



Clinical trial results:

A randomized, parallel group, open-label, multicenter study to investigate the efficacy and safety of oral BAY 85-3934 and active comparator (darbepoetin alfa) in the maintenance treatment of anemia in pre-dialysis subjects with chronic kidney disease on darbepoetin treatment in Europe and Asia Pacific

Summary

EudraCT number	2013-001192-21
Trial protocol	DE HU IT ES BG PL
Global end of trial date	23 November 2015

Results information

Result version number	v1 (current)
This version publication date	19 November 2016
First version publication date	19 November 2016

Trial information

Trial identification

Sponsor protocol code	BAY85-3934/15261
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02021409
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee,, D-51368 Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 November 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	23 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of 16 weeks of titrated dose treatment with BAY85-3934 versus darbepoetin as measured by hemoglobin (Hb) levels during the last 4 weeks of treatment (evaluation period).

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Japan: 23
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 4
Country: Number of subjects enrolled	Romania: 18
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Bulgaria: 9
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 30
Country: Number of subjects enrolled	Italy: 22
Worldwide total number of subjects	124
EEA total number of subjects	93

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	42
From 65 to 84 years	78
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 47 study centers in 13 countries: Australia, Bulgaria, France, Germany, Hungary, Israel, Italy, Japan, Poland, Republic of Korea, Romania, Spain, and United Kingdom between 28 January 2014 (first subject first visit) and 23 November 2015 (last subject last visit).

Pre-assignment

Screening details:

A total of 196 subjects were screened, of them 72 were not included in the study due to screen failure, withdrawal by subjects and other reason. The remaining 124 subjects were randomized and assigned to treatment. Of the treated subjects, 39 entered the follow-up period and 77 subjects entered in an extension study.

Period 1

Period 1 title	Treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BAY85-3934 25 milligram (mg)

Arm description:

Subjects received BAY85-3934 tablet orally at a starting dose of 25 mg once daily up to 16 weeks which was titrated at 4-week intervals according to pre-defined criteria taking into account the subject's Hb response and the tolerability of the previous dose.

Arm type	Experimental
Investigational medicinal product name	BAY85-3934
Investigational medicinal product code	BAY85-3934
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received BAY85-3934 tablet orally at a starting dose of 25 mg once daily up to 16 weeks which was titrated at 4-week intervals.

Arm title	BAY85-3934 50 mg
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Arm description:

Subjects received BAY85-3934 tablet orally at a starting dose of 50 mg once daily up to 16 weeks which was titrated at 4-week intervals according to pre-defined criteria taking into account the subject's Hb response and the tolerability of the previous dose.

Arm type	Experimental
Investigational medicinal product name	BAY85-3934
Investigational medicinal product code	BAY85-3934
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received BAY85-3934 tablet orally at a starting dose of 50 mg once daily up to 16 weeks which was titrated at 4-week intervals.

Arm title	BAY85-3934 75 mg
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Arm description:

Subjects received BAY85-3934 tablet orally at a starting dose of 75 mg once daily up to 16 weeks which was titrated at 4-week intervals according to pre-defined criteria taking into account the subject's Hb

response and the tolerability of the previous dose.

Arm type	Experimental
Investigational medicinal product name	BAY85-3934
Investigational medicinal product code	BAY85-3934
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received BAY85-3934 tablet orally at a starting dose of 75 mg once daily up to 16 weeks which was titrated at 4-week intervals.

Arm title	Darbepoetin
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Arm description:

Subjects received Darbepoetin injection intravenously (IV) or subcutaneously (SC) once every 1, 2, or 4 weeks as per individual subject regimen according to the local label up to 16 weeks which was titrated at 4-week intervals according to pre-defined criteria taking into account the subject's Hb response and the tolerability of the previous dose.

Arm type	Active comparator
Investigational medicinal product name	Darbepoetin
Investigational medicinal product code	
Other name	Aranesp
Pharmaceutical forms	Injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Subjects received darbepoetin injection IV or SC once every 1, 2, or 4 weeks as per individual subject regimen according to the local label up to 16 weeks which was titrated at 4-week intervals.

Number of subjects in period 1	BAY85-3934 25 milligram (mg)	BAY85-3934 50 mg	BAY85-3934 75 mg
Started	30	30	32
Completed	21	25	26
Not completed	9	5	6
Physician Decision	1	-	1
Protocol violation	1	-	-
Protocol driven decision point	3	-	3
Death	1	-	-
Adverse event	2	4	2
Sponsor Decision	-	1	-
Withdrawal by subject	1	-	-

Number of subjects in period 1	Darbepoetin
Started	32
Completed	27
Not completed	5
Physician Decision	1
Protocol violation	-
Protocol driven decision point	2

Death	1
Adverse event	1
Sponsor Decision	-
Withdrawal by subject	-

Period 2

Period 2 title	Follow-up Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BAY85-3934 25 mg

Arm description:

Subjects entered a follow-up period for a duration of 8 weeks after completing treatment.

Arm type	Experimental
Investigational medicinal product name	BAY85-3934
Investigational medicinal product code	BAY85-3934
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received BAY85-3934 tablet orally at a starting dose of 25 mg once daily up to 16 weeks which was titrated at 4-week intervals during treatment period.

