



Clinical trial results:

An Open-Label Multi-center, Multiple Dose Study to Determine the Optimum Starting Dose of Intravenous MIRCERA for Maintenance Treatment of Anemia in Pediatric Participants With chronic Kidney Disease on Hemodialysis

Summary

EudraCT number	2007-007758-70
Trial protocol	BE DE ES FR HU IT
Global end of trial date	28 March 2016

Results information

Result version number	v2 (current)
This version publication date	24 August 2017
First version publication date	15 October 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	NH19707
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00717366
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com

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	28 March 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the optimum starting dose of methoxy polyethylene glycol-epoetin beta (MIRCERA) in pediatric participants with chronic kidney disease (CKD) on hemodialysis when switching from stable maintenance treatment with epoetin alfa, epoetin beta or darbepoetin alfa; to demonstrate changes in hemoglobin (Hb) over time in response to different intravenous (IV) doses of MIRCERA; to study the pharmacokinetics (PK) and exposure-response relationship of MIRCERA; to assess the safety and tolerability of multiple doses of MIRCERA; and to document long-term safety and efficacy of MIRCERA.

Protection of trial subjects:

The study was conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research was conducted, whichever affords the greater protection to the individual. The study fully adhered to the principles outlined in "Guideline for Good Clinical Practice (GCP)" International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Tripartite Guideline and ensured compliance with the EU Clinical Trial Directive [2001/20/EC]. Approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and the relevant Competent Authority was obtained before study start.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 July 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Thailand: 2
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Ukraine: 3
Worldwide total number of subjects	64
EEA total number of subjects	59

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)	0
Children (2-11 years)	25
Adolescents (12-17 years)	39
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 112 participants were screened at 28 sites in 10 countries, of which 64 participants were enrolled (16 initially in MIRCERA Group 1 and then 48 in MIRCERA Group 2, following a preliminary analysis of MIRCERA Group 1).

Period 1

Period 1 title	Core Study Period (20 weeks)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	MIRCERA Group 1: Intermediate-Conversion-Factor Group

Arm description:

Participants received MIRCERA IV injection at a starting dose based on an intermediate conversion factor from their previous Erythropoiesis-Stimulating Agent (ESA) dose ($4 \times$ previous weekly epoetin dose [international units {IU}]/250 or $4 \times$ previous weekly darbepoetin alfa dose [micrograms {mcg}]/1.1) once every 4 weeks for 20 weeks. Participants who completed the 20 weeks of treatment and had hemoglobin (Hb) level within ± 1 grams per deciliter (g/dL) of their baseline Hb level and within the target range of 10-12 g/dL, entered an optional 52-weeks safety extension period. During this period, the participants continued to receive MIRCERA IV injection 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 in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

MIRCERA was administered IV, every 4 weeks.

Arm title	MIRCERA Group 2: High-Conversion-Factor Group
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Arm description:

Participants received MIRCERA IV injection based on a high conversion factor from their previous ESA dose ($4 \times$ previous weekly epoetin dose [IU]/125 or $4 \times$ previous weekly darbepoetin alfa dose [mcg]/0.55) once every 4 weeks for 20 weeks. Participants who completed the 20 weeks of treatment and had Hb level within ± 1 g/dL of their baseline Hb level and within the target range of 10-12 g/dL, entered an optional 52-weeks safety extension period. During this period, the participants continued to receive MIRCERA IV injection 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 in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

MIRCERA was administered IV, every 4 weeks.

Number of subjects in period 1	MIRCERA Group 1: Intermediate- Conversion-Factor Group	MIRCERA Group 2: High-Conversion- Factor Group
Started	16	48
Completed	12	35
Not completed	4	13
Death	-	1
Refused treatment/Did not cooperate	-	1
Renal transplant	4	9
Admin/Other than specified	-	2

Period 2

Period 2 title	Extension Period (52 weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	MIRCERA Group 1: Intermediate-Conversion-Factor Group

Arm description:

Participants received MIRCERA IV injection at a starting dose based on an intermediate conversion factor from their previous ESA dose (4 * previous weekly epoetin dose [IU]/250 or 4 * previous weekly darbepoetin alfa dose [mcg]/1.1) once every 4 weeks for 20 weeks. Participants who completed the 20 weeks of treatment and had Hb level within ± 1 g/dL of their baseline Hb level and within the target range of 10-12 g/dL, entered an optional 52-weeks safety extension period. During this period, the participants continued to receive MIRCERA IV injection 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 in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

MIRCERA was administered IV, every 4 weeks.

Arm title	MIRCERA Group 2: High-Conversion-Factor Group
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Arm description:

Participants received MIRCERA IV injection based on a high conversion factor from their previous ESA dose (4 * previous weekly epoetin dose [IU]/125 or 4 * previous weekly darbepoetin alfa dose [mcg]/0.55) once every 4 weeks for 20 weeks. Participants who completed the 20 weeks of treatment and had Hb level within ± 1 g/dL of their baseline Hb level and within the target range of 10-12 g/dL, entered an optional 52-weeks safety extension period. During this period, the participants continued to receive MIRCERA IV injection once every 4 weeks.

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

Dosage and administration details:

MIRCERA was administered IV, every 4 weeks.

Number of subjects in period 2^[1]	MIRCERA Group 1: Intermediate-Conversion-Factor Group	MIRCERA Group 2: High-Conversion-Factor Group
Started	9	28
Received Visit/Week 21 Dose	8	28
Completed	5	12
Not completed	4	16
Renal transplant	3	13
Withdrew consent	1	1
Admin/Other than specified	-	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 3 participants of Group 1 and 7 participants of Group 2, who completed core study period, did not enter safety extension period.

Baseline characteristics

Reporting groups

Reporting group title	MIRCERA Group 1: Intermediate-Conversion-Factor Group
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Reporting group description:

Participants received MIRCERA IV injection at a starting dose based on an intermediate conversion factor from their previous Erythropoiesis-Stimulating Agent (ESA) dose ($4 \times$ previous weekly epoetin dose [international units {IU}]/250 or $4 \times$ previous weekly darbepoetin alfa dose [micrograms {mcg}]/1.1) once every 4 weeks for 20 weeks. Participants who completed the 20 weeks of treatment and had hemoglobin (Hb) level within ± 1 grams per deciliter (g/dL) of their baseline Hb level and within the target range of 10-12 g/dL, entered an optional 52-weeks safety extension period. During this period, the participants continued to receive MIRCERA IV injection once every 4 weeks.

Reporting group title	MIRCERA Group 2: High-Conversion-Factor Group
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Reporting group description:

Participants received MIRCERA IV injection based on a high conversion factor from their previous ESA dose ($4 \times$ previous weekly epoetin dose [IU]/125 or $4 \times$ previous weekly darbepoetin alfa dose [mcg]/0.55) once every 4 weeks for 20 weeks. Participants who completed the 20 weeks of treatment and had Hb level within ± 1 g/dL of their baseline Hb level and within the target range of 10-12 g/dL, entered an optional 52-weeks safety extension period. During this period, the participants continued to receive MIRCERA IV injection once every 4 weeks.

Reporting group values	MIRCERA Group 1: Intermediate- Conversion-Factor Group	MIRCERA Group 2: High-Conversion- Factor Group	Total
Number of subjects	16	48	64
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	11.3 ± 3.24	13 ± 3.06	-
Gender categorical Units: Subjects			
Female	5	25	30
Male	11	23	34

End points

End points reporting groups

Reporting group title	MIRCERA Group 1: Intermediate-Conversion-Factor Group
Reporting group description: Participants received MIRCERA IV injection at a starting dose based on an intermediate conversion factor from their previous Erythropoiesis-Stimulating Agent (ESA) dose ($4 \times$ previous weekly epoetin dose [international units {IU}]/250 or $4 \times$ previous weekly darbepoetin alfa dose [micrograms {mcg}]/1.1) once every 4 weeks for 20 weeks. Participants who completed the 20 weeks of treatment and had hemoglobin (Hb) level within ± 1 grams per deciliter (g/dL) of their baseline Hb level and within the target range of 10-12 g/dL, entered an optional 52-weeks safety extension period. During this period, the participants continued to receive MIRCERA IV injection once every 4 weeks.	
Reporting group title	MIRCERA Group 2: High-Conversion-Factor Group
Reporting group description: Participants received MIRCERA IV injection based on a high conversion factor from their previous ESA dose ($4 \times$ previous weekly epoetin dose [IU]/125 or $4 \times$ previous weekly darbepoetin alfa dose [mcg]/0.55) once every 4 weeks for 20 weeks. Participants who completed the 20 weeks of treatment and had Hb level within ± 1 g/dL of their baseline Hb level and within the target range of 10-12 g/dL, entered an optional 52-weeks safety extension period. During this period, the participants continued to receive MIRCERA IV injection once every 4 weeks.	
Reporting group title	MIRCERA Group 1: Intermediate-Conversion-Factor Group
Reporting group description: Participants received MIRCERA IV injection at a starting dose based on an intermediate conversion factor from their previous ESA dose ($4 \times$ previous weekly epoetin dose [IU]/250 or $4 \times$ previous weekly darbepoetin alfa dose [mcg]/1.1) once every 4 weeks for 20 weeks. Participants who completed the 20 weeks of treatment and had Hb level within ± 1 g/dL of their baseline Hb level and within the target range of 10-12 g/dL, entered an optional 52-weeks safety extension period. During this period, the participants continued to receive MIRCERA IV injection once every 4 weeks.	
Reporting group title	MIRCERA Group 2: High-Conversion-Factor Group
Reporting group description: Participants received MIRCERA IV injection based on a high conversion factor from their previous ESA dose ($4 \times$ previous weekly epoetin dose [IU]/125 or $4 \times$ previous weekly darbepoetin alfa dose [mcg]/0.55) once every 4 weeks for 20 weeks. Participants who completed the 20 weeks of treatment and had Hb level within ± 1 g/dL of their baseline Hb level and within the target range of 10-12 g/dL, entered an optional 52-weeks safety extension period. During this period, the participants continued to receive MIRCERA IV injection once every 4 weeks.	

Primary: Change in Average Hb Concentration Between Baseline and Evaluation Period

End point title	Change in Average Hb Concentration Between Baseline and Evaluation Period ^[1]
End point description: A time adjusted average baseline Hb concentration for each individual was calculated using an area under the curve (AUC) approach from all available Hb measurements taken during the baseline period (Day -20 to Day 1). The average evaluation period Hb concentration for each individual was calculated using the same method, from all their available measurements taken during the evaluation period (Week 17 to Week 21). The change in Hb concentration between the baseline and evaluation periods was calculated by subtracting the baseline Hb concentration from the evaluation period Hb concentration. Intention-to-treat (ITT) population included all enrolled participants. Hb values within 21 days after blood transfusion(s) were excluded from analysis. Here 'n' signifies number of participants evaluable at specified time-points.	
End point type	Primary
End point timeframe: Baseline (Day -20 to Day 1), Evaluation Period (Week 17 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: Since analysis is descriptive in nature, statistical data could not be provided.

End point values	MIRCERA Group 1: Intermediate-Conversion-Factor Group	MIRCERA Group 2: High-Conversion-Factor Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	48		
Units: g/dL				
arithmetic mean (standard deviation)				
Baseline (n=16,48)	11.26 (± 0.496)	11.08 (± 0.493)		
Change at Evaluation Period (n=12,36)	-0.78 (± 1.237)	-0.15 (± 1.014)		

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

End point title	Number of Participants With an Average Hb Concentration During the Evaluation Period Within ±1 g/dL of Their Baseline Hb
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End point description:

Baseline Hb value was defined as the average Hb concentration from all available Hb measurements taken during the baseline period (Day -20 to Day 1). The evaluation period Hb concentration was defined as the average Hb concentration from all available Hb measurements taken during the evaluation period (Week 17 to Week 21). ITT population. Hb values within 21 days after blood transfusion(s) were excluded from analysis. Number of participants analyzed = participants with Hb concentration assessment at specified time-points.

End point type	Secondary
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End point timeframe:

Evaluation Period (Week 17 to Week 21)

End point values	MIRCERA Group 1: Intermediate-Conversion-Factor Group	MIRCERA Group 2: High-Conversion-Factor Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	36		
Units: participants	7	27		

Statistical analyses

No statistical analyses for this end point

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

The evaluation period Hb concentration was defined as the average Hb concentration from all available Hb measurements taken during the evaluation period (Week 17 to Week 21). ITT population. Hb values within 21 days after blood transfusion(s) were excluded from analysis. Number of participants analyzed = participants with Hb concentration assessment at specified time-points.

End point type	Secondary
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End point timeframe:

Evaluation Period (Week 17 to Week 21)

End point values	MIRCERA Group 1: Intermediate-Conversion-Factor Group	MIRCERA Group 2: High-Conversion-Factor Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	36		
Units: participants				
Above 12 g/dL	0	3		
Within 10-12 g/dL	9	29		
Below 10 g/dL	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Blood Transfusions

End point title	Number of Participants With Blood Transfusions
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End point description:

ITT population.

End point type	Secondary
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End point timeframe:

Baseline to Week 20

End point values	MIRCERA Group 1: Intermediate-Conversion-Factor Group	MIRCERA Group 2: High-Conversion-Factor Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	48		
Units: participants	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Average Reticulocyte Count Between the Baseline and Evaluation Period

End point title	Change in Average Reticulocyte Count Between the Baseline and Evaluation Period
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End point description:

A time adjusted average baseline reticulocyte count for each individual was calculated using an AUC approach from all available reticulocyte counts taken during the baseline period (Day -20 to Day 1). The average evaluation period reticulocyte count for each individual was calculated using the same method, from all their available measurements taken during the evaluation period (Week 17 to Week 21). The change in reticulocyte count between the baseline and evaluation periods was calculated by subtracting the baseline reticulocyte count from the evaluation period reticulocyte count. Relative reticulocytes were recorded conversion to absolute values was performed. ITT population. Reticulocyte values within 21 days after blood transfusion(s) were excluded from analysis. Here, number of participants analyzed = participants evaluable for this outcome measure and 'n' signifies number of participants evaluable at specified time-points.

End point type	Secondary
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End point timeframe:

Baseline (Day -20 to Day 1), Evaluation Period (Week 17 to Week 21)

End point values	MIRCERA Group 1: Intermediate-Conversion-Factor Group	MIRCERA Group 2: High-Conversion-Factor Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	48		
Units: 10 ³ cells/microliter				
arithmetic mean (standard deviation)				
Baseline (n=15,48)	46.08 (± 26.472)	43.7 (± 25.984)		
Change at Evaluation Period (n=11,36)	23.38 (± 29.279)	24.8 (± 32.428)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of MIRCERA

End point title	Maximum Observed Serum Concentration (Cmax) of MIRCERA
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End point description:

PK evaluable population included all enrolled participants who received at least one dose of study drug and had evaluable PK assessment.

End point type	Secondary
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End point timeframe:

Pre-dose (with 1 hour before drug administration) and 2, 48 hours post dose on Week 9, at Weeks 10, 11, and 12, pre-dose (with 1 hour before drug administration) on Week 13

End point values	MIRCERA Group 1: Intermediate-Conversion-Factor Group	MIRCERA Group 2: High-Conversion-Factor Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	34		
Units: picograms per milliliter (pg/mL)				
geometric mean (geometric coefficient of variation)	37700 (\pm 74.5)	66100 (\pm 149.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Serum Concentration-Time Curve From 0 to 672 Hours (AUC0-672h) of MIRCERA

End point title	Area Under the Serum Concentration-Time Curve From 0 to 672 Hours (AUC0-672h) of MIRCERA
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End point description:

Area under the serum concentration versus time curve over 672 hours. AUC0-672h represents area under the serum concentration versus time curve from time zero to end of dosing interval (AUC0-tau). PK evaluable population. Number of participants analyzed = participants with AUC0-672h assessment at specified time-points.

End point type	Secondary
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End point timeframe:

Pre-dose (with 1 hour before drug administration) and 2, 48 hours post dose on Week 9, at Weeks 10, 11, and 12, pre-dose (with 1 hour before drug administration) on Week 13

End point values	MIRCERA Group 1: Intermediate-Conversion-Factor Group	MIRCERA Group 2: High-Conversion-Factor Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	32		
Units: picograms*hour/milliliter (pg*h/mL)]				

geometric mean (geometric coefficient of variation)	3630000 (\pm 91.8)	7170000 (\pm 140)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Cmax (Tmax) of MIRCERA

End point title	Time to Reach Cmax (Tmax) of MIRCERA
End point description:	
PK evaluable population.	
End point type	Secondary
End point timeframe:	
Pre-dose (with 1 hour before drug administration) and 2, 48 hours post dose on Week 9, at Weeks 10, 11, and 12, pre-dose (with 1 hour before drug administration) on Week 13	

End point values	MIRCERA Group 1: Intermediate-Conversion-Factor Group	MIRCERA Group 2: High-Conversion-Factor Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	34		
Units: hours				
median (full range (min-max))	2 (1.98 to 2.17)	2 (1.83 to 164)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Terminal Phase Half-Life (t1/2) of MIRCERA

End point title	Apparent Terminal Phase Half-Life (t1/2) of MIRCERA
End point description:	
PK evaluable population. Number of participants analyzed = participants evaluable for t1/2 assessments.	
End point type	Secondary
End point timeframe:	
Pre-dose (with 1 hour before drug administration) and 2, 48 hours post dose on Week 9, at Weeks 10, 11, and 12, pre-dose (with 1 hour before drug administration) on Week 13	

End point values	MIRCERA Group 1: Intermediate- Conversion- Factor Group	MIRCERA Group 2: High- Conversion- Factor Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	32		
Units: hours				
geometric mean (geometric coefficient of variation)	147 (\pm 30.1)	121 (\pm 43.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 73

