Clinical trial results:
A controlled, parallel group, open-label, multicenter extension study to investigate efficacy and safety of oral BAY 85-3934 and darbepoetin alfa comparator in the long term treatment of anemia in pre-dialysis subjects with chronic kidney disease in Europe and Asia Pacific

Summary

EudraCT number	2013-001190-24
Trial protocol	GB DE IT HU ES BG PL
Global end of trial date	12 December 2016

Results information

Result version number	v1 (current)
This version publication date	07 December 2017
First version publication date	07 December 2017

Trial information

Trial identification

Sponsor protocol code	BAY85-3934/15653

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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, 0049 30300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, 0049 30300139003, 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	12 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 December 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were to:
• evaluate efficacy of treatment with BAY85-3934 (molidustat) compared with darbepoetin alfa as measured by change from baseline to post-baseline time points in haemoglobin (Hb) levels.
• evaluate safety and tolerability of treatment with BAY85-3934 compared with darbepoetin by events of special interest, adjudicated serious adverse events (SAEs), and SAEs.

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 Council for 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	24 June 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: 2
Country: Number of subjects enrolled	Japan: 37
Country: Number of subjects enrolled	Korea, Republic of: 16
Country: Number of subjects enrolled	Romania: 19
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Bulgaria: 11
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 34
Country: Number of subjects enrolled	Italy: 25
Worldwide total number of subjects	164
EEA total number of subjects	109

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)	44
From 65 to 84 years	120
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 50 active study centers in 12 countries: Bulgaria, France, Germany, Hungary, Israel, Italy, Japan, Poland, Republic of Korea, Romania, Spain, and United Kingdom (UK), between 24 June 2014 (first subject first visit) and 12 December 2016 (last subject last visit).

Pre-assignment

Screening details:

Overall, 166 subjects were included in this extension study from parent studies 15141 (2013-001193-14); 15261 (2013-001192-21), of whom 2 were excluded (no reliable treatment data); 4 were not treated. 144 subjects entered main phase (97 subjects entered directly; 47 subjects rolled over from HbS phase). Finally, 128 subjects completed follow-up.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BAY85-3934

Arm description:

Subjects received initial doses of BAY85-3934 tablet as per parent study once daily (OD) and then all the doses were titrated to 15, 25, 50, 75, 100, and 150 milligram per day (mg/day) up to a maximum of 36 months. Treatment included two phases: the hemoglobin (Hb) stabilization phase (HbS) (up to 16 weeks) for subjects who were outside of target Hb range at start of the extension study and the main phase (up to 36 months). In the HbS phase, subjects received initial doses of BAY85-3934 OD dose assigned by interactive voice or web response system (IXRS) and then titrated at each scheduled visit to maintain Hb in the target range of 10.0 to 12.0 gram per deciliter (g/dL). In the main phase, subjects received titrated dose of BAY85-3934 OD assigned by IXRS.

Arm type	Experimental
Investigational medicinal product name	Molidustat
Investigational medicinal product code	BAY85-3934
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

In the HbS phase, subjects received initial doses of BAY85-3934 OD dose assigned by IXRS and then titrated at each scheduled visit to maintain Hb in the target range of 10.0 to 12.0 g/dL. In the main phase, subjects received titrated dose of BAY85-3934 OD assigned by IXRS.

Arm title	Darbepoetin

Arm description:

Subjects received initial doses of darbepoetin intravenously (IV) or subcutaneously (SC) and all the doses were titrated at the scheduled dose up to a maximum of 36 months. Treatment included two phases: HbS (up to 16 weeks) and main phase (up to 36 months). In the HbS phase, subjects who were on placebo in the parent study or were out of Hb target range at start of the extension study received initial doses of darbepoetin IV or SC according to local label and then titrated at each scheduled visit to maintain Hb in the target range of 10.0 to 12.0 g/dL. In the main phase, subjects received titrated dose of darbepoetin IV or SC according to the local label and titrated at each scheduled visit for every 4 weeks.

Arm type	Active comparator

Investigational medicinal product name	Darbepoetin
Investigational medicinal product code	
Other name	Aranesp
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

In the HbS phase, subjects who were on placebo in the parent study or were out of Hb target range at start of the extension study received initial doses of darbepoetin IV or SC according to local label and then titrated at each scheduled visit to maintain Hb in the target range of 10.0 to 12.0 g/dL. In the main phase, subjects received titrated dose of darbepoetin IV or SC according to the local label and titrated at each scheduled visit for every 4 weeks.

Number of subjects in period 1[1]	BAY85-3934	Darbepoetin
Started	103	41
Entered HbS phase	49	18
Entered main phase from HbS phase	31	16
Entered main phase directly	72	25
Completed follow-up	97	31
Completed	0	0
Not completed	103	41
Physician decision	1	-
Logistical difficulties	1	-
Lost to follow-up	1	-
Protocol driven decision point	12	7
Protocol violation	1	1
Death	4	-
Other	1	-
Adverse event	18	3
Study terminated by sponsor	62	25
Withdrawal by subject	2	5

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Not all the enrolled subjects were treated with study drugs. As baseline only included treated subjects, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	BAY85-3934

Reporting group description:

Subjects received initial doses of BAY85-3934 tablet as per parent study once daily (OD) and then all the doses were titrated to 15, 25, 50, 75, 100, and 150 milligram per day (mg/day) up to a maximum of 36 months. Treatment included two phases: the hemoglobin (Hb) stabilization phase (HbS) (up to 16 weeks) for subjects who were outside of target Hb range at start of the extension study and the main phase (up to 36 months). In the HbS phase, subjects received initial doses of BAY85-3934 OD dose assigned by interactive voice or web response system (IXRS) and then titrated at each scheduled visit to maintain Hb in the target range of 10.0 to 12.0 gram per deciliter (g/dL). In the main phase, subjects received titrated dose of BAY85-3934 OD assigned by IXRS.

Reporting group title	Darbepoetin

Reporting group description:

Subjects received initial doses of darbepoetin intravenously (IV) or subcutaneously (SC) and all the doses were titrated at the scheduled dose up to a maximum of 36 months. Treatment included two phases: HbS (up to 16 weeks) and main phase (up to 36 months). In the HbS phase, subjects who were on placebo in the parent study or were out of Hb target range at start of the extension study received initial doses of darbepoetin IV or SC according to local label and then titrated at each scheduled visit to maintain Hb in the target range of 10.0 to 12.0 g/dL. In the main phase, subjects received titrated dose of darbepoetin IV or SC according to the local label and titrated at each scheduled visit for every 4 weeks.

Reporting group values	BAY85-3934	Darbepoetin	Total
Number of subjects	103	41	144
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	69.6	67.9	
standard deviation	± 10.36	± 11.72	-
Gender categorical Units: Subjects			
Female	55	20	75
Male	48	21	69

End points

End points reporting groups

Reporting group title	BAY85-3934

Reporting group description:

Subjects received initial doses of BAY85-3934 tablet as per parent study once daily (OD) and then all the doses were titrated to 15, 25, 50, 75, 100, and 150 milligram per day (mg/day) up to a maximum of 36 months. Treatment included two phases: the hemoglobin (Hb) stabilization phase (HbS) (up to 16 weeks) for subjects who were outside of target Hb range at start of the extension study and the main phase (up to 36 months). In the HbS phase, subjects received initial doses of BAY85-3934 OD dose assigned by interactive voice or web response system (IXRS) and then titrated at each scheduled visit to maintain Hb in the target range of 10.0 to 12.0 gram per deciliter (g/dL). In the main phase, subjects received titrated dose of BAY85-3934 OD assigned by IXRS.

Reporting group title	Darbepoetin

Reporting group description:

Subjects received initial doses of darbepoetin intravenously (IV) or subcutaneously (SC) and all the doses were titrated at the scheduled dose up to a maximum of 36 months. Treatment included two phases: HbS (up to 16 weeks) and main phase (up to 36 months). In the HbS phase, subjects who were on placebo in the parent study or were out of Hb target range at start of the extension study received initial doses of darbepoetin IV or SC according to local label and then titrated at each scheduled visit to maintain Hb in the target range of 10.0 to 12.0 g/dL. In the main phase, subjects received titrated dose of darbepoetin IV or SC according to the local label and titrated at each scheduled visit for every 4 weeks.

Subject analysis set title	Modified intent-to-treat (mITT)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT (N=144) included all subjects who received at least 1 dose of study treatment during the main phase and had at least 1 post-baseline Hb value in the main phase.

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

SAF (N=144) included all subjects who received at least 1 dose of study treatment during the main phase.

Primary: Change in Local Laboratory Hemoglobin Level from Baseline to Each Post-Baseline Visit During Main Phase

End point title	Change in Local Laboratory Hemoglobin Level from Baseline to Each Post-Baseline Visit During Main Phase

End point description:

Change in local laboratory Hb level from baseline to each post-baseline visit during the main phase was reported. Here 'n' signifies those subjects who were evaluable for this measure at given time points for each group respectively, and '99999' here indicates that data was not calculated as the evaluable subjects were less than 3, as 2 or less collected values were not sufficient to calculate a reliable estimation. EOT refers to end of treatment. Treatment duration for main phase was defined as date of last study drug (EOT day) – date of first study drug + 1. For subjects entering main phase directly, treatment duration = date of last non-zero dose - date of first dose at main phase + 1; for subjects entering main phase from HbS phase, treatment duration = date of last non-zero dose - main phase Day 1 + 1.