Arm title	BAY85-3934 50 mg
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Arm description:

Subjects entered a follow-up period for a duration of 8 weeks after completing treatment.

Arm type	Experimental
Investigational medicinal product name	BAY85-3934
Investigational medicinal product code	BAY85-3934
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received BAY85-3934 tablet orally at a starting dose of 50 mg once daily up to 16 weeks which was titrated at 4-week intervals during treatment period.

Arm title	BAY85-3934 75 mg
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Arm description:

Subjects entered a follow-up period for a duration of 8 weeks after completing treatment.

Arm type	Experimental
Investigational medicinal product name	BAY85-3934
Investigational medicinal product code	BAY85-3934
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received BAY85-3934 tablet orally at a starting dose of 75 mg once daily up to 16 weeks which was titrated at 4-week intervals during treatment period.

Arm title	Darbepoetin
Arm description: Subjects entered a follow-up period for a duration of 8 weeks after completing treatment.	
Arm type	Active comparator
Investigational medicinal product name	Darbepoetin
Investigational medicinal product code	
Other name	Aranesp
Pharmaceutical forms	Injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Subjects received darbepoetin injection IV or SC once every 1, 2, or 4 weeks as per individual subject regimen according to the local label up to 16 weeks which was titrated at 4-week intervals during treatment period.

Number of subjects in period 2^[1]	BAY85-3934 25 mg	BAY85-3934 50 mg	BAY85-3934 75 mg
Started	8	12	14
Completed	8	10	14
Not completed	0	2	0
Other	-	1	-
Lost to follow-up	-	1	-

Number of subjects in period 2^[1]	Darbepoetin
Started	5
Completed	5
Not completed	0
Other	-
Lost to follow-up	-

Notes:

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

Justification: Few of the participants entered the extension study and few of them discontinued the treatment, so there is a difference in number of subjects starting the subsequent period compared to the number completing the preceding period.

Baseline characteristics

Reporting groups

Reporting group title	BAY85-3934 25 milligram (mg)
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Reporting group description:

Subjects received BAY85-3934 tablet orally at a starting dose of 25 mg once daily up to 16 weeks which was titrated at 4-week intervals according to pre-defined criteria taking into account the subject's Hb response and the tolerability of the previous dose.

Reporting group title	BAY85-3934 50 mg
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Reporting group description:

Subjects received BAY85-3934 tablet orally at a starting dose of 50 mg once daily up to 16 weeks which was titrated at 4-week intervals according to pre-defined criteria taking into account the subject's Hb response and the tolerability of the previous dose.

Reporting group title	BAY85-3934 75 mg
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Reporting group description:

Subjects received BAY85-3934 tablet orally at a starting dose of 75 mg once daily up to 16 weeks which was titrated at 4-week intervals according to pre-defined criteria taking into account the subject's Hb response and the tolerability of the previous dose.

Reporting group title	Darbepoetin
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Reporting group description:

Subjects received Darbepoetin injection intravenously (IV) or subcutaneously (SC) once every 1, 2, or 4 weeks as per individual subject regimen according to the local label up to 16 weeks which was titrated at 4-week intervals according to pre-defined criteria taking into account the subject's Hb response and the tolerability of the previous dose.

Reporting group values	BAY85-3934 25 milligram (mg)	BAY85-3934 50 mg	BAY85-3934 75 mg
Number of subjects	30	30	32
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	65.5 ± 8.82	64.5 ± 10.18	72.5 ± 10.63
Gender categorical Units: Subjects Female Male	18 12	13 17	16 16
Number of Japanese and Non-Japanese Subjects Units: Subjects Japanese Subjects Non-Japanese Subjects	6 24	6 24	5 27
Estimated Glomerular Filtration Rate (eGFR)			
The eGFR was used to determine eligibility for the study and whether subjects of different stages of renal impairment / chronic kidney disease (CKD) respond differently to BAY85-3934 and to assess renal function by treatment.			
Units: milliliter/minute/1.73 square meter arithmetic mean standard deviation	20.025 ± 10.4051	17.674 ± 8.8648	23.261 ± 13.8266

Local Laboratory Hemoglobin Levels Units: gram/deciliter (g/dL) arithmetic mean standard deviation	10.85 ± 0.732	10.74 ± 0.689	10.66 ± 0.748
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Reporting group values	Darbepoetin	Total	
Number of subjects	32	124	
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	68.8 ± 8.74	-	
Gender categorical Units: Subjects			
Female	14	61	
Male	18	63	
Number of Japanese and Non-Japanese Subjects Units: Subjects			
Japanese Subjects	6	23	
Non-Japanese Subjects	26	101	
Estimated Glomerular Filtration Rate (eGFR)			
The eGFR was used to determine eligibility for the study and whether subjects of different stages of renal impairment / chronic kidney disease (CKD) respond differently to BAY85-3934 and to assess renal function by treatment.			
Units: milliliter/minute/1.73 square meter arithmetic mean standard deviation	21.929 ± 12.0731	-	
Local Laboratory Hemoglobin Levels Units: gram/deciliter (g/dL) arithmetic mean standard deviation	10.85 ± 0.678	-	

