NI PASS PROTOCOL (SECONDARY DATA USE)

TITLE:	**REAL WORLD EVIDENCE OF SAFETY AND DOSING OF MIRCERA IN CHILDREN WITH CHRONIC KIDNEY DISEASE**
PROTOCOL NUMBER:	MH40258
VERSION NUMBER:	1.0
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FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
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[redacted]	QPPV	21-Jan-2019 14:13:06

DATE FINAL:	See electronic date stamp on first page
EU PAS REGISTER NUMBER:	To be determined
ACTIVE SUBSTANCE:	B03XA03 methoxy polyethylene glycol-epoetin beta
STUDIED MEDICINAL PRODUCT	Mircera (methoxy polyethylene glycol-epoetin beta)
PRODUCT REFERENCE NUMBER:	Mircera (RO0503821)
PROCEDURE NUMBER:	N/A
JOINT PASS	No
RESEARCH QUESTION AND OBJECTIVES:	The study aims to further characterize safety, dosing and related hemoglobin concentrations and to validate the dose simulation models of Mircera in pediatric patients with anemia due to CKD in a real-world setting.
COUNTRY OF STUDY POPULATION:	Germany
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany
MAH CONTACT PERSON:	[redacted], global regulatory leader established products

TABLE OF CONTENTS

LIST OF APPENDICES

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE inhibitors	Angiotensin converting enzyme inhibitors
AE	Adverse events
ARBs	Angiotensin receptor blockers
AVF	Arteriovenous fistulas;
AVG	Arteriovenous grafts
C.E.R.A.	Continuous erythropoietin receptor activator
CAKUT	Congenital anomalies of the kidney and urinary tract
CKD	Chronic kidney disease
CSR	Clinical study report
eGFR	Estimated glomerular filtration rate
EPO	Erythropoietin
EMA	European Medicines Agency
ESA	Erythropoiesis-stimulating agent
EU PAS (register)	European Union electronic Register of Post-Authorisation Studies
FDA	Food and Drug Administration
Hb	Hemoglobin
HD	Hemodialysis
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IPDN	International Pediatric Dialysis Network
IPHN	International Pediatric Hemodialysis Network
IPPN	International Pediatric Peritoneal Network
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
NI-PASS	Non-interventional post-authorization safety study
NIS	Non-interventional study
PD	Peritoneal dialysis
PK/PD	Pharmacokinetic /pharmacodynamics
PDCO	Paediatric Committee
SAE	Serious adverse event

SD	Standard deviation
SID	Strong ion difference
SDU	Secondary data use
URR	Urea rate ratio

2. RESPONSIBLE PARTIES

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Complementary information is given in Appendix 1.

3. ABSTRACT/SYNOPSIS

TITLE:	**REAL WORLD EVIDENCE OF SAFETY AND DOSING OF MIRCERA IN CHILDREN WITH CHRONIC KIDNEY DISEASE**
PROTOCOL NUMBER:	MH40258
VERSION NUMBER:	1.0
DATE OF SYNOPSIS:	Date of submission to IDM
EU PAS REGISTER NUMBER:	To be determined
STUDIED MEDICINAL PRODUCT:	MIRCERA (methoxy polyethylene glycol-epoetin beta)
SCIENTIFIC RESPONSIBLE	[redacted], PDMA EP, Roche
MAIN AUTHOR	[redacted], PHC Data Science, Roche
PHASE:	IV, non-interventional study
INDICATION:	Anemia due to chronic kidney disease (CKD)
MARKETING AUTHORIZATION HOLDER:	Roche Registration GmbH Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany

Rationale and Background

This study aims to further characterize the safety and efficacy of Mircera in a real-world pediatric population setting. These data are needed to supplement data obtained from two clinical trials of Mircera in pediatric patients: NH19707 (DOLPHIN) and NH19708, which form the basis of a pediatric study plan (FDA) / pediatric investigation plan (PDCO/EMA) for Mircera®.

NH19707 (DOLPHIN) was an open-label multi-center, single-arm, multiple dose trial to determine the optimum starting dose of Mircera IV for the maintenance treatment of anemia in pediatric patients (5–17 years old) with kidney disease on hemodialysis (HD). This trial was completed in 2016 and formed the basis of the Food and Drug Administration (FDA) approval of Mircera for the treatment of anemia associated with chronic kidney disease (CKD) in pediatric patients (aged 5–17 years) on HD converting from another erythropoiesis-stimulating agent (ESA) after their hemoglobin (Hb) level was stabilized with an ESA.

