



## Clinical trial results:

### 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.

#### Summary

EudraCT number	2016-004779-39
Trial protocol	ES LT HU FR PL IT
Global end of trial date	19 July 2021

#### Results information

Result version number	v1 (current)
This version publication date	04 February 2022
First version publication date	04 February 2022

#### Trial information

##### Trial identification

Sponsor protocol code	NH19708
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03552393
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
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Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000172-PIP01-07
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 July 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 July 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this trial was to ascertain the starting dose of Mircera given subcutaneously (SC) in pediatric participants with chronic kidney disease (CKD) on dialysis or not yet on dialysis when switching from stable SC maintenance treatment with epoetin alfa, epoetin beta, or darbepoetin alfa.

Protection of trial subjects:

A signed Informed Consent Form (ICF) was obtained for all study subjects: written informed consent from the parent/legal guardian was required and written informed consent or assent from the child, where appropriate, was obtained.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 August 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	40
EEA total number of subjects	31

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	4

Children (2-11 years)	19
Adolescents (12-17 years)	17
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The core study was 23 weeks and consisted of three periods: screening (3 weeks), dose titration (16 weeks) and evaluation (4 weeks). Participants completing the 20 weeks of treatment with hemoglobin (Hb) within +/- 1g/dL of their baseline and within the target range of 10-12 g/dL were eligible to enter an optional 24-week safety extension period.

### Pre-assignment

Screening details:

Forty pediatric participants (ages 3 months to 17 years) with a diagnosis of anemia due to chronic kidney disease (CKD) who may or may not have been on dialysis at the time of study start were switched from stable subcutaneous (SC) maintenance treatment with epoetin alfa/beta or darbepoetin to methoxy polyethylene glycol-epoetin beta (Mircera).

### Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	Mircera
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Arm description:

Mircera was administered subcutaneously once every 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Methoxy Polyethylene Glycol-Epoetin Beta
Investigational medicinal product code	RO0503821
Other name	MIRCERA
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Mircera was administered subcutaneously once every 4 weeks

Number of subjects in period 1	Mircera
Started	40
Completed	38
Not completed	2
Kidney Transplant	1
Prohibited Medication	1

## Baseline characteristics

### Reporting groups

Reporting group title	Overall Period
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Reporting group description: -

Reporting group values	Overall Period	Total	
Number of subjects	40	40	
Age categorical			
Units: subjects			
Infants and toddlers (28 days-23 months)	4	4	
Children (2-11 years)	19	19	
Adolescents (12-17 years)	17	17	
Age Continuous			
Units: years			
arithmetic mean	10.32		
standard deviation	± 5.69	-	
Sex: Female, Male			
Units: subjects			
Female	17	17	
Male	23	23	

## End points

### End points reporting groups

Reporting group title	Mircera
Reporting group description:	
Mircera was administered subcutaneously once every 4 weeks.	

### Primary: Change in Hemoglobin (Hb) Concentration Between the Baseline and the Evaluation Period for Each Patient

End point title	Change in Hemoglobin (Hb) Concentration Between the Baseline and the Evaluation Period for Each Patient <sup>[1]</sup>
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End point description:

The Hb change from baseline was calculated on a per-participant 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 the time between the day of first study dose and the previous 35 days. The evaluation period was defined as the period between Week 17 and Week 21 inclusive. ITT population included all participants enrolled in the study. Number analyzed is the number of participants with Hb concentration assessment at specified time points.

End point type	Primary
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End point timeframe:

Baseline up to Week 21

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical testing was planned to be performed for the primary endpoint.

End point values	Mircera			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: g/dL				
arithmetic mean (standard deviation)				
Baseline	11.05 (± 0.51)			
Change at Evaluation Period	0.48 (± 1.03)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With an Average Hb Concentration During the Evaluation Period Within ± 1 g/dL of Their Baseline Hb and Above, Within or Below the Range of 10-12 g/dL

End point title	Number of Participants With an Average Hb Concentration During the Evaluation Period Within ± 1 g/dL of Their Baseline Hb and Above, Within or Below the Range of 10-12 g/dL
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End point description:

Number of participants with an average Hb concentration during the evaluation period within ± 1 g/dL of their baseline Hb is reported as well as the number of participants with an average Hb concentration above, within or below the range of 10-12 g/dL. The evaluation period was defined as the period between Week 17 and Week 21 inclusive. ITT population included all participants enrolled in the study. Hb values within 21 days after blood transfusion(s) were excluded from analysis.