End points

End points reporting groups

Reporting group title	BAY85-3934 25 milligram (mg)
Reporting group description: Subjects received BAY85-3934 tablet orally at a starting dose of 25 mg once daily up to 16 weeks which was titrated at 4-week intervals according to pre-defined criteria taking into account the subject's Hb response and the tolerability of the previous dose.	
Reporting group title	BAY85-3934 50 mg
Reporting group description: Subjects received BAY85-3934 tablet orally at a starting dose of 50 mg once daily up to 16 weeks which was titrated at 4-week intervals according to pre-defined criteria taking into account the subject's Hb response and the tolerability of the previous dose.	
Reporting group title	BAY85-3934 75 mg
Reporting group description: Subjects received BAY85-3934 tablet orally at a starting dose of 75 mg once daily up to 16 weeks which was titrated at 4-week intervals according to pre-defined criteria taking into account the subject's Hb response and the tolerability of the previous dose.	
Reporting group title	Darbepoetin
Reporting group description: Subjects received Darbepoetin injection intravenously (IV) or subcutaneously (SC) once every 1, 2, or 4 weeks as per individual subject regimen according to the local label up to 16 weeks which was titrated at 4-week intervals according to pre-defined criteria taking into account the subject's Hb response and the tolerability of the previous dose.	
Reporting group title	BAY85-3934 25 mg
Reporting group description: Subjects entered a follow-up period for a duration of 8 weeks after completing treatment.	
Reporting group title	BAY85-3934 50 mg
Reporting group description: Subjects entered a follow-up period for a duration of 8 weeks after completing treatment.	
Reporting group title	BAY85-3934 75 mg
Reporting group description: Subjects entered a follow-up period for a duration of 8 weeks after completing treatment.	
Reporting group title	Darbepoetin
Reporting group description: Subjects entered a follow-up period for a duration of 8 weeks after completing treatment.	
Subject analysis set title	Modified Intent-To-Treat (mITT)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: mITT (N= 124) included all subjects randomized to study treatment who received at least one dose of study treatment and who have at least one post-baseline efficacy value available.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description: SAF (N= 124) included all randomized subjects who received at least one dose of study treatment.	

Primary: Mean Change From Baseline in Local Laboratory Hemoglobin Level During Evaluation Period

End point title	Mean Change From Baseline in Local Laboratory Hemoglobin Level During Evaluation Period
End point description: Evaluation Period was defined as the last 4 planned weeks of the study treatment period.	
End point type	Primary

End point timeframe:
Baseline, Weeks 13 to 16

End point values	BAY85-3934 25 milligram (mg)	BAY85-3934 50 mg	BAY85-3934 75 mg	Darbepoetin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26 ^[1]	26 ^[2]	28 ^[3]	28 ^[4]
Units: g/dL				
arithmetic mean (standard deviation)	0.09 (± 1.096)	0.39 (± 0.561)	0.87 (± 0.824)	0.18 (± 0.777)

Notes:

[1] - mITT with number of subjects evaluable for this end point.

[2] - mITT with number of subjects evaluable for this end point.

[3] - mITT with number of subjects evaluable for this end point.

[4] - mITT with number of subjects evaluable for this end point.

Statistical analyses

Statistical analysis title	Statistical Analysis for BAY85-3934 25 mg
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Statistical analysis description:

Results were reported including Least square mean (LS-mean) difference and 95 percent (%) confidence intervals (CI). LS-mean difference was based on constrained longitudinal data analysis (cLDA) model including the response vector consisting of baseline and values at each post-baseline time point, and the repeated measures model including treatment, randomization stratification factors, time (visit), the interaction of time by treatment, and the interaction of time by randomization factors.

Comparison groups	BAY85-3934 25 milligram (mg) v Darbepoetin
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	0.42
Variability estimate	Standard error of the mean
Dispersion value	0.246

Statistical analysis title	Statistical Analysis for BAY85-3934 50 mg
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Statistical analysis description:

Results were reported including LS-mean difference and 95 % CI. LS-mean difference was based on cLDA model including the response vector consisting of baseline and values at each post-baseline time point, and the repeated measures model including treatment, randomization stratification factors, time (visit), the interaction of time by treatment, and the interaction of time by randomization factors.

Comparison groups	BAY85-3934 50 mg v Darbepoetin
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Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.49
Variability estimate	Standard error of the mean
Dispersion value	0.182

Statistical analysis title	Statistical Analysis for BAY85-3934 75 mg
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Statistical analysis description:

Results were reported including LS-mean difference and 95 % CI. LS-mean difference was based on cLDA model including the response vector consisting of baseline and values at each post-baseline time point, and the repeated measures model including treatment, randomization stratification factors, time (visit), the interaction of time by treatment, and the interaction of time by randomization factors.

Comparison groups	BAY85-3934 75 mg v Darbepoetin
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS Mean Difference
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.86
Variability estimate	Standard error of the mean
Dispersion value	0.196

Secondary: Overall Rate of Responders in Local Hemoglobin During Evaluation Period

End point title	Overall Rate of Responders in Local Hemoglobin During Evaluation Period
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End point description:

A responder was defined as a subject who had a mean of the Hb levels during the evaluation period in the target range (10.0 to 12.0 g/dL, inclusive), greater than or equal to (\geq) 50 % of the Hb levels in the target range during the evaluation period, and no red blood cell (RBC) containing transfusion during active treatment. Evaluation Period was defined as the last 4 planned weeks of the study treatment period.

End point type	Secondary
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End point timeframe:

Weeks 13 to 16

End point values	BAY85-3934 25 milligram (mg)	BAY85-3934 50 mg	BAY85-3934 75 mg	Darbepoetin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24 ^[5]	26 ^[6]	28 ^[7]	28 ^[8]
Units: Percentage of responders				
number (not applicable)	70.8	80.8	60.7	89.3

Notes:

[5] - mITT number of subjects evaluable for this end point.

[6] - mITT number of subjects evaluable for this end point.

[7] - mITT number of subjects evaluable for this end point.

[8] - mITT number of subjects evaluable for this end point.

Statistical analyses

Statistical analysis title	Statistical Analysis for BAY85-3934 25 mg
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Statistical analysis description:

Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 42. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.

Comparison groups	BAY85-3934 25 milligram (mg) v Darbepoetin
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	-18.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.2
upper limit	9.4

Statistical analysis title	Statistical Analysis for BAY85-3934 50 mg
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Statistical analysis description:

Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 46. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.

Comparison groups	BAY85-3934 50 mg v Darbepoetin
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	-8.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.9
upper limit	17.5

Statistical analysis title	Statistical Analysis for BAY85-3934 75 mg
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Statistical analysis description:

Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 42. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.

Comparison groups	BAY85-3934 75 mg v Darbepoetin
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	-28.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.3
upper limit	-0.7

Secondary: Time Within Hemoglobin Target Range During Active Treatment

End point title	Time Within Hemoglobin Target Range During Active Treatment
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End point description:

Time within the treatment target was defined as the sum of all days where subject Hb values were within protocol defined treatment target. Hb target range was defined as 10.0 to 12.0 g/dL, inclusive.

End point type	Secondary
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End point timeframe:

From baseline up to 16 weeks

End point values	BAY85-3934 25 milligram (mg)	BAY85-3934 50 mg	BAY85-3934 75 mg	Darbepoetin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30 ^[9]	30 ^[10]	32 ^[11]	32 ^[12]
Units: days				
median (full range (min-max))	87.35 (0 to 112)	84.35 (0 to 114)	65.15 (0 to 111)	106.4 (11.8 to 118)

Notes:

[9] - mITT

[10] - mITT

[11] - mITT

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Hemoglobin During Active Treatment

End point title	Change From Baseline in Hemoglobin During Active Treatment
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End point description:

Hb was analysed using the blood samples drawn during the active treatment period of the study.

End point type	Secondary
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End point timeframe:

Baseline, Weeks 2, 3, 5, 7, 9, 11, 13, 14, 15, 16 and 17

End point values	BAY85-3934 25 milligram (mg)	BAY85-3934 50 mg	BAY85-3934 75 mg	Darbepoetin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30 ^[13]	30 ^[14]	32 ^[15]	32 ^[16]
Units: g/dL				
arithmetic mean (standard deviation)				
Change at Week 2	-0.08 (± 0.594)	-0.07 (± 0.35)	-0.12 (± 0.553)	0 (± 0.531)
Change at Week 3	0.01 (± 0.671)	-0.06 (± 0.627)	0.17 (± 0.584)	0.12 (± 0.728)
Change at Week 5	0.13 (± 0.883)	0.22 (± 0.804)	0.31 (± 0.916)	0.2 (± 0.689)
Change at Week 7	-0.01 (± 1.096)	0.18 (± 0.598)	0.53 (± 1.048)	0.34 (± 0.71)
Change at Week 9	0.02 (± 1.142)	0.23 (± 0.817)	0.62 (± 1.123)	0.37 (± 0.804)
Change at Week 11	-0.06 (± 1.284)	0.04 (± 0.808)	0.6 (± 1.262)	0.21 (± 0.735)
Change at Week 13	-0.01 (± 1.361)	0.17 (± 0.85)	0.95 (± 1.242)	0.26 (± 0.746)
Change at Week 14	0.05 (± 1.309)	0.08 (± 0.735)	0.86 (± 1.148)	0.29 (± 0.729)
Change at Week 15	0.01 (± 1.2)	0.33 (± 0.856)	0.8 (± 1.036)	0.24 (± 0.815)
Change at Week 16	0.07 (± 1.236)	0.27 (± 0.854)	0.63 (± 1.073)	0.2 (± 0.918)
Change at Week 17	0.01 (± 1.045)	0.19 (± 0.902)	0.56 (± 1.1)	0.11 (± 0.924)

Notes:

[13] - mITT

[14] - mITT

[15] - mITT

[16] - mITT

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Meeting Specific Local Hemoglobin Criteria in Evaluation Period

End point title	Number of Subjects Meeting Specific Local Hemoglobin Criteria in Evaluation Period
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End point description:

Evaluation Period was defined as the last 4 planned weeks of the study treatment period. The following were the specific hemoglobin criteria that were to be met: greater than (>) 50 % of the Hb levels below the lower limit of 10.0 g/dL, mean of the Hb levels below the lower limit of 10.0 g/dL, > 50% of the Hb levels above the upper limit of 12.0 g/dL, mean of the Hb levels above the upper limit of 12.0 g/dL.

End point type	Secondary
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End point timeframe:

Weeks 13 to 16

End point values	BAY85-3934 25 milligram (mg)	BAY85-3934 50 mg	BAY85-3934 75 mg	Darbepoetin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24 ^[17]	26 ^[18]	28 ^[19]	28 ^[20]
Units: Subjects				
> 50% of the Hb levels below the lower limit of 10	2	1	1	2
Mean of the Hb levels below the lower limit of 10	4	2	2	2
> 50% of the Hb levels above the upper limit of 12	2	1	7	1
Mean of the Hb levels above the upper limit of 12	3	3	8	1

Notes:

[17] - mITT number of subjects evaluable for this end point.

[18] - mITT number of subjects evaluable for this end point.

[19] - mITT number of subjects evaluable for this end point.

[20] - mITT number of subjects evaluable for this end point.

Statistical analyses

Statistical analysis title	BAY85-3934 25mg (> 50% of Hb levels below 10 g/dL)
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Statistical analysis description:

Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 4. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.

Comparison groups	BAY85-3934 25 milligram (mg) v Darbepoetin
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.8
upper limit	28.3

Statistical analysis title	BAY85-3934 50mg (> 50% of Hb levels below 10 g/dL)
Statistical analysis description:	
Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 3. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.	
Comparison groups	BAY85-3934 50 mg v Darbepoetin
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.8
upper limit	23.9

Statistical analysis title	BAY85-3934 75mg (> 50% of Hb levels below 10 g/dL)
Statistical analysis description:	
Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 3. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.	
Comparison groups	BAY85-3934 75 mg v Darbepoetin
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.7
upper limit	23.9

Statistical analysis title	BAY85-3934 25 mg (Mean of Hb levels below 10 g/dL)
Statistical analysis description:	
Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 6. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.	
Comparison groups	BAY85-3934 25 milligram (mg) v Darbepoetin

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	9.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.8
upper limit	35.9

Statistical analysis title	BAY85-3934 50 mg (Mean of Hb levels below 10 g/dL)
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Statistical analysis description:

Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 4. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.

Comparison groups	BAY85-3934 50 mg v Darbepoetin
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26
upper limit	27.6

Statistical analysis title	BAY85-3934 75 mg (Mean of Hb levels below 10 g/dL)
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Statistical analysis description:

Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 4. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.

Comparison groups	BAY85-3934 75 mg v Darbepoetin
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.3
upper limit	27.3

Statistical analysis title	BAY85-3934 25mg (> 50% of Hb levels above 12 g/dL)
Statistical analysis description:	
Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 3. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.	
Comparison groups	BAY85-3934 25 milligram (mg) v Darbepoetin
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.5
upper limit	31.7

Statistical analysis title	BAY85-3934 50mg (> 50% of Hb levels above 12 g/dL)
Statistical analysis description:	
Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 2. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.	
Comparison groups	BAY85-3934 50 mg v Darbepoetin
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.5
upper limit	27.3

Statistical analysis title	BAY85-3934 75mg (> 50% of Hb levels above 12 g/dL)
Statistical analysis description:	
Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 8. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.	
Comparison groups	BAY85-3934 75 mg v Darbepoetin

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	21.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	47

Statistical analysis title	BAY85-3934 25 mg (Mean of Hb levels above 12 g/dL)
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Statistical analysis description:

Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 4. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.

Comparison groups	BAY85-3934 25 milligram (mg) v Darbepoetin
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.4
upper limit	35.5

Statistical analysis title	BAY85-3934 50 mg (Mean of Hb levels above 12 g/dL)
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Statistical analysis description:

Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 4. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.

Comparison groups	BAY85-3934 50 mg v Darbepoetin
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.8
upper limit	34.5

Statistical analysis title	BAY85-3934 75 mg (Mean of Hb levels above 12 g/dL)
Statistical analysis description:	
Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 9. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.	
Comparison groups	BAY85-3934 75 mg v Darbepoetin
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	50.2

Secondary: Treatment Exposure by Dose Level

End point title	Treatment Exposure by Dose Level
End point description:	
Treatment exposure was defined as number of days subject was on study treatment, calculated as last study treatment dose date - first study treatment dose date + 1. Here mcg/kg = microgram/kilogram.	
End point type	Secondary
End point timeframe:	
From baseline up to 16 weeks	

End point values	BAY85-3934 25 milligram (mg)	BAY85-3934 50 mg	BAY85-3934 75 mg	Darbepoetin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30 ^[21]	30 ^[22]	32 ^[23]	32 ^[24]
Units: mg for BAY85-3934;mcg/kg for Darbepoetin				
arithmetic mean (standard deviation)	26.3 (± 12.38)	45.6 (± 17.11)	63.1 (± 26.15)	0.03 (± 0.022)

Notes:

[21] - mITT

[22] - mITT

[23] - mITT

[24] - mITT

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Exposure

End point title	Duration of Exposure
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End point description:

Treatment duration (days) = date of last study drug - date of first study drug + 1.

End point type	Secondary
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End point timeframe:

From baseline up to 16 weeks

End point values	BAY85-3934 25 milligram (mg)	BAY85-3934 50 mg	BAY85-3934 75 mg	Darbepoetin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30 ^[25]	30 ^[26]	32 ^[27]	32 ^[28]
Units: days				
arithmetic mean (standard deviation)	102.6 (± 25.65)	104.6 (± 26.79)	107.7 (± 22.96)	103.2 (± 24.61)

Notes:

[25] - mITT

[26] - mITT

[27] - mITT

[28] - mITT

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Excessive Increase in Hemoglobin Levels and With Greater Than 13 gram/deciliter During Treatment Period

End point title	Number of Subjects With Excessive Increase in Hemoglobin Levels and With Greater Than 13 gram/deciliter During Treatment Period
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End point description:

Treatment period of the study is at least 16 weeks from randomisation of subjects. Excessive increase in Hb values was defined as an increase of > 1 g/dL over a 2-week period or > 2 g/dL over a 4-week period.

End point type	Secondary
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End point timeframe:

From baseline up to 16 weeks

End point values	BAY85-3934 25 milligram (mg)	BAY85-3934 50 mg	BAY85-3934 75 mg	Darbepoetin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30 ^[29]	30 ^[30]	32 ^[31]	32 ^[32]
Units: subjects				
Hb > 13 g/dL at any time	2	2	5	3
Excessive increase of Hb with >1 g/dL over 2 weeks	3	7	9	5
Excessive increase of Hb with >2 g/dL over 4 weeks	0	3	3	0

Notes:

[29] - mITT

[30] - mITT

[31] - mITT

[32] - mITT

Statistical analyses

Statistical analysis title	Statistical analysis-BAY85-3934 25mg v Darbepoetin
Statistical analysis description:	
Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 5. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.	
Comparison groups	BAY85-3934 25 milligram (mg) v Darbepoetin
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.3
upper limit	22.7

Statistical analysis title	Statistical analysis-BAY85-3934 50mg v Darbepoetin
Statistical analysis description:	
Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 5. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.	
Comparison groups	BAY85-3934 50 mg v Darbepoetin
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.3
upper limit	22.7

Statistical analysis title	Statistical analysis-BAY85-3934 75mg v Darbepoetin
Statistical analysis description:	
Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method) stratified by randomization stratification factor(s) (if the total observed subjects were less than 5) and without	

stratification factors if the total observed subjects were more than 5. Number of subjects in this analysis was 8. The number of subjects mentioned in the table is auto-generated and therefore cannot be edited.

Comparison groups	BAY85-3934 75 mg v Darbepoetin
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.5
upper limit	31.4

Secondary: Number of Subjects Requiring Titration of Dose (Down-Titration, Up-Titration)

End point title	Number of Subjects Requiring Titration of Dose (Down-Titration, Up- Titration)
End point description:	Individual dose-titration was based on regular local laboratory Hb levels measured. Dose of study treatment (for BAY 85-3934 and darbepoetin) was titrated according to pre-defined criteria taking into account the subject's Hb response and the tolerability of the previous dose.
End point type	Secondary
End point timeframe:	
From baseline up to 16 weeks	

End point values	BAY85-3934 25 milligram (mg)	BAY85-3934 50 mg	BAY85-3934 75 mg	Darbepoetin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30 ^[33]	30 ^[34]	32 ^[35]	32 ^[36]
Units: subjects				
Number of dose down-titration: 0	16	15	8	26
Number of dose down-titration: 1	14	7	12	3
Number of dose down-titration: 2	0	8	9	3
Number of dose down-titration: 3	0	0	3	0
Number of dose up-titration: 0	20	22	21	27
Number of dose up-titration: 1	5	3	6	3
Number of dose up-titration: 2	4	4	5	2
Number of dose up-titration: 3	1	1	0	0

Notes:

[33] - mITT

[34] - mITT

[35] - mITT

[36] - mITT

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Serious Adverse Events (SAEs)

End point title	Number of Subjects With Serious Adverse Events (SAEs)
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End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A Serious Adverse Event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly; any other medically important serious event as judged by the investigator.

End point type	Secondary
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End point timeframe:

From baseline up to 16 weeks

End point values	BAY85-3934 25 milligram (mg)	BAY85-3934 50 mg	BAY85-3934 75 mg	Darbepoetin
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30 ^[37]	30 ^[38]	32 ^[39]	32 ^[40]
Units: subjects	5	7	7	6

Notes:

[37] - SAF

[38] - SAF

[39] - SAF

[40] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of study drug administration up to the end of the treatment plus 3 days (Up to 119 days)

Adverse event reporting additional description:

Treatment Emergent AEs for Safety Population

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	BAY85-3934 25 mg
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Reporting group description:

Subjects received BAY85-3934 tablet orally at a dose of 25 mg once daily up to 16 weeks which was titrated at 4-week intervals according to pre-defined criteria taking into account the subject's Hb response and the tolerability of the previous dose.

Reporting group title	BAY85-3934 50 mg
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Reporting group description:

Subjects received BAY85-3934 tablet orally at a dose of 50 mg once daily up to 16 weeks which was titrated at 4-week intervals according to pre-defined criteria taking into account the subject's Hb response and the tolerability of the previous dose.

Reporting group title	BAY85-3934 75 mg
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Reporting group description:

Subjects received BAY85-3934 tablet orally at a dose of 75 mg once daily up to 16 weeks which was titrated at 4-week intervals according to pre-defined criteria taking into account the subject's Hb response and the tolerability of the previous dose.