Adverse event reporting additional description:

Safety population included all participants who received at least one dose of study drug and had a safety follow-up visit.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	MIRCERA Group 1: Intermediate-Conversion-Factor Group
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Reporting group description:

Participants received MIRCERA IV injection at a starting dose based on an intermediate conversion factor from their previous ESA dose (4 * previous weekly epoetin dose [IU]/250 or 4 * previous weekly darbepoetin alfa dose [mcg]/1.1) once every 4 weeks for 20 weeks. Participants who completed the 20 weeks of treatment and had Hb level within ± 1 g/dL of their baseline Hb level and within the target range of 10-12 g/dL, entered an optional 52-weeks safety extension period. During this period, the participants continued to receive MIRCERA IV injection once every 4 weeks.

Reporting group title	MIRCERA Group 2: High-Conversion-Factor Group
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Reporting group description:

Participants received MIRCERA IV injection based on a high conversion factor from their previous ESA dose (4 * previous weekly epoetin dose [IU]/125 or 4 * previous weekly darbepoetin alfa dose [mcg]/0.55) once every 4 weeks for 20 weeks. Participants who completed the 20 weeks of treatment and had Hb level within ± 1 g/dL of their baseline Hb level and within the target range of 10-12 g/dL, entered an optional 52-weeks safety extension period. During this period, the participants continued to receive MIRCERA IV injection once every 4 weeks.

Serious adverse events	MIRCERA Group 1: Intermediate- Conversion-Factor Group	MIRCERA Group 2: High-Conversion- Factor Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 16 (25.00%)	17 / 48 (35.42%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	1 / 16 (6.25%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial injury			

subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	0 / 16 (0.00%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transplant failure			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 16 (0.00%)	3 / 48 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericarditis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Intracranial haematoma			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Thrombosis in device			

subjects affected / exposed	0 / 16 (0.00%)	3 / 48 (6.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Uterine haemorrhage			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Lupus nephritis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 16 (0.00%)	3 / 48 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal scalded skin syndrome			

subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	1 / 16 (6.25%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	MIRCERA Group 1: Intermediate- Conversion-Factor Group	MIRCERA Group 2: High-Conversion- Factor Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 16 (68.75%)	28 / 48 (58.33%)	
Investigations			
Haemoglobin			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 16 (6.25%)	9 / 48 (18.75%)	
occurrences (all)	1	12	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 16 (6.25%)	13 / 48 (27.08%)	
occurrences (all)	1	25	
General disorders and administration site conditions			

Malaise subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 48 (0.00%) 0	
Pyrexia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	3 / 48 (6.25%) 3	
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	4 / 48 (8.33%) 5	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 2	0 / 48 (0.00%) 0	
Ear pain subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	3 / 48 (6.25%) 3	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	3 / 48 (6.25%) 3	
Vomiting subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	5 / 48 (10.42%) 5	
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 48 (2.08%) 1	
Nausea subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	3 / 48 (6.25%) 3	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	4 / 48 (8.33%) 5	
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	2 / 48 (4.17%) 2	
Endocrine disorders Hyperparathyroidism secondary subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 48 (2.08%) 1	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	14 / 48 (29.17%) 16	
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	2 / 48 (4.17%) 2	
Bronchitis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	3 / 48 (6.25%) 4	
Pharyngitis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	3 / 48 (6.25%) 4	
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 48 (2.08%) 1	
Viral infection subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	2 / 48 (4.17%) 3	
Catheter site infection subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 48 (2.08%) 1	
H1N1 influenza subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	0 / 48 (0.00%) 0	
Oral herpes subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 48 (0.00%) 0	
Conjunctivitis			

subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 48 (0.00%) 0	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 48 (0.00%) 0	
Metabolism and nutrition disorders			
Hyperphosphataemia subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	3 / 48 (6.25%) 3	
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 3	3 / 48 (6.25%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2008	- Changes were made in reporting guidelines for serious adverse events (SAEs) and roles were clarified within the Data and Safety Monitoring Board (DSMB).
21 November 2008	- Use of pre-filled syringes adopted instead of vials. - Medical judgment rather than numerical values was used to assess hypertension as an exclusion criterion.
09 November 2012	- The sample size increased from 25 to 36 participants 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 were made due to a planned change in the electronic data capture system. - Handling of missing Hb values for the analysis was changed.
23 July 2014	- Clarifications were made regarding informed consent, prior medications, exclusion of pregnant participants. - Guidance was added in case of suspected antierythropoietin antibody-mediated pure red cell aplasia.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported