



Clinical trial results:

A Multi-Center, Double-Blind, Randomized Study Evaluating De Novo Weekly and Once Every Two Week Darbepoetin Alfa Dosing for the Correction of Anemia in Pediatric Subjects with Chronic Kidney Disease Receiving and Not Receiving Dialysis

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2008-003418-88 |
| Trial protocol | SK LV BE LT GB Outside EU/EEA |
| Global end of trial date | 03 March 2014 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 20 June 2016 |
| First version publication date | 31 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 20050256 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00436748 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Amgen, Inc. |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, CA, United States, 91320 |
| Public contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000329-PIP02-09 |
| 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 | 03 March 2014 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 03 March 2014 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study are the following:

1. To test if the proportion of participants achieving a hemoglobin value greater than or equal to 10.0 g/dL at any time point after the first dose during the study is greater than 0.8 when administered de novo darbepoetin alfa once a week (QW) for treatment of anemia in pediatric patients with chronic kidney disease receiving and not receiving dialysis, and
2. To test if the proportion of participants achieving a hemoglobin value greater than or equal to 10.0 g/dL at any time point after the first dose during the study is greater than 0.8 when administered de novo darbepoetin alfa every 2 weeks (Q2W) for treatment of anemia in pediatric patients with chronic kidney disease receiving and not receiving dialysis.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines and applicable country regulations. Assent from the child, except if the child was very young, and consent from the parents or legal guardian were obtained as defined by local law for all subjects by the investigator or designee after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any study-specific procedures were performed or investigational product was administered. The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 01 September 2008 |
| 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 | Latvia: 1 |
| Country: Number of subjects enrolled | Lithuania: 5 |
| Country: Number of subjects enrolled | Mexico: 5 |
| Country: Number of subjects enrolled | Poland: 1 |
| Country: Number of subjects enrolled | Russian Federation: 16 |
| Country: Number of subjects enrolled | Slovakia: 8 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | United States: 79 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 116 |
| EEA total number of subjects | 16 |

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) | 41 |
| Adolescents (12-17 years) | 73 |
| Adults (18-64 years) | 2 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This trial enrolled pediatric patients with chronic kidney disease (CKD) who were anemic and not treated with an erythropoiesis-stimulating agent (ESA). The study was conducted at 43 centers in the US, Europe and Mexico. The first participant was enrolled on 16 September 2008 and the last participant was enrolled on 02 December 2013.

Pre-assignment

Screening details:

A total of 189 participants were screened, 116 participants were enrolled, and 73 screen failed. The primary reasons for screen failure were hemoglobin concentration > 10 g/dL or transferrin saturation < 20%. Randomization was stratified by age and dialysis status.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer |

Arms

| | |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Darbepoetin Alfa QW |

Arm description:

Participants received darbepoetin alfa once a week (QW) for 24 weeks. The initial dose was 0.45 µg/kg; thereafter, active doses were administered to achieve and then maintain hemoglobin levels within a target range of 10.0 to 12.0 g/dL. Participants not on dialysis or who were receiving peritoneal dialysis were administered darbepoetin alfa subcutaneously; participants receiving hemodialysis were administered darbepoetin alfa intravenously.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Darbepoetin Alfa |
| Investigational medicinal product code | |
| Other name | Aranesp® |
| Pharmaceutical forms | Solution for injection/infusion in pre-filled syringe |
| Routes of administration | Intravenous use, Subcutaneous use |

Dosage and administration details:

Subjects not receiving dialysis and subjects receiving peritoneal dialysis were administered darbepoetin alfa subcutaneously; subjects receiving hemodialysis were administered darbepoetin alfa intravenously.

| | |
|------------------|----------------------|
| Arm title | Darbepoetin Alfa Q2W |
|------------------|----------------------|

Arm description:

Participants received darbepoetin alfa every 2 weeks (Q2W) and a placebo every other 2 weeks to maintain the blind for 24 weeks. The initial dose was 0.75 µg/kg; thereafter, active doses were administered to achieve and then maintain hemoglobin levels within a target range of 10.0 to 12.0 g/dL. Participants not on dialysis or who were receiving peritoneal dialysis were administered darbepoetin alfa subcutaneously; participants receiving hemodialysis were administered darbepoetin alfa intravenously.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Darbepoetin Alfa |
| Investigational medicinal product code | |
| Other name | Aranesp® |
| Pharmaceutical forms | Solution for injection/infusion in pre-filled syringe |
| Routes of administration | Intravenous use, Subcutaneous use |

Dosage and administration details:

Subjects not receiving dialysis and subjects receiving peritoneal dialysis were administered darbepoetin alfa subcutaneously; subjects receiving hemodialysis were administered darbepoetin alfa intravenously.

| Number of subjects in period 1 | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W |
|---------------------------------------|---------------------|----------------------|
| Started | 59 | 57 |
| Received Treatment | 58 | 56 |
| Completed | 48 | 45 |
| Not completed | 11 | 12 |
| Ineligibility Determined | 1 | 1 |
| Adverse event, non-fatal | - | 2 |
| Other | 3 | - |
| Administrative Decision | 1 | - |
| Lost to follow-up | - | 1 |
| Protocol-specified Criteria | 5 | 4 |
| Consent Withdrawn | 1 | 4 |

Baseline characteristics

Reporting groups

| | |
|---|----------------------|
| Reporting group title | Darbepoetin Alfa QW |
| Reporting group description: | |
| Participants received darbepoetin alfa once a week (QW) for 24 weeks. The initial dose was 0.45 µg/kg; thereafter, active doses were administered to achieve and then maintain hemoglobin levels within a target range of 10.0 to 12.0 g/dL. Participants not on dialysis or who were receiving peritoneal dialysis were administered darbepoetin alfa subcutaneously; participants receiving hemodialysis were administered darbepoetin alfa intravenously. | |
| Reporting group title | Darbepoetin Alfa Q2W |
| Reporting group description: | |
| Participants received darbepoetin alfa every 2 weeks (Q2W) and a placebo every other 2 weeks to maintain the blind for 24 weeks. The initial dose was 0.75 µg/kg; thereafter, active doses were administered to achieve and then maintain hemoglobin levels within a target range of 10.0 to 12.0 g/dL. Participants not on dialysis or who were receiving peritoneal dialysis were administered darbepoetin alfa subcutaneously; participants receiving hemodialysis were administered darbepoetin alfa intravenously. | |

| Reporting group values | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | Total |
|---|---------------------|----------------------|-------|
| Number of subjects | 59 | 57 | 116 |
| Age, Customized Units: participants | | | |
| 1 to < 6 years | 2 | 1 | 3 |
| 6 to < 12 years | 19 | 19 | 38 |
| 12 to 18 years | 38 | 37 | 75 |
| Age Continuous Units: years | | | |
| arithmetic mean | 12.7 | 12.7 | |
| standard deviation | ± 3.6 | ± 3.7 | - |
| Gender, Male/Female Units: participants | | | |
| Female | 23 | 23 | 46 |
| Male | 36 | 34 | 70 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White or Caucasian | 31 | 31 | 62 |
| Black or African American | 4 | 5 | 9 |
| Hispanic or Latino | 23 | 20 | 43 |
| Other | 1 | 1 | 2 |
| Dialysis Status Units: Subjects | | | |
| Not receiving dialysis | 33 | 34 | 67 |
| Receiving hemodialysis | 15 | 14 | 29 |
| Receiving peritoneal dialysis | 11 | 9 | 20 |
| Hemoglobin Concentration Units: g/dL | | | |
| arithmetic mean | 8.59 | 8.73 | |
| standard deviation | ± 0.84 | ± 0.84 | - |

End points

End points reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Darbepoetin Alfa QW |
|-----------------------|---------------------|

Reporting group description:

Participants received darbepoetin alfa once a week (QW) for 24 weeks. The initial dose was 0.45 µg/kg; thereafter, active doses were administered to achieve and then maintain hemoglobin levels within a target range of 10.0 to 12.0 g/dL. Participants not on dialysis or who were receiving peritoneal dialysis were administered darbepoetin alfa subcutaneously; participants receiving hemodialysis were administered darbepoetin alfa intravenously.

| | |
|-----------------------|----------------------|
| Reporting group title | Darbepoetin Alfa Q2W |
|-----------------------|----------------------|

Reporting group description:

Participants received darbepoetin alfa every 2 weeks (Q2W) and a placebo every other 2 weeks to maintain the blind for 24 weeks. The initial dose was 0.75 µg/kg; thereafter, active doses were administered to achieve and then maintain hemoglobin levels within a target range of 10.0 to 12.0 g/dL. Participants not on dialysis or who were receiving peritoneal dialysis were administered darbepoetin alfa subcutaneously; participants receiving hemodialysis were administered darbepoetin alfa intravenously.

Primary: Proportion of Participants Achieving Hemoglobin ≥ 10.0 g/dL

| | |
|-----------------|--|
| End point title | Proportion of Participants Achieving Hemoglobin ≥ 10.0 g/dL ^[1] |
|-----------------|--|

End point description:

The proportion of participants achieving hemoglobin ≥ 10.0 g/dL (the correction proportion) was calculated as the number of participants achieving a hemoglobin ≥ 10.0 g/dL at any time point during the study when administered de novo darbepoetin alfa without receiving any red blood cell transfusion after randomization and within 90 days before the achievement, divided by the number of participants in the efficacy analysis set.

Analysis was performed using the efficacy analysis set, which includes all participants who received ≥ 1 dose of investigational product.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

24 weeks

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 comparisons between groups were planned or conducted for the primary efficacy endpoint. The null hypotheses were tested separately in subjects receiving darbepoetin alfa QW and Q2W, however, the EudraCT system does not accept statistical analyses for single arms.

| End point values | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | | |
|-----------------------------------|---------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 58 | 56 | | |
| Units: proportion of participants | | | | |
| number (confidence interval 95%) | 0.983 (0.908 to 1) | 0.839 (0.717 to 0.924) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Hemoglobin Value ≥ 10.0 g/dL

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|--|---|
| End point title | Time to First Hemoglobin Value \geq 10.0 g/dL |
| End point description: The time from study Day 1 to the day a participant first achieved hemoglobin \geq 10.0 g/dL for participants who achieved hemoglobin \geq 10.0 g/dL. | |
| End point type | Secondary |
| End point timeframe: 24 weeks | |

| End point values | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | | |
|---------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 57 ^[2] | 47 ^[3] | | |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 24 (15 to 50) | 22 (14 to 41) | | |

Notes:

[2] - Efficacy analysis set responders

[3] - Efficacy analysis set responders

Statistical analyses

No statistical analyses for this end point

Secondary: Hemoglobin Concentration Over Time

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|--|------------------------------------|
| End point title | Hemoglobin Concentration Over Time |
| End point description: | |
| End point type | Secondary |
| End point timeframe: Baseline and Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25. | |

| End point values | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | | |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 58 | 56 | | |
| Units: g/dL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=58, 56) | 8.59 (\pm 0.84) | 8.73 (\pm 0.84) | | |
| Week 1 (n=53, 50) | 8.64 (\pm 0.9) | 8.65 (\pm 0.95) | | |
| Week 2 (n=52, 52) | 8.74 (\pm 1.09) | 8.96 (\pm 1.2) | | |
| Week 3 (n=51, 55) | 9.28 (\pm 1.27) | 9.09 (\pm 1.27) | | |
| Week 4 (n=53, 53) | 9.79 (\pm 1.3) | 9.55 (\pm 1.23) | | |
| Week 5 (n=53, 52) | 10.18 (\pm 1.29) | 9.87 (\pm 1.32) | | |
| Week 6 (n=54, 50) | 10.54 (\pm 1.43) | 10.19 (\pm 1.33) | | |
| Week 7 (n=52, 48) | 10.96 (\pm 1.53) | 10.17 (\pm 1.25) | | |
| Week 8 (n=53, 51) | 11.05 (\pm 1.37) | 10.47 (\pm 1.21) | | |
| Week 9 (n=50, 51) | 11.03 (\pm 1.48) | 10.6 (\pm 1.34) | | |

| | | | | |
|---------------------|----------------|----------------|--|--|
| Week 10 (n=54, 51) | 11.32 (± 1.33) | 10.6 (± 1.29) | | |
| Week 11 (n=51, 48) | 11.34 (± 1.33) | 10.73 (± 1.22) | | |
| Week 12 (n=51, 48) | 11.45 (± 1.25) | 10.87 (± 1.38) | | |
| Week 13 (n=50, 47) | 11.68 (± 1.19) | 10.82 (± 1.33) | | |
| Week 14 (n=52, 50) | 11.27 (± 1.28) | 10.92 (± 1.31) | | |
| Week 15 (n=49, 50) | 11.25 (± 1.13) | 11 (± 1.23) | | |
| Week 16 (n=48, 47) | 11.36 (± 1.19) | 10.86 (± 1.21) | | |
| Week 17 (n=48, 48) | 11.21 (± 1.23) | 11.05 (± 1) | | |
| Week 18 (n=49, 46) | 11.14 (± 1.2) | 10.91 (± 1.09) | | |
| Week 19 (n=48, 46) | 11.06 (± 0.91) | 10.91 (± 1.09) | | |
| Week 20 (n=48, 45) | 11.09 (± 1.03) | 10.76 (± 1) | | |
| Week 21 (n=48, 46) | 11.2 (± 1.04) | 10.64 (± 0.99) | | |
| Week 22 (n=48, 45) | 11 (± 1.19) | 10.58 (± 1.04) | | |
| Week 23 (n=48, 44) | 10.93 (± 1.1) | 10.5 (± 1.05) | | |
| Week 24 (n=45, 46) | 10.93 (± 1.16) | 10.43 (± 0.97) | | |
| Week 25 (n= 32, 31) | 11.13 (± 1.1) | 10.65 (± 0.75) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Weight-adjusted Darbepoetin Alfa Dose at Time of Achieving First Hemoglobin ≥ 10.0 g/dL

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|-----------------|---|
| End point title | Weight-adjusted Darbepoetin Alfa Dose at Time of Achieving First Hemoglobin ≥ 10.0 g/dL |
|-----------------|---|

End point description:

The darbepoetin alfa dose at the time a participant achieved a first hemoglobin level ≥ 10.0 g/dL, divided by the participant's weight measured at the closest study week prior to the dosing, post dialysis.

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

End point timeframe:

24 weeks

| End point values | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | | |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 54 ^[4] | 44 ^[5] | | |
| Units: µg/kg | | | | |
| arithmetic mean (standard deviation) | 0.48 (± 0.24) | 0.76 (± 0.21) | | |

Notes:

[4] - Efficacy analysis set responders for whom dosing data were available.

[5] - Efficacy analysis set responders for whom dosing data were available.

Statistical analyses

No statistical analyses for this end point

Secondary: Darbepoetin Alfa Weight-Adjusted Dose Over Time

| | |
|-----------------|---|
| End point title | Darbepoetin Alfa Weight-Adjusted Dose Over Time |
|-----------------|---|

End point description:

Arithmetic means are provided; Withheld doses are counted as 0 µg.

Numbers > 0 on non-darbepoetin alfa dosing weeks for the Q2W group reflect participants who did not receive the assigned placebo dose (eg, dose withheld per investigator decision based on hemoglobin value or missed visit).

"9999" indicates not applicable since subjects received dosing every 2 weeks.

"99999" indicates values that could not be calculated since sample size = 1.

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

End point timeframe:

Day 1 (initial dose) and Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25.

| End point values | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | | |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 58 | 56 | | |
| Units: µg/kg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Initial Dose (n=58, 56) | 0.45 (± 0.07) | 0.73 (± 0.13) | | |
| Week 2 (n=55, 0) | 0.45 (± 0.07) | 9999 (± 9999) | | |
| Week 3 (n=55, 52) | 0.44 (± 0.07) | 0.72 (± 0.11) | | |
| Week 4 (n=54, 0) | 0.4 (± 0.11) | 9999 (± 9999) | | |
| Week 5 (n=54, 51) | 0.43 (± 0.26) | 0.72 (± 0.25) | | |
| Week 6 (n=54, 0) | 0.42 (± 0.29) | 9999 (± 9999) | | |
| Week 7 (n=54, 51) | 0.38 (± 0.25) | 0.7 (± 0.28) | | |
| Week 8 (n=53, 1) | 0.34 (± 0.24) | 0 (± 99999) | | |
| Week 9 (n=52, 52) | 0.32 (± 0.23) | 0.64 (± 0.26) | | |
| Week 10 (n=55, 3) | 0.33 (± 0.26) | 0 (± 0) | | |
| Week 11 (n=54, 50) | 0.32 (± 0.28) | 0.61 (± 0.35) | | |
| Week 12 (n=54, 2) | 0.26 (± 0.28) | 0 (± 0) | | |
| Week 13 (n=54, 50) | 0.24 (± 0.28) | 0.56 (± 0.35) | | |
| Week 14 (n=53, 4) | 0.21 (± 0.27) | 0 (± 0) | | |
| Week 15 (n=52, 48) | 0.31 (± 0.33) | 0.53 (± 0.36) | | |
| Week 16 (n=50, 5) | 0.35 (± 0.44) | 0 (± 0) | | |
| Week 17 (n=51, 47) | 0.29 (± 0.34) | 0.61 (± 0.97) | | |
| Week 18 (n=50, 3) | 0.32 (± 0.4) | 0 (± 0) | | |
| Week 19 (n=50, 46) | 0.31 (± 0.33) | 0.45 (± 0.3) | | |
| Week 20 (n=48, 4) | 0.35 (± 0.34) | 0 (± 0) | | |
| Week 21 (n=48, 46) | 0.38 (± 0.63) | 0.47 (± 0.36) | | |
| Week 22 (n=48, 3) | 0.38 (± 0.64) | 0 (± 0) | | |
| Week 23 (n=47, 44) | 0.39 (± 0.63) | 0.49 (± 0.4) | | |
| Week 24 (n=46, 1) | 0.41 (± 0.63) | 0 (± 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 13 and Week 25 in Parent-reported

Pediatric Quality of Life Inventory (PedsQL) Scores

| | |
|-----------------|--|
| End point title | Change From Baseline at Week 13 and Week 25 in Parent-reported Pediatric Quality of Life Inventory (PedsQL) Scores |
|-----------------|--|

End point description:

The PedsQL is a health-related quality of life (HRQOL) questionnaire that can be used to measure quality of life in children ≥ 2 years old. The 23-item PedsQL 4.0 includes physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). Separate questionnaires for ages 2 to 4 (toddler), 5-7, 8-12, and 13-18 years are used for parent proxy-reporting, which assesses parents' perceptions of their child's HRQOL. The instructions ask how much of a problem each item has been during the past 1 month; each item is answered on a 5-point scale: 0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem. Scores from the 4 subscales, the total score, and the psychosocial composite score were generated using standard algorithms. Each item's score in the questionnaire was converted to a 0 to 100 scale (with higher scores indicating better HRQOL).

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

End point timeframe:

Baseline, Week 13 and Week 25 (or end of study visit if earlier than Week 25)

| End point values | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | | |
|---|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 ^[6] | 46 ^[7] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard error) | | | | |
| Week 13 Total Score (n=45, 46) | 4.5 (\pm 2.19) | 0.58 (\pm 2.43) | | |
| Week 13 Psychosocial composite score (n=45, 46) | 5.12 (\pm 2.16) | -0.41 (\pm 2.57) | | |
| Week 13 Physical function score (n=45, 46) | 3.61 (\pm 3.2) | 2.31 (\pm 3.35) | | |
| Week 13 Emotional function score (n=45, 46) | 1 (\pm 3) | -3.89 (\pm 2.74) | | |
| Week 13 Social function score (n=45, 46) | 6.89 (\pm 3.54) | 0.76 (\pm 3.56) | | |
| Week 13 School function score (n=42, 42) | 7.3 (\pm 2.47) | 4.17 (\pm 3.63) | | |
| Week 25 Total Score (n=38, 41) | 1.9 (\pm 2.06) | 0.65 (\pm 2.66) | | |
| Week 25 Psychosocial composite score (n=38, 41) | 2.52 (\pm 1.83) | -1.84 (\pm 3.13) | | |
| Week 25 Physical function score (n=38, 41) | 0.66 (\pm 3.89) | 5.18 (\pm 3.59) | | |
| Week 25 Emotional function score (n=38, 41) | -0.66 (\pm 2.61) | -3.51 (\pm 3.16) | | |
| Week 25 Social function score (n=38, 41) | 5.13 (\pm 2.64) | -2.2 (\pm 4.1) | | |
| Week 25 School function score (n=36, 37) | 3.9 (\pm 2.51) | 2.03 (\pm 3.94) | | |

Notes:

[6] - Efficacy analysis set with available data

[7] - Efficacy analysis set with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Week 13 and Week 25 in Child Self-reported

Pediatric Quality of Life Inventory (PedsQL) Scores

| | |
|-----------------|--|
| End point title | Change From Baseline at Week 13 and Week 25 in Child Self-reported Pediatric Quality of Life Inventory (PedsQL) Scores |
|-----------------|--|

End point description:

The PedsQL child self-reported questionnaire was used in children > 5 years old. The 23-item PedsQL 4.0 includes physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). Separate questionnaires for ages 5-7, 8-12, and 13-18 years was used for child self-reporting. The instructions asked how much of a problem each item has been during the past 1 month; each item is answered on a 5-point scale for ages 8 to 18 (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem), or simplified to a 3-point scale for ages 5 to 7 (0 = not at all a problem; 2 = sometimes a problem; 4 = a lot of a problem). Scores from the 4 subscales, the total score, and the psychosocial composite score were generated using standard algorithms. Each item's score in the questionnaire was converted to a 0 to 100 scale (with higher scores indicating better HRQOL).

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

End point timeframe:

Baseline, Week 13 and Week 25 (or end of study visit if earlier than Week 25)

| End point values | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | | |
|---|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 ^[8] | 46 ^[9] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard error) | | | | |
| Week 13 Total Score (n=46, 46) | 2.94 (± 1.7) | -1.23 (± 2.04) | | |
| Week 13 Psychosocial composite score (n=46, 46) | 2.59 (± 1.92) | -0.45 (± 2.23) | | |
| Week 13 Physical function score (n=46, 46) | 3.78 (± 2.43) | -2.79 (± 2.59) | | |
| Week 13 Emotional function score (n=46, 46) | 0.43 (± 2.52) | -0.76 (± 2.79) | | |
| Week 13 Social function score (n=46, 46) | 3.26 (± 2.93) | -2.28 (± 3.02) | | |
| Week 13 School function score (n=45, 43) | 2.89 (± 2.98) | 2.44 (± 3.83) | | |
| Week 25 Total Score (n=40, 42) | 5 (± 1.75) | 2.58 (± 1.78) | | |
| Week 25 Psychosocial composite score (n=40, 42) | 3.81 (± 1.97) | 3.53 (± 2.01) | | |
| Week 25 Physical function score (n=40, 42) | 7.42 (± 2.48) | 0.74 (± 2.8) | | |
| Week 25 Emotional function score (n=40, 42) | -0.25 (± 2.51) | 3.93 (± 3.1) | | |
| Week 25 Social function score (n=40, 42) | 7 (± 3.1) | 2.5 (± 2.67) | | |
| Week 25 School function score (n=40, 39) | 4.25 (± 3.14) | 3.85 (± 3.09) | | |

Notes:

[8] - Efficacy analysis set aged > 5 years and with available data

[9] - Efficacy analysis set aged > 5 years and with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-emergent Adverse Events

| | |
|--|---|
| End point title | Number of Participants with Treatment-emergent Adverse Events |
| End point description: A serious adverse event (SAE) is defined as an adverse event that meets at least one of the following serious criteria: • is fatal, • is life threatening, • requires in-patient hospitalization or prolongation of existing hospitalization, • results in persistent or significant disability/incapacity, • is a congenital anomaly/birth defect, and/or • other significant medical hazard. The investigator assessed whether the adverse event was related to the investigational product (IP). Events of interest included hypertension, ischemic heart disease, cardiac failure, cerebrovascular disorders, convulsions, embolic and thrombotic events, embolic and thrombotic events: venous, embolic and thrombotic events: arterial, embolic and thrombotic events: vessel type unspecified and mixed arterial and venous, dialysis vascular access thrombosis, antibody-mediated pure red cell aplasia, hypersensitivity, lack of efficacy-effect, and malignancies. | |
| End point type | Secondary |
| End point timeframe: 25 weeks | |

| End point values | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | | |
|--|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 58 ^[10] | 56 ^[11] | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| All adverse events | 48 | 50 | | |
| Serious adverse events | 16 | 14 | | |
| Leading to discontinuation of IP | 0 | 2 | | |
| Leading to discontinuation from study | 0 | 2 | | |
| Fatal adverse events | 0 | 0 | | |
| Events of interest | 18 | 20 | | |
| Treatment-related adverse events (TRAE) | 14 | 16 | | |
| Treatment-related serious adverse events | 1 | 2 | | |
| TRAE leading to discontinuation of IP | 0 | 2 | | |
| TRAE leading to discontinuation from study | 0 | 2 | | |
| Treatment-related fatal adverse events | 0 | 0 | | |
| Treatment-related events of interest | 6 | 9 | | |

Notes:

[10] - Safety analysis set

[11] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Hemoglobin Serial Rate of Change (ROC) Over Time

| | |
|---|--|
| End point title | Hemoglobin Serial Rate of Change (ROC) Over Time |
| End point description: Calculated using the serial method as the change in hemoglobin from the previous non-missing hemoglobin level divided by number of days in between, and then multiplied by 7. | |
| End point type | Secondary |

End point timeframe:

Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25.

| End point values | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | | |
|-------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 58 ^[12] | 56 ^[13] | | |
| Units: g/dL/week | | | | |
| median (full range (min-max)) | | | | |
| Week 2 (n=49, 47) | 0.263 (-0.9 to 1.17) | 0.35 (-1.82 to 2.1) | | |
| Week 3 (n=50, 53) | 0.53 (-1 to 1.7) | 0.2 (-1.23 to 1.4) | | |
| Week 4 (n=53, 52) | 0.56 (-0.4 to 2.2) | 0.513 (-1.6 to 3.33) | | |
| Week 5 (n=53, 49) | 0.438 (-2 to 2) | 0.117 (-3.92 to 1.52) | | |
| Week 6 (n=54, 48) | 0.4 (-2.5 to 2.4) | 0.231 (-1.05 to 2.4) | | |
| Week 7 (n=51, 45) | 0.2 (-1.2 to 2.9) | 0.1 (-1.75 to 2.57) | | |
| Week 8 (n=52, 49) | 0.163 (-1.98 to 1.63) | 0.3 (-2.71 to 1.17) | | |
| Week 9 (n=49, 50) | 0.1 (-2.8 to 1.4) | 0.089 (-1.3 to 2.2) | | |
| Week 10 (n=53, 50) | 0.117 (-1.4 to 3.9) | 0 (-2.1 to 1.52) | | |
| Week 11 (n=51, 48) | 0.1 (-2.1 to 1.87) | 0.138 (-1.49 to 1.49) | | |
| Week 12 (n=51, 48) | 0 (-1.4 to 4.4) | 0.2 (-2.2 to 1.1) | | |
| Week 13 (n=50, 47) | 0.128 (-2.8 to 2.7) | -0.064 (-2.57 to 2.19) | | |
| Week 14 (n=52, 50) | -0.419 (-1.87 to 2.4) | 0.023 (-1.4 to 1.4) | | |
| Week 15 (n=49, 50) | 0.2 (-1.6 to 2.33) | 0.128 (-2.38 to 1.63) | | |
| Week 16 (n=48, 47) | 0 (-2.1 to 3.27) | -0.1 (-3.2 to 1.1) | | |
| Week 17 (n=47, 48) | -0.1 (-2.8 to 2.4) | 0.139 (-1 to 2) | | |
| Week 18 (n=48, 46) | -0.188 (-2.3 to 1.4) | 0.094 (-2.33 to 1.4) | | |
| Week 19 (n=47, 46) | 0.1 (-1.52 to 1.2) | -0.1 (-2.22 to 3.9) | | |
| Week 20 (n=47, 44) | 0 (-1.9 to 2.6) | -0.05 (-3.2 to 1.1) | | |
| Week 21 (n=47, 45) | 0.1 (-1.48 to 2.45) | -0.14 (-1.2 to 1.4) | | |
| Week 22 (n=48, 44) | -0.2 (-2.6 to 1.1) | 0 (-1.7 to 1.6) | | |
| Week 23 (n=47, 43) | -0.1 (-2.8 to 1.75) | 0 (-1.54 to 1.82) | | |
| Week 24 (n=44, 46) | 0.1 (-3.03 to 4.34) | 0.05 (-1.6 to 6.44) | | |
| Week 25 (n=32, 31) | 0.188 (-1.2 to 2.1) | 0 (-1.05 to 1.68) | | |

Notes:

[12] - Safety analysis set with available data

[13] - Safety analysis set with available data

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Hemoglobin > 12.0, > 13.0, and > 14.0 g/dL During the Study

| | |
|-----------------|---|
| End point title | Number of Participants with Hemoglobin > 12.0, > 13.0, and > 14.0 g/dL During the Study |
|-----------------|---|

End point description:

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

End point timeframe:

25 weeks

| End point values | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | | |
|--|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 58 | 56 | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Number of participants with hemoglobin > 12.0 g/dL | 44 | 33 | | |
| Number of participants with hemoglobin > 13.0 g/dL | 24 | 6 | | |
| Number of participants with hemoglobin > 14.0 g/dL | 6 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Increase in Hemoglobin Over Any 2 Week Period

| | |
|-----------------|---|
| End point title | Maximum Increase in Hemoglobin Over Any 2 Week Period |
|-----------------|---|

End point description:

The maximum increase between any 2 non-missing hemoglobin measurements over any 2-week period from Day 1.

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

End point timeframe:

25 weeks

| End point values | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | | |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 58 | 56 | | |
| Units: g/dL/2 weeks | | | | |
| arithmetic mean (standard deviation) | 2.06 (± 0.88) | 1.61 (± 0.76) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Systolic Blood Pressure Over Time

| | |
|-----------------|---|
| End point title | Change from Baseline in Systolic Blood Pressure Over Time |
|-----------------|---|

End point description:

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

End point timeframe:

Baseline and Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25.

| End point values | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | | |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 58 | 56 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 2 (n=55, 54) | 1.7 (± 11.6) | -3.9 (± 11.1) | | |
| Week 3 (n=55, 56) | 1.1 (± 14.1) | 0 (± 12.7) | | |
| Week 4 (n=55, 54) | 1.3 (± 13) | 1.2 (± 11.5) | | |
| Week 5 (n=55, 52) | 1.1 (± 13.7) | -3 (± 13.7) | | |
| Week 6 (n=54, 51) | 0.2 (± 14.2) | -2.9 (± 12.5) | | |
| Week 7 (n=54, 52) | -1 (± 14.2) | -3.7 (± 13.4) | | |
| Week 8 (n=55, 52) | 0.5 (± 16) | -2.7 (± 13.8) | | |
| Week 9 (n=54, 52) | 1 (± 18.3) | -3.1 (± 14.5) | | |
| Week 10 (n=55, 52) | -0.2 (± 16.6) | -3.7 (± 14.6) | | |
| Week 11 (n=54, 51) | -2 (± 15.6) | -1.8 (± 15.9) | | |
| Week 12 (n=55, 49) | -2.4 (± 17.2) | -2.8 (± 15.4) | | |
| Week 13 (n=53, 50) | 0.5 (± 14.8) | -2.1 (± 14.2) | | |
| Week 14 (n=54, 50) | -2.3 (± 19.5) | -1.8 (± 15.8) | | |
| Week 15 (n=53, 50) | 0.1 (± 17.4) | -2.4 (± 13) | | |
| Week 16 (n=50, 48) | 1.9 (± 16.4) | -3.8 (± 16.3) | | |
| Week 17 (n=51, 47) | 1 (± 17.7) | 0.1 (± 10.6) | | |
| Week 18 (n=50, 46) | 0.5 (± 18.5) | 0 (± 15.5) | | |

| | | | | |
|--------------------|---------------|---------------|--|--|
| Week 19 (n=50, 47) | 3.4 (± 16) | -2.5 (± 14.2) | | |
| Week 20 (n=48, 46) | -0.9 (± 18.3) | -4 (± 13) | | |
| Week 21 (n=49, 46) | 1.9 (± 15.7) | -2.2 (± 15) | | |
| Week 22 (n=48, 46) | -0.6 (± 18.2) | -0.9 (± 15) | | |
| Week 23 (n=47, 45) | -0.6 (± 16.5) | -1.2 (± 15.7) | | |
| Week 24 (n=46, 46) | 0 (± 17.8) | -2 (± 11.8) | | |
| Week 25 (n=34, 32) | -0.5 (± 14.3) | -2.3 (± 12.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Diastolic Blood Pressure Over Time

| | |
|-----------------|--|
| End point title | Change from Baseline in Diastolic Blood Pressure Over Time |
|-----------------|--|

End point description:

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

End point timeframe:

Baseline and Weeks 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 25.

| End point values | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | | |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 58 | 56 | | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 2 (n=55, 54) | 1.4 (± 9.4) | 0.8 (± 11.1) | | |
| Week 3 (n=55, 56) | 2.2 (± 11) | 3.1 (± 10.8) | | |
| Week 4 (n=55, 54) | 2.8 (± 11) | 1.8 (± 12.6) | | |
| Week 5 (n=55, 52) | 3 (± 12.4) | -0.2 (± 11.2) | | |
| Week 6 (n=54, 51) | 2.6 (± 10.1) | -0.1 (± 11.4) | | |
| Week 7 (n=54, 52) | 1.2 (± 10.4) | -1 (± 12.3) | | |
| Week 8 (n=55, 52) | 3.9 (± 11.9) | 1.1 (± 15) | | |
| Week 9 (n=54, 52) | 4.8 (± 14.7) | -0.3 (± 12.9) | | |
| Week 10 (n=55, 52) | 1.5 (± 13.7) | 0.9 (± 15.9) | | |
| Week 11 (n=54, 51) | 3.9 (± 11.8) | 0.9 (± 14.4) | | |
| Week 12 (n=55, 49) | 1.6 (± 10.4) | 2.8 (± 13.7) | | |
| Week 13 (n=54, 50) | 2.7 (± 13.8) | 2.2 (± 10.6) | | |
| Week 14 (n=54, 50) | 3.4 (± 14.4) | 1.7 (± 12) | | |
| Week 15 (n=53, 50) | 3.7 (± 12.9) | 1.4 (± 11.7) | | |
| Week 16 (n=50, 48) | 4.6 (± 13.7) | 0.7 (± 11.9) | | |
| Week 17 (n=51, 47) | 4.1 (± 15.6) | 2.6 (± 10.6) | | |
| Week 18 (n=50, 46) | 3 (± 16.4) | 0.4 (± 11.7) | | |
| Week 19 (n=50, 47) | 3.7 (± 12.9) | 0.6 (± 12.2) | | |
| Week 20 (n=48, 46) | 1.7 (± 13.8) | 2 (± 13.2) | | |
| Week 21 (n=49, 46) | 2.9 (± 15.1) | 0.6 (± 12.9) | | |

| | | | | |
|--------------------|--------------|---------------|--|--|
| Week 22 (n=48, 46) | 3.2 (± 14.7) | 0.3 (± 13.9) | | |
| Week 23 (n=47, 45) | 5 (± 13.8) | -2 (± 14) | | |
| Week 24 (n=46, 46) | 4 (± 13.8) | -0.3 (± 12.8) | | |
| Week 25 (n=34, 32) | 3 (± 13) | -1.5 (± 10.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Developed Anti-erythropoiesis Antibodies

| | |
|-----------------|---|
| End point title | Number of Participants who Developed Anti-erythropoiesis Antibodies |
|-----------------|---|

End point description:

Participants who were negative for anti-erythropoiesis antibodies at Baseline (pre-dose) and who developed anti-erythropoiesis antibodies during the study. Serum samples were tested using Amgen's Surface Plasmon Resonance Immunoassay (SPRIA) method.

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

End point timeframe:

25 weeks

| End point values | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | | |
|-----------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 49 ^[14] | 49 ^[15] | | |
| Units: participants | | | | |
| number (not applicable) | 2 | 4 | | |

Notes:

[14] - Safety analysis set with both pre and postdose immunoassay antibody results

[15] - Safety analysis set with both pre and postdose immunoassay antibody results

Statistical analyses

No statistical analyses for this end point

Secondary: Darbepoetin Alfa Serum Concentrations for Participants Less Than 6 Years of Age

| | |
|-----------------|---|
| End point title | Darbepoetin Alfa Serum Concentrations for Participants Less Than 6 Years of Age |
|-----------------|---|

End point description:

Serum concentrations of darbepoetin alfa were measured by an enzyme-linked immunosorbent assay (ELISA).

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

End point timeframe:

Weeks 1, 2, and 3 before the investigational product dose and 2 days after the first investigational product dose

| End point values | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | | |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[16] | 0 ^[17] | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[16] - Due to the low number of subjects <6 years of age summary concentration analyses were not performed.

[17] - Due to the low number of subjects <6 years of age summary concentration analyses were not performed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

25 weeks

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Darbepoetin Alfa QW |
|-----------------------|---------------------|

Reporting group description:

Participants received darbepoetin alfa once a week (QW) for 24 weeks. The initial dose was 0.45 µg/kg; thereafter, active doses were administered to achieve and then maintain hemoglobin levels within a target range of 10.0 to 12.0 g/dL. Participants not on dialysis or who were receiving peritoneal dialysis were administered darbepoetin alfa subcutaneously; participants receiving hemodialysis were administered darbepoetin alfa intravenously.

| | |
|-----------------------|----------------------|
| Reporting group title | Darbepoetin Alfa Q2W |
|-----------------------|----------------------|

Reporting group description:

Participants received darbepoetin alfa every 2 weeks (Q2W) and a placebo every other 2 weeks to maintain the blind for 24 weeks. The initial dose was 0.75 µg/kg; thereafter, active doses were administered to achieve and then maintain hemoglobin levels within a target range of 10.0 to 12.0 g/dL. Participants not on dialysis or who were receiving peritoneal dialysis were administered darbepoetin alfa subcutaneously; participants receiving hemodialysis were administered darbepoetin alfa intravenously.

| Serious adverse events | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | |
|---|---------------------|----------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 58 (27.59%) | 14 / 56 (25.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 3 / 56 (5.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 0 / 58 (0.00%) | 2 / 56 (3.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Device failure | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device malfunction | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Local swelling | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Medical device complication | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract inflammation | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Arteriovenous fistula site complication | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous fistula site haematoma | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrostomy failure | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Headache | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 2 / 58 (3.45%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive encephalopathy | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Histiocytosis haematophagic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 56 (1.79%) | |
| 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 | 2 / 58 (3.45%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Decubitus ulcer | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Swelling face | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (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 | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure chronic | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 2 / 58 (3.45%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vesical fistula | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site infection | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related sepsis | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epstein-Barr virus infection | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis clostridial | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 58 (0.00%) | 2 / 56 (3.57%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis bacterial | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (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 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shunt infection | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (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 | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid overload | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 58 (1.72%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | 0 / 56 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 58 (0.00%) | 1 / 56 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 0 | 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 | Darbepoetin Alfa QW | Darbepoetin Alfa Q2W | |
|---|---------------------|----------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 42 / 58 (72.41%) | 43 / 56 (76.79%) | |
| Investigations | | | |
| Blood pressure increased | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | 3 / 56 (5.36%) | |
| occurrences (all) | 3 | 3 | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 58 (1.72%) | 3 / 56 (5.36%) | |
| occurrences (all) | 1 | 4 | |
| Procedural hypotension | | | |
| subjects affected / exposed | 3 / 58 (5.17%) | 3 / 56 (5.36%) | |
| occurrences (all) | 24 | 15 | |
| Vascular disorders | | | |

| | | | |
|---|-----------------------|------------------------|--|
| Hypertension subjects affected / exposed occurrences (all) | 9 / 58 (15.52%) 29 | 8 / 56 (14.29%) 12 | |
| Hypotension subjects affected / exposed occurrences (all) | 2 / 58 (3.45%) 2 | 3 / 56 (5.36%) 3 | |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 3 / 58 (5.17%) 3 | 3 / 56 (5.36%) 3 | |
| Headache subjects affected / exposed occurrences (all) | 4 / 58 (6.90%) 5 | 10 / 56 (17.86%) 17 | |
| General disorders and administration site conditions | | | |
| Catheter site pain subjects affected / exposed occurrences (all) | 3 / 58 (5.17%) 3 | 1 / 56 (1.79%) 1 | |
| Fatigue subjects affected / exposed occurrences (all) | 5 / 58 (8.62%) 6 | 2 / 56 (3.57%) 2 | |
| Injection site pain subjects affected / exposed occurrences (all) | 3 / 58 (5.17%) 3 | 2 / 56 (3.57%) 3 | |
| Medical device complication subjects affected / exposed occurrences (all) | 2 / 58 (3.45%) 2 | 3 / 56 (5.36%) 3 | |
| Pyrexia subjects affected / exposed occurrences (all) | 5 / 58 (8.62%) 10 | 10 / 56 (17.86%) 13 | |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 6 / 58 (10.34%) 6 | 5 / 56 (8.93%) 6 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 3 / 58 (5.17%) 3 | 2 / 56 (3.57%) 2 | |

| | | | |
|--|------------------------|-----------------------|--|
| Constipation subjects affected / exposed occurrences (all) | 4 / 58 (6.90%) 4 | 4 / 56 (7.14%) 4 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 3 / 58 (5.17%) 3 | 4 / 56 (7.14%) 4 | |
| Nausea subjects affected / exposed occurrences (all) | 5 / 58 (8.62%) 6 | 4 / 56 (7.14%) 4 | |
| Vomiting subjects affected / exposed occurrences (all) | 10 / 58 (17.24%) 12 | 9 / 56 (16.07%) 13 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 7 / 58 (12.07%) 10 | 4 / 56 (7.14%) 4 | |
| Nasal congestion subjects affected / exposed occurrences (all) | 4 / 58 (6.90%) 4 | 1 / 56 (1.79%) 1 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 2 / 58 (3.45%) 2 | 3 / 56 (5.36%) 3 | |
| Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) | 4 / 58 (6.90%) 6 | 1 / 56 (1.79%) 1 | |
| Rash subjects affected / exposed occurrences (all) | 3 / 58 (5.17%) 5 | 1 / 56 (1.79%) 1 | |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 2 / 58 (3.45%) 2 | 3 / 56 (5.36%) 3 | |
| Muscle spasms subjects affected / exposed occurrences (all) | 5 / 58 (8.62%) 5 | 2 / 56 (3.57%) 3 | |

| | | | |
|---|--|---|--|
| Pain in extremity subjects affected / exposed occurrences (all) | 4 / 58 (6.90%) 4 | 1 / 56 (1.79%) 2 | |
| Infections and infestations Catheter site infection subjects affected / exposed occurrences (all) Ear infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) | 4 / 58 (6.90%) 5 4 / 58 (6.90%) 4 4 / 58 (6.90%) 4 2 / 58 (3.45%) 4 3 / 58 (5.17%) 3 4 / 58 (6.90%) 5 | 3 / 56 (5.36%) 3 0 / 56 (0.00%) 0 6 / 56 (10.71%) 9 5 / 56 (8.93%) 5 7 / 56 (12.50%) 10 0 / 56 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 20 August 2007 | <p>The study design was changed from an open-label, single-arm study assessing the safety and efficacy of darbepoetin alfa administered Q2W to a double-blind, randomized, parallel-group study assessing the safety and efficacy of darbepoetin alfa administered QW or Q2W. The objectives, endpoints, procedure, and sample informed consent form were revised to reflect this change. The number of subjects and study centers were increased, and a new region (Canada) was added. In addition, the following changes were made:</p> <ul style="list-style-type: none">- The targeted age distribution was revised to enroll a greater percentage of subjects < 12 years.- The Hb target range was revised from 11.0 - 13.0 g/dL to 11.0 - 12.0 g/dL.- Collection of samples for pharmacokinetic analyses was added for subjects < 6 years old.- The frequency of Hb measurements was changed from biweekly to weekly.- Known positive HIV or hepatitis B status was removed from and immunosuppressive agent use was added to the exclusion criteria. The prohibition period for RBC transfusions before randomization was changed from 8 to 12 weeks.- The Epoetin alfa washout period for subjects receiving dialysis was deleted and the prohibition period for any ESA use before randomization was changed from 4 to 12 weeks for all subjects.- Darbepoetin alfa product used in this study was changed from vials to prefilled syringes, and the dosing procedures, including dose adjustment rules, were updated to reflect unit dosing.- Subjects who progressed to dialysis were allowed to remain in the study. In addition, subjects who declined to receive investigational product were allowed to continue with other study procedures.- Analyses sets for efficacy and safety were further defined. |
| 08 November 2007 | <p>The Hb target range was revised to 10.0-12.0 g/dL and the study objectives, endpoints, inclusion criteria, and dose adjustment procedures were updated accordingly. Physical examination procedures were defined in greater detail. The procedures section was updated to reflect the use of a central laboratory for analyses. Language regarding contraception was updated for consistency between the protocol and informed consent template.</p> |
| 26 August 2008 | <p>The following changes were implemented to improve study enrollment: minor updates were made to the eligibility criteria, the number of blood samples collected were reduced by removing samples required for future analysis, and regions outside North America were allowed to participate. The informed consent form template was updated accordingly, and to reflect the most current safety language for darbepoetin alfa and remove Canadian-specific text since Canada was not participating in the study.</p> |
| 04 May 2010 | <p>The exclusion criteria were revised to allow the use of low dose corticosteroids (such as those used for asthma treatment); this change was implemented to avoid unnecessary exclusion of subjects without altering the study safety for subjects. The informed consent form template was also updated to include additional safety information for darbepoetin alfa from clinical trials.</p> |

| | |
|-------------------|--|
| 30 January 2012 | <p>The protocol was primarily amended to allow a 5 µg dose so that subjects who required treatment with < 10 µg darbepoetin alfa (lowest dose previously specified) could receive investigational product.</p> <p>Darbepoetin alfa product was changed from prefilled syringes to vials in order to accommodate this dose while retaining the blind. Dosing procedures, including dose adjustment rules, were updated accordingly.</p> <p>The following changes were also implemented to improve enrollment.</p> <ul style="list-style-type: none"> - The prohibition period prior to enrollment was changed from 12 to 8 weeks for ESAs and from 12 to 1 week(s) for RBC transfusions. The primary study endpoints were adjusted to account for the shortened period prohibiting RBC transfusions. - The time between consecutive Hb samples was changed from 7 to 5 days for purposes of inclusion - The exclusion criteria for hematologic disease (ie, likely to affect RBC production or turnover) and seizure (ie, nonfebrile) were clarified. - An age group of 1 to < 12 years was added to the subgroup analyses. |
| 13 September 2012 | <p>The protocol was amended to include the occurrence of an unplanned interim analysis of data from all subjects who ended the study by 31 July 2012 in order to fulfill regulatory requirements. In addition, the language regarding serious adverse event reporting was updated, and the sample informed consent was also updated for consistency with current Amgen templates.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---------------|---|--------------|
| 03 March 2014 | <p>Following review of the interim CSR, agreement was reached with both the US FDA (10 July 2012) and the Paediatric Committee (PDCO) of the European Medicines Agency (EMA) (17 January 2014) to terminate the study early on the basis of availability of sufficient data in the targeted population. Study 20050256 was terminated early (last patient completed follow-up 03 March 2014) after enrolling 116 out of 150 planned subjects.</p> | - |

Notes:

Limitations and caveats

None reported