NH19708 is a planned Phase II, open-label randomized, controlled, multi-center parallel group trial to confirm the optimal starting dose of Mircera SC and IV for the maintenance treatment of anemia in pediatric patients (2–17 yrs) with CKD on dialysis or not yet on dialysis.

Study (MH40258) will provide RWD and supplement the data from clinical trials NH19707 and NH19708. Aggregated safety data and patient level data on Mircera dosing and Hb levels will be obtained from an independent pediatric registry (International Pediatric Dialysis Network; IPDN) to provide real-world experience (primary study objective). Study MH40258 will also provide data which will help to inform the modeling/simulation from NH19708 (secondary study objective).

Research question and objectives

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

The two co-primary objectives for the study are to:

- describe the safety profile of Mircera by assessment of aggregate patient level safety data (mortality and hospitalizations only)
- assess the relationship between Mircera dosing and Hb concentrations using patient level data.

The secondary objectives for the study are to:

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

Study design

Non-interventional study secondary data use (NIS SDU) and voluntary post-authorization safety study (PASS) of pediatric patients from the International Pediatric Peritoneal Network (IPPN) and International Pediatric Hemodialysis Network (IPHN) registries who received Mircera.

Population

Pediatric patients aged from 0 months to less than 18 years old on chronic peritoneal dialysis (PD) or HD, with at least one visit while treated with Mircera, who are included in two international, prospective, multicenter registries (IPPN and IPHN).

Variables

- Demographics (age, gender, geographic region)
- Clinical characteristics (height, weight, body mass index; blood pressure)
- Dialysis: (dialysis type; time on dialysis; dialysis prescription and adequacy; comorbidities; reasons for discontinuation of dialysis)
- Treatments (Mircera: dose and dosing interval; prior ESA type: route of administration, dose and dosing interval; concomitant RAS inhibitors; iron therapy and type)

- Hemoglobin levels
- Safety data (deaths and causes of hospitalization)

Data sources

IPPN and IPHN registries, which collect prospective observational data from pediatric PD and HD centers worldwide. The only safety data available from these registries are deaths and causes of hospitalization.

Study size

As of April 2018, there were 125 PD patients and 32 HD patients treated with Mircera with at least one observation in the IPPN and IPHN registries, respectively. Data will be extracted from all eligible patients enrolled in the two registries during the study period.

Data analysis

The primary objective will be addressed by conducting descriptive analyses for selected patient characteristics at the first observation under Mircera. The patient characteristics to be evaluated include demographics, clinical characteristics, treatments, and laboratory measures. Time varying patient characteristics will be presented as change from first observation to most recent observation under Mircera.

The secondary objectives will be addressed by conducting an external validation of the Modeling and Simulation Framework for MIRCERA that has been developed on Phase II and III adult data and the first pediatric study DOLPHIN (NH19707, Fischbach et al. 2018). Simulations will be performed and compared to observed data from the present study. The dose conversions from previous ESA treatment to Mircera that were determined and tested in study NH19707 (IV) and NH19708 (SC) will be evaluated.

Milestones

The data collection periods for this study are from 2007 through Q3 2021 for IPPN and from 2013 through Q3 2021 for IPHN.

Start Date of Study

The study start date will be the date of the contract execution.

End of Study

The end of the study will be the date from which analysis of data required to fulfill study objectives is complete. The planned end of study date is Q4/ 2021.

4. AMENDMENTS AND UPDATES

Substantial protocol amendments/updates so far: None.

5. MILESTONES

Milestone	Planned date
Registration of protocol in the EU PAS register	01 February 2019
Start of study dataset creation	01 March 2019
End of study	October 2021
Interim report*	September 2019
Final report of study results (CSR)	December 2021
Registration of the results in the EU PAS register	01 February 2022

** date based on the actual time of the Interim Report for NH19708 being issued*

6. RATIONALE AND BACKGROUND

6.1 BACKGROUND ON CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is characterized by a progressive decline in renal function. As CKD progresses, inadequate levels of erythropoietin (EPO)—synthesized in the kidneys and stimulating the production of red blood cells in the bone marrow—are produced (Caro et al. 1979) and the resulting anemia becomes progressively more severe (Astor et al. 2002; McClellan et al. 2004). If left untreated, anemia impairs quality of life (Klang et al. 1996; Gerson et al. 2004) and may lead to cardiovascular dysfunction (Mitsnefes et al. 2000; Chavers and Herzog 2004) and reduced physical activity (Sietsema et al. 2002; Pattaragarn et al. 2004). The anemia of CKD is also associated with increased hospitalization and mortality rates in both adults and children (Ma et al. 1999; Xia et al. 1999; Warady and Ho 2003).

Exogenous replacement of EPO by erythropoietic agents is an established method for anemia treatment in CKD in conjunction with iron supplementation (Locatelli et al. 2004). The currently available treatment options include short-acting human recombinant erythropoietins (epoetin alfa and beta), requiring several injections per week due to their short half-life, and longer acting erythropoiesis-stimulating agents (ESAs) (hyperglycosylated [darbepoetin alfa] and pegylated [Mircera®] recombinant human erythropoietin [RHuEPO]), which need less frequent dosing due to their prolonged half-life. Until recently, only epoetin alfa/beta and darbepoetin alfa were approved treatments for anemia associated with CKD in pediatric patients. In June 2018 the Food and Drug Administration (FDA) granted approval for a new indication for Mircera administered by intravenous route for the treatment of anemia associated

with CKD in pediatric patients 5 to 17 years of age on hemodialysis (HD) who are converting from another ESA after their hemoglobin (Hb) level was stabilized.

As a post-marketing requirement, the FDA requested a summary report and registry data that describes the dosing, aggregate level safety data, and Hb concentrations in a cohort of pediatric patients with anemia associated with CKD treated with Mircera.

6.2 BACKGROUND ON MIRCERA

Methoxy polyethylene glycol-epoetin beta (Mircera) is a chemically synthesized continuous EPO receptor activator. Mircera differs from EPO through integration of amide bonds between amino groups and methoxy polyethylene glycol butanoic acid. This results in a calculated molecular weight of approximately 60 kDa.

Mircera has a long elimination half-life (approximately 130 hours after single-dose SC administration and approximately 90 hours after single-dose IV administration) (Locatelli and Reigner, 2007). The serum concentrations of Mircera are not affected by standard HD or hemofiltration.

In contrast with EPO, Mircera shows a different activity at the receptor level, characterized by a slower association to the receptor, reduced specific activity in vitro with an increased activity in vivo, as well as an increased half-life (Jarsch et al. 2008). These pharmacological properties are relevant in achieving a monthly dosing regimen with Mircera.

The global clinical development adult program for Mircera included 13 Phase I clinical pharmacology studies and 10 therapeutic studies comprising 4 Phase II and 6 Phase III studies in patients with CKD, including patients on dialysis and not on dialysis (Del Vecchio et al. 2008). Administration of Mircera for the treatment of anemia associated with CKD was generally well tolerated, with no difference in the safety profile in comparison to reference ESAs.

Mircera was efficacious in correcting anemia associated with CKD in adult patients who were on dialysis or not on dialysis and who were not currently treated with an ESA, regardless of route of administration (IV or SC). Mircera, with its effect on erythropoiesis and its long elimination half-life requiring infrequent administration, offers potential benefits compared to other ESAs (Mircera Summary of Product Characteristics and Mircera Prescribing Information)

Data are available on the efficacy and safety of Mircera administered once every 4 weeks by IV application in pediatric patients (64 children, ages 6−17 years old). The completed Phase II Study NH19707 showed that pediatric patients with CKD on HD can be switched from maintenance treatment with epoetin alfa, epoetin beta, or darbepoetin to Mircera using defined conversion factors (CFs).

In addition to Study NH19707, Mircera has been studied in children in two independent investigator-initiated trials. Cano et al. (2011) evaluated the efficacy and safety of Mircera in the management of anemia in 16 pediatric patients (ages 2−14 years) on stable peritoneal dialysis (PD) receiving EPO who converted to Mircera SC, scheduled every 2 weeks. Wedekin et al. (2011) conducted a study with Mircera administered intravenously every 4 weeks in 12 pediatric patients (ages 6−17 years) in a post-transplant setting. In both studies, no AEs attributable to Mircera were reported and Hb levels were effectively controlled. In Study NH19707, the adverse event (AE) profile observed during the core study period and in the safety extension period did not reveal any unexpected safety concerns.

6.3 STUDY RATIONALE

The pediatric study plan (FDA)/ pediatric investigation plan (PDCO/EMA) for Mircera comprises two studies. The first study, NH19707 – DOLPHIN – an open-label multi-center, single-arm, multiple dose study to determine the optimum starting dose of Mircera IV for the maintenance treatment of anemia in pediatric patients (5–17 years of age) with kidney disease on hemodialysis was completed (n=64) in 2016 and recruitment took 8 years.

The second, initially proposed study, NH19708, was a Phase II, open-label randomized, controlled, multi-center parallel group study (n=150) to confirm the optimal starting dose of Mircera SC and IV for the maintenance treatment of anemia in pediatric patients (2–17 years of age) with CKD on dialysis or not yet on dialysis.

The finalization of NH19707 took 8 years during which time additional scientific knowledge became available. Therefore, the second study, NH19708, was re-designed and agreed with FDA and PDCO in 2016 to the following design: a 40-patient study to assess the use of Mircera in younger children (<6 years old, on PD or not yet on dialysis) utilizing SC administration of Mircera. In addition, the results of the modeling and simulation studies based on DOLPHIN (NH19707) are to be confirmed.

To supplement the data base from both pediatric clinical trials (NH19707 and NH19708), it has been agreed with the FDA to provide additional aggregated safety data and patient level data on Mircera dosing and Hb values from an independent pediatric registry (IPDN) providing real world experience (primary study objective). In addition, study MH40258 will provide data which will help to inform the modeling/simulation from NH19708 (secondary study objectives). The current study is a secondary data use NIS and voluntary PASS which will take place over 3 years to provide the agreed level of supplemental information.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTION

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

7.2 OBJECTIVES

The primary objectives for the study are to:

- describe the safety profile of Mircera by aggregate assessment of patient level safety data
- assess the relationship between Mircera dosing and Hb concentrations using patient level data.

The secondary objectives for the study are to:

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

8. RESEARCH METHODS

8.1 STUDY DESIGN

In this non-interventional study secondary data use (NIS SDU) and voluntary post-authorization safety study (PASS), selected data elements among patients who received Mircera will be extracted from two existing registries within the IPDN (International Pediatric Peritoneal Network [IPPN] and International Pediatric Hemodialysis Network [IPHN]).

Inclusion criteria of the analytic study population:

- aged 0 months to <18 years at initial visit
- on chronic PD or HD
- with at least one visit while treated with Mircera

Data elements to be described among the study population meeting the inclusion criteria are provided in 2, and include:

- Demographics

- Clinical characteristics
- Treatments
- Hemoglobin levels
- Safety data (deaths and causes of hospitalizations)

The data collection periods for this study are from 2007 through Q3 2021 for IPPN and from 2013 through Q3 2021 for IPHN. Note that the start of the observational time period corresponds to the earliest date with available data from each registry.

8.2 SETTING

The IPDN is a global consortium of pediatric nephrology centers dedicated to the care of children on chronic dialysis. IPDN entertains two registries: The IPPN registry for children on chronic PD, and the IPHN registry for children on HD. As of July 2018, 242 institutions participate in the network (http://www.pedpd.org).

The IPDN aims to:

- improve the quality of pediatric dialysis care worldwide
- collect basic information regarding pediatric dialysis practices and outcomes
- provide useful tools and management algorithms for daily dialysis practice
- provide global benchmarking of pediatric dialysis outcomes
- perform prospective observational studies on important clinical issues in pediatric dialysis.

The registries collect prospective (baseline and every 6 months) information from pediatric PD and HD centers worldwide. The participating centers are asked to enroll all incident and prevalent patients and enter data longitudinally until chronic PD or HD is discontinued. Data input to registries is performed exclusively via an internet–based web platform (www.pedpd.org). Data entries are automatically checked for plausibility and completeness. Data protection is ensured by pseudonymized data input.

Between 2007 and 2015, a total of 2453 infants, children, and adolescents aged 11 days to 18.8 years (median, 10.5 years; IQR, 3.4–14.2 years) were enrolled from 105 pediatric dialysis centers in 38 countries (Borzych-Duzalka et al. 2017). As of September 2018 (www.pedpd.org), 3551 patients have been enrolled at 125 contributing centers in 43 countries in the IPPN registry, and 847 patients have been enrolled at 82 contributing centers in 36 countries in the IPHN registry.

In 2017, there were 681 patients in the registries with at least one observation (Table 1). There were four patients switched from PD to HD and one patient switched from HD to PD.

Table 1 Patients in the IPDN registries in 2017

Number of observations	IPPN, n (%)	IPHN, n (%)
1	327 (69)	139 (67)
2	142 (30)	67 (32)
3	4 (1)	2 (1)
Total	473	208

IPDN: International Pediatric Dialysis Network; IPHN: International Pediatric Hemodialysis Network; IPPN: International Pediatric Peritoneal Network.

8.3 VARIABLES

The analytic variables of interest are provided in Table 2.