End point type	Secondary
End point timeframe:	
Week 17 up to Week 21	

End point values	Mircera			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: participants				
Hb Above 1 g/dL of Baseline	15			
Hb Maintained Within $\pm$ 1 g/dL of Baseline	19			
Hb Below 1 g/dL of Baseline	4			
Hb Above 12 g/dL	12			
Hb Maintained Within 10-12 g/dL	24			
Hb Below 10 g/dL	2			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Hb Values and Change from Baseline

End point title	Mean Hb Values and Change from Baseline
End point description:	
The mean Hb concentration over time and the mean change in Hb from baseline over time are presented. ITT population included all participants enrolled in the study. Here 'n' signifies the number of participants evaluable at specified time-points.	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 3, 5, 9, 13, 17,19, 21, 25, 29, 33, 37, 41, 45	

End point values	Mircera			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: g/dL				
arithmetic mean (standard deviation)				
Baseline (n=40)	11.02 ( $\pm$ 0.53)			
Week 3 (n=40)	11.69 ( $\pm$ 0.97)			
Change at Week 3 (n=40)	0.67 ( $\pm$ 0.74)			
Week 5 (n=40)	11.21 ( $\pm$ 1.02)			
Change at Week 5 (n=40)	0.19 ( $\pm$ 0.94)			
Week 9 (n=39)	11.68 ( $\pm$ 1.42)			
Change at Week 9 (n=39)	0.64 ( $\pm$ 1.21)			
Week 13 (n=38)	11.56 ( $\pm$ 1.17)			
Change at Week 13 (n=38)	0.51 ( $\pm$ 1.10)			

Week 17 (n=37)	11.46 (± 1.33)			
Change at Week 17 (n=37)	0.42 (± 1.39)			
Week 19 (n=37)	11.81 (± 1.11)			
Change at Week 19 (n=37)	0.77 (± 1.14)			
Week 21 (n=38)	11.10 (± 0.91)			
Change at Week 21 (n=38)	0.05 (± 0.99)			
Week 25 (n=25)	11.29 (± 1.04)			
Change at Week 25 (n=25)	0.21 (± 1.12)			
Week 29 (n=23)	11.22 (± 1.18)			
Change at Week 29 (n=23)	0.15 (± 1.11)			
Week 33 (n=24)	11.09 (± 1.11)			
Change at Week 33 (n=24)	0.02 (± 1.24)			
Week 37 (n=24)	11.04 (± 0.77)			
Change at Week 37 (n=24)	-0.03 (± 0.90)			
Week 41 (n=22)	10.83 (± 0.83)			
Change at Week 41 (n=22)	-0.22 (± 1.03)			
Week 45 (n=21)	10.68 (± 1.02)			
Change at Week 45 (n=21)	-0.35 (± 1.13)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in Mircera Dose Over Time

End point title	Change in Mircera Dose Over Time
End point description:	
A dose change was defined as a change in the administered dose strength compared to the preceding dose. Safety population included all participants who received at least one dose of study drug regardless of whether they withdrew prematurely or not. Here 'n' signifies number of participants evaluable at specified time points.	
End point type	Secondary
End point timeframe:	
Week 1 to Week 17	

End point values	Mircera			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: micrograms (µg)				
median (full range (min-max))				
Week 1 (n=40)	75.00 (15.0 to 360.0)			
Week 5 (n=39)	75.00 (15.0 to 360.0)			
Change at Week 5 (n=39)	0.00 (-50.0 to 75.0)			
Week 9 (n=39)	50.00 (0.0 to 360.0)			



Change at Week 9 (n=39)	0.00 (-250.0 to 190.0)			
Week 13 (n=38)	50.00 (0.0 to 360.0)			
Change at Week 13 (n=38)	-25.00 (-120.0 to 210.0)			
Week 17 (n=38)	50.00 (0.0 to 250.0)			
Change at Week 17 (n=38)	-20.00 (-250.0 to 120.0)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Ratio of Mircera Starting Dose (Week 1) to the Dose at Week 17

End point title	Ratio of Mircera Starting Dose (Week 1) to the Dose at Week 17
End point description: The ratio of Mircera dose was calculated as the median (min-max) ratio of starting dose (Week 1) to the dose at Week 17. Participants who withdrew before Week 17 or who were not administered a Mircera dose at Week 17 visit due to the applicable dose adjustment rules were excluded from the ratio computation.	
End point type	Secondary
End point timeframe: Week 1, Week 17	

End point values	Mircera			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: ratio				
median (full range (min-max))	1.44 (0.2 to 3.8)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Adverse Events by Severity as Assessed by Highest World Health Organization (WHO) Toxicity Grade

End point title	Number of Participants With Adverse Events by Severity as Assessed by Highest World Health Organization (WHO) Toxicity Grade
End point description: An adverse event is 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 existing disease (a worsening in the character, frequency, or severity of a known condition), recurrence of an intermittent	

medical condition or any deterioration in a laboratory value or other clinical test. Safety population included all participants who received at least one dose of study drug regardless of whether they withdrew prematurely or not.

End point type	Secondary
End point timeframe:	
Baseline up to Week 45	

<b>End point values</b>	Mircera			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: participants				
Grade 1-2	25			
Grade 3-4	8			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Bioavailability (F) of Mircera in Pediatric Participants Based on Population PK Model

End point title	Bioavailability (F) of Mircera in Pediatric Participants Based on Population PK Model
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End point description:

Bioavailability (F) is defined as the percentage of the administered drug, that reaches the systemic circulation. A population PK model was developed for Mircera that adequately describes pediatric data: a 1-compartment model with first order absorption and elimination processes.

End point type	Secondary
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End point timeframe:

Pre-dose at Week 1, 9, 17; post-dose at Week 3 and Week 19 and additional sample taken between 24 hours and 5 days at participant's convenience

<b>End point values</b>	Mircera			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percentage				
number (not applicable)	67			

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Week 45

Adverse event reporting additional description:

Safety population included all participants who received at least one dose of study drug regardless of whether they withdrew prematurely or not.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22
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### Reporting groups

Reporting group title	Mircera
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Reporting group description:

Mircera was administered subcutaneously once every 4 weeks.

Serious adverse events	Mircera		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 40 (32.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Device related thrombosis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Enterovirus infection			

subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	3 / 40 (7.50%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pharyngotonsillitis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus bronchiolitis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhinovirus infection				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device malfunction			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Mircera		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 40 (70.00%)		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Hypotension			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	6		
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
General disorders and administration site conditions Injection site pain subjects affected / exposed occurrences (all)  Pyrexia subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2  5 / 40 (12.50%) 5		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3  3 / 40 (7.50%) 4		
Respiratory, thoracic and mediastinal disorders Rhinorrhoea subjects affected / exposed occurrences (all)  Oropharyngeal pain subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3  3 / 40 (7.50%) 3		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2		
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3		

Gastroenteritis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Pharyngitis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	6		
Urinary tract infection			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Hyperphosphataemia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2018	<ul style="list-style-type: none"><li>- An additional time point for immunogenicity sampling was added at Week 9 (Visit 6 [V6]).</li><li>- An additional blood sample should be stored for an anti-PEG antibody determination after the assay has been developed in those participants where loss of efficacy was observed.</li></ul>
11 July 2018	<ul style="list-style-type: none"><li>- Lab assessments required for calculating transferrin saturation (TSAT) were clarified. TSAT calculation with either serum transferrin or total iron-binding capacity was added.</li><li>- Blood sampling volume limits were added to ensure the safety of the participants in the study in accordance with the ethical considerations for clinical trials on medicinal products conducted with a pediatric population as published by the Directorate- General for Health and Food Safety.</li><li>- To further strengthen safety monitoring for special situations that may or may not result in an adverse event, instructions regarding the reporting of accidental overdose or medication error were added.</li><li>- The grading scale for assessment of severity of adverse events was revised to use the universally accepted and current World Health Organization toxicity scale.</li><li>- Requirements for the reporting of injection reactions were added.</li><li>- Reporting requirements for medical device complaints were added. In accordance with the Kidney Disease Outcomes Quality Initiative guidelines, Kt/V assessments for PD patients was reduced to one assessment every 6 months. Kt/V assessments at V3, V6 and V13 were removed.</li></ul>
07 December 2018	<ul style="list-style-type: none"><li>- Requirements for scheduling the screening visits and the approximate length of the screening period were clarified.</li><li>- Exclusion Criteria were amended to exclude participants who have undergone a kidney transplant with use of immunosuppressive therapies known to exacerbate anemia, as inclusion of these participants would add a bias to the studied patient population.</li><li>- Mircera Dose Adjustments, were amended to clarify the dose adjustment rules for Mircera.</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported