EU Clinical Trials Register

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)	EMEA-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

End point title	Time to First Hemoglobin Value ≥ 10.0 g/dL
End point description:	
The time from study Day 1 to the day a participant first achieved hemoglobin ≥ 10.0 g/dL for participants who achieved hemoglobin ≥ 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

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 (± 0.84)	8.73 (± 0.84)		
Week 1 (n=53, 50)	8.64 (± 0.9)	8.65 (± 0.95)		
Week 2 (n=52, 52)	8.74 (± 1.09)	8.96 (± 1.2)		
Week 3 (n=51, 55)	9.28 (± 1.27)	9.09 (± 1.27)		
Week 4 (n=53, 53)	9.79 (± 1.3)	9.55 (± 1.23)		
Week 5 (n=53, 52)	10.18 (± 1.29)	9.87 (± 1.32)		
Week 6 (n=54, 50)	10.54 (± 1.43)	10.19 (± 1.33)		
Week 7 (n=52, 48)	10.96 (± 1.53)	10.17 (± 1.25)		
Week 8 (n=53, 51)	11.05 (± 1.37)	10.47 (± 1.21)		
Week 9 (n=50, 51)	11.03 (± 1.48)	10.6 (± 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

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.

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 (± 2.19)	0.58 (± 2.43)		
Week 13 Psychosocial composite score (n=45, 46)	5.12 (± 2.16)	-0.41 (± 2.57)		
Week 13 Physical function score (n=45, 46)	3.61 (± 3.2)	2.31 (± 3.35)		
Week 13 Emotional function score (n=45, 46)	1 (± 3)	-3.89 (± 2.74)		
Week 13 Social function score (n=45, 46)	6.89 (± 3.54)	0.76 (± 3.56)		
Week 13 School function score (n=42, 42)	7.3 (± 2.47)	4.17 (± 3.63)		
Week 25 Total Score (n=38, 41)	1.9 (± 2.06)	0.65 (± 2.66)		
Week 25 Psychosocial composite score (n=38, 41)	2.52 (± 1.83)	-1.84 (± 3.13)		
Week 25 Physical function score (n=38, 41)	0.66 (± 3.89)	5.18 (± 3.59)		
Week 25 Emotional function score (n=38, 41)	-0.66 (± 2.61)	-3.51 (± 3.16)		
Week 25 Social function score (n=38, 41)	5.13 (± 2.64)	-2.2 (± 4.1)		
Week 25 School function score (n=36, 37)	3.9 (± 2.51)	2.03 (± 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 analyis set with available data

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 August 2007	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: - 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	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.
26 August 2008	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.
04 May 2010	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.

30 January 2012	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. 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. The following changes were also implemented to improve enrollment. - 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	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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
03 March 2014	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.	-

Notes:

Limitations and caveats

None reported