Reporting group title	Darbepoetin
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Reporting group description:

Subjects received Darbepoetin injection IV or SC as per individual subject regimen according to the local label up to 16 weeks which was titrated at 4-week intervals according to pre-defined criteria taking into account the subject's Hb response and the tolerability of the previous dose.

Serious adverse events	BAY85-3934 25 mg	BAY85-3934 50 mg	BAY85-3934 75 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 30 (16.67%)	7 / 30 (23.33%)	7 / 32 (21.88%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Refractory anaemia with an excess of blasts			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Vascular disorders			

Hypotension			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Ileus			

subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Oedematous pancreatitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Azotaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	3 / 32 (9.38%)
occurrences causally related to treatment / all	2 / 2	2 / 2	3 / 3
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Infections and infestations			
Encephalitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

Serious adverse events	Darbepoetin		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 32 (18.75%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Refractory anaemia with an excess of blasts			

subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Haemorrhagic stroke			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Diarrhoea			

subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Ileus			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Oedematous pancreatitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Azotaemia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Chronic kidney disease			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Renal failure			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		

Renal impairment			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Intervertebral disc protrusion			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Infections and infestations			
Encephalitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Pneumonia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		
Hyponatraemia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	1 / 1		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	BAY85-3934 25 mg	BAY85-3934 50 mg	BAY85-3934 75 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 30 (66.67%)	23 / 30 (76.67%)	19 / 32 (59.38%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 30 (10.00%)	6 / 30 (20.00%)	5 / 32 (15.63%)
occurrences (all)	4	8	5
Hypotension			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	1 / 32 (3.13%)
occurrences (all)	1	1	1
Pallor			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Arteriovenous fistula operation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Dialysis device insertion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Haemodialysis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Peritoneal dialysis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Tooth extraction			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	1 / 32 (3.13%)
occurrences (all)	0	2	1
Chest pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0
Chills			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Influenza like illness			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Oedema			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	2 / 30 (6.67%)	4 / 30 (13.33%)	1 / 32 (3.13%)
occurrences (all)	2	4	1
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Prostatitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	2	1	0
Dyspnoea			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Epistaxis			

subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Interstitial lung disease			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Psychiatric disorders			
Initial insomnia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	2 / 32 (6.25%)
occurrences (all)	2	0	2
Investigations			
Amylase increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Blood chloride decreased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Blood pressure decreased			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Blood pressure increased			

subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Electrocardiogram pr prolongation			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences (all)	1	0	1
Electrocardiogram qt prolonged			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	3
Haemoglobin decreased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Haemoglobin increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Lipase increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Mycobacterium tuberculosis complex test positive			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Pancreatic enzymes increased			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Serum ferritin decreased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Venous pressure jugular increased			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Weight increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	1 / 32 (3.13%)
occurrences (all)	0	1	1

Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Thermal burn			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Traumatic haematoma			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Wound			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Wrist fracture			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			
Ichthyosis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0
Cardiac failure			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Sinus arrhythmia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	2	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			

subjects affected / exposed	1 / 30 (3.33%)	3 / 30 (10.00%)	1 / 32 (3.13%)
occurrences (all)	1	3	1
Headache			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Neuropathy peripheral			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Nephrogenic anaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Vitreous haemorrhage			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Anal haemorrhage			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	2 / 32 (6.25%)
occurrences (all)	2	0	2
Diarrhoea			
subjects affected / exposed	1 / 30 (3.33%)	4 / 30 (13.33%)	0 / 32 (0.00%)
occurrences (all)	1	4	0
Dyspepsia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Enterocolitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Gastric ulcer			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal pain			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Glossodynia			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	1 / 32 (3.13%)
occurrences (all)	2	1	2

Umbilical hernia subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	0 / 32 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 2	0 / 30 (0.00%) 0	2 / 32 (6.25%) 2
Hepatobiliary disorders Cholecystitis acute subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	0 / 32 (0.00%) 0
Skin and subcutaneous tissue disorders Eczema asteatotic subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	0 / 32 (0.00%) 0
Hyperhidrosis subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	0 / 32 (0.00%) 0
Prurigo subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	1 / 32 (3.13%) 1
Pruritus subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	2 / 32 (6.25%) 2
Urticaria subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	0 / 32 (0.00%) 0
Renal and urinary disorders Chronic kidney disease subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	4 / 32 (12.50%) 4
Renal failure subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	0 / 32 (0.00%) 0
Renal impairment subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	1 / 32 (3.13%) 1
Urethral stenosis			

subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	0 / 32 (0.00%) 0
Endocrine disorders Hyperparathyroidism secondary subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	0 / 32 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 2	0 / 30 (0.00%) 0	1 / 32 (3.13%) 1
Arthritis subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	0 / 32 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	0 / 30 (0.00%) 0	2 / 32 (6.25%) 2
Gouty arthritis subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	1 / 32 (3.13%) 1
Muscle spasms subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	0 / 32 (0.00%) 0
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0	0 / 32 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	0 / 32 (0.00%) 0
Spinal osteoarthritis subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1	0 / 32 (0.00%) 0
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	1 / 30 (3.33%) 1	0 / 32 (0.00%) 0
Cellulitis			

subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Cystitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Infected fistula			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	2 / 30 (6.67%)	2 / 30 (6.67%)	2 / 32 (6.25%)
occurrences (all)	2	2	2
Pharyngitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	1	1	0
Rhinitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	2 / 32 (6.25%)
occurrences (all)	0	0	3
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			

