



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 | 29 March 2016 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 |
| This version publication date | 15 October 2016 |
| First version publication date | 15 October 2016 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | NH19707 |
|-----------------------|---------|

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 | 29 March 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 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 | 28 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 |
|------------------|---|

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 |
|------------------|---|

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 |
|----------|--------------|

| | |
|--|--|
| 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 |
|-----------------------|---|

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 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 | 11.3 | 13 | |
| standard deviation | ± 3.24 | ± 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

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|--|--|
| 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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

End point description:

ITT population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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) | | |
|---|-----------------------|----------------------|--|--|

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 |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| 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 * 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.

| | |
|-----------------------|---|
| 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 * 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.

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

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

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

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

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 48 (2.08%) | 1 / 16 (6.25%) | |
| 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 2: High-Conversion- Factor Group | MIRCERA Group 1: Intermediate- Conversion-Factor Group | |
|---|--|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 28 / 48 (58.33%) | 11 / 16 (68.75%) | |
| Investigations | | | |
| Haemoglobin | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 2 | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 9 / 48 (18.75%) | 1 / 16 (6.25%) | |
| occurrences (all) | 12 | 1 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 13 / 48 (27.08%) | 1 / 16 (6.25%) | |
| occurrences (all) | 25 | 1 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 48 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 25 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. |
| 24 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