End point type	Primary

End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 60, 72, 96, 108 and EOT

End point values	BAY85-3934	Darbepoetin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[1]	41[2]		
Units: gram per deciliter (g/dL)				
arithmetic mean (standard deviation)				
Baseline (n=103, 41)	11.28 (± 0.552)	11.08 (± 0.505)		
Change at Week 12 (n=100, 40)	-0.01 (± 0.962)	-0.02 (± 0.868)		
Change at Week 24 (n=93, 37)	-0.18 (± 0.875)	-0.15 (± 0.961)		
Change at Week 36 (n=84, 31)	-0.34 (± 0.965)	-0.11 (± 0.931)		
Change at Week 48 (n=77, 28)	-0.21 (± 0.923)	-0.06 (± 0.941)		
Change at Week 60 (n=59, 21)	-0.39 (± 1.321)	0.05 (± 0.915)		
Change at Week 72 (n=32, 15)	-0.13 (± 0.842)	-0.25 (± 1.039)		
Change at Week 96 (n=12, 5)	-0.57 (± 1.168)	-0.27 (± 0.337)		
Change at Week 108 (n=1, 2)	0.83 (± 99999)	-0.41 (± 0.018)		
Change at EOT (n=93, 39)	-0.33 (± 1.214)	-0.14 (± 1.215)		

Notes:

[1] - mITT

[2] - mITT

Statistical analyses

Statistical analysis title	Statistical Analysis for Week 12

Statistical analysis description:

Results were reported including least square mean (LS-mean) difference and 95% confidence intervals (CIs) which was based on constrained longitudinal data analysis (cLDA) model. Erroneously, database auto calculates the total number of subjects for the selected arms. Number of subjects evaluated in this analysis was 140.

Comparison groups	BAY85-3934 v Darbepoetin
Number of subjects included in analysis	144
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	-0.18
upper limit	0.45
Variability estimate	Standard error of the mean
Dispersion value	0.161

Statistical analysis title	Statistical Analysis for Week 24

Statistical analysis description:

Results were reported including LS-mean difference and 95% CI. LS mean difference was based on cLDA model. Erroneously, database auto calculates the total number of subjects for the selected arms. Number of subjects evaluated in this analysis was 130.

Comparison groups	Darbepoetin v BAY85-3934
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.43
Variability estimate	Standard error of the mean
Dispersion value	0.166

Statistical analysis title	Statistical Analysis for Week 36

Statistical analysis description:

Results were reported including LS-mean difference and 95% CI. LS mean difference was based on cLDA model. Erroneously, database auto calculates the total number of subjects for the selected arms. Number of subjects evaluated in this analysis was 115.

Comparison groups	BAY85-3934 v Darbepoetin
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.29
Variability estimate	Standard error of the mean
Dispersion value	0.177

Statistical analysis title	Statistical Analysis for Week 48

Statistical analysis description:

Results were reported including LS-mean difference and 95% CI. LS mean difference was based on cLDA model. Erroneously, database auto calculates the total number of subjects for the selected arms. Number of subjects evaluated in this analysis was 105.

Comparison groups	BAY85-3934 v Darbepoetin

Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.43
Variability estimate	Standard error of the mean
Dispersion value	0.185

Statistical analysis title	Statistical Analysis for Week 60

Statistical analysis description:

Results were reported including LS-mean difference and 95% CI. LS mean difference was based on cLDA model. Erroneously, database auto calculates the total number of subjects for the selected arms. Number of subjects evaluated in this analysis was 80.

Comparison groups	BAY85-3934 v Darbepoetin
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.209

Statistical analysis title	Statistical Analysis for Week 72

Statistical analysis description:

Results were reported including LS-mean difference and 95% CI. LS mean difference was based on cLDA model. Erroneously, database auto calculates the total number of subjects for the selected arms. Number of subjects evaluated in this analysis was 47.

Comparison groups	BAY85-3934 v Darbepoetin
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.74

Variability estimate	Standard error of the mean
Dispersion value	0.252

Statistical analysis title	Statistical Analysis for Week 96

Statistical analysis description:

Results were reported including LS-mean difference and 95% CI. LS mean difference was based on cLDA model. Erroneously, database auto calculates the total number of subjects for the selected arms. Number of subjects evaluated in this analysis was 17.

Comparison groups	BAY85-3934 v Darbepoetin
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	0.89
Variability estimate	Standard error of the mean
Dispersion value	0.415

Statistical analysis title	Statistical Analysis for Week 108

Statistical analysis description:

Results were reported including LS-mean difference and 95% CI. LS mean difference was based on cLDA model. Erroneously, database auto calculates the total number of subjects for the selected arms. Number of subjects evaluated in this analysis was 3.

Comparison groups	BAY85-3934 v Darbepoetin
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	2.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	3.95
Variability estimate	Standard error of the mean
Dispersion value	0.939

Statistical analysis title	Statistical Analysis for EOT

Statistical analysis description:

Results were reported including LS-mean difference and 95% CI. LS mean difference was based on cLDA model. Erroneously, database auto calculates the total number of subjects for the selected arms.

Number of subjects evaluated in this analysis was 132.

Comparison groups	BAY85-3934 v Darbepoetin
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	0.163

Primary: Number of Subjects With Treatment Emergent Serious Adverse Events During Main Phase

End point title	Number of Subjects With Treatment Emergent Serious Adverse Events During Main Phase[3]

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; life threatening experience (immediate risk of dying); inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; congenital anomaly; any other medically important serious event as judged by the investigator. Treatment duration for main phase was defined as date of last study drug (EOT day) – date of first study drug + 1. For subjects entering main phase directly, treatment duration = date of last non-zero dose - date of first dose at main phase + 1; for subjects entering main phase from HbS phase, treatment duration = date of last non-zero dose - main phase Day 1 + 1.

End point type	Primary

End point timeframe:

From start of study drug administration up to 3 days after the end of treatment

Notes:

[3] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	BAY85-3934	Darbepoetin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[4]	41[5]		
Units: subjects	51	22		

Notes:

[4] - SAF

[5] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Rate of Responders in Local Hemoglobin During Main Phase

End point title	Overall Rate of Responders in Local Hemoglobin During Main

	Phase

End point description:

A responder was defined as a subject who had a mean of the Hb levels during the main phase in the target range (10.0 to 12.0 g/dL, inclusive), greater than or equal to (>=) 50 percent (%) of the Hb levels in the target range during the main phase, and no red blood cell (RBC) containing transfusion during main phase. Treatment duration for main phase was defined as date of last study drug (EOT day) – date of first study drug + 1. For subjects entering main phase directly, treatment duration = date of last non-zero dose - date of first dose at main phase + 1; for subjects entering main phase from HbS phase, treatment duration = date of last non-zero dose - main phase Day 1 + 1.

End point type	Secondary

End point timeframe:

Baseline up to 36 months

End point values	BAY85-3934	Darbepoetin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[6]	41[7]		
Units: percentage of responders				
number (not applicable)	89.3	73.2		

Notes:

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method). If the total observed subjects were less than 5 who met or did not meet specific criterion in any one of compared groups, unconditional confidence limits for the proportion difference were presented in 95% CI of difference.

Comparison groups	BAY85-3934 v Darbepoetin
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Percentage difference from darbepoetin
Point estimate	16.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	32.2

Secondary: Time Within Hemoglobin Target Range During Main Phase

End point title	Time Within Hemoglobin Target Range During Main Phase

End point description:

Hb target range was defined as 10.0 to 12.0 g/dL, inclusive. Treatment duration for main phase was defined as date of last study drug (EOT day) – date of first study drug + 1. For subjects entering main phase directly, treatment duration = date of last non-zero dose - date of first dose at main phase + 1; for subjects entering main phase from HbS phase, treatment duration = date of last non-zero dose - main phase Day 1 + 1.

End point type	Secondary

End point timeframe:

up to 36 months

End point values	BAY85-3934	Darbepoetin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[8]	41[9]		
Units: days				
median (full range (min-max))	335 (9 to 696)	325.3 (22.9 to 813.5)		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Exposure During Main Phase

End point title	Duration of Exposure During Main Phase

End point description:

Treatment duration for main phase was defined as date of last study drug (EOT day) – date of first study drug + 1. For subjects entering main phase directly, treatment duration = date of last non-zero dose - date of first dose at main phase + 1; for subjects entering main phase from HbS phase, treatment duration = date of last non-zero dose - main phase Day 1 + 1.

End point type	Secondary

End point timeframe:

From baseline up to 36 months

End point values	BAY85-3934	Darbepoetin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[10]	41[11]		
Units: days				
arithmetic mean (standard deviation)	399.8 (± 185.92)	414.6 (± 205.63)		

Notes:

[10] - SAF with number of subjects evaluable for this specific end point.

[11] - SAF with number of subjects evaluable for this specific end point.

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects Requiring Titration of Dose (Down-Titration, Up-Titration) During Main Phase

End point description:

Individual dose-titration for BAY 85-3934 was based on the subject's Hb response and tolerability of previous dose, IXRS assigned the titrated dose for each subject and as per local label for darbepoetin. Treatment duration for main phase was defined as date of last study drug (EOT day) – date of first study drug + 1. For subjects entering main phase directly, treatment duration = date of last non-zero dose - date of first dose at main phase + 1; for subjects entering main phase from HbS phase, treatment duration = date of last non-zero dose - main phase Day 1 + 1. In the below table, > is greater than.