Acidosis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Gout			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	0 / 32 (0.00%)
occurrences (all)	0	2	0
Hyperkalaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	1 / 32 (3.13%)
occurrences (all)	0	1	1
Hyperuricaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	0 / 32 (0.00%)
occurrences (all)	0	3	0
Metabolic acidosis			
subjects affected / exposed	0 / 30 (0.00%)	3 / 30 (10.00%)	1 / 32 (3.13%)
occurrences (all)	0	3	1

Non-serious adverse events	Darbepoetin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 32 (50.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Lipoma subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Vascular disorders			
Hypertension subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 7		
Hypotension subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Pallor subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Surgical and medical procedures			
Arteriovenous fistula operation subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Dialysis device insertion subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Haemodialysis subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Peritoneal dialysis subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Tooth extraction subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Chest pain subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		

Chills			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Oedema			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Prostatitis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Interstitial lung disease			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Pleural effusion			

subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Rhinitis allergic			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Initial insomnia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Investigations			
Amylase increased			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Blood chloride decreased			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Blood pressure decreased			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Blood pressure increased			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Electrocardiogram pr prolongation			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Electrocardiogram qt prolonged			

subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Haemoglobin decreased			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Haemoglobin increased			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Lipase increased			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Mycobacterium tuberculosis complex test positive			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Pancreatic enzymes increased			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Serum ferritin decreased			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Venous pressure jugular increased			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Weight increased			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Thermal burn			

<p>subjects affected / exposed</p> <p>0 / 32 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Traumatic haematoma</p> <p>subjects affected / exposed</p> <p>0 / 32 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Wound</p> <p>subjects affected / exposed</p> <p>1 / 32 (3.13%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Wrist fracture</p> <p>subjects affected / exposed</p> <p>0 / 32 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Congenital, familial and genetic disorders</p> <p>Ichthyosis</p> <p>subjects affected / exposed</p> <p>0 / 32 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Cardiac disorders</p> <p>Atrioventricular block first degree</p> <p>subjects affected / exposed</p> <p>0 / 32 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Cardiac failure</p> <p>subjects affected / exposed</p> <p>0 / 32 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Sinus arrhythmia</p> <p>subjects affected / exposed</p> <p>0 / 32 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Sinus tachycardia</p> <p>subjects affected / exposed</p> <p>0 / 32 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Nervous system disorders</p> <p>Dizziness</p> <p>subjects affected / exposed</p> <p>0 / 32 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Headache</p> <p>subjects affected / exposed</p> <p>0 / 32 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Neuropathy peripheral</p>			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sciatica</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Somnolence</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 32 (0.00%)</p> <p>0</p> <p>0 / 32 (0.00%)</p> <p>0</p> <p>0 / 32 (0.00%)</p> <p>0</p>		
<p>Blood and lymphatic system disorders</p> <p>Anaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Leukopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nephrogenic anaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thrombocytopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 32 (3.13%)</p> <p>1</p> <p>0 / 32 (0.00%)</p> <p>0</p> <p>0 / 32 (0.00%)</p> <p>0</p> <p>0 / 32 (0.00%)</p> <p>0</p>		
<p>Eye disorders</p> <p>Diabetic retinopathy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vitreous haemorrhage</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 32 (0.00%)</p> <p>0</p> <p>0 / 32 (0.00%)</p> <p>0</p>		
<p>Gastrointestinal disorders</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain upper</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Anal haemorrhage</p>	<p>0 / 32 (0.00%)</p> <p>0</p> <p>1 / 32 (3.13%)</p> <p>1</p>		

subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Enterocolitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Gastric ulcer			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Gastrointestinal pain			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Glossodynia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Umbilical hernia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			

Cholecystitis acute subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Skin and subcutaneous tissue disorders			
Eczema asteatotic subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1		
Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Prurigo subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Pruritus subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Urticaria subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Renal and urinary disorders			
Chronic kidney disease subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Renal failure subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Renal impairment subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Urethral stenosis subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Endocrine disorders			
Hyperparathyroidism secondary subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0		
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Arthritis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Gouty arthritis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Spinal osteoarthritis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Cellulitis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Infected fistula			

subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Infection			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Decreased appetite			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		

Gout			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Hypercalcaemia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Hyperkalaemia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Hyperphosphataemia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Hyperuricaemia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	0 / 32 (0.00%)		
occurrences (all)	0		
Metabolic acidosis			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2014	This protocol amendment included the following modifications: changed the lower value of the baseline Hb range from 10.0 to 9.0 gram/deciliter, added heart failure as an adjudicated SAE, removed exclusion criterion regarding phosphodiesterase type 5 (PDE5) inhibitors or nitrates, removed atrial fibrillation from exclusion criteria, changed timing of Hb assessment from within "2" to "3" days prior to visit, updated the status of the BAY85-3934 phase I studies, clarified hyporesponsiveness to darbepoetin by total dose at microg/kilogram/week, allowed re-screening of subjects who fail the criterion regarding folate and vitamin B12.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Decimal places were automatically truncated if last decimal equals zero.

Notes: