdrawal by Subject	0
Study Terminated by sponsor	0
Physician Decision	0
Other	2 (5.0%)
Kidney Transplant	1 (2.5%)
Prohibited Medication	1 (2.5%)
Patients discontinued safety extension period	4 (10.0%)
Adverse events	0
Pregnancy	0
Death	0
Lack of Efficacy	0
Lost to Follow-up	0
Protocol Deviation	0
Withdrawal by Subject	0
Study Terminated by sponsor	0
Physician Decision	0
Other	4 (10.0%)
Kidney Transplant	4 (10.0%)

Percentages are based on N.

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A total of 62 patients were screened, 34 patients were enrolled after initial screening and 28 patients failed the screening. Among the 28 screen failure patients, 7 patients were re-screened, 6 patients were enrolled, and 1 patient failed the re-screening.

A total of 40 patients (100%) were enrolled in the core period of the study from 20 centres distributed across 7 countries.

The majority of patients (38 patients [95%]) completed and 2 patients (5%) discontinued during the core period. The reasons for discontinuation from the core period were kidney transplant (1 patient [2.5%]) and use of prohibited medication (1 patient [2.5%]).

A total of 38 patients completed the core period; of these, 25 eligible patients (62.5%) opted to enter the safety extension period. Of the 13 patients who did not enter the safety extension, 7 would have been eligible based on Hb within 10-12 g/dL and ±1 g/dL of the baseline value. The majority of the patients entering the safety extension have completed this period (21 of 25 patients), and 4 patients had discontinued. The only reason for discontinuation of patients from the safety extension period was kidney transplant (4 patients).

Recruitment/Numbers analysed

All ITT patients (40 patients) received at least one dose of the treatment and were included in the safety population. Therefore, the ITT and safety population were the same.

In the PP population, 33 patients were included and 7 patients were excluded. The main reasons for exclusion of patients from the PP population were overdose of Mircera at Week 17 (2 patients) and treatment with prohibited concomitant medication (2 patients).

All 25 patients who entered the optional safety extension period of the study were included in the safety extension population.

To meet the target patient population, no replacement of patients was required to complete the targeted sample size in the study.

Table 39. Summary of Populations

Protocol: NH19708
Analysis Populations

Reasons for Exclusion	MIRCERA SC
Intent-to-treat Population	40
Safety Population	40
Per Protocol Population	33
Exclusions Per Protocol Population	
Patients with an incorrect starting dose of Mircera	1
Patients with an overdose of Mircera at Week 17	2
Patients with prohibited concomitant medication	2
Patients who do not fulfill the inclusion criteria:	
Change in dose > 25% of previous ESA	1
HB value outside range (10-12 g/dL)	1
Inadequate dialysis	1
Included in Safety Extension	25
Excluded from Safety Extension	15

Note: One subject did not fulfill two inclusion criteria.

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Conduct of the study

Version	Date	Summary of Main Changes
V2	19.01.2018 (FDA comments)	- Additional time point for immunogenicity sampling at Week 9 (Visit 6). - Additional assessment of anti-PEG antibodies in those patients where loss of efficacy was observed. - Age range categories for additional statistical analyses of the primary efficacy endpoint were amended to align with the study goal of including as many patients under 5 years old as possible.
V3	11.07.2018 (European health authorities comments)	- Update of the rationale for Mircera dose and schedule with results from real word data from the International Paediatric Dialysis Network registries. - Clarification of lab assessments required for calculating transferrin saturation (TSAT). - Blood sampling volume limits were added (ethical considerations).
V4	07.12.2018	- Exclusion Criteria were amended to exclude patients who have undergone a kidney transplant with use of immunosuppressive therapies known to exacerbate anaemia, as inclusion of these patients would add a bias to the studied patient population. - Table Mircera Dose Adjustments, were amended to clarify the dose adjustment rules for Mircera. - Updated with information regarding sample storage and the use of samples after withdrawal of patient consent.

Baseline data

The patients' demographic and baseline characteristics were consistent with the target patient population. Demographics and baseline characteristics of the ITT population is included below (Table 40).

The mean (±SD) weight and height of patients at baseline was 34.21 (21.04) kg and 126.74 (32.95) cms, respectively. The median Z-score was negative for both weight (-1.2) and height (-1.6), indicating that the patient population had lower weight and height than the normal population for the same age and sex, which is as expected in this patient population with anaemia of CKD.

A similar proportion of patients were previously treated with darbepoetin alfa or epoetin alfa/beta were enrolled (20 patients [50%] treated with previous ESA).

Overall, there were 23 male patients (57,5%). The majority of patients were caucasian (30 patients, 75%), and the mean ± SD age was 10.32 ± 5.69 years. The graphical distribution of patients among age categories (Figure 25) (<5, 5-11, ≥12 years) is presented below. 12 patients (30%) were younger than 5 years old, 4 of them between 0-2 years old.

There were 18 patients (45%) who were on peritoneal dialysis, 17 patients (42.5%) who were not on dialysis, and 5 patients (12.5%) who were on haemodialysis. The number of patients on haemodialysis was comparatively lower than the number of patients not on dialysis or on peritoneal dialysis. This was because to be eligible for enrolment in this Study NH19708, these patients had to previously receive their ESA treatment SC.

The mean (±SD) weight and height of patients at baseline was 34.21 (21.04) kg and 126.74 (32.95) cms, respectively. The median Z-score was negative for both weight (-1.2) and height (-1.6), indicating that the patient population had lower weight and height than the normal population for the same age and sex, which is as expected in this patient population with anaemia of CKD.

A similar proportion of patients were previously treated with darbepoetin alfa or epoetin alfa/beta were enrolled (20 patients [50%] treated with each previous ESA).

Table 40. Demographics and baseline characteristics: ITT population (1/2)

Protocol: NH19708

	MIRCERA SC (N=40)
Age (yr)	
n	40
Mean (SD)	10.32 (5.69)
Median	11.35
Min - Max	0.4 - 17.7
Age group (yr)	
n	40
Less than 5 Years	12 (30.0%)
5 - 11 Years	11 (27.5%)
Greater /Equal to 12 Years	17 (42.5%)
Sex	
n	40
Male	23 (57.5%)
Female	17 (42.5%)
Ethnicity	
n	40
Hispanic or Latino	4 (10.0%)
Not Hispanic or Latino	27 (67.5%)
Not Reported	2 (5.0%)
Unknown	7 (17.5%)
Race	
n	40
Black or African American	3 (7.5%)
White	30 (75.0%)
Unknown	7 (17.5%)
Dialysis status	
Not on dialysis	17 (42.5%)
Peritoneal dialysis	18 (45.0%)
Hemodialysis	5 (12.5%)
Previous ESA Therapy	
Darbepoetin alfa	20 (50.0%)
Epoetin alfa or Epoetin beta or Biosimilars	20 (50.0%)

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 standardized 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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Demographics and Baseline Characteristics : ITT Population
Protocol: NH19708

Table 41. Demographics and baseline characteristics: ITT population (2/2)

	MIRCERA SC (N=40)
Weight (kg)	
n	40
Mean (SD)	34.213 (21.043)
Median	29.800
Min - Max	6.90 - 90.00
Height (cm)	
n	39
Mean (SD)	126.746 (32.953)
Median	135.000
Min - Max	62.00 - 172.50
Z - score for Height*	
n	39
Mean (SD)	-1.566 (1.148)
Median	-1.630
Min - Max	-6.03 - 1.06
Z - score for Weight*	
n	40
Mean (SD)	-1.019 (1.558)
Median	-1.210
Min - Max	-6.83 - 1.60
Smoker	
n	40
No	40 (100%)

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 standardized 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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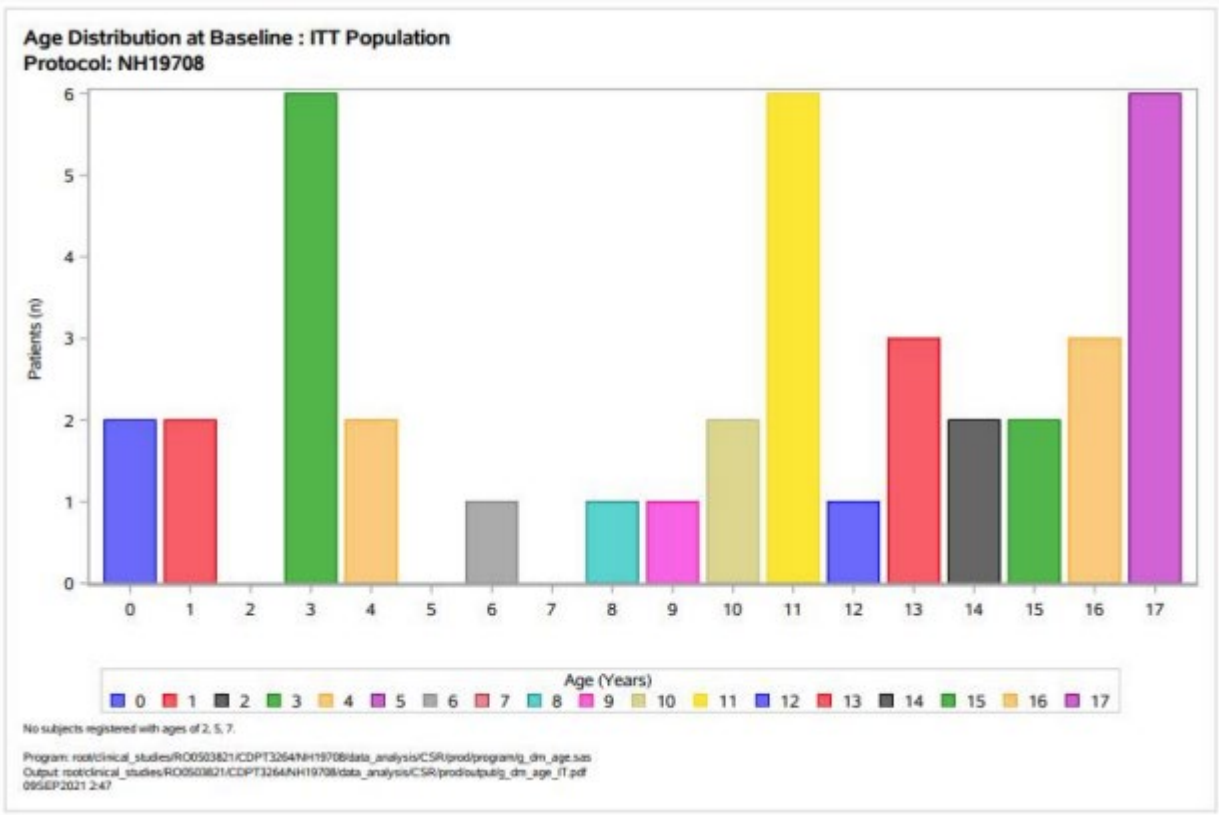

Figure 25. Age distribution at baseline

Baseline Laboratory Parameters

Median baseline haemoglobin levels were 11. 2 ± 0,53 g/dL (Table 42).

Table 42. Baseline Haemoglobin and Iron Parameters- Safety Population

Protocol: NH19708

Parameter	Statistic	MIRCERA SC (N=40)
Hemoglobin (g/dL)		
	n	40
	Mean (SD)	11.02 (0.53)
	Median	11.08
	Min - Max	10.1 - 12.2
	Q1 - Q3	10.61 - 11.39
Serum Iron (umol/L)		
	n	40
	Mean (SD)	14.58 (4.14)
	Median	14.98
	Min - Max	6.5 - 24.5
	Q1 - Q3	12.05 - 17.92
Ferritin (ng/mL)		
	n	40
	Mean (SD)	199.19 (205.92)
	Median	139.65
	Min - Max	18.9 - 939.5
	Q1 - Q3	71.20 - 245.81
Transferrin Saturation* (%)		
	n	39
	Mean (SD)	29.45 (8.57)
	Median	29.95
	Min - Max	10.9 - 46.2
	Q1 - Q3	22.27 - 35.92

* Transferrin saturation has been recalculated, based on the values for serum iron and serum transferrin or TIBC.

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Previous ESA Therapy

A similar proportion of patients that were previously treated with darbepoetin alfa or epoetin alfa/beta were enrolled (20 patients [50%] treated with each previous ESA).

The last median (min-max) weekly epoetin alfa/beta dose before administering the first Mircera dose was 2000 IU (range: 375-8000 IU). The majority of patients (60%) received epoetin alfa/beta at a frequency of once a week (8 patients [40%]) or twice a week (4 patients [20%]).

The last median (min-max) weekly darbepoetin alfa dose before administering the first Mircera dose was 10 μg (range: 2.5-50 μg). Nine patients (45%) received darbepoetin alfa at a frequency of once every two weeks.

Table 43. Summary of Previous ESA Therapy: Safety population

Protocol: NH19708

	Statistics	MIRCERA SC (N=40)
Previous ESA Drug		
Epoetin Alfa/Beta (IU)	n	20 (50.0%)
Darbepoetin alfa (ug)	n	20 (50.0%)
Last Weekly Epoetin Alfa/ Beta Dose before first Mircera Dose (IU)		
	Mean (SD)	2664.9 (2164.1)
	Median	2000.0
	Min - Max	375 - 8000
	Q1 - Q3	683.4 - 4250.0
Frequency of Injections		
QS (Once a Week)	n	8 (40.0%)
BIS (Twice a Week)	n	4 (20.0%)
TIS (Three Times a Week)	n	1 (5.0%)
Q3S (Every 3 Weeks)	n	2 (10.0%)
Q4S (Every 4 Weeks)	n	1 (5.0%)
Q5D (Every 5 Days)	n	2 (10.0%)
Q10D (Every 10 Days)	n	2 (10.0%)
Time from Start Date (days)		
	Mean (SD)	-218.2 (350.5)
	Median	-59.0
	Min - Max	-1410 - -42
	Q1 - Q3	-239.5 - -46.5
Last Weekly Darbepoetin alfa Dose before first Mircera Dose (ug)		
	Mean (SD)	13.78 (11.69)
	Median	10.00
	Min - Max	2.5 - 50.0
	Q1 - Q3	8.75 - 14.50
Frequency of Injections		
QS (Once a Week)	n	4 (20.0%)
Q2S (Every 2 Weeks)	n	9 (45.0%)
Q3S (Every 3 Weeks)	n	1 (5.0%)
Q4S (Every 4 Weeks)	n	2 (10.0%)
QM (Every Month)	n	2 (10.0%)
Q10D (Every 10 Days)	n	1 (5.0%)
Q12D (Every 12 Days)	n	1 (5.0%)
Time from Start Date (days)		
	Mean (SD)	-342.1 (345.5)
	Median	-196.5
	Min - Max	-1344 - -42
	Q1 - Q3	-479.0 - -83.5

Note: Time from start date (days) is the number of days the subject has been treated with ESA prior to first dose of Mircera.
Epoetin Alfa/ Beta group consists of Epoetin alfa, Epoetin beta and Biosimilars.

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Previous and Concurrent Diseases

Aetiology of Chronic Kidney Disease

The most frequent (≥10% patients) nephrological diseases were hypoplastic/dysplastic kidneys (12 patients [30%]), reflux nephropathy (7 patients [17.5%]), and hereditary nephropathy (5 patients [12.5%]).

Risk Factors for Vascular Events and Haemorrhage

Twelve patients (30%) had at least one of the risk factors for vascular events and haemorrhage at or before enrolment. Arterial hypertension was the only predominant risk factor reported in 10 patients (25%).

Previous and Concomitant Treatments

All patients (40 patients) were receiving at least one previous treatment at baseline. Previous treatments by class taken by ≥ 30% of patients were Vitamin D and analogues (27 patients [67.5%]), calcium (21 patients [52.5%]), folic acid and derivatives (18 patients [45%]), iron bivalent, oral preparations (16 patients [40%]), iron trivalent, oral preparations and ACE inhibitors (15 patients [37.5%]), antacids with sodium bicarbonate and drugs for treatment of hyperkalemia and hyperphosphatemia (13 patients [32.5%]), and dihydropyridine derivatives (12 patients [30%]).

All patients (40 patients) continued receiving at least one concomitant treatment during the study including the extension period. The concomitant treatment classes taken by ≥ 30% of patients were Vitamin D and analogues (29 patients [72.5%]), calcium (22 patients [55%]), folic acid and derivatives (19 patients [47.5%]), ACE inhibitors (18 patients [45%]), iron bivalent, oral preparations and iron trivalent, oral preparations (17 patients [42.5%] in each class), drugs for treatment of hyperkalemia and hyperphosphatemia (16 patients [40%] in each class), dihydropyridine derivatives (13 patients [32.5%]), antibiotics and antacids with sodium bicarbonate and other antipsoriatics for topical use (14 patients [35%] in each class), somatropin and somatropin agonists and sulfonamides (12 patients [30%] in each class).

Anticoagulation Treatment

Two patients (5%) were receiving anticoagulation treatment at baseline and continued to receive it during the study. One patient received enoxaparin sodium and another patient received nadroparin calcium.

Iron Supplementation

A majority of patients (35 patients [87.5%]) were receiving iron supplementation at baseline. Most enrolled patients (36 patients [90.0%]) continued receiving iron supplementation during the study including the extension period

Outcomes and estimation

Primary efficacy endpoint: Change in Hb concentration (g/dl) between the baseline and the evaluation period

During the evaluation period (weeks 17-21), the data was evaluable for 38 patients. The mean (±SD) change in Hb concentration level during the evaluation period showed a 0.48 (1.03) g/dL increase above the baseline level. The 90% CI for the mean change in Hb concentration levels from baseline was within the protocol specified range of ±1,1 g/dL and the SD was <1.5 g/dL.

Table 44. 90% confidence interval for haemoglobin values (g/dl) and change from baseline: ITT population

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

Table 45. Haemoglobin values (g/dL) and change from baseline: ITT population

Visit	MIRCERA SC (N=40) Value at Visit	Change from Baseline
Baseline (Day -35 to Day 1)		
n	40	
Mean (SD)	11.02 (0.53)	
Median	11.08	
Min - Max	10.1 - 12.2	
Q1 - Q3	10.61 - 11.39	
Week 3		
n	40	40
Mean (SD)	11.69 (0.97)	0.67 (0.74)
Median	12.00	0.74
Min - Max	9.5 - 14.0	-1.2 - 2.2
Q1 - Q3	10.90 - 12.25	0.16 - 1.00
Week 5		
n	40	40
Mean (SD)	11.21 (1.02)	0.19 (0.94)
Median	11.15	0.27
Min - Max	8.2 - 13.2	-2.5 - 2.3
Q1 - Q3	10.55 - 11.85	-0.47 - 0.62
Week 9		
n	39	39
Mean (SD)	11.68 (1.42)	0.64 (1.21)
Median	11.70	0.82
Min - Max	7.5 - 14.4	-3.2 - 3.0
Q1 - Q3	11.00 - 12.50	-0.13 - 1.49
Week 13		
n	38	38
Mean (SD)	11.56 (1.17)	0.51 (1.10)
Median	11.70	0.50
Min - Max	7.7 - 13.5	-3.0 - 2.8
Q1 - Q3	11.00 - 12.20	0.06 - 1.10
Week 17		
n	37	37
Mean (SD)	11.46 (1.33)	0.42 (1.39)
Median	11.50	0.33
Min - Max	8.4 - 15.0	-2.6 - 4.4
Q1 - Q3	10.70 - 12.40	-0.18 - 1.05
Week 19		
n	37	37
Mean (SD)	11.81 (1.11)	0.77 (1.14)
Median	12.00	0.82
Min - Max	9.2 - 15.1	-2.0 - 3.5
Q1 - Q3	11.20 - 12.50	0.05 - 1.61
Week 21		
n	38	38
Mean (SD)	11.10 (0.91)	0.05 (0.99)
Median	11.10	0.04
Min - Max	9.3 - 12.7	-2.4 - 1.5
Q1 - Q3	10.40 - 11.90	-0.79 - 0.92
Evaluation Period (Weeks 17 - 21)		
n	38	38
Mean (SD)	11.54 (0.96)	0.48 (1.03)
Median	11.64	0.59
Min - Max	9.2 - 13.9	-1.8 - 2.5
Q1 - Q3	10.65 - 12.13	-0.03 - 1.20

The mean Hb concentration level was maintained within the targeted range of 10-12 g/dL and the mean change in Hb level was within ±1 g/dL of the baseline Hb levels. At all-time points, the mean Hb concentration levels showed an increase above the baseline levels.

A total of 3 patients out of the 40 enrolled patients were excluded from the analysis of change in mean Hb concentration levels at Weeks 17 and 19:

- At Week 17, two patients had discontinued the study and one patient underwent RBC transfusion within the previous 3 Weeks of the scheduled visit at Week 17.

- At Week 19, along with the 2 discontinued patients, one patient had missed the visit scheduled at Week 19.

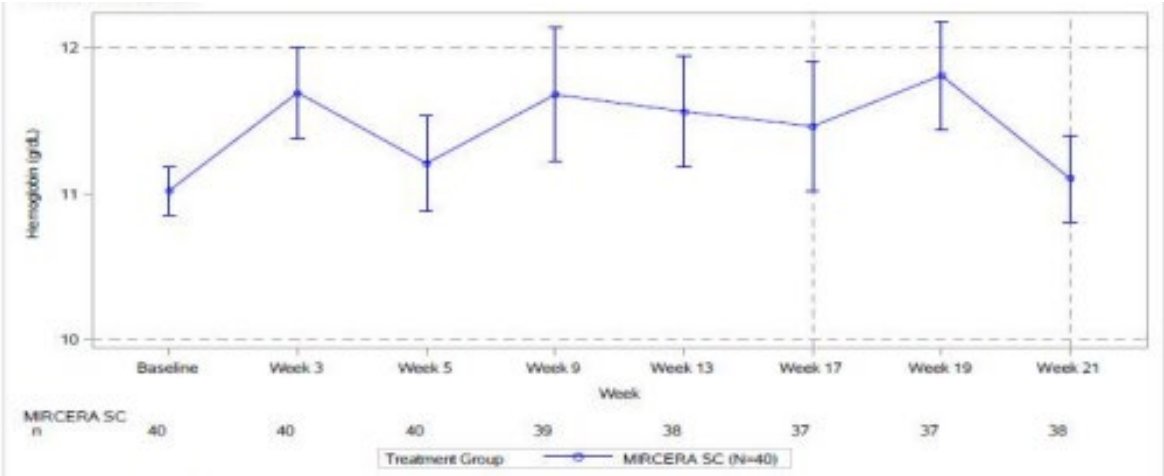


Figure 26. Mean haemoglobin values during the core study period: ITT population

Secondary efficacy endpoints

Patients with Mean Hb within 10-12 g/dL and Change from Baseline within ±1 g/dL during Evaluation Period

During the evaluation period, the data was evaluable for 38 patients (Table 46). The numbers of patients who had maintained mean Hb concentration level during the evaluation period were as follows:

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

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

Table 46. Summary of patients maintaining stable haemoglobin during the evaluation period: ITT

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

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

The number of patients outside of the targeted mean Hb range of 10-12 g/dL and ± 1 g/dL of the baseline Hb levels during the evaluation period is provided in Table 47 and Table 48, respectively.

Table 47. Number of patients with mean Hb outside of the target range (10-12 g/dL) during the evaluation period

Hb Categories	Number of Patients
Hb Level below 10 g/dL	
9 to 9.5 g/dL	1
9.5 to 10 g/dL	1
Total	2
Hb Level Above 12 g/dL	
12 to 12.5 g/dL	7
12.5 to 13 g/dL	3
13 to -13.5 g/dL	1
13.5 to 14 g/dL	1
Total	12

Table 48. Number of patients with mean Hb outside of the target range (±1g/dL) during the evaluation period

Hb Categories	Number of Patients
Change in Hb below 1 g/dL of baseline	
–1 to –1.5 g/dL	2
–1.5 to –2 g/dL	2
Total	4
Change in Hb during Above 1 g/dL of baseline	
1 to 1.5 g/dL	10
1.5 to 2 g/dL	3
2 to 2.5 g/dL	2
Total	15

Mircera dose over time

Overall, the Mircera dose was decreased over time from the starting dose at Week 1 until Week 17. The median was considered for reporting Mircera dose.

Ratio Mircera Dose: Overall, the median (min-max) ratio of starting dose (Week 1) to the dose at the Week 17 was 1.44 (range: 0.2 -3.8), indicating that the Mircera dose was decreased over the course of the core study period. Patients who were not administered a Mircera dose at Week 17 visit due to the applicable dose adjustment rules were excluded from the ratio computation. There were 5 such patients; therefore, at Week 17, the data of 33 patients were available for calculation of the median ratio of Mircera dose.

Mircera Dose in core period: The median (min-max) Mircera dose at Week 1 was 75 μg (range: 15-360 μg) and it was 50 μg (range: 0-250 μg) at Week 17. This was a median (min-max) decrease by 20 μg (–250.0 - 120 μg) compared to the starting dose at Week 1 (Table 49). All patients received a median of 5 doses (range: 1-5) of Mircera. The median Mircera dose was 67 μg over a median duration of 16.14 weeks (range: 0.1-18.3 weeks).

By body weight and by surface area at Week 17, the median (min-max) Mircera dose decreased by –0.81 μg/kg (range: –6.3-3.8 μg/kg) and by –20.30 μg/ m2 (range: –182.6-110.4) compared to the starting dose at Week 1, respectively.

Table 49. Summary of Mircera dose over time during the core study period: safety population

	MIRCERA SC (N=40)
Treatment duration (weeks)	
n	40
Mean (SD)	15.00 (3.20)
Median	16.14
Min - Max	0.1 - 18.3
Average dose (ug)	
n	40
Mean (SD)	78.65 (62.92)
Median	67.00
Min - Max	8.0 - 338.0
Number of doses	
n	40
Mean (SD)	4.9 (0.7)
Median	5.0
Min - Max	1 - 5
Week 1	
Dose (ug)	
n	40
Mean (SD)	91.50 (70.08)
Median	75.00
Min - Max	15.0 - 360.0
Week 5	
Dose (ug)	
n	39
Mean (SD)	88.85 (67.25)
Median	75.00
Min - Max	15.0 - 360.0
Change from Baseline (ug)	
n	39
Mean (SD)	-3.08 (20.28)
Median	0.00
Min - Max	-50.0 - 75.0
Week 9	
Dose (ug)	
n	39
Mean (SD)	70.38 (78.76)
Median	50.00
Min - Max	0.0 - 360.0
Change from Baseline (ug)	
n	39
Mean (SD)	-21.54 (67.83)
Median	0.00
Min - Max	-250.0 - 190.0
Week 13	
Dose (ug)	
n	38
Mean (SD)	75.72 (80.83)
Median	50.00
Min - Max	0.0 - 360.0
Change from Baseline (ug)	
n	38
Mean (SD)	-16.64 (52.49)
Median	-25.00
Min - Max	-120.0 - 210.0
Week 17	
Dose (ug)	
n	38
Mean (SD)	65.84 (61.39)
Median	50.00
Min - Max	0.0 - 250.0
Change from Baseline (ug)	
n	38
Mean (SD)	-26.53 (69.02)
Median	-20.00
Min - Max	-250.0 - 120.0
Ratio of dose (Week 1/ Week 17)	
n	33
Mean (SD)	1.39 (0.72)
Median	1.44
Min - Max	0.2 - 3.8

Patients with dose adjustments

Mircera dose adjustments (increase, decrease, or both) were made for the majority of the patients (34 patients [85%]) during the core period. Five patients (12.5%) did not require any adjustment in their Mircera dose. For most of the patients, Mircera dose was decreased (25 patients [62.5%]). The Mircera dose was increased in 7 patients (17.5%). The predominant reason for these dose modifications was as per protocol (33 patients [82.5%]), which allowed the Mircera dose adjustments to maintain the individual patient's Hb concentration levels within a target range of 10–12 g/dL or within ±1 g/dL of baseline Hb levels. 2 (5%) dose modification was due to a medication error and 3 (7,5%) due to physician decision.

Table 50. Summary of Patients with dose adjustments of the 4-weekly dose during the core study period: ITT population

	MIRCERA SC (N=40) No. (%)
No Dose Change	5 (12.5%)
Any Dose Change	34 (85.0%)
Dose Increase(s) only	7 (17.5%)
Dose Decrease(s) only	25 (62.5%)
Dose Decrease(s) and Increase(s)	2 (5.0%)

Criterion for dose adjustment: Current 4-weekly dose differs more than +- 20% from previous dose.
One patient had only one dose and so was not counted in any category.

Ancillary analyses

Subgroup analyses

Subgroup analyses by the key stratification factors age group (<5, 5-11, ≥12 years), dialysis status at the start of the study (no dialysis, PD or HD), and previous ESA treatment (epoetin [alfa or beta] or darbepoetin alpha) were performed.

Age group (<5, 5-11, ≥12 years)

Change in Mean Hb concentration (Primary Efficacy Endpoint) (Table 51)

In the age group of <5 years, the mean (±SD) Hb concentration level at baseline was 11.02 (0.33) g/dL and it was 11.63 (0.90) g/dL in the evaluation period, which was an increase of 0.57 g/dL (0.88) from the baseline level.

In the age group of 5-11 years, the mean (±SD) Hb concentration level at baseline was 10.85 (0.50) g/dL and it was 11.23 (1.07) g/dL in the evaluation period, which was an increase of 0.38 (1.16) g/dL from the baseline level.

In the age group of ≥12 years, the mean (±SD) Hb concentration level at baseline was 11.12 (0.64) g/dL and it was 11.68 (0.92) g/dL in the evaluation period, which was an increase of 0.50 (1.08) g/dL from the baseline level.

Table 51. Haemoglobin values (g/dL) and Change from Baseline by Age Group: ITT population

	MIRCERA SC (N=40)					
	<5 (N=12)		5 - 11 (N=11)		>=12 (N=17)	
Visit	Value at Visit	Change from Baseline	Value at Visit	Change from Baseline	Value at Visit	Change from Baseline
Baseline (Day -35 to Day 1)						
n	12		11		17	
Mean (SD)	11.02 (0.33)		10.85 (0.50)		11.12 (0.64)	
Median	11.06		10.89		11.24	
Min - Max	10.4 - 11.5		10.2 - 11.5		10.1 - 12.2	
Q1 - Q3	10.79 - 11.32		10.29 - 11.37		10.63 - 11.56	
Week 3						
n	12	12	11	11	17	17
Mean (SD)	11.71 (0.54)	0.69 (0.58)	11.40 (1.01)	0.55 (0.60)	11.86 (1.17)	0.74 (0.93)
Median	11.85	0.85	11.60	0.52	12.20	0.71
Min - Max	10.7 - 12.3	-0.4 - 1.4	10.0 - 12.6	-0.2 - 1.7	9.5 - 14.0	-1.2 - 2.2
Q1 - Q3	11.35 - 12.10	0.32 - 1.09	10.40 - 12.20	-0.17 - 0.95	11.30 - 12.50	0.26 - 1.02
Week 5						
n	12	12	11	11	17	17
Mean (SD)	11.02 (0.91)	0.00 (0.85)	11.29 (0.82)	0.44 (0.57)	11.28 (1.23)	0.16 (1.17)
Median	11.00	-0.08	11.40	0.42	11.10	-0.03
Min - Max	9.8 - 12.7	-1.5 - 1.4	9.7 - 12.5	-0.6 - 1.4	8.2 - 13.2	-2.5 - 2.3
Q1 - Q3	10.25 - 11.75	-0.64 - 0.58	10.80 - 11.80	0.18 - 0.61	10.60 - 12.30	-0.47 - 0.85
Week 9						
n	12	12	11	11	16	16
Mean (SD)	11.63 (1.25)	0.61 (1.12)	11.59 (1.22)	0.74 (0.97)	11.78 (1.71)	0.59 (1.47)
Median	11.80	0.84	12.10	1.03	11.55	0.41
Min - Max	8.8 - 13.5	-1.8 - 2.4	9.3 - 13.1	-1.0 - 1.7	7.5 - 14.4	-3.2 - 3.0
Q1 - Q3	10.95 - 12.45	0.05 - 1.28	10.90 - 12.50	-0.23 - 1.61	11.05 - 12.85	-0.19 - 1.65
Week 13						
n	11	11	11	11	16	16
Mean (SD)	11.88 (1.11)	0.82 (0.91)	11.76 (1.08)	0.91 (1.03)	11.20 (1.23)	0.01 (1.12)
Median	12.10	0.65	11.90	0.70	11.35	0.20
Min - Max	9.8 - 13.5	-0.6 - 2.4	9.0 - 13.0	-1.3 - 2.8	7.7 - 12.8	-3.0 - 1.7
Q1 - Q3	11.00 - 12.90	0.17 - 1.67	11.40 - 12.20	0.49 - 1.43	10.90 - 11.90	-0.61 - 0.74
Week 17						
n	11	11	10	10	16	16
Mean (SD)	11.30 (1.16)	0.24 (1.11)	11.05 (1.41)	0.25 (1.45)	11.83 (1.36)	0.64 (1.56)
Median	11.30	0.18	11.80	0.71	11.55	0.23
Min - Max	9.3 - 13.0	-2.2 - 1.7	8.4 - 12.4	-2.6 - 1.9	10.0 - 15.0	-2.2 - 4.4
Q1 - Q3	10.60 - 12.40	-0.59 - 1.05	10.30 - 12.00	-0.18 - 0.99	10.80 - 12.65	-0.17 - 1.38

	MIRCERA SC (N=40)					
	<5 (N=12)		5 - 11 (N=11)		>=12 (N=17)	
Visit	Value at Visit	Change from Baseline	Value at Visit	Change from Baseline	Value at Visit	Change from Baseline
Week 19						
n	11	11	11	11	15	15
Mean (SD)	11.95 (0.98)	0.89 (0.93)	11.49 (1.27)	0.64 (1.37)	11.94 (1.11)	0.79 (1.17)
Median	12.30	0.98	11.90	1.12	12.00	0.71
Min - Max	10.3 - 13.1	-0.5 - 2.2	9.2 - 13.2	-2.0 - 1.9	10.6 - 15.1	-1.4 - 3.5
Q1 - Q3	11.00 - 12.80	-0.08 - 1.67	10.50 - 12.30	-1.00 - 1.68	11.20 - 12.30	0.05 - 1.33
Week 21						
n	11	11	11	11	16	16
Mean (SD)	11.30 (1.06)	0.24 (1.11)	10.88 (0.81)	0.03 (0.81)	11.11 (0.89)	-0.07 (1.06)
Median	11.30	0.92	11.00	-0.07	11.10	0.04
Min - Max	9.3 - 12.4	-1.5 - 1.4	9.8 - 12.6	-1.4 - 1.5	9.5 - 12.7	-2.4 - 1.3
Q1 - Q3	10.40 - 12.30	-1.05 - 1.17	10.10 - 11.30	-0.50 - 0.62	10.50 - 11.90	-0.82 - 0.71
Evaluation Period (Weeks 17 - 21)						
n	11	11	11	11	16	16
Mean (SD)	11.63 (0.90)	0.57 (0.88)	11.23 (1.07)	0.38 (1.16)	11.68 (0.92)	0.50 (1.08)
Median	11.95	0.63	11.63	1.01	11.57	0.40
Min - Max	10.5 - 12.8	-0.9 - 1.8	9.2 - 12.5	-1.7 - 1.6	10.4 - 13.9	-1.8 - 2.5
Q1 - Q3	10.58 - 12.35	-0.10 - 1.23	10.32 - 12.07	-1.12 - 1.18	11.14 - 12.04	-0.02 - 1.04
Week 25						
n	5	5	7	7	13	13
Mean (SD)	11.44 (0.35)	0.32 (0.53)	11.57 (0.93)	0.71 (0.71)	11.08 (1.26)	-0.10 (1.37)
Median	11.40	0.31	11.70	0.77	11.10	0.08
Min - Max	11.1 - 12.0	-0.3 - 1.1	10.3 - 12.9	-0.2 - 1.7	9.4 - 13.3	-2.2 - 2.4
Q1 - Q3	11.20 - 11.50	-0.12 - 0.57	10.70 - 12.40	0.08 - 1.51	10.10 - 11.40	-1.14 - 0.83
Week 29						
n	4	4	6	6	13	13
Mean (SD)	11.30 (0.85)	0.19 (1.04)	10.72 (0.83)	-0.08 (0.63)	11.42 (1.39)	0.25 (1.34)
Median	11.50	0.43	10.50	-0.30	11.10	0.45
Min - Max	10.1 - 12.1	-1.3 - 1.2	9.7 - 11.8	-0.8 - 0.7	8.9 - 13.7	-2.7 - 1.9
Q1 - Q3	10.80 - 11.80	-0.54 - 0.92	10.20 - 11.60	-0.47 - 0.67	10.60 - 12.40	-0.48 - 1.63
Week 33						
n	4	4	7	7	13	13
Mean (SD)	11.30 (0.34)	0.19 (0.59)	10.90 (0.80)	0.04 (0.92)	11.12 (1.41)	-0.05 (1.56)
Median	11.30	0.16	11.10	0.41	11.30	0.00
Min - Max	10.9 - 11.7	-0.4 - 0.9	9.7 - 11.8	-1.8 - 0.9	8.2 - 14.1	-2.5 - 3.5
Q1 - Q3	11.05 - 11.55	-0.29 - 0.67	10.10 - 11.70	-0.38 - 0.57	10.40 - 11.70	-0.94 - 0.53

	MIRCERA SC (N=40)					
	<5 (N=12)		5 - 11 (N=11)		>=12 (N=17)	
Visit	Value at Visit	Change from Baseline	Value at Visit	Change from Baseline	Value at Visit	Change from Baseline
Week 37						
n	4	4	7	7	13	13
Mean (SD)	11.18 (0.71)	0.07 (0.96)	10.76 (0.63)	-0.11 (0.85)	11.15 (0.86)	-0.02 (0.97)
Median	11.30	0.23	10.60	-0.29	11.00	-0.34
Min - Max	10.3 - 11.8	-1.1 - 0.9	10.0 - 11.7	-1.5 - 1.2	10.0 - 12.7	-1.7 - 1.9
Q1 - Q3	10.60 - 11.75	-0.74 - 0.87	10.10 - 11.40	-0.38 - 0.57	10.40 - 11.80	-0.47 - 0.45
Week 41						
n	4	4	7	7	11	11
Mean (SD)	10.55 (0.73)	-0.56 (0.96)	10.91 (1.14)	0.05 (1.33)	10.88 (0.69)	-0.27 (0.89)
Median	10.80	-0.28	10.70	-0.32	10.70	-0.27
Min - Max	9.5 - 11.1	-1.9 - 0.2	9.5 - 12.5	-1.8 - 2.2	9.4 - 11.9	-2.5 - 0.7
Q1 - Q3	10.05 - 11.05	-1.29 - 0.17	10.10 - 12.40	-0.60 - 1.37	10.60 - 11.40	-0.64 - 0.35
Week 45						
n	4	4	7	7	10	10
Mean (SD)	11.05 (1.59)	-0.06 (1.84)	10.59 (1.02)	-0.28 (0.88)	10.59 (0.83)	-0.52 (1.05)
Median	11.10	0.03	10.20	-0.28	10.60	-0.54
Min - Max	9.4 - 12.6	-2.0 - 1.7	9.4 - 12.0	-1.9 - 0.9	9.5 - 12.1	-2.2 - 1.0
Q1 - Q3	9.70 - 12.40	-1.64 - 1.52	9.90 - 12.00	-0.72 - 0.50	10.00 - 11.20	-1.07 - 0.43

Mircera dose over time

The ratio (Week 1: Week 17) of median Mircera dose indicated a greater decrease in dose among patients in 5-11 years (1.50 [range: 0.2 – 2.5]) and <5 years (1.50 [range: 0.6 – 3.8]) age groups compared with ≥12 years age group (1.23 [range: 0.6 – 2.5]) (Table 52).

Table 52. Ratio (Week 1:Week 17) of median Mircera dose by age group

	MIRCERA SC (N=40)		
	<5 (N=12)	5 - 11 (N=11)	>=12 (N=17)
Ratio of dose (Week 1/ Week 17)			
n	10	11	12
Mean (SD)	1.44 (0.91)	1.49 (0.77)	1.26 (0.51)
Median	1.50	1.50	1.23
Min - Max	0.6 - 3.8	0.2 - 2.5	0.6 - 2.5

At Week 1 and Week 17, the median Mircera dose by body weight was higher among patients in the <5 years (3.57 at week 1 and 2.22 at week 17) compared to the 5-11 years (2.52 at week 1 and 1.47 at week 17) and ≥12 years (2.38 at week 1 and 1.32 at week 17) age groups.

Table 53. Dose by bodyweight over time during the core study period by age group: safety population

	MIRCERA SC (N=40)		
	<5 (N=12)	5 - 11 (N=11)	>=12 (N=17)
Treatment duration (weeks)			
n	12	11	17
Mean (SD)	14.82 (3.07)	16.21 (0.10)	14.34 (4.12)
Median	16.00	16.14	16.14
Min - Max	8.3 - 16.9	16.1 - 16.4	0.1 - 18.3
Average dose/kg (ug/kg)			
n	12	11	17
Mean (SD)	4.03 (2.93)	2.19 (1.09)	2.22 (1.72)
Median	3.38	1.88	1.61
Min - Max	1.1 - 11.9	0.8 - 4.7	0.8 - 6.5
Number of doses			
n	12	11	17
Mean (SD)	4.8 (0.6)	5.0 (0.0)	4.8 (1.0)
Median	5.0	5.0	5.0
Min - Max	3 - 5	5 - 5	1 - 5
Week 1			
Dose/kg (ug/kg)			
n	12	11	17
Mean (SD)	4.41 (2.47)	2.55 (1.46)	2.63 (1.67)
Median	3.57	2.52	2.38
Min - Max	2.1 - 10.0	1.0 - 5.5	0.8 - 6.7
Week 5			
Dose/kg (ug/kg)			
n	12	11	16
Mean (SD)	4.43 (2.77)	2.52 (1.44)	2.57 (1.75)
Median	3.79	2.30	2.37
Min - Max	2.0 - 12.4	0.8 - 5.6	0.8 - 7.0
Change from baseline dose/kg (ug/kg)			
n	12	11	16
Mean (SD)	0.02 (1.24)	-0.02 (0.29)	-0.13 (0.66)
Median	-0.10	-0.01	-0.05
Min - Max	-2.9 - 2.4	-0.5 - 0.6	-1.1 - 1.9
Week 9			
Dose/kg (ug/kg)			
n	12	11	16
Mean (SD)	4.21 (3.15)	1.98 (1.16)	1.91 (2.41)
Median	3.30	1.81	1.03
Min - Max	1.3 - 12.1	0.0 - 4.3	0.0 - 7.9
Change from baseline dose/kg (ug/kg)			
n	12	11	16
Mean (SD)	-0.19 (1.59)	-0.57 (1.14)	-0.78 (2.15)
Median	-0.22	-0.80	-0.07
Min - Max	-3.1 - 2.9	-2.8 - 1.4	-5.6 - 4.6
Week 13			
Dose/kg (ug/kg)			
n	11	11	16
Mean (SD)	3.11 (3.31)	1.68 (1.03)	2.43 (2.40)
Median	3.06	1.64	1.60
Min - Max	0.0 - 11.5	0.0 - 3.6	0.0 - 8.9
Change from baseline dose/kg (ug/kg)			
n	11	11	16
Mean (SD)	-1.24 (2.09)	-0.87 (1.73)	-0.27 (1.77)
Median	-1.37	-0.88	-0.48
Min - Max	-5.2 - 1.6	-4.8 - 2.3	-2.7 - 5.6
Week 17			
Dose/kg (ug/kg)			
n	11	11	16
Mean (SD)	3.55 (3.75)	2.20 (1.71)	1.68 (1.74)
Median	2.22	1.47	1.37
Min - Max	0.0 - 13.6	0.7 - 5.3	0.0 - 6.1
Change from baseline dose/kg (ug/kg)			
n	11	11	16
Mean (SD)	-0.80 (2.53)	-0.34 (1.61)	-1.01 (1.92)
Median	-1.07	-0.81	-0.68
Min - Max	-6.3 - 3.7	-1.7 - 3.8	-5.6 - 2.8
Ratio of dose/kg (Week 1/ Week 17)			
n	10	11	12
Mean (SD)	1.57 (1.01)	1.54 (0.80)	1.26 (0.48)
Median	1.59	1.55	1.21
Min - Max	0.7 - 4.2	0.2 - 2.6	0.5 - 2.4

Patients with dose adjustments

During the core study period, a higher proportion of patients in the age group of <5 years (11 patients [91.7%]) and 5-11 years (10 patients [90.9%]) required adjustments (increase, decrease, or both) in Mircera dose compared with patient in ≥12 years age group (13 patients [76.5%]) during the core period.

A decrease in the Mircera dose was noted in 7 patients [58.3%]) in the age group of <5 years, 7 patients (63.6%) in the age group of 5-11 years, and 11 patients (64.7%) in the age group of ≥12 years.

An increase in the Mircera dose was noted in 4 patients (33.3%) in the age group of <5 years, 2 patients (18.2%) in the age group of 5-11 years, and 1 patient (5.9%) in the age group ≥12 years.

One patient each in the age groups 5-11 years (1 patient [9.1%]) and ≥12 years (1 patient [5.9%]) had both an increase as well as a decrease in the Mircera dose during the core study period. No patient in the age group of <5 years required both increase and decrease in the Mircera dose (Table 54).

In terms of absolute number of Mircera dose changes, the mean (±SD) number of dose decrease was 1.0 (1.0), 1.2 (0.9), and 1.0 (0.7) in the age groups of <5 years, 5-11 years, and ≥12 years, respectively. The mean number of dose increase was 0.3 (0.5), 0.5 (1.2), and 0.3 (0.6) in the age groups of <5 years, 5-11 years, and of ≥12 years, respectively (Table 55).

Table 54. Summary of patients with dose adjustments of the 4-weeks dose during the core study period by age group: ITT population

	MIRCERA SC (N=40)		
	<5 (N=12) No. (%)	5 - 11 (N=11) No. (%)	>=12 (N=17) No. (%)
No Dose Change	1 (8.3%)	1 (9.1%)	3 (17.6%)
Any Dose Change	11 (91.7%)	10 (90.9%)	13 (76.5%)
Dose Increase(s) only	4 (33.3%)	2 (18.2%)	1 (5.9%)
Dose Decrease(s) only	7 (58.3%)	7 (63.6%)	11 (64.7%)
Dose Decrease(s) and Increase(s)	0	1 (9.1%)	1 (5.9%)

Criterion for dose adjustment: Current 4-weekly dose differs more than +- 20% from previous dose.
One patient had only one dose and so was not counted in any category.

Table 55. Summary of number of dose adjustments in the 4-weeks dose during the core study period by age groups: ITT population

	MIRCERA SC (N=40)		
	<5 (N=12)	5 - 11 (N=11)	>=12 (N=17)
N of Dose administrations			
n	12	11	17
Mean (SD)	4.8 (0.6)	5.0 (0.0)	4.8 (1.0)
Median	5.0	5.0	5.0
Min - Max	3 - 5	5 - 5	1 - 5
N of Any Dose Changes			
n	12	11	16
Mean (SD)	1.3 (0.8)	1.7 (1.1)	1.3 (0.9)
Median	1.0	2.0	1.0
Min - Max	0 - 3	0 - 4	0 - 3
N of Dose Decreases			
n	12	11	16
Mean (SD)	1.0 (1.0)	1.2 (0.9)	1.0 (0.7)
Median	1.0	1.0	1.0
Min - Max	0 - 3	0 - 2	0 - 2
N of Dose Increases			
n	12	11	16
Mean (SD)	0.3 (0.5)	0.5 (1.2)	0.3 (0.6)
Median	0.0	0.0	0.0
Min - Max	0 - 1	0 - 4	0 - 2
N of Constant Doses			
n	12	11	16
Mean (SD)	2.5 (0.9)	2.3 (1.1)	2.8 (0.9)
Median	3.0	2.0	3.0
Min - Max	1 - 4	0 - 4	1 - 4
Total number of patients with at least one dose modification	11 (91.7%)	10 (90.9%)	13 (76.5%)
Number of patients with at least one dose modification due to			
MEDICATION ERROR	0	1 (9.1%)	1 (5.9%)
PER PROTOCOL	11 (91.7%)	10 (90.9%)	12 (70.6%)
PHYSICIAN DECISION	0	0	3 (17.6%)

Criterion for dose adjustment: Current dose differs more than +- 20% from previous dose.

Dyalisis status

Change in Mean Hb concentration (Primary Efficacy Endpoint)

In patients not on dialysis, the mean (±SD) Hb concentration level at baseline was 10.89 (0.45) g/dL and it was 11.66 (0.95) g/dL during the evaluation period, which was an increase of 0.73 (0.75) g/dL from the baseline level.

In patients on peritoneal dialysis, the mean (±SD) Hb concentration level at baseline was 11.14 (0.53) g/dL and it was 11.57 (0.98) g/dL in the evaluation period, which was an increase of 0.40 (1.18) g/dL from the baseline level.

In patients on haemodialysis, the mean (±SD) Hb concentration level at baseline was 11.02 (0.74) g/dL and it was 11.01 (0.90) g/dL in the evaluation period, which was a decrease of 0.01 (1.23) g/dL from the baseline level.

Mircera dose over time

The ratio (Week 1: Week 17) of median Mircera dose indicated a greater decrease in dose among patients on peritoneal dialysis (1.50 [range: 0.6 – 2.5]) and patients not on dialysis (1.50 [range: 0.2 – 3.8]) compared with patients on haemodialysis (1.00 [range: 0.6 – 1.3]).

Table 56. Ratio (Week 1: Week 17) of median Mircera dose by dialysis status

	MIRCERA SC (N=40)		
	Not on dialysis (N=17)	Peritoneal dialysis (N=18)	Hemodialysis (N=5)
Ratio of dose (Week 1/ Week 17)			
n	15	13	5
Mean (SD)	1.56 (0.91)	1.33 (0.55)	1.04 (0.29)
Median	1.50	1.50	1.00
Min - Max	0.2 - 3.8	0.6 - 2.5	0.6 - 1.3

Patients with dose adjustments

During the core study period, all patients (18 patients [100%]) on peritoneal dialysis required adjustments (increase, decrease, or both) in Mircera dose compared with 14 patients (82.4%) not on dialysis. There were 2 patients (40.0%) on haemodialysis who required adjustments (increase, decrease, or both) in Mircera dose.

A decrease in Mircera dose was noted in 11 patients (64.7%) not on dialysis, 13 patients (72.2%) on peritoneal dialysis and 1 patient (20%) on haemodialysis at study start.

An increase in Mircera dose was noted in 3 patients (17.6%) not on dialysis, 3 patients (16.7%) on peritoneal dialysis and 1 patient (20%) on haemodialysis at study start.

In terms of absolute number of Mircera dose changes, the mean (±SD) number of dose decrease was 1.2 (1.0), 1.2 (0.7), and 0.2 (0.4) in patients not on dialysis, on peritoneal dialysis, and on haemodialysis, respectively. The mean (±SD) number of dose increase was 0.4 (1.0), 0.3 (0.6), and 0.2 (0.4) in patients not on dialysis, on peritoneal dialysis, and on haemodialysis, respectively.

Previous ESA treatment

Change in Mean Hb concentration (Primary Efficacy Endpoint)

In patients previously on darbepoetin alfa treatment, the mean (±SD) Hb concentration level at baseline was 11.01 (0.52) g/dL and it was 11.67 (1.11) g/dL during the evaluation period, which was an increase of 0.65 (1.09) g/dL from the baseline level.

In patients previously on epoetin alfa/beta treatment, the mean (±SD) Hb concentration level at baseline was 11.03 (0.54) g/dL and it was 11.40 (0.78) g/dL during the evaluation period, which was an increase by 0.32 (0.96) g/dL from the baseline level.

Mircera dose over time

The ratio (Week 1: Week 17) of median Mircera dose indicated a greater decrease in dose among patients previously on darbepoetin alfa (1.50 [range: 0.2 – 2.5]) compared with the patients on epoetin alfa/ beta (1.00 [range: 0.6 – 3.8]).

Table 57. Ratio (Week 1:Week 17) of median Mircera dose by dialysis status

	MIRCERA SC (N=40)	
	Darbepoetin Alfa (N=20)	Epoetin Alfa/ Beta (N=20)
Ratio of dose (Week 1/ Week 17)		
n	16	17
Mean (SD)	1.54 (0.59)	1.25 (0.81)
Median	1.50	1.00
Min - Max	0.2 - 2.5	0.6 - 3.8

Patients with dose adjustments

During the core study period, all patients (20 patients [100%]) previously on darbepoetin alfa treatment required adjustments (increase, decrease, or both) in Mircera dose compared with patients previously treated with epoetin alfa/beta (14 patients [70.0%]).

A decrease in Mircera dose was noted in higher proportion of patients (17 patients [85.0%]) previously treated with darbepoetin alfa compared with patients on previous epoetin alfa/beta treatment (8 patients [40.0%]).

An increase in Mircera dose was noted in higher proportion of patients (5 patients [25%]) previously treated with epoetin alfa/beta compared with patients on previous darbepoetin alfa treatment (2 patients [10.0%]).

In terms of absolute number of Mircera dose changes, the mean (±SD) number of dose decrease was 1.3 (0.7) and 0.8 (1.0) in patients previously treated with darbepoetin alfa and epoetin alfa/beta, respectively. The mean (±SD) number of dose increases was 0.4 (0.9) and 0.4 (0.6) in patients previously treated with darbepoetin alfa and epoetin alfa/beta, respectively.

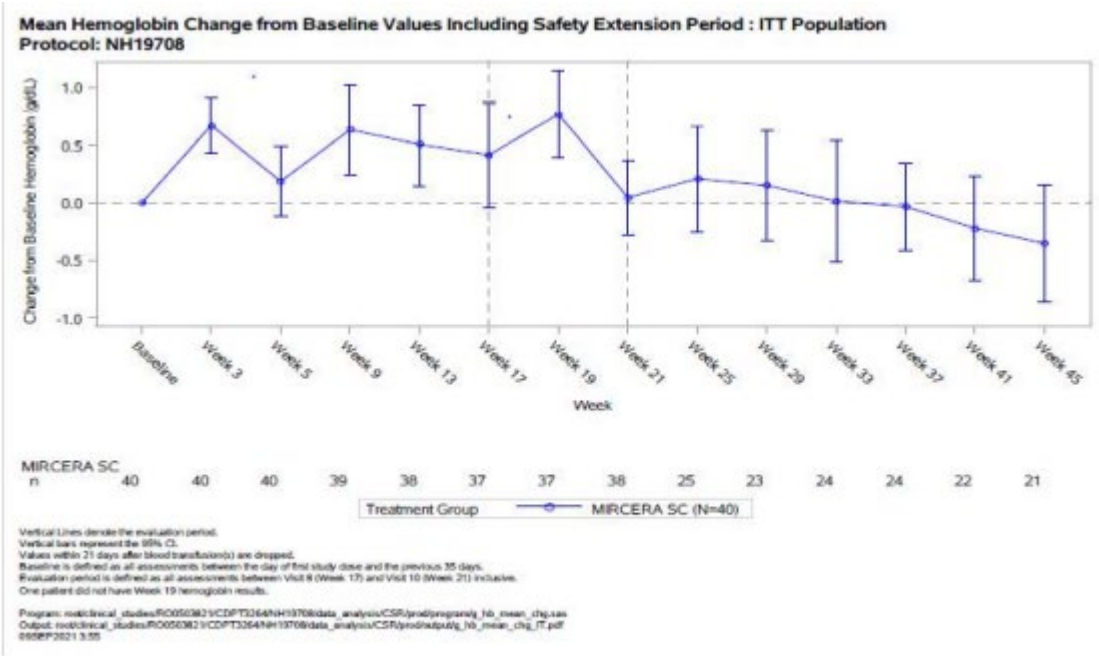
Efficacy evaluations during the safety extension period

Haemoglobin over time

A total of 25 patients who were eligible entered the safety extension period. At baseline, the mean (±SD) Hb concentration value was 11.02 (0.53) g/dL. The mean change in Hb values from baseline during the safety extension was maintained around baseline (0), indicating stable mean Hb concentration levels.

In Group 2, during the safety extension period, all mean Hb values remained within the 10-12 g/dL range. 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. The change from baseline in Group 2 during the safety extension period fluctuated around baseline.



SC=subcutaneous; ITT=Intent-to-Treat.

Figure 27. Mean Hb Change from Baseline Values Including Safety Extension Period: ITT Population

The Hb concentration levels were maintained within the target range of 10-12 g/dL by 13/21 patients (61.9%) at Week 45. Five patients (23.8%) had Hb concentration levels below 10 g/dL and 3 patients (14.3%) had Hb concentration levels above 12 g/dL at Week 45.

Table 58. Summary of patients maintaining stable haemoglobin over time within 10-12 g/dl-including safety extension period: ITT population

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

Mircera dose over time

The median (min-max) Mircera dose at Week 1 was 75 μg (range: 15-360 μg) and it was 50 μg (range: 10.0-560.0 μg) at Week 41. This was a median (min-max) decrease by −25 μg (−150.0-200.0 μg) at Week 41 compared to Week 1.

Dose adjustments

During the safety extension period, Mircera dose adjustments (increase, decrease, or both) were made in majority of the patients (18 patients [72%]). Seven patients (28%) did not require any dose change. Mircera dose increase as well as decrease were made in 10 patients (40%). Six patients (24%) had dose decrease only, and 2 patients (8%) had dose increase only (Table 59).

Table 59. Summary of patients with 4-weekly dose during the safety extension period: ITT population

	MIRCERA SC (N=25) No. (%)
No Dose Change	7 (28.0%)
Any Dose Change	18 (72.0%)
Dose Increase(s) only	2 (8.0%)
Dose Decrease(s) only	6 (24.0%)
Dose Decrease(s) and Increase(s)	10 (40.0%)

Patient-reported outcomes

Injection pain

5 minutes following ESA administration was assessed using a VAS scale at screening (both visits) when the patients were on previous ESA treatment (darbepoetin alfa or epoetin alfa/beta) and after transitioning to Mircera treatment at Week 1 (Visit 3) and at Week 9 (Visit 6).

A plot of mean (±SD) pain score over time by nurse's, patient's and parent's assessment indicated a higher injection pain scores during screening while the patients were on treatment with previous darbepoetin alfa or epoetin alfa/beta compared to treatment with Mircera at both injection time points at Week 1 and Week 9.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial NH19707

Title: An Open-Label, Multi-Center, Multiple Dose Study to Determine the Optimum Starting Dose of Intravenous MIRCERA for Maintenance Treatment of Anemia in Pediatric Patients with Chronic Kidney Disease on Hemodialysis.	
Study identifier	NH19707 (EudraCT 2007-007758-70 and NCT00717366)
Design	Phase II, open-label, single-arm, multicenter, sequential dose-finding study with Mircera administered once every 4 weeks IV in paediatric patients with CKD receiving haemodialysis who had switched from other ESAs (epoetin alfa/beta or darbepoetin alfa).

	Duration of main phase:	22 weeks (screening 2 weeks, dose titration 16 weeks, evaluation core period 4 weeks) (First patient entered 28 July 2008)
	Duration of Extension phase (optional safety extension period):	52 weeks (LPLV 29 March 2016)
Hypothesis	This was an exploratory study without a powered statistical group comparison. Due to the nature of the study, no formal testing was planned and all tests and p-values were descriptive.	
Treatments groups	Mircera Group 1: Intermediate-conversion-factor Group	Mircera was administered IV once every 4 weeks for the duration of the study. The starting dose was based on an intermediate conversion factor and the previous Erythropoiesis-Stimulating Agent (ESA) dose: *For patients previously on epoetin alfa or beta:* Intermediate dose (Group 1): Mircera starting dose: 4 × weekly EPO dose (IU)/250, 1×/4 weeks IV *For patients previously on darbepoetin alfa:* Intermediate dose (Group 1): Mircera starting dose: 4 × weekly darbepoetin alfa dose (µg)/1.1, 1×/4 weeks IV. Dose adjustments could be performed during the entire study.
	Mircera Group 2: High-Conversion-Factor Group	Mircera was administered IV once every 4 weeks for the duration of the study. The starting dose was based on an high dose conversion factor and the previous Erythropoiesis-Stimulating Agent (ESA) dose: *For patients previously on epoetin alfa or beta:* High dose (Group 2): Mircera starting dose: 4 × weekly EPO dose (IU)/125, 1×/4 weeks IV. *For patients previously on darbepoetin alfa:* High dose (Group 2): Mircera starting dose: 4 × weekly darbepoetin alfa dose (µg)/0.55, 1×/4 weeks IV. Dose adjustments could be performed during the entire study.
Endpoints and definitions	Primary efficacy endpoint	Change in Hb concentration (g/dL) between the baseline period and the evaluation period (weeks 17- 20)
	Secondary efficacy endpoints	Number of patients with an average Hb concentration during the evaluation period within ±1 g/dL of their baseline Hb. Number of patients with an average Hb concentration during the evaluation period above, within or below the range of 10-12 g/dL Incidence of red blood cell (RBC) transfusions Change in reticulocyte count

	Exploratory efficacy endpoints	Change in Mircera dose over time, including the change between the starting dose and the evaluation period.	
Database lock	28 April 2016		
Results and Analysis			
Analysis description	Descriptive statistics		
Analysis population and time point description	Intent to treat population included all patients enrolled in the study.		
Descriptive statistics and estimate variability	Treatment group	Mircera Group 1 (intermediate-conversion factor)	Mircera Group 2 (high-conversion factor)
	Number of subjects	16	48
	Primary endpoint: adjusted mean estimated from ANCOVA model for average change in Hb from baseline and during evaluation period	-0.74 g/dL	-0.09 g/dL
	95% CI	-1.32 to -0.16	-0.45 to 0.26
	Standard Error	0.2876	0.1767
	Secondary endpoint: Number of patients with an average Hb concentration during the evaluation period above, within or below the range of 10-12 g/dL and change from baseline ±1g/dL	Hb maintained within ±1g/dL of baseline: 58.3% Hb maintained within 10-12 g/dL: 75% Hb above 12g/dL: 0% Hb below 10 g/dL: 25% Hb within ± 1g/dL and within 10-12 g/dL: 58.3%	Hb maintained within ±1g/dL of baseline: 75.0% Hb maintained within 10-12 g/dL: 80.6% Hb above 12g/dL: 8.3% Hb below 10 g/dL: 11.1% Hb within +/- 1g/dL and within 10-12 g/dL: 69.4%
	Summary of patients with dose adjustments	No dose change: 3 (18.8%) Any dose change: 13 (81.3%) Dose increase only: 9 (56.3%) Dose decrease only: 2 (12.5%) Dose decrease and increase: 2 (12.5%)	No dose change: 11 (22.9%) Any dose change: 37 (77.1%) Dose increase only: 14 (29.2%) Dose decrease only: 5 (10.4%) Dose decrease and increase: 18 (37.5%)
Analysis description	Change in Hb concentration (g/dL) between the baseline and evaluation periods (primary efficacy endpoint) was calculated on a per-patient basis, using an area under the curve (AUC) approach. For all analyses concerning Hb, no imputation was made for missing values and analysis was performed on observed cases only. 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.		

Summary of Efficacy for trial NH19708

Title: An Open-Label, Single-Arm, Multicenter Study to Ascertain the Optimal Starting Dose of Mircera Given Subcutaneously for the Maintenance Treatment of Anemia in Pediatric Patients with Chronic Kidney Disease on Dialysis or Not Yet on Dialysis.		
Study identifier	NH19708 (EudraCT 2016-004779-39 - NCT03552393)	
Design	Open-label, single-arm, multicenter study to ascertain the optimal starting dose of Mircera given subcutaneously for the maintenance treatment of anemia in pediatric patients with CKD on dialysis or not yet on dialysis.	
	Duration of main phase:	23 Weeks (screening 3 weeks, dose titration 16 weeks, evaluation 4 weeks) (First Patient Enrolled: 03 August 2018)
	Duration of Extension phase (optional safety extension period):	24 Weeks (LPLV 19 July 2021)
Hypothesis	This was an exploratory study without a powered statistical group comparison. Due to the nature of the study, no formal testing was planned and all tests and p-values were descriptive.	
Treatments groups	Single Arm	MIRCERA SC injection once every 4 weeks. The starting dose was based on an high dose conversion factor and the previous Erythropoiesis-Stimulating Agent (ESA) dose: *For patients previously on epoetin alfa or beta:* High dose (Group 2): Mircera starting dose: 4 × weekly EPO dose (IU)/125, 1×/4 weeks IV. *For patients previously on darbepoetin alfa:* High dose (Group 2): Mircera starting dose: 4 × weekly darbepoetin alfa dose (µg)/0.55, 1×/4 weeks IV. Dose adjustments could be performed during the entire study.
Endpoints and definitions	Primary endpoint	Change in Hb concentration (g/dL) between the baseline and the evaluation period for each patient
	Secondary endpoint	Number of patients with an average Hb concentration during the evaluation period within ±1 g/dL of their baseline Hb or above, within or below the range of 10-12 g/dL Change in Mircera dose over time, including the change between the starting dose and the evaluation period
Database lock	30 August 2021	
Results and Analysis		

Analysis description	Descriptive statistics	
Analysis population and time point description	Intent to treat population consists of all patients enrolled in the study.	
Descriptive statistics and estimate variability	Treatment group	Core study
	Number of subjects	40
	Primary endpoint: change in Hb (g/dL) concentration at evaluation period	0.48
	Standard deviation	1.03
	90% CI for mean	(0.20, 0.76)
	Secondary endpoint: Number of patients with an average Hb concentration during the evaluation period within ±1 g/dL of their baseline Hb or above, within or below the range of 10-12 g/dL.	Hb maintained within ±1g/dL of baseline: 50.0% Hb maintained within 10-12 g/dL: 63.2% Hb above 12g/dL: 31.6% Hb below10 g/dL: 5.3% Hb within ± 1g/dL and within 10-12 g/dL: 47.7%
	Summary of patients with dose adjustments	No dose change: 5 (12.5%) Any dose change: 34 (85.0%) Dose increase only: 7 (17.5%) Dose decrease only: 25 (62.5%) Dose decrease and increase: 2 (5.0%)
Analysis description	No formal statistical testing was performed. The primary and secondary efficacy analyses were performed on the intent-to treat population consisting of all enrolled patients. The Hb change from baseline was calculated on a per-patient basis, using an Area Under the curve (AUC) approach to calculate an individual's average for both the baseline and evaluation periods and taking the difference. This per-patient change was then averaged over all patients and the confidence intervals calculated.	

Supportive studies

MH40258 -Real world evidence of safety and dosing of Mircera in children with chronic kidney disease

This is a non-interventional study secondary data use (NIS SDU) and voluntary post-authorization safety study (PASS) of paediatric patients from the two existing registries within the International Paediatric Dialysis Network (IPDN): International Paediatric Peritoneal Dialysis Network (IPPN) and International Paediatric Haemodialysis Network (IPHN) registries. The registries collect prospective (baseline and every 6 months) information from paediatric PD and HD centers worldwide.

The data collection periods for this study were from 2007 through Q2 2021 for IPPN and from 2013 through Q2 2021 for IPHN.

The study aims to further characterize safety, dosing and related Hb concentrations and to validate the dose simulation models of Mircera in paediatric patients (<18 years of age) with anaemia due to CKD in a real-world setting.

Patients aged 0 months to <18 years at initial Mircera visit, on chronic PD or HD were included.

A total of 229 paediatric dialysis patients (177 PD, 52 HD) receiving Mircera were analysed in this study. The median age at first visit was 10.6 (interquartile range 4.2-14.6) years for the PD and 14.1 (10.4-16.2) years for the HD cohort, respectively. The median observation time under Mircera exposure was 6.1 (0-12.5) months and 11.9 (0-17.9) months for the PD and HD patients, respectively. More than PD patients 50% were from Europe, and almost all HD patients were from Europe (96,2%).

Safety results- hospitalizations events and deaths

The safety of Mircera was assessed by aggregate analysis of the hospitalization events and deaths during exposure to the drug. Hospitalizations and deaths were monitored from 6 months before the first visit under Mircera until the last visit under Mircera or, if available, for 6 months after the last visit with reported Mircera exposure.

During a median observation time of 13.5 months, 121 (68.4%) PD patients under Mircera had at least one hospitalization while using Mircera. There were 5 (2.8%) deaths observed in the PD cohort under Mircera. 121 (68.4%) PD patients had at least one hospitalization while using Mircera and a total of 370 hospitalizations occurred during 270 observation years (calculated as mean observation time * number of patients), i.e., 1.37 per year of observation. 77% of the hospitalizations (1.03 per year) were non-elective. Infections (thereof 56% PD-related) accounted for 85/277 (31%), non-elective PD technique complications for 37/277 (14%), and cardiovascular, fluid and electrolyte complications for 62/277 (23%) of the non-elective hospitalizations. The latter included 18 admissions for hypertensive crisis in 14 patients.

A total of 6 hospitalizations in three patients were related to anaemia, including two transfusions performed in one patient and two episodes of bleeding in another patient. No episodes of thrombotic or thromboembolic events were reported in any of the children undergoing PD.

In the HD cohort, 36 patients (69.2%) had 132 hospitalizations during 83.6 observation years while using Mircera, corresponding to a rate of 1.58 hospitalization events per year of observation. 106/132 (80%) of these hospitalizations (1.27 per year) were non-elective. 43/106 (41%) of the non-elective hospitalization events were due to HD technique complications, 30/106 (28%) to infections, and 16/106 (15%) to cardiovascular/fluid imbalance events. 10 admissions in seven patients were due to hypertensive crises. No access-unrelated thrombotic or thromboembolic events and no blood transfusions were reported.

Five children in the PD cohort and 2 of the children undergoing HD died while receiving Mircera (i.e. 3% of the total population), corresponding to an overall mortality rate of 19.8 cases per 1000 observation years. The causes of death included infections (n=2), intracranial bleeding (n=2), congestive heart failure (n=2), and one case of sudden death at home.

Haemoglobin concentration and Mircera dose

The mean (SD) Hb level was 11.0 (1.9) g/dL at first observation and 10.9 (1.7) g/dL at last observation under Mircera in the PD cohort, and 10.2 (1.6) g/dL at first and 10.4 (1.7) g/dL at last observation under Mircera in the HD group. In both cohorts, Hb levels were stable over time and did not differ by age group. At last observation, 46.9% of the children on PD and 48.1% of those on HD had a Hb value in the target range of 10-12 g/dL, while 24.9% of PD and 13.5% of HD displayed higher and 28.2% of PD and 38.5% of HD patients lower Hb levels.

In the PD cohort the median (Q1, Q3) Mircera monthly dose at first visit was 100 (50, 120) µg, 3.4 (2.3, 5.4) µg/kg body weight, or 94 (67, 144) µg/m2 body surface area, and at last visit 100 (50, 150) µg, 3.5 (2.3, 5.1) µg/kg, or 95 (62, 145) µg/m2. In the HD cohort, the median monthly Mircera dose at first visit was 107 (80, 129) µg, 2.9 (1.7, 4.0) µg/kg, or 89 (59, 115) µg/m2, and at last visit 80 (54, 129) µg, 2.1 (1.2, 3.4) µg/kg, or 63 (40, 98) µg/m2.

In general, the absolute monthly Mircera dose increased with age. At the first visit, in the PD cohort, it changed from median (interquartile range) 30 (30-100) µg in infants younger than 2 years to 114 (75-161) µg in the adolescent age group. In the HD cohort it changed from median (interquartile range) 91 (54-129) µg in children 2 to <5-year-old to 107 (80-129) µg in the adolescent age group. At the last visit, in the PD cohort, it changed from median (interquartile range) 50 (30-100) µg in infants younger than 2 years to 146 (78-170) µg in the adolescent age group. In the HD cohort it changed from median (interquartile range) 91 (54-129) µg in 2 children 2 to <5-year-old to 80 (54-129) µg in the adolescent age group.

While absolute Mircera doses increased with age, the weight-related doses decreased substantially with increasing body size in both cohorts. In the children on PD aged <2, 2-<5, 5-<12 and 12-<18 years, the median Mircera monthly dose was 7.9 (4.9, 11.6), 5.4 (3.0, 7.5), 3.2 (2.7, 4.9) and 2.6 (1.9, 3.9) µg/kg at first observation and 5.1 (3.4, 9.8), 5.2 (2.7, 6.9), 3.0 (2.3, 4.7) and 3.0 (1.7, 4.5) µg/kg at last observation. In children on HD aged 2-<5, 5-<12 and 12-<18 years, the median monthly dose was 6.5 (4.5, 8.6), 4.0 (3.2, 4.9), and 2.2 (1.3, 3.0) µg/kg at first observation and 6.5 (4.5, 8.6), 2.9 (2.1, 4.0), and 1.5 (0.9, 2.4) µg/kg at last observation, respectively.

The age-related dosing differences were smaller when doses were normalized to body surface area rather than body weight, with median doses at last visit of 114 (69, 218), 121 (69, 166), 87 (62, 120) and 98 (59, 145) µg/m2/month at <2, 2-<5, 5-<12 and 12-<18 years in the PD cohort and 155 (100, 211), 83 (59, 104) and 53 (35, 81) µg/m2/month at 2-<5, 5-<12 and 12-<18 years in the HD group.

2.4.2. Discussion on clinical efficacy

This application is an extension of indication to include treatment of symptomatic anaemia associated with CKD in paediatric patients from 3 months to less than 18 years of age on ESA maintenance treatment. Mircera is already approved for the treatment of symptomatic anaemia associated with CKD in adult patients and, according to the SmPC, can be used both in adult patients not currently treated with an erythropoiesis stimulating agent (ESA) and in those currently treated with an ESA (epoetins or dabepoetin).

Epoetins and darbepoetin are usually given on a weekly basis while Mircera is proposed to be administered every 4 weeks. This, in principle, could be considered an advantage for patients.

In the clinical development, a paediatric formulation has not been developed, as indicated in the agreed PIP. The formulation and strengths used in the paediatric studies supporting this extension of indication were those authorised for adults (solution for injection in single-use pre-filled syringes and a number of different strengths). The MAH has provided data to support that few patients included in the clinical studies received doses below 30 mcg. Due to the rarity of CKD in paediatric patients, it is agreed that few patients would have an uncovered need. Furthermore, taking into account the therapeutic indication requested (ESA conversion), and the fact that other ESAs are also authorised in vials, this question has not been further pursued. Nevertheless, as Mircera is manufactured in pre-filled syringes and partial doses should not be administered due to the risk of medication errors, this has been properly reflected in the SmPC sections 4.2, 4.4 and 6.6.

The efficacy of Mircera is based on extrapolation from data adults and on 2 dose finding studies (NH19707 and NH19708). Supportive data from a non-interventional study has also been provided (study MH40258). Overall, the extrapolation concept is acceptable considering the availability of PK data in children compared to adults, the data in adults from adequate and controlled trials and that the physiopathology and the mechanism of action for efficacy is the same in adults and children.

Study NH19707 was a phase II, open-label, multicentre, dose finding study designed to provide evidence on the optimal dose of Mircera in the paediatric population (5-17 years old) with CKD anaemia on haemodialysis, following iv administration of Mircera after switching from other ESAs (i.e., epoetin alfa/beta or darbepoetin alfa). The duration of study NH19707 was 20 weeks (core phase). 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.

This study was exploratory without a powered statistical group comparison.

The main objective was to determine the optimum starting dose of Mircera in paediatric patients with CKD on haemodialysis when switching from stable maintenance treatment with other ESA.

The protocol included two different groups with different conversion factors based on their previous ESA dose to find the optimum Mircera starting dose. Group 1 comprised patients who started with an intermediate conversion factor dose. In the adaptive design, this starting dose was assessed. A group 2 was enrolled for treatment with a higher conversion factor dose, double than that of group 1. 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-week safety extension period. During this period, the patients continued to receive Mircera once every 4 weeks with Hb concentration measurements occurred less frequently (every 4 weeks).

A total of 112 patients were screened. Of these, 64 were enrolled (16 initially in Group 1 and then 48 in group 2). The mean age was 11 and 13 years in groups 1 and 2, respectively. Children recruited in Group 2 were a bit older. The number of patients between 5 to 11 years of age was greater in group 1 than in group 2 with a low representation of patients younger than 8 years of age (3 and 2 patients <8 years in groups 1 and 2, respectively).

During the evaluation phase, 4 patients in Group 1 and 13 in Group 2 withdrew from treatment due to renal transplant. The MAH replaced these patients with new ones in order to maintain the sample size planned at the beginning of the study. Baseline characteristics of patients who withdrew and replaced patients were similar. Replacement is agreeable taking into account the single-arm study design. Twelve patients in group 1 and 35 patients in group 2 completed the evaluation period. Thirty-seven of these completers went on to participate in the optional 1-year safety extension, which was completed by 17 patients.

The primary efficacy endpoint was the change in Hb concentration (g/dL) between the baseline period and the evaluation period (weeks 17-21). Only results for group 2 were presented, as this was the dose conversion factor, proposed also for study NH19708.

In study NH19707, the adjusted mean change in Hb from baseline to the evaluation period was -0.09 g/dl (95%IC: -0.45 to 0.26) in group 2. During the evaluation period, 75% of patients maintained Hb values within the range of ± 1 g/dL of the baseline levels, and 81% within the range of 10-12 g/dL. The proportions of patients with Hb values within ± 1 g/dL and within 10-12 g/dL were 69%. During the core phase the dose administered could be adjusted in order to maintain Hb levels between 10-12 g/dL. IV Mircera dose changes occurred frequently (77% of patients in Group 2), as expected for patients receiving ESA.

Twenty-eight patients entered the extension study. Overall, the mean dose of Mircera was maintained stable within the Hb range. These results should be considered with caution as there was a high withdrawal rate.

Avoiding/reducing number of transfusions is a relevant goal of the treatment with ESAs. In this study 3 patients needed blood transfusions, one in Group 1 and 2 in Group 2, due to Hb reduction, procedural haemorrhage and intracranial hematoma. Due to the single arm design of the study it is not possible to interpret this data.

Study NH19708 was a phase II, open-label, single-arm, multicenter study designed to ascertain the starting dose of Mircera given subcutaneously in 3 months-17 years paediatric patients with CKD anaemia on dialysis or not yet on dialysis when switching with epoetin alfa, epoetin beta or dabepoetin alfa.

The main objective was to ascertain the starting dose of Mircera given subcutaneously in paediatric patients with CKD on dialysis or not yet on dialysis when switching from stable SC maintenance treatment with other ESA.

The core study was for 23 weeks and consisted of three periods: Screening (3 weeks), dose titration (16 weeks), and evaluation (4 weeks). Patients completing the 20 weeks of treatment with Hb within ±1 g/dL of their baseline Hb and within the target range of 10-12 g/dL, were eligible to enter an optional 24-week safety extension period. Mircera was administered subcutaneously once every 4 weeks for the duration of the study. Dose adjustments were permitted to maintain target Hb levels. The starting dose was based on conversion factors obtained from the dose-finding study (group 2, Study NH19707).

In both studies patients had to be receiving maintenance treatment with ESA therapy at least 8 weeks before enrolment with no weekly dose change > 25% (increase or decrease) for at least 4 weeks before the first dose of Mircera, IV or SC for studies NH19707 and NH19708, respectively.

Overall, 64 patients were screened and 40 of them were enrolled. The majority of patients completed (95%), and 2 patients discontinued during the core period; the reason for discontinuation were kidney transplant and use of prohibited medication. 25 eligible patients (62.5%) opted to enter the safety extension period. Of the 13 patients who did not enter the safety extension, 7 would have been eligible.

Mean age of patients included in study NH19708 was 10.2 years. Twelve (30% patients) were < 5 years, 11 (27.5%) 5-11 years, and 17 patients 12-17 years. A minimum enrolment of 10 patients below 5 years was considered of interest by the PDCO to provide the needed PK data.

The primary efficacy endpoint was the change in Hb concentration (g/dL) between the baseline period and the evaluation period (weeks 17-21). The mean change (±SD) in Hb concentration level during the evaluation period for study NH19708 showed a 0.48 (1.03) g/dL increase above the baseline level. The 90% CI for the mean change in Hb concentration levels from baseline was within the protocol specified range of ±1.1 g/dL and the SD was <1.5 g/dL.

During the evaluation period, 50% of patients maintained Hb values within the range of ± 1 g/dL of the baseline levels, and 63.2% within the range of 10-12 g/dL. The proportions of patients with Hb values within ± 1 g/dL and within 10-12 g/dL were 47.4%.

During the evaluation phase the dose administered could be adjusted in order to maintain Hb levels between 10-12 g/dL. The mean dose was decreased over time approximately by 30%. Furthermore, 62.5% of patients had dose decreases only, and a considerable number of patients had an Hb value above the target range (31.6%). Although dose adjustments are considered common during ESA therapy, results from study NH19708 suggested the conversion factor proposed might not be adequate for the switch to the SC route and that the Mircera dose could be too high.

Theoretical safety concerns have been raised following the SC to SC switch (AEs related to high Hb levels), and the popPK model was updated. Uncertainties of differences in paediatric SC bioavailability between other ESAs have been described, and these differences may have an impact on the apparently too high initial Mircera SC dose. Results from an additional analysis showed that the high PK and PD variability for Mircera lead to an overlap on PD outcomes considering or not differences in bioavailability between ESAs. However, due to the limitations on the PK/PD model, these results are considered rather limited. For practical reasons the high conversion factor for IV to IV and SC to SC switch was the MAH's preferred option, which is acknowledged by the CHMP. However, taking into account that a substantial percentage of patients in the SC to SC switch had Hb levels above the upper limit of the accepted range, and the potential AEs related to too high Hb levels, the intermediate conversion factor is considered more appropriate by the CHMP. Also, this is not expected to affect efficacy due to frequent monitoring is still required for these patients, and Mircera dose can be titrated.

Subgroup analysis, in general, are aligned with primary efficacy results.

2.4.3. Conclusions on the clinical efficacy

The efficacy of Mircera is based on extrapolation from data in adults and on 2 dose finding studies (NH19707 and NH19708). Supportive data from a non-interventional study has also been provided (study MH40258). Overall, the extrapolation is acceptable considering the availability of PK data in children compared to adults, the data in adults from adequate and controlled trials and that the physiopathology and the mechanism of action for efficacy is the same in adults and children.

For study NH19707 in which patients on haemodialysis were switched from IV ESA to Mircera IV route efficacy results show that mean Hb concentration level remained stable during the evaluation period. These results support the proposed posology as well as the possibility to switch to IV Mircera paediatric patients 5 to 17 years of age on haemodialysis who are stabilised with an ESA.

Results from study NH19708 in which patients were switched from stable SC maintenance treatment with epoetin alfa, epoetin beta, or darbepoetin alfa to Mircera SC route support the SC use in the paediatric population (3 months to 17 years of age).

2.5. Clinical safety

Introduction

ESA therapy is an established treatment option for alleviate signs and symptoms associated with anaemia in patients with CKD. However, ESA therapy has been associated with risks, including pure red cell aplasia, stroke, vascular access loss and hypertension. In clinical trials, an increased risk of death, serious cardiovascular events including thrombosis or cerebrovascular events including stroke was observed when ESAs were administered to target a haemoglobin of greater than 12 g/dl.

The primary safety information in paediatric patients is derived from studies NH19707 and NH19708, that included patients 5-17 years old with clinically stable chronic renal anaemia on haemodialysis treatment and patients 3 months-17 years paediatric patients with CKD anaemia on dialysis or not yet on dialysis, respectively. Patients included in both studies were receiving maintenance treatment with an erythropoiesis stimulating agent (ESA) prior to switching to methoxy polyethylene glycol-epoetin beta (Mircera).

The duration of core period study was 20 weeks and 23 weeks for studies NH19707 and NH19708, respectively. Patients completing the core period 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-week and 24-week safety extension period, respectively.

After the first administration of Mircera, dose adjustments were permitted to maintain target Hb levels, which were measured once a week during the core study period and once every four weeks during the safety extension.

The clinical safety of Mircera in paediatric patients is further supported by analysis of post-marketing adverse event (AE) reports and data from international registries recording use of Mircera in paediatric patients as well as reports of paediatric Mircera use in the literature.

Patient exposure

Study NH19707

A total of 64 paediatric patients received at least one dose of Mircera in this study. The extent of exposure (core study and safety extension) is summarized in Table 60. Nineteen patients were exposed to Mircera for at least 15 months.

Table 60. Summary of patient exposure, including safety extension period of study NH19707: Safety population

Age Category	Group 1	Group 2	Total
All patients	**16**	**48**	**64**
Exposure			
At least 1 month	14 (87.5%)	44 (91.7%)	58 (90.6%)
At least 6 months	7 (43.8%)	26 (54.2%)	33 (51.6%)
At least 12 months	5 (31.3%)	15 (31.3%)	20 (31.3%)
At least 15 months	5 (31.3%)	14 (29.2%)	19 (29.7%)
Mean ± SD exposure, years	0.67 ± 0.532	0.72 ± 0.501	0.70 ± 0.506
Sum exposure, years	10.7	34.4	45.1
5-11 years	**9**	**16**	**25**
Exposure			
At least 1 month	8 (88.9%)	16 (100.0%)	24 (96.0%)
At least 6 months	5 (55.6%)	9 (56.3%)	14 (56.0%)
At least 12 months	3 (33.3%)	4 (25.0%)	7 (28.0%)
At least 15 months	3 (33.3%)	4 (25.0%)	7 (28.0%)
Mean ± SD exposure, years	0.69 ±0.569	0.72 ±0.490	0.71 ±0.508
Sum exposure, years	6.2	11.5	17.7
12-17 years	**7**	**32**	**39**
Exposure			
At least 1 month	6 (85.7%)	28 (87.5%)	34 (87.2%)
At least 6 months	2 (28.6%)	17 (53.1%)	19 (48.7%)
At least 12 months	2 (28.6%)	11 (34.4%)	13 (33.3%)
At least 15 months	2 (28.6%)	10 (31.3%)	12 (30.8%)
Mean ± SD exposure, years	0.64 ± 0.525	0.72 ± 0.515	0.70 ± 0.511
Sum exposure, years	4.5	22.9	27.4

During the core study period, the median cumulative total dose of Mircera was 466 µg in 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 18 administrations and one in Group 2 received 19.

Study NH19708

A total of 40 paediatric patients received at least one dose of Mircera in this study. The extent of exposure (core study and safety extension) is summarized in Table 61.
Overall, the patients received a median of 5 Mircera administrations (range: 1-5 administrations) during the core period. The majority of patients (38 patients [95%]) received at least 5 Mircera administrations.

Table 61. Summary of number of Mircera administrations- including safety extension period: safety

	MIRCERA SC (N=40)
Exposure:	
At least 1 Administration	40 (100%)
At least 2 Administrations	39 (97.5%)
At least 3 Administrations	39 (97.5%)
At least 4 Administrations	38 (95.0%)
At least 5 Administrations	38 (95.0%)
At least 6 Administrations	25 (62.5%)
At least 7 Administrations	25 (62.5%)
At least 8 Administrations	24 (60.0%)
At least 9 Administrations	24 (60.0%)
At least 10 Administrations	24 (60.0%)
At least 11 Administrations	22 (55.0%)
Overall Exposure (Administrations) :	
n	40
Mean (SD)	8.5 (3.2)
Median	11.0
Min - Max	1 - 11
Q1 - Q3	5.0 - 11.0

Adverse events

Study NH19707

Core period

For the Core Period, overall, 49/64 patients (77%) reported at least one AE (12/16 [75%] in Group 1 and 37/48 [77%] in Group 2) (Table 62).

Table 62. Summary of Adverse Events Reported in the core period of study NH19707: Safety population

	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)

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

The most commonly affected SOCs (with > 15% of patients overall with AEs) were Infections and infestations (30/64 patients overall [47%]), General disorders and administration site conditions (12/64 patients [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%]).

Adverse events with a frequency ≥ 2% by SOC during the core period is shown in Table 63. Most of the AEs were associated with CKD, other previous and concurrent risk factors/diseases and treatments, and/or dialysis-induced, and considered by the investigator to be unrelated to the study drug.

Seven AEs in 5/64 patients (8%) overall (1 AE [decreased Hb] in 1 patient in Group 1 and 6 AEs [arteriovenous fistula thrombosis, extensive interdialytic weight gain, hyperkalemia, hyperphosphatemia, dental caries, thrombosis in device] in 4 patients in Group 2) were considered by the investigator to be related to the study drug.

Table 63. Summary of Adverse Events (⩾2% of patients overall) by SOC during the Core Period of Study NH19707: 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	12 (75.0)	37 (77.1)	49 (76.6)
Total Number of AEs	23	112	135
INFECTIONS AND INFESTATIONS			
Total Pts With at Least one AE	7 (43.8)	23 (47.9)	30 (46.9)
NASOPHARYNGITIS	-	9 (18.8)	9 (14.1)
BRONCHITIS	1 (6.3)	3 (6.3)	4 (6.3)
DEVICE RELATED INFECTION	-	3 (6.3)	3 (4.7)
VIRAL INFECTION	1 (6.3)	2 (4.2)	3 (4.7)
GASTROENTERITIS	1 (6.3)	1 (2.1)	2 (3.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Total Pts With at Least one AE	3 (18.8)	9 (18.8)	12 (18.8)
PYREXIA	1 (6.3)	2 (4.2)	3 (4.7)
FATIGUE	-	2 (4.2)	2 (3.1)
PAIN	-	2 (4.2)	2 (3.1)
THROMBOSIS IN DEVICE	-	2 (4.2)	2 (3.1)
GASTROINTESTINAL DISORDERS			
Total Pts With at Least one AE	2 (12.5)	10 (20.8)	12 (18.8)
VOMITING	2 (12.5)	4 (8.3)	6 (9.4)
ABDOMINAL PAIN	1 (6.3)	3 (6.3)	4 (6.3)
DENTAL CARIES	-	2 (4.2)	2 (3.1)
NERVOUS SYSTEM DISORDERS			
Total Pts With at Least one AE	2 (12.5)	10 (20.8)	12 (18.8)
HEADACHE	1 (6.3)	8 (16.7)	9 (14.1)
METABOLISM AND NUTRITION DISORDERS			
Total Pts With at Least one AE	2 (12.5)	7 (14.6)	9 (14.1)
HYPERKALAEMIA	1 (6.3)	2 (4.2)	3 (4.7)
FLUID OVERLOAD	1 (6.3)	1 (2.1)	2 (3.1)
HYPERPHOSPHATAEMIA	-	2 (4.2)	2 (3.1)
VASCULAR DISORDERS			
Total Pts With at Least one AE	1 (6.3)	7 (14.6)	8 (12.5)
HYPERTENSION	1 (6.3)	7 (14.6)	8 (12.5)
HYPOTENSION	-	2 (4.2)	2 (3.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Total Pts With at Least one AE	2 (12.5)	5 (10.4)	7 (10.9)
ARTERIOVENOUS FISTULA THROMBOSIS	1 (6.3)	1 (2.1)	2 (3.1)
PROCEDURAL HAEMORRHAGE	-	2 (4.2)	2 (3.1)
EAR AND LABYRINTH DISORDERS			
Total Pts With at Least one AE	1 (6.3)	4 (8.3)	5 (7.8)
EAR PAIN	-	3 (6.3)	3 (4.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Total Pts With at Least one AE	1 (6.3)	3 (6.3)	4 (6.3)
COUGH	-	2 (4.2)	2 (3.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Total Pts With at Least one AE	-	3 (6.3)	3 (4.7)
THROMBOCYTOPENIA	-	2 (4.2)	2 (3.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Total Pts With at Least one AE	-	2 (4.2)	2 (3.1)
BACK PAIN	-	2 (4.2)	2 (3.1)

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.
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Overall, there were 2 life-threatening AEs (both in group 2, intracranial hematoma and procedural haemorrhage, not related with treatment) 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 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

During the safety extension period, 27 patients (73%) experienced at least one AE (4 [44%] in Group 1 and 23 [82%] in Group 2) (Table 64).

Table 64. Summary of Adverse Events Reported in the safety extension period of study NH19707: Safety population

	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

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: anaemia and urinary tract infection.

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.

Study NH19708

Core period

A majority of patients (32 patients [80%]) experienced at least one AE (Table 65). A total of 106 AEs were reported during the core period. A total of 13 patients (32.5%) experienced SAEs; however, none of these SAEs was considered related to Mircera treatment by the investigator and none resulted in withdrawal or dose modification/interruption. No deaths were reported.

AEs of severe intensity were reported in 6 patients (15%). Two patients (5%) each reported related AEs and AEs leading to dose modification/interruption. One patient required blood transfusion (2.5%).

Table 65. Adverse Events - Core Period: Safety Population

	MIRCERA SC (N=40)
Total number of patients with at least one AE	32 (80.0%)
Total number of AEs	106
Total number of deaths	0
Total number of patients with blood transfusions	1 (2.5%)
Total number of patients withdrawn from study due to an AE	0
Total number of patients with at least one	
AE with fatal outcome	0
Serious AE	13 (32.5%)
Serious AE leading to withdrawal from treatment	0
Serious AE leading to dose modification/interruption	0
Related Serious AE	0
AE leading to withdrawal from treatment	0
AE leading to dose modification/interruption	2 (5.0%)
Related AE	2 (5.0%)
Related AE leading to withdrawal from treatment	0
Related AE leading to dose modification/interruption	0
Severe AE (at greatest intensity)	6 (15.0%)

Investigator text for AEs encoded using MedDRA version 24.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset from first dose of study drug to date of last contact or 28 days after last dose of study drug.

The SOCs in which AEs were experienced by ≥ 15% patients were Infections and infestations (25 patients [62.5%]), Injury, poisoning and procedural complications and Respiratory, thoracic and mediastinal disorders (7 patients [17.5%] in each SOC), Gastrointestinal disorders and General disorders and administration site conditions (6 patients [15%] in each SOC).

The most frequent AEs experienced by ≥5% patients were upper respiratory tract infection (5 patients [12.5%]), accidental overdose (4 patients [10%]), oropharyngeal pain, pyrexia, gastroenteritis, peritonitis (3 patients [7.5%] in each PT), and anaemia, abdominal pain, diarrhea, bronchitis, conjunctivitis, nasopharyngitis, pharyngitis, hyperphosphataemia, headache, and hypertension (2 patients [5%] in each PT).

A total of 4 patients were reported with accidental overdoses in the study. Two accidental overdoses were because of an issue with the functioning of IXRS system. The remaining two accidental overdoses were due to medical error and did not exceed 25% of the dose that should have been administered. In all 4 patients the Mircera dose was corrected at the next visit and the overdosing had no safety impact.

During the core period, two patients experienced 3 AEs of administration site pain and ecchymosis (1 patient [2.5]), and injection site pain (1 patient [2.5%]) considered to be related to Mircera by the investigator.

Table 66. All Adverse Events by System Organ Class and Preferred Term – Core Period: Safety Population

MedDRA System Organ Class MedDRA Preferred Term	MIRCERA SC (N=40) No. (%)
Total number of patients with at least one adverse event	32 (80.0%)
Overall total number of events	106
Infections and infestations	
Total number of patients with at least one adverse event	25 (62.5%)
Total number of events	37
Upper respiratory tract infection	5 (12.5%)
Gastroenteritis	3 (7.5%)
Peritonitis	3 (7.5%)
Bronchitis	2 (5.0%)
Conjunctivitis	2 (5.0%)
Nasopharyngitis	2 (5.0%)
Pharyngitis	2 (5.0%)
Abscess	1 (2.5%)
Appendicitis	1 (2.5%)
COVID-19	1 (2.5%)
Catheter site infection	1 (2.5%)
Device related infection	1 (2.5%)
Ear infection	1 (2.5%)
Enterovirus infection	1 (2.5%)
Escherichia peritonitis	1 (2.5%)
Laryngitis	1 (2.5%)
Pharyngotonsillitis	1 (2.5%)
Pneumonia	1 (2.5%)
Pyelonephritis	1 (2.5%)
Respiratory syncytial virus bronchiolitis	1 (2.5%)

MedDRA System Organ Class	MIRCERA SC (N=40)
MedDRA Preferred Term	No. (%)
Respiratory tract infection viral	1 (2.5%)
Rhinitis	1 (2.5%)
Rhinovirus infection	1 (2.5%)
Viral infection	1 (2.5%)
Injury, poisoning and procedural complications	
Total number of patients with at least one adverse event	7 (17.5%)
Total number of events	9
Accidental overdose	4 (10.0%)
Anaemia postoperative	1 (2.5%)
Contusion	1 (2.5%)
Foot fracture	1 (2.5%)
Incorrect dose administered	1 (2.5%)
Respiratory, thoracic and mediastinal disorders	
Total number of patients with at least one adverse event	7 (17.5%)
Total number of events	8
Oropharyngeal pain	3 (7.5%)
Cough	1 (2.5%)
Hypoxia	1 (2.5%)
Pharyngeal erythema	1 (2.5%)
Rhinorrhoea	1 (2.5%)
Gastrointestinal disorders	
Total number of patients with at least one adverse event	6 (15.0%)
Total number of events	11
Abdominal pain	2 (5.0%)
Diarrhoea	2 (5.0%)
Abdominal pain lower	1 (2.5%)
Enteritis	1 (2.5%)
Gingival bleeding	1 (2.5%)
Vomiting	1 (2.5%)
General disorders and administration site conditions	
Total number of patients with at least one adverse event	6 (15.0%)
Total number of events	6
Pyrexia	3 (7.5%)
Administration site pain	1 (2.5%)
Catheter site injury	1 (2.5%)
Injection site pain	1 (2.5%)
Skin and subcutaneous tissue disorders	
Total number of patients with at least one adverse event	4 (10.0%)
Total number of events	5
Dermatitis	1 (2.5%)
Ecchymosis	1 (2.5%)
Pruritus	1 (2.5%)
Rash papular	1 (2.5%)
Rash pruritic	1 (2.5%)
Blood and lymphatic system disorders	
Total number of patients with at least one adverse event	3 (7.5%)
Total number of events	3
Anaemia	2 (5.0%)
Neutropenia	1 (2.5%)
Musculoskeletal and connective tissue disorders	
Total number of patients with at least one adverse event	3 (7.5%)
Total number of events	3
Arthralgia	1 (2.5%)
Back pain	1 (2.5%)
Limb discomfort	1 (2.5%)

Investigator text for AEs is coded using MedDRA version 24.0.
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset from first dose of study drug to date of last contact or 28 days after last dose of study drug.

MedDRA System Organ Class MedDRA Preferred Term	MIRCERA SC (N=40) No. (%)
Vascular disorders	
Total number of patients with at least one adverse event	3 (7.5%)
Total number of events	5
Hypertension	2 (5.0%)
Hypotension	1 (2.5%)
Metabolism and nutrition disorders	
Total number of patients with at least one adverse event	2 (5.0%)
Total number of events	3
Hyperphosphataemia	2 (5.0%)
Hyperkalaemia	1 (2.5%)
Nervous system disorders	
Total number of patients with at least one adverse event	2 (5.0%)
Total number of events	4
Headache	2 (5.0%)
Reproductive system and breast disorders	
Total number of patients with at least one adverse event	2 (5.0%)
Total number of events	2
Heavy menstrual bleeding	1 (2.5%)
Vulvovaginal erythema	1 (2.5%)
Congenital, familial and genetic disorders	
Total number of patients with at least one adverse event	1 (2.5%)
Total number of events	1
Hydrocele	1 (2.5%)
Endocrine disorders	
Total number of patients with at least one adverse event	1 (2.5%)
Total number of events	1
Hyperparathyroidism	1 (2.5%)
Hepatobiliary disorders	
Total number of patients with at least one adverse event	1 (2.5%)
Total number of events	1
Hepatic cirrhosis	1 (2.5%)
Investigations	
Total number of patients with at least one adverse event	1 (2.5%)
Total number of events	1
Staphylococcus test positive	1 (2.5%)
Product issues	
Total number of patients with at least one adverse event	1 (2.5%)
Total number of events	4
Device malfunction	1 (2.5%)
Product contamination microbial	1 (2.5%)
Thrombosis in device	1 (2.5%)
Renal and urinary disorders	
Total number of patients with at least one adverse event	1 (2.5%)
Total number of events	2
Dysuria	1 (2.5%)
Haematuria	1 (2.5%)

Investigator text for AEs is coded using MedDRA version 24.0.
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset from first dose of study drug to date of last contact or 28 days after last dose of study drug.

The majority of patients (25 patients [62.5%]) experienced AEs of WHO Grade 1-2. The AEs of WHO Grade 3-4 was experienced by 6 patients (15%): 2 patients (5%) experienced Grade 3 AEs and 4 patients (10%) experienced Grade 4 AEs.

Two patients experienced a total of 3 Grade 3 SAEs of respiratory syncytial virus bronchiolitis (1 patient [2.5%]), and peritonitis and device malfunction (1 patient [2.5%]). All 3 SAEs were considered unrelated to Mircera by the investigator and had resolved.

Four patients experienced a total of 4 Grade 4 SAEs of gastroenteritis, appendicitis, anaemia postoperative, and pneumonia (1 patient [2.5%] in each PT). All 4 SAEs were considered unrelated to Mircera by the investigator. Except for gastroenteritis, all the remaining Grade 4 AEs had resolved by the end of core period.

Safety extension period

A total of 16 patients (64%) experienced at least one AE in the safety extension period (Table 67). A total of 53 AEs were reported in the safety extension period. Three patients (12%) each experienced SAEs and AEs of severe intensity. One patient (4%) experienced an AE considered related to Mircera by the investigator. One patient (4%) required blood transfusion. None of the patients experienced AEs leading to treatment withdrawal or AEs leading to dose modification/interruption during the safety extension period.

No major difference was noted in the pattern of AEs between the core and safety extension period.

The SOCs in which AEs were experienced by ≥ 15% patients were Infections and infestations (8 patients [32%]), and General disorders and administration site conditions (5 patients [20%]).

The most frequent AEs experienced by ≥5% patients were upper respiratory tract infection, urinary tract infection, pyrexia, rhinitis, muscle spasms, hypotension, and headache (2 patients [8%] in each PT).

During the safety extension period, one patient experienced an AE of injection site pain (1 patient [4%]) considered to be related to Mircera by the investigator.

Table 67. Adverse Events – Safety Extension Period: Safety Population

	MIRCERA SC (N=25)
Total number of patients with at least one AE	16 (64.0%)
Total number of AEs	53
Total number of deaths	0
Total number of patients with blood transfusions	1 (4.0%)
Total number of patients withdrawn from study due to an AE	0
Total number of patients with at least one	
AE with fatal outcome	0
Serious AE	3 (12.0%)
Serious AE leading to withdrawal from treatment	0
Serious AE leading to dose modification/interruption	0
Related Serious AE	0
AE leading to withdrawal from treatment	0
AE leading to dose modification/interruption	0
Related AE	1 (4.0%)
Related AE leading to withdrawal from treatment	0
Related AE leading to dose modification/interruption	0
Severe AE (at greatest intensity)	3 (12.0%)

Investigator text for AEs encoded using MedDRA version 24.0.
Percentages are based on N in the column headings.
Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset from start of safety extension period to date of last contact or 28 days after last dose of study drug.

The pattern of AEs by intensity was similar between the core and safety extension period.

The AEs of WHO Grade 1-2 were experienced by 12 patients (48%) and WHO Grade 3-4 AEs were experienced by 3 patients (12%). One patient (4%) experienced a non-serious Grade 3 AE of pyrexia and had resolved. Two patients (8%) experienced 2 SAEs of Grade 4 hypotension and anaemia postoperative, both the SAEs had resolved.

Serious adverse event/deaths/other significant events

Deaths

Study NH19707

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.

Study NH19708

No deaths were reported in the study.

Serious adverse event

Study NH19707

Core period

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).

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

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). Of the AEs classified as serious, none were considered related to the study medication.

Study NH19708

During the core period 13 patients (32.5%) experienced a total of 23 SAEs and 3 patients experienced a total of 4 SAEs in the safety extension period. All SAEs were considered unrelated to Mircera treatment by the investigator.

Other significant events

Hypertension

Study NH19707

Core period

Overall, at baseline, 32 patients (50%) had hypertension reported by the investigator as one of the risk factors for vascular events and hemorrhage and 37 (58%) were already receiving or had received

antihypertensive and/or diuretic agents. During the core study period, 8 patients (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 enrolment or within 12 weeks prior to enrolment, and 1 had previously received antihypertensive therapy although this patient was not reported to have hypertension at enrolment or within 12 weeks of enrolment. In 1 patient, 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 increased antihypertensive treatment compared with baseline (5 of these already had increased antihypertensive treatment in the core period).

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.

Study NH19708

At study entry, a total of 21 patients (52.5%) had hypertension.

During the core period, after initiating Mircera treatment, 2 patients reported with 3 non-serious, Grade 2 AEs of hypertension. One patient reported 2 non-serious, Grade 2 AEs of hypertension and 1 patient reported 1 non serious, Grade 2 AE of hypertension. All 3 hypertension AEs were considered unrelated to Mircera treatment by the investigator and resolved with treatment.

No patients experienced any AE of hypertension during the safety extension period.

Overall, in all patients, the median Z-score for the SBP and DBP showed small variation across all visits compared to the median score at baseline during core and safety extension period.

Vascular Access Thrombosis (VAS)

Study NH19707

Core Study Period

During the core study period, 4 patients (3 in Group 2 and 1 in Group 1) reported 5 events that may be classified as vascular access thrombosis. These events were defined as 'arteriovenous fistula thrombosis' in 2 patients and 'thrombosis in device' in 2 patients (1 patient experienced 2 such events).

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

During the safety extension period, 3 patients reported 5 events classified as 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.

Study NH19708

One patient experienced a total of 9 AEs of VAS. Of these 9 events, one was a serious Grade 2 AE and 8 were non-serious. All were considered unrelated to Mircera treatment by the investigator. From Day 128 to day 277, this patient had recurrent thrombosis in device. The patient changed dialysis modality from PD to HD on study day 127 due to PD catheter malfunction.

Anti-Erythropoietin Antibody-Induced Pure Red Cell Aplasia

Study NH19707

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

Study NH19708

Two patients tested positive for anti-EPO antibodies. No effect on Hb or Mircera doses were seen and no AE of PRCA was reported.

Laboratory findings and vital signs

Study NH19707

Hematology

In this study, Hb concentrations, reticulocytes, and red blood cell counts were considered part of the efficacy assessment. One patient had a moderate AE of Hb decreased due, according to the investigator, to the latency effect of Mircera. This AE resolved.

In clinical trials of Mircera in adults, slight decreases in platelet counts have been observed. In study NH19707, 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 but remained within 16% and 20% of baseline, respectively. There was substantial within and between-patient variability of platelets in both groups. In Group 1, 1/16 patients had one or more postbaseline 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 postbaseline values below normal range, of whom 6/19 already had low values at baseline, and 4/47 patients had one or more postbaseline 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 who had one or more post-baseline platelet counts below normal. Thrombocytopenia was reported as an AE in four patients; in all cases, the event was classified as mild and unrelated to study drug.

During the core study period, median haematocrit remained within 15% of baseline for both groups and remained stable during the safety extension period.

Chemistry

Over the entire study period, median changes from baseline for aspartate aminotransferase, alanine aminotransferase, serum albumin, calcium, blood glucose parameters, as well as for potassium and phosphate, were minor, with no obvious trends over time. Abnormal post-baseline values for these parameters were observed only sporadically. The only abnormalities in these parameters reported as AEs were hyperkalemia (4 patients in total), hyperphosphatemia (3 patients in total) and hypocalcemia (1 patient in total). Two of these AEs were reported as severe (hyperkalemia and hyperphosphatemia).

Post baseline values ≥ 800 U/L were seen at some timepoint throughout the study for alkaline phosphatase in 4 and 3 patients in Group 1 and Group 2, respectively. None of these abnormalities were associated with AEs.

C-reactive protein

Median C-reactive protein (CRP) levels remained close to or below the baseline value throughout the study. The majority of patients had normal CRP levels at baseline and these values remained within normal range throughout the study. None of these patients experienced AEs.

Iron parameters

In Group 2, the largest median changes from baseline were observed at Week 13 for iron (+6.75 µM/L from 12.00 µM/L at baseline), at Week 61 for ferritin (245.38 µg/L from 328.00 µg/L for ferritin) and Week 53 for transferrin saturation (13.11% from 26.82% at baseline). A similar pattern was observed in Group 1. In all cases, median values for these parameters remained within normal values. Two patients reported AEs related to iron parameters: iron deficiency and iron overload. Neither of these events was considered related to Mircera.

Vital signs, Physical findings and other observations related to safety

During the core period, plots of pre-dialysis Z scores for systolic blood pressure (SBP) and diastolic blood pressure (DBP) showed no clear trend throughout the study, with median Z scores within ± 1 of the baseline. During the safety extension period, changes from baseline remained small in Group 2. Group 1 showed greater fluctuation, particularly after Week 57, although this may be a consequence of the low patient numbers.

In both dose groups approximately 60% of patients had at least three consecutive predialysis and postdialysis SBP or DBP values at or above the age, sex, and weight specific 95th percentile. Median sitting pulse rate did not change by more than 10 bpm with respect to baseline at any time during the study.

Changes in height and weight

Analysis of changes in height and weight did not reveal any indication of an impact of Mircera on growth.

Study NH19708

Hematology

In this study, Hb concentrations, reticulocytes, and red blood cell counts were considered part of the efficacy assessment.

Mean Hb concentrations raised during the study period although Mircera dose was decreased. This should be further discussed (See efficacy MO/OC).

The red blood cell count was consistent as expected in patients with anemia due to CKD at baseline. The median RBC count showed a slight improvement over time during the core and safety extension period.

No clinically significant change was noted in the platelet count during the core period. Overall, a slight decrease in median platelet count was noted in all visits from the baseline value of 262.50 × 109 / L to 235 ×109/L at Week 21 and to 234 ×10 9/L at Week 45 but was within the normal range during the entire study period.

One patient showed a shift in platelet values from normal to low post baseline and 2 patients shifted from normal to high post baseline value. The patient with shift from normal to low post baseline value did not have any AE related to low platelet count.

Chemistry

No major change in median values was noted for albumin (g/L), alkaline phosphatase, SGOT, SGPT, and calcium over the course of the study. Although there were a few patients who had shifts from normal to low or high for these analytes, these were not clinically significant.

Serum electrolytes (phosphorus and potassium) showed a minor change in median values from baseline. A total of 14 patients (35%) and 10 patients (25%) shifted from normal to high during the study for phosphorous and potassium, respectively. However, these changes in serum electrolytes or phosphorous and potassium were not clinically significant.

C-reactive protein

A decrease in median (min-max) C-reactive protein levels was noted across all visits from baseline value (2.40 mg/L [range: 0.0 - 145.0 mg/L]) to Week 21 (1.75 mg/L, [range: 0.0 - 84.0 mg/L]); however, there was no major change noted at Week 45 (2.66 mg/L [range: 0.0 - 16.2 mg/L]) compared to baseline.

The majority of patients (25 patients [62.5%]) had normal CRP levels post baseline. Seven patients (17.5%) shifted from normal to high CRP levels. These changes in C-reactive protein levels were not clinically significant.

Iron parameters

Overall, the iron parameters were increased but remained within the normal range throughout the study period.

The median baseline value for iron was 14.98 μmol/L (range: 6.5-24.5 μmol/L). The lowest and highest median change from baseline in iron was 2.82 μmol/L (range: −14.2 - 26.4) and 5.08 μmol/L (range: −12.1- 35) at Week 29, respectively.

The median baseline value for ferritin was 139.65 ng/mL (range: 18.9 - 939.5 ng/mL). The lowest and highest median change from baseline in ferritin was 13.66 ng/mL (range: -375.0 - 300.1) and 47.30 ng/mL (range: −379.0 - 673.2) at Week 37 and Week 21, respectively.

The median baseline value for transferrin saturation was 29.95% (range: 10.9%- 46.2%). The lowest and highest median change from baseline in transferrin saturation was 4.24% (range: -24.7 – 64%) and 9.64% (range: −20.8 - 139.8%) at Week 17 and Week 29, respectively.

Dialysis Modality Over Time

Three patients (7.5%) had dialysis modality change in the study. All three patients changed to haemodialysis.

Vital signs, Physical findings and other observations related to safety

At baseline, the median Z-score was 0.99 for SBP and 0.71 for DBP in patients not on dialysis/on peritoneal dialysis (above values in the reference population). During the core and safety extension period, the median Z-score for the SBP and DBP showed small variation (within ±1 of baseline) across all visits compared to the median score at baseline; the greatest change was 0.37 at Week 5 for SBP and −0.33 at Week 17 for DBP.

In haemodialysis patients, the pre-dialysis baseline median Z-score was 1.16 for SBP, suggesting slightly higher pre-dialysis median SBP than the mean SBP in the reference population. The pre-dialysis baseline median Z-score was 0.28 for DBP. The post-dialysis baseline median Z-score was 0.78 for SBP and −0.18 at DBP.

In haemodialysis patients during the pre-dialysis assessments, the median Z-score for the SBP and DBP showed small variation (within ±1 of baseline) across all visits compared to the median score at baseline during the core period; during the safety extension period BP showed greater variation at the later visits compared to the median score at baseline. The MAH justifies these large variations during safety extension period due to low number of patients.

Changes in height and weight

Analysis of changes in height and weight did not reveal any indication of an impact of Mircera on growth.

Immunogenicity

Study NH19707

No patients tested positive for erythropoietin antibodies or anti-drug antibodies at any time during the study, including the safety extension period.

Study NH19708

Blood samples were collected for anti-drug antibody (ADA) testing at Week 1, 9, 21 and 45. In all patients a total of 131 samples were tested for anti-Mircera and anti-EPO antibodies. Overall, two samples tested positive for anti-Mircera antibodies and four samples tested positive for anti-EPO antibodies in two patients.

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

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

In both of these patients, there was no evidence of PRCA and both continued to show response to Mircera treatment.

Discontinuation due to adverse events

Study NH19707

One patient died and did not complete study treatment during the core study period. No patients were withdrawn from study treatment due to a non-fatal AE in either study period.

No AEs led to dose modification at any time during the study.

Study NH19708

None of the patients experienced any AE that led to withdrawal of the study treatment during the core or extension period.

Two patients (5%) experienced one non-serious AE each of Grade 2 anaemia during the core period. Both the AEs required Mircera dose to be increased. Both the AEs were considered to be unrelated to Mircera treatment by the investigator and had resolved.

Supportive data

In addition to the safety data derived from clinical studies, the MAH has provided data from supportive paediatric registry study MH40258 (see supportive studies in clinical efficacy).

As reported by the MAH, the drug is well tolerated with long-term exposure. In adults, safety data from long-term exposure (BA16528 and BH21260) did not reveal any safety concerns and safety of Mircera was consistent with the known profile of Mircera.

The MAH also claims the long-term safety of the drug in paediatric patients is further supported by data from other ESAs. Schaefer *et al*., 2016 has published the outcomes of long-term treatment (up to 2 years) in children with darbepoetin alfa. In that study, which included 319 patients aged from < 1 years upwards (approximately half not yet on dialysis), no new safety signals were identified.

Additional safety issues

Several pegylated products have been assessed by CHMP for marketing authorization. PEG accumulation has been discussed thoroughly by the Committee for Medicinal Products for Human Use (CHMP) and the Paediatric Committee (PDCO) with a positive benefit/risk balance for adolescents and adults (age >12 years). The major issue for this age restriction was the limited efficacy, which did not outweigh the (theoretical) risk of the vacuolisation.

Following the CHMP request, a discussion has been provided by the MAH regarding the biodistribution of the PEGylated drug product and the risk of vacuolation due to mPEG accumulation in choroid plexus and other tissues, and the risk for the paediatric population. *In vivo* distribution data indicated that Mircera can reach the brain, but at low levels, and it should be considered that PEG-induced cell vacuolation observed in toxicity studies performed with other PEGylated medicinal products were not associated to functional consequences. Furthermore, clinical experience with Mircera in adults and paediatric patients also did not raise any safety concerns pertaining to the PEG-induced vacuolation. As a consequence, no safety concern is expected related to PEG accumulation with Mircera (see non-clinical aspects).

2.5.1. Discussion on clinical safety

ESA therapy is an established treatment option to alleviate signs and symptoms associated with anaemia in patients with CKD. However, ESA therapy has been associated with risks, including pure red cell aplasia, stroke, vascular access loss and hypertension. In clinical trials, an increased risk of death, serious cardiovascular events including thrombosis or cerebrovascular events including stroke was observed when ESAs were administered to target a haemoglobin of greater than 12 g/dl.

The primary safety information in paediatric patients is derived from studies NH19707 and NH19708, that included patients 5-17 years old with clinically stable chronic renal anaemia on haemodialysis

treatment and patients 3 months-17 years paediatric patients with CKD anaemia on dialysis or not yet on dialysis, respectively. Patients included in both studies were receiving maintenance treatment with an erythropoiesis stimulating agent (ESA) prior to switching to methoxy polyethylene glycol-epoetin beta (Mircera).

During the whole study NH19707, the cumulative total exposure was 45.5 patient-exposure-year (PEY) with a mean of 0.7 PEY per patient. Nineteen patients were exposed to Mircera for at least 15 months. During study NH19708, a total of 40 paediatric patients received at least one dose of Mircera. Overall, the patients received a median of 11 Mircera administrations (range: 1-11 administrations) during the core and safety extension periods. Twenty-two patients [55%]) received at least 11 Mircera administrations.

Overall, the safety data set in the paediatric population is rather limited. It is acknowledged that this disease is uncommon in children and that the paediatric population tolerate better the anaemia and therefore are less likely to be treated with ESA. Also, limited data from patients <1 year is available. Considering the nature of the patients with symptomatic anaemia associated with CKD, the physiologically normal low kidney function is not regarded as an issue, as ESA response is not influenced by the function or immaturity of the kidneys, but it is by the severity of kidney impairment. Also, considering the shift to Mircera is occurring in patients in stable maintenance, monthly Hb monitoring and dose adjustments will allow to adapt doses to each patient. Although, considering long-half-life of Mircera, fragility of paediatric population, and limited low-doses available presentations, it is considered that ESA-treated patients <1 year of age should only be switched if there is a compelling need for the switch. This has been reflected in the SmPC (section 4.4). Furthermore, lower doses than 30 µg cannot be administered with the prefilled pens. A warning has been included in the SmPC to reflect that subjects with stabilized Hb and with an expected need of lower doses of Mircera than 30 µg should not be switched.

Safety results from this phase II studies showed that 77% and 73% of patients in the core period and safety extension period reported at least one adverse event in study NH19707, and 80% and 64% of patients in the core period and safety extension period in study NH19708 respectively. These percentages seem lower than those obtained from pooled phase II/III trials conducted in adult patients with chronic renal anaemia where around 88% of patients reported at least one adverse event.

The most commonly affected SOCs (with >15% of patients overall with AEs) were Infections and infestations, General disorders and administration site conditions, Injury, poisoning and procedural complications, Respiratory, thoracic and mediastinal disorders, Gastrointestinal disorders, administration site conditions and Nervous system disorders (12/64 patients [19%]).

The adverse events considered related to treatment in paediatric patients (study NH19707) were 7.8% in the core period and 5.4% in the extension period, and 5.0% and 4.0% for the same periods in study NH19708, respectively. For adult patients (pooled phase II/III trials) this data was around 6%.

One death occurred during study NH19707 due to intracranial hematoma related to head trauma in a domestic accident that was considered unrelated to treatment.

In the evaluation period of study NH19707, 25% of patients (12/48) reported SAEs in Group, 2 were considered serious, and 2 were considered related to study medication: arteriovenous thrombosis and thrombosis in device. During the extension phase none were considered related to the study medication.

During NH19708 13 patients (32.5%) experienced 23 SAEs and three 4 SAEs in the safety extension period. None was considered related to Mircera treatment by the investigator.

Hypertension, vascular access thrombosis and anti-erythropoietin antibody-induced pure red cell aplasia (AEAB-PRCA) as potential safety concerns. These adverse events, along with decrease in platelet count and thromboembolic events (including pulmonary embolism), were considered of special interest during the clinical development of Mircera in adult patients with chronic renal anaemia and are described as adverse events in the product information.

During the evaluation period in study NH19707, 8 patients (12.5%) reported hypertension as adverse event, 7 of which showed hypertension prior to inclusion in the study. The other one had previously received antihypertensive therapy. Two of these cases reported (3.1%) were classified as serious adverse events, and not considered related to the study medication. In the safety extension period of study NH19707 five patients (13.5%) reported hypertension, however two (5.4%) was classified as serious and not related to the study medication.

During the core period in study NH19708, 2 patients (5%) reported with 3 non-serious, Grade 2 AEs of hypertension, that were considered unrelated Mircera and resolved with treatment. No patients experienced any AE of hypertension during the safety extension period. One patient (2,5%) reported a total of 9 AEs of vascular access thrombosis in study NH19708; all of them were considered unrelated to treatment, and one was a serious grade 2 AE.

As with other ESA, blood pressure can increase during treatment and should be monitored while on ESA, and uncontrolled hypertension is a contraindication in the SmPC of Mircera. However, given the single-arm, open label nature of the studies it is difficult to conclude on the contribution of Mircera to these increases of blood pressure.

Four patients reported vascular access thrombosis in study NH19707 (2 patients (3.1%) described as thrombosis in device and 2 patients (3.1%) as arteriovenous fistula thrombosis). All cases were classified as serious adverse events but only two of them were considered related to the study medication (one case each). During the safety extension period of study NH19707 arteriovenous fistula thrombosis and thrombosis in device were reported in 2 patients each (5.4%). Two of them were classified as serious adverse event (one arteriovenous fistula thrombosis and the other one thrombosis in device) and none of them was considered related to the study drug.

No patients developed anti-drug antibodies or anti-erythropoietin antibodies during Study NH19707, neither pure red cell aplasia. Two patients tested positive for anti-EPO antibodies in study NH19708. No effect on Hb or Mircera doses were seen and no AE of PRCA was reported.

In study NH19708 mean Hb concentrations raised during the study period although Mircera dose was decreased. Mircera dose decreases were greater in younger patients. Following these safety concerns, the popPK model was updated (see Clinical efficacy section). Results for an additional analysis showed that the high variability PK and PD for Mircera lead to an overlap on PD outcomes between considering

or not differences in bioavailability between ESAs, and, taking into account frequent monitoring is still required for these patients, the clinical impact could be considered not relevant.

In both studies platelet count decreased along evaluation the extension phase. This had been previously observed in adult treated patients. No bleeding events were reported in any patients who had post-baseline platelet counts below normal range.

In addition to the safety data derived from Study NH19707, the MAH has provided data from a paediatric registry study MH40258. No new safety concerns have been reported.

According to the data provided the safety profile of Mircera in the paediatric population seems similar to that of adults and no new AEs have been identified.

Nevertheless, clinicians should be warned that Hb level fluctuations may occur after conversion, and a warning in section 4.4 of the SmPC has been included to reflect that after ESA conversion, a monthly/every 4-week Hb control is recommended (similar to the recommendation during ESA initiation therapy).

Given the information coming from non-clinical studies related to other PEGylated products, there is a possible risk of accumulation of PEG causing vacuolation in tissues such as brain, liver and kidney as seen in animals. The implication of this finding in humans is at the time being unclear. Following the CHMP request, the MAH has included a discussion of the potential concerns for use of Mircera, which is a PEGylated medicinal product in paediatric patients. Results provided support that Mircera is not expected to cause any safety concern as consequence of PEG accumulation and its possible vacuolisation to the CNS and other tissues (see non-clinical assessment).

2.5.2. Conclusions on clinical safety

According to the data provided the safety profile of Mircera in the paediatric population appears to be similar to that of adults as no new safety adverse events have been identified. The safety database is quite limited, especially in the youngest children and especially in patients <1 year. However, considering clinical experience of Mircera in adult patients, and the similar safety profile of Mircera in adults and children, no new safety concerns are raised at this moment.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to update the Instruction for Use in the Package Leaflet.

2.6.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- No extensive changes have been made to the Package Leaflet to incorporate the paediatric indication, and no new descriptions related to contra-indications, warnings and precautions or undesirable effects have been added.

- Few precautions have been added to mitigate potential choking-risk for children (e.g., "immediately throw away the cotton ball or the gauze after use"). These are considered minor changes.

3. Benefit-Risk Balance

3.1.1. Disease or condition

Treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in paediatric patients from 3 months to less than 18 years of age who are converting from another erythropoiesis stimulating agent (ESA) after their haemoglobin level was stabilised with the previous ESA.

Anaemia is a common comorbidity in patients with CKD, including children. This condition is associated with multiple adverse clinical consequences and its management is a core component of nephrology care. Although numerous complex factors interact in the development of this anaemia, erythropoietin deficiency and iron dysregulation (including iron deficiency and iron-restricted erythropoiesis) are the primary causes.

3.1.1. Available therapies and unmet medical need

Currently available treatment options for the management of symptomatic anaemia associated with CKD include short-acting human recombinant erythropoietins and longer-acting erythropoiesis stimulating agents (ESAs). In Europe, epoetin alfa, epoetin beta, epoetin zeta and darbepoetin alfa are approved for the treatment of anaemia due to CKD in paediatric patients. Epoetin alfa and zeta are approved for patients aged 1 to 18 years on haemodialysis (HD), and epoetin beta is approved for treating symptomatic anaemia caused by CKD in paediatric patients on dialysis and not yet on dialysis. Darbepoetin was approved by EMA for paediatric patients on and not yet on dialysis in 2015. Darbepoetin and epoetin beta are approved for IV as well as SC use in paediatric patients. Epoetin alfa and epoetin zeta are approved for paediatric patients on HD, and dosing recommendations are given for IV use only.

Mircera (methoxy polyethylene glycol-epoetin beta) is an erythropoiesis stimulating agent currently approved for the treatment of symptomatic anaemia associated with CKD in adult patients. Mircera was first approved in Europe on 20 July 2007.

3.1.2. Main clinical studies

In this submission the MAH is seeking an extension of indication to include treatment of symptomatic anaemia associated with CKD in paediatric patients from 3 months to less than 18 years of age on ESA

maintenance treatment. It is a switch indication from IV ESA to IV Mircera and from SC ESA to SC Mircera.

Efficacy is based on an extrapolation exercise, two dose finding studies in children with anaemia associated to CKD and a PopPK model. Overall, extrapolation is acceptable considering the availability of PK data in children compared to adults, the data in adults from adequate and controlled trials and that the physiopathology and the mechanism of action for efficacy is the same in adults and children.

Study NH19707 was a phase II, open-label, multicentre, dose finding study designed to provide evidence on the optimal dose of Mircera in the paediatric population (5-17 years old) with CKD anaemia on haemodialysis, following iv administration of Mircera after switching from other ESAs (i.e., epoetin alfa/beta or darbepoetin alfa). The duration of study NH19707 was 20 weeks (core phase). 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.

Study NH19708 was a phase II, open-label, single-arm, multicenter study designed to ascertain the starting dose of Mircera given subcutaneously in 3 months-17 years paediatric patients with CKD anaemia on dialysis or not yet on dyalisis when switching with epoetin alfa, epoetin beta or dabepoetin alfa. The core study was for 23 weeks and consisted of three periods: Screening (3 weeks), dose titration (16 weeks), and evaluation (4 weeks).

In both studies, dose adjustments were permitted to maintain target Hb levels and eligible patients were offered to enter a safety extension period.

3.2. Favourable effects

In study NH19707, the adjusted mean change in Hb from baseline to the evaluation period was -0.09 g/dl (95%IC: -0.45 to 0.26) in group 2. During the evaluation period, 75% of patients maintained Hb values within the range of ± 1 g/dL of the baseline levels, and 81% within the range of 10-12 g/dL. The proportion of patients with Hb values within ± 1 g/dL and within 10-12 g/dL were 69%. During the core phase the dose administered could be adjusted in order to maintain Hb levels between 10-12 g/dL.

In study NH19708, the change in Hb concentration (g/dL) between the baseline period and the evaluation period (weeks 17-21) was the primary efficacy endpoint. The mean change (±SD) in Hb concentration level during the evaluation period for study NH19708 showed a 0.48 (1.03) g/dL increase above the baseline level. The 90% CI for the mean change in Hb concentration levels from baseline was within the protocol specified range of ±1.1 g/dL and the SD was <1.5 g/dL.

During the evaluation period, 50% of patients maintained Hb values within the range of ± 1 g/dL of the baseline levels, and 63.2% within the range of 10-12 g/dL. The proportions of patients with Hb values within ± 1 g/dL and within 10-12 g/dL were 47.4%.

3.3. Uncertainties and limitations about favourable effects

In study NH19708 the Mircera mean dose was reduced approximately by 30% over the evaluation period, 62.5% of patients had dose decreases only and a considerable number of patients had an Hb value above the target range (30%). As mentioned in the Pharmacology Section, a 2.18-fold increase in SC bioavailability was estimated in paediatric patients compared to adult patients. In addition, the provided pcVPC for adult data following SC administration shows that the model excessively underpredicts the

median of the data, which indicates that the estimated bioavailability of 31% may be biased and the true SC bioavailability for adults is higher than this estimate. Safety concerns were raised following the SC switch, and the popPK model was updated.

Uncertainties of differences in paediatric SC bioavailability between other ESAs has been described, and these differences may have an impact on the apparently too high initial Mircera SC dose. Also, when the paediatric conversion doses are compared to the adult conversion doses, the paediatric conversion doses are considerably higher. For example, a 16-year-old subject on 60 µg darbepoetin would be switched to 360 µg Mircera whereas an 18-year-old with the same dose darbepoetin would be switched to 200 µg Mircera. Unfortunately, data provided by the MAH to address this question does not allow to conclude on the adequacy of the "high conversion factor". Considering that for practical and safety reasons the same conversion factor for IV to IV and SC to SC switch is the preferred option, and the already mentioned theorical safety concerns following SC to SC switch when the high CF is used, the intermediate CF is recommended to initiate the treatment with a lower dose, in order to avoid unnecessary high Hb levels, even when there is no clinical data supporting the use of that factor. This is taking on board that frequent monitoring is required for these patients, and patients can be uptitrated until reaching the appropriate Hb target. This would also avoid the discrepancies between paediatric dosing and adult dosing.

3.4. Unfavourable effects

Safety results from these phase II studies showed that 77% and 73% of patients in the core period and safety extension period reported at least one adverse event in study NH19707, and 80% and 64% of patients in the core period and safety extension period in study NH19708 respectively.

The most commonly affected SOCs (with > 15% of patients overall with AEs) were Infections and infestations, General disorders and administration site conditions, Injury, poisoning and procedural complications, Respiratory, thoracic and mediastinal disorders, Gastrointestinal disorders, administration site conditions and Nervous system disorders (12/64 patients [19%]).

During the core period of study NH19707, 8 patients (12.5%) reported hypertension as adverse event, 7 of which showed hypertension prior to inclusion in the study. The other one had previously received antihypertensive therapy. Two of these reported cases (3.1%) were classified as serious adverse events, and not considered related to the study medication. In the safety extension period of study NH19707, five patients (13.5%) reported hypertension, however two (5.4%) was classified as serious and not related to the study medication. Four patients reported vascular access thrombosis in study NH19707 (2 patients (3.1%) described as thrombosis in device and 2 patients (3.1%) as arteriovenous fistula thrombosis). All cases were classified as serious adverse events. However only two of them were considered related to the study medication (one case each). During the safety extension period of study NH19707 arteriovenous fistula thrombosis and thrombosis in device were reported in 2 patients each (5.4%). Two of them were classified as serious adverse event (one arteriovenous fistula thrombosis and the other one thrombosis in device) and none of them was considered related to the study drug. No thromboembolic events (i.e. pulmonary embolism) have been recorded in study NH19707.

During the core period of study NH19708, 2 patients (5%) reported with 3 non-serious, Grade 2 AEs of hypertension, that were considered unrelated Mircera and resolved with treatment. No patients experienced any AE of hypertension during the safety extension period. One patient (2,5%) reported a total of 9 AEs of vascular access thrombosis in study NH19708; all of them were considered unrelated to treatment, and ione was a serious grade 2 AE.

In both studies platelet count decreased along core and safety extension study period. This had been previously observed in adult treated patients. No bleeding events were reported in any patient who had post-baseline platelet counts below normal range.

3.5. Uncertainties and limitations about unfavourable effects

Overall, the safety data set is very limited. This is an uncommon disease in children who are usually less symptomatic and in less need of treatment with ESA. The difficulties to obtain a broader data set is acknowledged but this translates into a limited characterisation of the safety profile. Also, limited data from patients <1 year is available. Considering the nature of the patients with symptomatic anaemia associated with CKD, the physiologically normal low kidney function is not regarded as an issue, as ESA response is not influenced by the function or immaturity of the kidneys, rather than the severity of kidney impairment. Nevertheless, taking into consideration the long half-life of Mircera and that children <1 year with renal failure or severe renal dysfunction is a frail population with high morbidity, it is considered prudent to carefully evaluate before switching from a well-functioning dosing of another product. This has been reflected in section 4.4 of the SmPC. In addition, considering the shift to Mircera is occurring in patients in stable maintenance, monthly Hb monitoring and dose adjustments are recommended in the SmPC to allow to adapt doses to each patient.

3.6. Effects Table

Table 68. Effects Table for Mircera for symptomatic anaemia associated with chronic kidney disease (CKD) in paediatric patients from 3 months to less than 18 years of age who are converting from another erythropoiesis stimulating agent

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Change in Hb	Change from average Hb from baseline	g/dL	-0.74 (0.29)	-	Descriptive results	NH19707 Group 1 (intermediate conversion factor)
Hb within ±1 g/dL of baseline	Patients mantaining stable Hb	%	58.3	-	Descriptive results	NH19707 Group 1 (intermediate conversion factor)
Hb within 10-12 g/dL	Patients mantaining in range	%	75.0	-	Descriptive results	NH19707 Group 1 (intermediate conversion factor)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Hb within ±1 g/dL of baseline and within 10-12 g/dL	Patients mantaining in range	%	58.3	-	Descriptive results	NH19707 Group 1 (intermediate conversion factor)
Change in Hb	Change from average Hb from baseline	g/dL	-0.09 (0.18)	-	Descriptive results	NH19707 Group 2 (high conversion factor)
Hb within ±1 g/dL of baseline	Patients mantaining stable Hb	%	75.0	-	Descriptive results	NH19707 Group 2 (high conversion factor)
Hb within 10-12 g/dL	Patients mantaining in range	%	80.6	-	Descriptive results	NH19707 Group 2 (high conversion factor)
Hb within ±1 g/dL of baseline and within 10-12 g/dL	Patients mantaining in range	%	69.4	-	Descriptive results	NH19707 Group 2 (high conversion factor)
Change in Hb	Mean change in Hb levels from baseline	g/dL	0.48 (1.03)	-	IC90% 0.48 (0.2, 0.76)	NH19708 (high conversion factor)
Hb within ±1 g/dL of baseline	Patients mantaining stable Hb	%	63.2	-	Descriptive results	NH19708 (high conversion factor)
Hb within 10-12 g/dL	Patients mantaining in range	%	50.0	-	Descriptive results	NH19708 (high conversion factor)
Hb within ±1 g/dL of baseline and within 10-12 g/dL	Patients mantaining in range	%	47.4	-	Descriptive results	NH19708 (high conversion factor)

Abbreviations: Hb= haemoglobin

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The MAH has justified that the data available support the switch to Mircera of patients with anaemia associated with CKD who are clinically stable with epoetins or darbepoetin treatment, however data provided by the MAH to support the high conversion factor does not allow to conclude on its adequacy. It has been argued, that the high conversion factor with SC to SC switch administration results in Hb

values above the recommended level of 12 g/dL, especially in the youngest children (5/11 subjects). From this perspective, it has been considered more prudent to initiate treatment with a lower dose to avoid unnecessary high Hb levels and its potential associated safety issues. This also avoids discrepancies between paediatric dosing and adult dosing.

According to the data submitted it seems that no new safety adverse events have been described for Mircera in the paediatric population, although the safety database is considered limited, especially in children below 1 year old.

The risk of vacuolation due to PEG accumulation in choroid plexus and other tissues and the risk for the paediatric population has been previously described for other PEGylated products. Following the CHMP request, the MAH has included a discussion of the potential concerns for use of Mircera, which is a PEGylated medicinal product in paediatric patients. Results provided support that Mircera is not expected to cause any safety concern as consequence of PEG accumulation and its possible vacuolisation to the CNS and other tissues (see non-clinical assessment).

3.7.2. Balance of benefits and risks

The benefit risk balance of Mircera for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in paediatric patients from 3 months to less than 18 years of age who are converting from another erythropoiesis stimulating agent (ESA) after their haemoglobin level was stabilised with the previous ESA, is positive.

3.8. Conclusions

The overall B/R of Mircera is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include treatment of paediatric patients from 3 months to less than 18 years of age who are converting from another erythropoiesis stimulating agent (ESA) after their haemoglobin level was stabilised with the previous ESA. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to update the Instruction for Use in the Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA and IIIB are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0317/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Mircera-H-C-000739-II-0092.