End point type	Secondary

End point timeframe:

From baseline up to 36 months

End point values	BAY85-3934	Darbepoetin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[12]	41[13]		
Units: subjects				
Number of dose down-titration: 1	23	5		
Number of dose down-titration: 2 to 3	28	11		
Number of dose down-titration: >3 to 5	9	2		
Number of dose down-titration: >5	1	2		
Number of dose up-titration: 1	18	6		
Number of dose up-titration: 2 to 3	30	8		
Number of dose up-titration: >3 to 5	12	4		
Number of dose up-titration: >5	3	6		

Notes:

[12] - SAF with number of subjects evaluable for this specific end point.

[13] - SAF with number of subjects evaluable for this specific end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Reticulocyte Count During Main Phase

End point title	Change from Baseline in Reticulocyte Count During Main Phase

End point description:

Reticulocyte count (absolute reticulocyte counts and reticulocytes / erythrocyte %) was summarized for each post-baseline assessment until EOT during the main phase of study. Here 'n' signifies those subjects who were evaluable for this measure at given time points for each group respectively. In below table, '99999' here indicates that data was not calculated as the evaluable subjects were less than 3, as 2 or less collected values were not sufficient to calculate a reliable estimation. Treatment duration for main phase was defined as date of last study drug (EOT day) – date of first study drug + 1. For subjects entering main phase directly, treatment duration = date of last non-zero dose - date of first dose at main phase + 1; for subjects entering main phase from HbS phase, treatment duration = date of last non-zero dose - main phase Day 1 + 1.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108 and EOT

End point values	BAY85-3934	Darbepoetin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[14]	41[15]		
Units: giga per liter (giga/L)				
arithmetic mean (standard deviation)				
Baseline (n=76, 34)	71.7 (± 32.53)	69.4 (± 25.93)		
Change at Week 12 (n=67, 30)	0.6 (± 23.39)	-5.2 (± 19.91)		
Change at Week 24 (n=61, 29)	0.8 (± 24.45)	-9.1 (± 16.81)		
Change at Week 36 (n=56, 25)	-3 (± 21.88)	-4.7 (± 22.63)		
Change at Week 48 (n=48, 24)	-0.4 (± 24.82)	-3 (± 22.91)		
Change at Week 60 (n=33, 14)	-5.2 (± 26.54)	-8.5 (± 13.66)		
Change at Week 72 (n=13, 11)	5.4 (± 16.57)	-5.7 (± 19.86)		
Change at Week 84 (n=9, 6)	2.8 (± 28.27)	2 (± 16.28)		
Change at Week 96 (n=6, 5)	3.5 (± 28.93)	-10 (± 11.14)		
Change at Week 108 (n=1, 1)	-4 (± 99999)	-4 (± 99999)		
Change at EOT (n=66, 31)	-11.6 (± 26.17)	4 (± 24.77)		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Red Blood Cell Count During Main Phase

End point title	Change from Baseline in Red Blood Cell Count During Main Phase

End point description:

Red blood cell count was summarized for each post-baseline assessment until EOT during the main phase of study. Here 'n' signifies those subjects who were evaluable for this measure at given time points for each group respectively. In below table, '99999' here indicates that data was not calculated as the evaluable subjects were less than 3, as 2 or less collected values were not sufficient to calculate a reliable estimation. Treatment duration for main phase was defined as date of last study drug (EOT day) – date of first study drug + 1. For subjects entering main phase directly, treatment duration = date of last non-zero dose - date of first dose at main phase + 1; for subjects entering main phase from HbS phase, treatment duration = date of last non-zero dose - main phase Day 1 + 1.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108 and EOT

End point values	BAY85-3934	Darbepoetin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[16]	41[17]		
Units: millions per microliters (M/mcL)				
arithmetic mean (standard deviation)				
Baseline (n=98, 39)	3.73 (± 0.381)	3.71 (± 0.446)		
Change at Week 12 (n=88, 33)	-0.04 (± 0.349)	-0.02 (± 0.34)		
Change at Week 24 (n=80, 33)	-0.12 (± 0.36)	-0.05 (± 0.333)		