Table 2 List of data elements and related variables of interest for aggregate and patient-level analyses

Data Element	Variable	Aggregate-level data needed for primary objectives		Patient-level data needed for secondary objectives
		@First visit	@Follow-up visit(s)	@all available visits under Mircera
Demographics	Age	✓	✓	✓
	Gender	✓		✓
	Geographic region	✓		
Clinical characteristics	Body size (height, weight, body mass index)	✓	✓	✓
	Dialysis type	✓	✓	✓
	Dialysis type change (i.e., from PD to HD)	✓	✓	
	Time on any dialysis (months)	✓	✓	
	Time on PD (months)	✓	✓	
	Time on HD (months)	✓	✓	
	Dialysis prescription (frequency, duration, blood flow rate [measured by AVF or AVG in cc/min])	✓	✓	
	Dialysis adequacy (or fluid clearance measured as URR or Kt/V)	✓	✓	
	Blood pressure	✓	✓	
	Comorbidities (# and type by category and subcategory*)	✓	✓	

Data Element	Variable	Aggregate-level data needed for primary objectives		Patient-level data needed for secondary objectives
		@First visit	@Follow-up visit(s)	@all available visits under Mircera
	Reason for discontinuation (or termination) of dialysis (i.e., kidney transplantation, transfer to hemodialysis/peritoneal dialysis, transfer to another center, death, or other reason)		✓	
Treatment	Current Mircera: type and dose (µg)	✓	✓	✓
	Current Mircera: dosing interval	✓	✓	✓
	Prior ESA treatment: type, route of administration and dose	✓		✓
	Prior ESA: dosing interval		✓	✓
	Co-medications RAS inhibition (i.e., ACE inhibitors or ARBs)**	✓	✓	
	Iron therapy and type (iv or oral)	✓	✓	
Laboratory Measures	Hemoglobin levels (Hb)	✓	✓	✓
Safety related	Hospitalizations (# and leading cause)	✓	✓	
	Deaths	✓	✓	

** Comorbidity categories include: cognitive abnormality, motor abnormality, ocular abnormality, hearing abnormality, pulmonary abnormality, cardiac abnormality and whether it is with/without a syndrome, and whether CAKUT was the primary cause of end-stage kidney disease.*
*** Selected co-medications that may require higher dosing for same efficacy.*
ACE: angiotensin-converting-enzyme; ARBs: angiotensin II receptor blockers; AVF: arteriovenous fistulas; AVG: arteriovenous grafts; CAKUT: congenital anomalies of the kidney and the urinary tract; eGFR: estimated glomerular filtration rate; ESA: erythropoiesis-stimulating agent; Hb: hemoglobin; HD: hemodialysis; PD: peritoneal dialysis; RAS: renin-angiotensin system; URR: urea reduction ratio.

8.3.1 Safety Variables

The safety variables for this study are as follows:

- Deaths
- Cause of Hospitalizations

Information on whether the cause was treatment-related is not captured in the registries. A complete list of causes of hospitalizations captured is included in Appendix 2. This drop-down list was implemented in the IPDN registry in March 2018. Prior to March 2018 hospitalization causes were entered as free text and will be curated.

8.4 DATA SOURCE(S)

The IPPN and IPHN registries collect prospective (baseline and every 6 months) information from pediatric PD and HD centers worldwide. The only safety data

available from these existing registries are deaths and causes of hospitalization. The participating centers are asked to enroll all incident and prevalent patients and enter data longitudinally until chronic PD (or HD) is discontinued.

The data collection periods for this study are from 2007 through Q3 2021 for IPPN and from 2013 through Q3 2021 for IPHN.

The patient characteristics collected at entry to the registry are age, sex, cause of end-stage renal disease, age at initiation of dialysis, and presence of comorbidities, including a defined syndrome, cognitive impairment, motor impairment, cardiac abnormalities, pulmonary abnormalities, ocular abnormalities, and hearing impairment. A separate yes-or-no response is requested to indicate the presence or absence of each comorbidity (Neu et al. 2012). Termination forms are requested when a patient permanently discontinues dialysis at the enrolling center because of kidney transplantation, transfer to hemodialysis, transfer to another center, death, or other reason.

Any access revision due to infectious or noninfectious access-related complication is reported. Patient updates, including clinical and laboratory data, are requested at 6-month intervals. Data requested at each update include the number of hospitalizations and the number of hospital days in the preceding 6 months. Prior to March 2018, information on cause of hospitalizations were captured as free text in the physician notes. Currently, a drop-down menu is used to collect information on hospitalizations. The complete menu of hospitalization causes is provided in Appendix 2.

Data input to the registries is performed exclusively via an internet–based web platform (www.pedpd.org). Data entries are automatically checked for plausibility and completeness. Data protection is ensured by pseudonymized data input.

8.5 STUDY SIZE

As of April 2018, there were 125 PD patients and 32 HD patients treated with Mircera with at least one observation in the IPPN and IPHN registries, respectively. Data will be extracted from all eligible patients enrolled in the two registries during the study period.

8.6 DATA MANAGEMENT

For primary objective: Data processing and analysis will be performed by members of the Institute of Medical Biometry and Informatics, University Hospital Heidelberg, which are amongst others in charge of the IPDN data. [redacted] is responsible for the management of the underlying database

For secondary objectives: Data will be transferred electronically to the marketing authorization holder (MAH), and the MAH's standard procedures will be used to handle and process the electronic transfer of these data.

Data will be provided in spreadsheet form (or csv file) where each line will pertain to an individual patient at one-time point (i.e., at registry enrollment or follow-up visit), and each column will pertain to a requested data element/measurement. Thus, each patient will have at least two lines of data. Separate spreadsheets will be provided with data extracted from each IPDN registry (i.e., IPPN and IPHN). Data specifications will be provided that describe the data elements provided in the spreadsheet columns.

Data will be converted by the MAH from the spreadsheet into csv format for statistical analyses using R programming language. As a first step, prior to any data analyses, the data will be checked for potential data errors (i.e., duplicates, typos, inconsistencies, etc.) and missing data. If any potential errors or a high percentage of missing values are identified, these will be communicated to the IPDN biostatistician and a resolution will be discussed.

8.7 DATA ANALYSIS

8.7.1 Primary Objective Analyses

Descriptive analyses of aggregate-level safety data will be provided for the number of hospitalizations, leading cause of hospitalization, and deaths. These are the only safety data available in the IPDN. In addition, the relationship between Mircera dosing and Hb concentrations will be assessed using patient level data. The data will be presented by the following age groups: 0 months to <2 years, 2 years to <6 years, 6 years to <12 years and 12 years to <18 years.

The descriptive analyses will be conducted for the patient characteristics listed in Table 2 (Section 8.3) at the first observation. The patient characteristics to be evaluated include demographics, clinical characteristics, treatments, and hemoglobin levels. Time varying patient characteristics will be presented as change from first observation to most recent observation. Patient characteristics will be evaluated within each registry (IPPN and IPHN) separately among the following age groups: 0 months to <2 years, 2 years to <6 years, 6 years to <12 years and 12 years to <18 years. For continuous variables (e.g., body size, time on dialysis, etc.) the following descriptive statistics will be evaluated: mean, standard deviation, median, quartiles, minimum and maximum values. Examples of how the analyses will be presented are shown as table shells in Appendix 3.

8.7.2 Secondary Objective Analysis

The secondary objective will be addressed by conducting an external validation of the Modeling and Simulation Framework for MIRCERA that has been developed on Phase II and III adult data and the first pediatric study DOLPHIN (NH19707, Fischbach et al. 2018), external validation will be conducted. Simulations will be performed and compared to observed data from the present study.

The following analyses will be performed to confirm dose conversions from previous ESA treatment to Mircera; and to validate the previous dose simulation models:

a) External validation of the M&S framework: simulations will be performed and compared to observed data from the present study

b) If warranted and data quality allows, data will be pooled to the existing database to potentially update PK/PD parameters

c) In case PK/PD parameters were updated in step b., clinical trial simulations of SKIPPER will be rerun.

8.7.3 Other Analyses

All other analyses which will be performed are listed below:

1. Selected data analyses will be performed following the format used in the IPDN annual report (see Appendix 1):
   - Tables 2.1, 2.2, 2.3a (by region), 2.3b, and 2.3 by age group, 2.4a-d (by region), 3.1, 3.2, 3.4, and 3.5.
2. The following scatter plots will be created using patient data from the most recent observation under Mircera.
   - Mircera monthly dose/kg weight by age
   - Mircera monthly dose/body surface area by age.
3. Patients that received Mircera and are included in both the IPPN and IPHN will be identified to determine whether these patients have additional follow-up visit data that should be included in the analyses (e.g., if their first observation under Mircera was while in IPPN and the most recent observation was while in IPHN).
4. The analyses performed for the primary objective will be repeated among the following patient subgroups: (a) with data from only one visit and visit was while under Mircera (b) with two or more consecutive visits while under Mircera; and (c) with data from more than one visit.

8.8 DATA QUALITY ASSURANCE AND QUALITY CONTROL

The MAH must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, informed consent forms if applicable, and documentation of Institutional Review Board (IRB)/Independent Ethics Committee (IEC) (if required).

The MAH shall ensure that the datasets and statistical programs used by IPDN for generating the data included in the final study report are kept at IPDN electronic format for 25 years and are available for auditing and inspection.

Data not held within MAH systems will be accessible upon request from IPDN to the MAH. Patient-level data used for the secondary objective will be transferred from IPDN to MAH at one time (i.e., end of study). IPDN will comply with the MAH procedures regarding content, archiving, and records management of process documents.

Retention of Records

Records and documents pertaining to the conduct of this study must be retained for at least 25 years after completion of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the MAH. Written notification should be provided to the MAH prior to transferring any records to another party or moving them to another location.

8.9 LIMITATIONS OF THE RESEARCH METHOD

A potential limitation of this study is the relatively small number of dialysis patients (especially very young patients) who will have received Mircera. This issue unfortunately is inherent with the small size of the patient population being evaluated. Although the selected data source, IPDN, is the largest and most comprehensive registry available. This small number of patients may limit the strength of the conclusions that can be made from the proposed descriptive analyses. An additional limitation is that it is not known for certain that reported hospitalizations occurred while treated with Mircera, since treatment information is only available as 6-month snapshots. This limitation will be evaluated by conducting sensitivity analyses using different patient inclusion criteria based on number of visits while treated with Mircera.

9. PROTECTION OF HUMAN PATIENTS

9.1 INFORMED CONSENT

Whenever possible, the MAH shall ensure that patients at the occasion of the primary data collection have explicitly agreed to any secondary use of their data.

In case it is not possible/practical to obtain or retrieve informed consent for use of secondary data in a NIS, certain other precautions must be taken, including:

- Ensuring data are anonymized / pseudonymized
- Ensuring final analysis data are anonymized / pseudonymized
- Ensuring possibility of linkage back to individual identified patients is impossible or tightly controlled
- Obtaining ethical committee approval for use of data as proposed (e.g., the review of and extraction of information from individual medical charts), record for the proposed use ahead of study initiation.

In the unusual circumstance that individual patients can be identified directly from their data received, then approval to use that data should be sought where possible.

The ICF developed initially for the IPDN registries did not capture sharing of data with 3rd parties explicitly. Therefore, we have obtained ethical committee approval from the University of Heidelberg to use aggregated and anonymized patient level data.

9.2 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for Good Pharmacoepidemiology Practice published by the International Society of Pharmacoepidemiology and the laws and regulations of the country in which the research is conducted.

The study will comply with national and European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

9.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol and relevant supporting information must be submitted to the IRB/IEC by the Scientific Responsible and reviewed and approved by the IRB/IEC before the study is initiated.

The Scientific Responsible is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a non-interventional post-authorization safety study (NI-PASS) involving the use of secondary data and the reporting of adverse reactions in the form of ICSRs is not required.

It is assumed that safety reporting of data which are going to be extracted/analyzed as part of this study have been appropriately performed and documented at the time these data were collected through primary data collection mechanism.

As per protocol, the aggregate summaries may include the following SAE types:

- deaths
- causes of hospitalization

10.1 ADVERSE EVENTS

Adverse event data are not available and are not collected in the IPPN and IPHN registries, with the exception of deaths and causes of hospitalizations, as mentioned previously.

According to the International Conference of Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

10.2 SERIOUS ADVERSE EVENTS

A serious AE (SAE) is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life-threatening (NOTE: The term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires or prolongs inpatient hospitalization.
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study medicine
- Is a significant medical event in the physician's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

11. PLANS FOR DISSEMINATION AND COMMUNICATION OF STUDY RESULTS

Regardless of the outcome of NI-PASS, the MAH is dedicated to openly providing information on the NI-PASS to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The MAH will comply with all requirements for publication of study results.

PUBLICATION PLAN

The study results will be communicated in at least one peer-reviewed publication.

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Appendix 1
Stand-Alone Documents Not Included in the Protocol

INTERNATIONAL PEDIATRIC DIALYSIS NETWORK 2017 ANNUAL REPORT

IPDN (Fresenius)
Annual_Report 2017

(double-click icon to open report)

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Appendix 2
Complete List of Causes of Hospitalizations Captured

INTERNATIONAL PEDIATRIC HEMODIALYSIS NETWORK HOSPITALIZATION CAUSES (HEMODIALYSIS)

Hospitalizations in past 6 months

Please enter the number of hospitalizations and the total number of days per leading cause of hospitalization.
E.g., one hospitalization of 7 days for access revision and two because of hypertension, 5 days each:
Access revision 1 (7 days)
Hypertension 2 (10 days)

HD (non-infectious)
- HD initiation / access placement
- Access dysfunction
- Access revision
- Other

Infection
- CVC exit site infection
- CVC tunnel infection
- AVF/AVG infection
- UTI/urosepsis
- Gastroenteritis
- Upper respiratory infection
- Pulmonary infection
- Other bacterial infection
- Other viral infection

Cardiovascular
- Hypertension
- Hypotension
- Cardiac insufficiency
- Pulmonary thromboembolism
- Air embolism
- Arrhythmia
- Other

Electrolyte/ Fluid intolerance
- Fluid overload
- Dehydration
- Hypercalcemia
- Hypocalcemia
- Hyperkalemia
- Hypokalemia
- Hyperphosphatemia
- Hypophosphatemia
- Others

Anemia
- Anemia workup
- Bleeding
- Transfusion
- Others

Bone disease
- Hyperparathyroidism
- Fracture
- Other skeletal problem

Neurological complication
- Seizure
- Stroke/intracranial hemorrhage
- Neurological impairment
- Others

Gastrointestinal
- Malnutrition, failure to thrive
- G-tube placement
- G-tube dysfunction
- G-tube related infection
- Inflammatory bowel disease
- Others

Surgery
- Nephrectomy
- Bladder surgery
- Urological diagnostics
- Orthopedic surgery
- Parathyroidectomy
- Other Surgery

Social
- Patient / Family burden
- Non-compliance
- Medical treatment errors
- Abuse
- Other reasons

Others
- Workup for transplantation
- Annual work up

Other reasons (please specify

INTERNATIONAL PEDIATRIC PERITONEAL NETWORK (PERITONEAL DIALYSIS)

Hospitalizations in past 6 months

Please enter the number of hospitalizations and the total number of days per leading cause of hospitalization. E.g., one hospitalization of 7 days for peritonitis and two for PD training, 5 days each:

Peritonitis 1 (7 days)

PD training 2 (10 days)

PD (non-infectious)

- PD Initiation (including catheter insertion and initial training)
- PD training/retraining
- PD catheter exchange
- PD leakage/hernia
- Other PD catheter dysfunction
- PD related diagnostics (e.g. PET)

Infection

- Catheter exit site/tunnel infection
- Peritonitis
- UTI/urosepsis
- Gastroenteritis
- Upper respiratory tract infection
- Pneumonia
- Other bacterial infection
- Other viral infection

Cardiovascular

- Hypertension
- Hypotension
- Cardiac insufficiency
- Arrhythmia
- Other

Electrolyte/ Fluid intolerance

- Fluid overload
- Dehydration
- Hypercalcemia
- Hypocalcemia
- Hyperkalemia
- Hypokalemia
- Hyperphosphatemia
- Hypophosphatemia
- Others

Anemia

- Anemia workup
- Bleeding
- Transfusion
- Others

Bone disease

- Hyperparathyroidism
- Fracture
- Other skeletal problem

Neurological complication

- Seizure
- Stroke/intracranial hemorrhage
- Neurological impairment
- Others

Gastrointestinal

- Malnutrition, failure to thrive
- G-tube placement
- G-tube dysfunction
- G-tube related infection
- Inflammatory bowel disease
- Sclerosing peritonitis
- Others

Surgery

- Nephrectomy
- Bladder surgery
- Urological diagnostics
- Orthopedic surgery
- Parathyroidectomy
- Other surgery

Social

- Patient / family burden
- Non-compliance
- Medical treatment errors
- Abuse
- Other reasons

Others

- Workup for transplantation
- Annual work up
- Other reasons (please specify)

Appendix 3
Example Table Shells

Table A. Patient characteristics at first visitby age group

	Age groups				
	0 mo– <2	**2 – <6**	**6 – <12**	**12 - <18**	**all**
N					
For each Continuous variable					
Mean (SD)					
Median (Q1, Q3)					
Min, Max					
For each Categorical variable					
Example					
Sex, n (%)					
Female					
Male					

Q: quartile; SD: standard deviation.

For all variables listed in 2 with baseline and follow-up information:

Table B. Change in patient characteristics from first visit to most recent visit by age group at first visit

	Age groups (years)				
	0mo– <2	**2 – <6**	**6 – <12**	**12 - <18**	**all**
N					
Continuous variables					
Mean (SD)					
Median (Q1, Q3)					
Min, Max					
Categorical variables					
Example					
Iron therapy type, n (%)					
IV to oral					
Oral to IV					
Any to none					
None to any					

IV: intravenous; Q: quartile; SD: standard deviation.