Change at Week 36 (n=71, 30)	-0.12 (± 0.359)	-0.05 (± 0.395)		
Change at Week 48 (n=62, 27)	-0.12 (± 0.332)	-0.07 (± 0.296)		
Change at Week 60 (n=42, 16)	-0.2 (± 0.446)	-0.03 (± 0.328)		
Change at Week 72 (n=19, 13)	-0.01 (± 0.373)	-0.02 (± 0.28)		
Change at Week 84 (n=13, 7)	-0.05 (± 0.45)	0.1 (± 0.379)		
Change at Week 96 (n=6, 5)	-0.12 (± 0.36)	-0.08 (± 0.164)		
Change at Week 108 (n=0, 1)	99999 (± 99999)	-4 (± 99999)		
Change at EOT (n=81, 33)	-0.25 (± 0.399)	-0.15 (± 0.442)		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Hematocrit During Main Phase

End point title	Change from Baseline in Hematocrit During Main Phase

End point description:

Hematocrit values were summarized for each post-baseline assessment until EOT during the main phase of study. Here 'n' signifies those subjects who were evaluable for this measure at given time points for each group respectively. In below table, '99999' here indicates that data was not calculated as the evaluable subjects were less than 3, as 2 or less collected values were not sufficient to calculate a reliable estimation. Treatment duration for main phase was defined as date of last study drug (EOT day) – date of first study drug + 1. For subjects entering main phase directly, treatment duration = date of last non-zero dose - date of first dose at main phase + 1; for subjects entering main phase from HbS phase, treatment duration = date of last non-zero dose - main phase Day 1 + 1.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108 and EOT

End point values	BAY85-3934	Darbepoetin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[18]	41[19]		
Units: percentage				
arithmetic mean (standard deviation)				
Baseline (n=98, 39)	35.1 (± 2.51)	34.1 (± 2.31)		
Change at Week 12 (n=87, 33)	-0.2 (± 3.17)	-0.4 (± 2.64)		
Change at Week 24 (n=80, 33)	-1 (± 3.55)	-0.4 (± 3.44)		
Change at Week 36 (n=71, 30)	-1 (± 3.4)	-0.5 (± 3.94)		
Change at Week 48 (n=61, 26)	-0.8 (± 3.39)	-0.6 (± 2.7)		
Change at Week 60 (n=42, 16)	-1.5 (± 4.31)	-0.3 (± 3.55)		
Change at Week 72 (n=19, 13)	0.5 (± 2.86)	-0.1 (± 2.84)		
Change at Week 84 (n=13, 7)	-0.1 (± 4.57)	0.4 (± 3.87)		
Change at Week 96 (n=6, 5)	-0.8 (± 2.99)	-0.4 (± 2.3)		

Change at Week 108 (n=0, 1)	99999 (± 99999)	-3 (± 99999)		
Change at EOT (n=81, 33)	-2.8 (± 3.93)	-1 (± 4.24)		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Central Laboratory Hemoglobin During Main Phase

End point title	Change from Baseline in Central Laboratory Hemoglobin During Main Phase

End point description:

Hb was analysed using the blood samples drawn during the main phase of the study. Here 'n' signifies those subjects who were evaluable for this measure at given time points for each group respectively. In below table, "99999" denotes that data was not calculated as no subjects were evaluated for the specified arm / standard deviation cannot be calculated as there was only one subject in the specified arm. Treatment duration for main phase was defined as date of last study drug (EOT day) – date of first study drug + 1. For subjects entering main phase directly, treatment duration = date of last non-zero dose - date of first dose at main phase + 1; for subjects entering main phase from HbS phase, treatment duration = date of last non-zero dose - main phase Day 1 + 1.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108 and EOT

End point values	BAY85-3934	Darbepoetin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102[20]	40[21]		
Units: gram per deciliter (g/dL)				
arithmetic mean (standard deviation)				
Baseline (n=102,40)	11.54 (± 0.719)	10.99 (± 0.746)		
Change at Week 12 (n=94,34)	-0.11 (± 1.015)	0.17 (± 1.059)		
Change at Week 24 (n=87,36)	-0.42 (± 1.016)	0.03 (± 1.059)		
Change at Week 36 (n=77,30)	-0.52 (± 0.938)	0.13 (± 1.084)		
Change at Week 48 (n=67,27)	-0.43 (± 1.110)	0.09 (± 1.104)		
Change at Week 60 (n=47,18)	-0.74 (± 1.341)	0.18 (± 1.084)		
Change at Week 72 (n=24,13)	-0.39 (± 0.723)	-0.01 (± 0.941)		
Change at Week 84 (n=19,7)	-0.35 (± 1.200)	0.34 (± 1.041)		
Change at Week 96 (n=7,5)	-0.81 (± 0.938)	-0.26 (± 0.500)		
Change at Week 108 (n=0,1)	99999 (± 99999)	-0.58 (± 99999)		
Change at Week EOT (n=36,14)	-0.7 (± 1.489)	-0.7 (± 1.288)		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Meeting Specific Local Hemoglobin Criteria During Main Phase

End point title	Number of Subjects Meeting Specific Local Hemoglobin Criteria During Main Phase

End point description:

The following were the specific hemoglobin criteria: > 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. Treatment duration for main phase was defined as date of last study drug (EOT day) – date of first study drug + 1. For subjects entering main phase directly, treatment duration = date of last non-zero dose - date of first dose at main phase + 1; for subjects entering main phase from HbS phase, treatment duration = date of last non-zero dose - main phase Day 1 + 1.

End point type	Secondary

End point timeframe:

From baseline up to 36 months

End point values	BAY85-3934	Darbepoetin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[22]	41[23]		
Units: subjects				
> 50% of Hb levels below lower limit of 10 g/dL	2	2		
Mean of Hb levels below lower limit of 10 g/dL	3	3		
> 50% of Hb levels above upper limit of 12 g/dL	3	2		
Mean of Hb levels above upper limit of 12 g/dL	2	2		

Notes:

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

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

Statistical analyses

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

Statistical analysis description:

Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method). If the total observed subjects were less than 5 who met or did not meet specific criterion in any one of compared groups, unconditional confidence limits for the proportion difference were presented in 95% CI of difference.

Comparison groups	BAY85-3934 v Darbepoetin

Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.8
upper limit	15.1

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

Statistical analysis description:

Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method). If the total observed subjects were less than 5 who met or did not meet specific criterion in any one of compared groups, unconditional confidence limits for the proportion difference were presented in 95% CI of difference.

Comparison groups	BAY85-3934 v Darbepoetin
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.2
upper limit	13.6

Statistical analysis title	BAY85-3934 (> 50% of Hb levels above 12 g/dL)

Statistical analysis description:

Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method). If the total observed subjects were less than 5 who met or did not meet specific criterion in any one of compared groups, unconditional confidence limits for the proportion difference were presented in 95% CI of difference.

Comparison groups	BAY85-3934 v Darbepoetin
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.8
upper limit	16

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

Statistical analysis description:

Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method). If the total observed subjects were less than 5 who met or did not meet specific criterion in any one of compared groups, unconditional confidence limits for the proportion difference were presented in 95% CI of difference.

Comparison groups	BAY85-3934 v Darbepoetin
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.8
upper limit	15.1

Secondary: Number of Subjects with Hemoglobin Levels >13 g/dL or Excessive Increase During Main Phase

End point title	Number of Subjects with Hemoglobin Levels >13 g/dL or Excessive Increase During Main Phase

End point description:

Excessive increase in Hb values was defined as an increase of >1 g/dL in 2 weeks or >2 g/dL in 4 weeks. Treatment duration for main phase was defined as date of last study drug (EOT day) – date of first study drug + 1. For subjects entering main phase directly, treatment duration = date of last non-zero dose - date of first dose at main phase + 1; for subjects entering main phase from HbS phase, treatment duration = date of last non-zero dose - main phase Day 1 + 1.

End point type	Secondary

End point timeframe:

From baseline up to 36 months

End point values	BAY85-3934	Darbepoetin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[24]	41[25]		
Units: subjects				
Hb > 13 g/dL at any time	10	5		
Excessive increase of Hb with >2 g/dL over 4 weeks	5	0		

Notes:

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

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

Statistical analyses

Statistical analysis title	BAY85-3934 (Hb >13 g/dL at any time)

Statistical analysis description:

Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method). If the total observed subjects were less than 5 who met or did not meet specific criterion in any one of compared groups, unconditional confidence limits for the proportion difference were presented in 95% CI of difference.

Comparison groups	BAY85-3934 v Darbepoetin
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.7
upper limit	7.7

Statistical analysis title	BAY85-3934 (Excessive increase of Hb over 4 weeks)

Statistical analysis description:

Analysis was based on Miettinen and Nurminen method (an unconditional, asymptotic method). If the total observed subjects were less than 5 who met or did not meet specific criterion in any one of compared groups, unconditional confidence limits for the proportion difference were presented in 95% CI of difference.

Comparison groups	BAY85-3934 v Darbepoetin
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference from darbepoetin
Point estimate	4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.2
upper limit	22.7

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration up to 3 days after the end of treatment

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	BAY85-3934

Reporting group description:

Subjects received initial doses of BAY85-3934 tablet as per parent study OD and then all the doses were titrated to 15, 25, 50, 75, 100, and 150 milligram per day (mg/day) up to a maximum of 36 months. Treatment included two phases: the HbS (up to 16 weeks) for subjects who were outside of target Hb range at start of the extension study and the main phase (up to 36 months). In the HbS phase, subjects received initial doses of BAY85-3934 OD dose assigned by IXRS and then titrated at each scheduled visit to maintain Hb in the target range of 10.0 to 12.0 g/dL. In the main phase, subjects received titrated dose of BAY85-3934 OD assigned by IXRS.

Reporting group title	Darbepoetin

Reporting group description:

Subjects received initial doses of darbepoetin IV or SC and all the doses were titrated at the scheduled dose up to a maximum of 36 months. Treatment included two phases: HbS (up to 16 weeks) and main phase (up to 36 months). In the HbS phase, subjects who were on placebo in the parent study or were out of Hb target range at start of the extension study received initial doses of darbepoetin IV or SC according to local label and then titrated at each scheduled visit to maintain Hb in the target range of 10.0 to 12.0 g/dL. In the main phase, subjects received titrated dose of darbepoetin IV or SC according to the local label and titrated at each scheduled visit for every 4 weeks.

Serious adverse events	BAY85-3934	Darbepoetin	
Total subjects affected by serious adverse events			
subjects affected / exposed	56 / 118 (47.46%)	22 / 42 (52.38%)	
number of deaths (all causes)	5	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal adenocarcinoma			

subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic gastric cancer			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 118 (1.69%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			

subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column injury			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 118 (1.69%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	2 / 118 (1.69%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	4 / 118 (3.39%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 118 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery occlusion			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 118 (1.69%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 118 (1.69%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrogenic anaemia			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Inguinal hernia			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (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			
Pruritus			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (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			
Acute kidney injury			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	16 / 118 (13.56%)	6 / 42 (14.29%)	
occurrences causally related to treatment / all	0 / 18	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			

subjects affected / exposed	4 / 118 (3.39%)	3 / 42 (7.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 118 (1.69%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	2 / 118 (1.69%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Catheter site infection			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gangrene			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 118 (5.08%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis			

subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	2 / 118 (1.69%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (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			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (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	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	0 / 118 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 118 (0.85%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BAY85-3934	Darbepoetin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	94 / 118 (79.66%)	34 / 42 (80.95%)	
Injury, poisoning and procedural complications			
Laceration			
subjects affected / exposed	0 / 118 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Vascular disorders			
Hypertension			
subjects affected / exposed	23 / 118 (19.49%)	14 / 42 (33.33%)	
occurrences (all)	36	21	
Hypotension			
subjects affected / exposed	8 / 118 (6.78%)	0 / 42 (0.00%)	
occurrences (all)	10	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 118 (0.00%)	4 / 42 (9.52%)	
occurrences (all)	0	4	
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	7 / 118 (5.93%)	0 / 42 (0.00%)	
occurrences (all)	10	0	
Oedema peripheral			
subjects affected / exposed	6 / 118 (5.08%)	4 / 42 (9.52%)	
occurrences (all)	7	4	

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	10 / 118 (8.47%)	0 / 42 (0.00%)	
occurrences (all)	12	0	
Diarrhoea			
subjects affected / exposed	11 / 118 (9.32%)	4 / 42 (9.52%)	
occurrences (all)	13	4	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 118 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	14 / 118 (11.86%)	4 / 42 (9.52%)	
occurrences (all)	17	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 118 (5.93%)	0 / 42 (0.00%)	
occurrences (all)	7	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	7 / 118 (5.93%)	0 / 42 (0.00%)	
occurrences (all)	7	0	
Nasopharyngitis			
subjects affected / exposed	15 / 118 (12.71%)	7 / 42 (16.67%)	
occurrences (all)	23	9	
Urinary tract infection			
subjects affected / exposed	0 / 118 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 118 (5.08%)	0 / 42 (0.00%)	
occurrences (all)	7	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2014	Following modifications were made in this amendment: •To improve study feasibility and safety monitoring, Day 8 of HbS phase was removed and the subjects from Study 15141 who had an Hb stopping event after Day 15 in that study were added to the safety monitoring at Day 15 of HbS phase •Heart failure was added to the list of adjudicated AEs as it was the most frequently observed event amongst all components of the composite safety endpoint in this population •To improve study feasibility, ECG assessments were reduced from triplicate to single measurements and clarified to reflect the use of ECG as a safety measure. In addition information on ECG central review was removed which had been included in error since it was not applicable to the study •Following statement was included in the protocol: prescribed continuous dosing of acetaminophen / paracetamol was not allowed •Atrial fibrillation as an exclusion criterion was removed as it was considered common in the study population •Clarification on time separation of intake of BAY85-3934 and breast cancer resistant protein substrates
24 November 2015	Discrepancy was identified between the BAY85-3934 dose titrations (dose increase, dose decrease, and dose suspension) and those utilized in the IXRS system, the IXRS system was programmed to allow dose suspension in case of high Hb (Hb > 11.7 g/dL).

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.

Analyses on changes of the following measures from baseline in parent study were not performed: reticulocyte count, red blood cell count, haematocrit and central laboratory hemoglobin.

Notes: