Clinical trial results:
A Phase 3, Multicenter, Randomized, Open-Label, Active-Controlled Study of the Efficacy and Safety of FG-4592 in the Treatment of Anemia in Incident-dialysis Patients.

Summary

EudraCT number	2013-002753-30
Trial protocol	EE BG LV PL
Global end of trial date	21 September 2018

Results information

Result version number	v1 (current)
This version publication date	17 October 2019
First version publication date	17 October 2019

Trial information

Trial identification

Sponsor protocol code	FGCL-4592-063/CFG13001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02052310
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	FibroGen, Inc.
Sponsor organisation address	409 Illinois Street, San Francisco, United States, CA 94158
Public contact	Lona Poole, MD (medical monitor), FibroGen, Inc., 415 9781344, lpoole@fibrogen.com
Scientific contact	Lona Poole, MD (medical monitor), FibroGen, Inc., 415 9781344, lpoole@fibrogen.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	21 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 September 2018
Global end of trial reached?	Yes
Global end of trial date	21 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the efficacy and safety of roxadustat in the treatment of anemia in incident-dialysis subjects, compared with active control.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline and the local law and regularions of the counties of clinical sites.

A Data Safety Monitoring Board (DSMB) reviewed safety data periodically in collaboration with the sponsor to ensure subject safety. An Independent Event Review Committee (IERC), blinded to treatment group, adjudicated pre-specified cardiovascular, cerebrovascular, and thromboembolic safety events of interest.

Background therapy:

Oral iron was allowed as first-line iron supplementation without restriction; IV iron was allowed per protocol specification.

Evidence for comparator:

For subjects on HD, doses of epoetin alfa were administered IV three times weekly according to the United States Package Insert (USPI) or Summary of Product Characteristics (SmPC) by appropriately trained personnel. For subjects requiring ultra-low dose of EPO (e.g., ≤1000 IU/per week), the frequency of administration could have been adjusted per local standard of care.
For subjects on home-hemodialysis (HHD) or peritoneal dialysis (PD), doses of epoetin alfa were administered by appropriately trained personnel, including the subject or caregiver, according to the USPI, SmPC, or local standard of care.
All epoetin alfa was supplied to the study sites from commercial sources. Within the United States (U.S.), sites obtained commercially available epoetin alfa; outside of the U.S., FibroGen provided commercially available epoetin alfa for use by the sites. Epoetin alfa was stored according to the USPI or SmPC.

Actual start date of recruitment	04 December 2013
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	Poland: 9
Country: Number of subjects enrolled	Bulgaria: 96
Country: Number of subjects enrolled	Latvia: 6
Country: Number of subjects enrolled	Argentina: 53
Country: Number of subjects enrolled	Belarus: 3
Country: Number of subjects enrolled	Brazil: 30
Country: Number of subjects enrolled	Chile: 6

Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Korea, Republic of: 34
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Malaysia: 23
Country: Number of subjects enrolled	Peru: 6
Country: Number of subjects enrolled	Romania: 21
Country: Number of subjects enrolled	Russian Federation: 340
Country: Number of subjects enrolled	Thailand: 11
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Ukraine: 143
Country: Number of subjects enrolled	United States: 252
Worldwide total number of subjects	1043
EEA total number of subjects	132

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)	772
From 65 to 84 years	261
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

The study population consisted of anaemic patients that received hemodialysis (HD) or peritoneal dialysis (PD) for end-stage renal disease (ESRD) for a minimum of 2 weeks and a maximum of 4 months, prior to randomization AND with none or limited (≤ 3 weeks) ESA exposure.

Pre-assignment

Screening details:

The Screening Period lasted up to 6 weeks. A total of 1043 subjects were randomized to received one of the 2 treatment arms in a 1:1 ratio to receive either open label roxadustat or epoetin alfa.

Period 1

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

Blinding implementation details:

Automated randomization and treatment assignments were provided by an Interactive Voice and Web Response System (IXRS) for this open label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Roxadustat

Arm description:

Roxadustat was dosed orally 3 times weekly (TIW) throughout the Treatment Period (minimum of 52 weeks, maximum up to approximately 4 years), except if a subject required <20 mg TIW (i.e., <60 mg per week) to maintain Hb levels.

Arm type	Experimental
Investigational medicinal product name	Roxadustat
Investigational medicinal product code	
Other name	FG 4592
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Roxadustat was orally self-administered by subjects. Roxadustat was dosed TIW throughout the Treatment Period, except if a subject required <20 mg TIW (i.e., <60 mg per week) to maintain Hb levels in the Maintenance Phase, then the dosing frequency could have been reduced in a step-wise fashion (e.g., TIW to BIW, BIW to QW, QW to Q-2 Week [every 2 weeks]).
The initial roxadustat dose (per dose amount) was based on a tiered, weight based dosing scheme with a starting dose of 70 mg for subjects who weighed <70 kg or 100 mg for subjects who weighed ≥70 kg at Day 1. The maximum roxadustat dose was 3.0 mg/kg per dose or 400 mg per administration (whichever was lower).

Arm title	Epoetin Alfa

Arm description:

Epoetin alfa was supplied to the study site from commercial sources. Within the U.S., sites obtained commercially available epoetin alfa; outside of the U.S., FibroGen provided commercially available epoetin alfa for use by the sites. Epoetin alfa was stored according to the USPI or SmPC.

Arm type	Active comparator
Investigational medicinal product name	Epoetin alfa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

For subjects on HD, doses of epoetin alfa were administered IV TIW according to the United States Package Insert (USPI) or Summary of Product Characteristics (SmPC) by appropriately trained personnel. For subjects requiring ultra-low dose of EPO (e.g., ≤1000 IU/per week), the frequency of administration could have been adjusted per local standard of care.
For subjects on home-hemodialysis (HHD) or PD, doses of epoetin alfa were administered by appropriately trained personnel, including the subject or caregiver, according to the USPI, SmPC, or local standard of care.

Number of subjects in period 1	Roxadustat	Epoetin Alfa
Started	522	521
Completed	307	309
Not completed	215	212
Adverse event, serious fatal	64	54
Consent withdrawn by subject	37	49
Physician decision	14	7
Adverse event, non-fatal	29	22
Lost to follow-up	4	2
Other - subject moved or relocated	32	29
Study/Site Termination by Sponsor	5	13
Kidney transplant	23	29
Lack of efficacy	6	1
Protocol deviation	1	6

Baseline characteristics

Reporting groups	
Reporting group title	Roxadustat
Reporting group description:	
Roxadustat was dosed orally 3 times weekly (TIW) throughout the Treatment Period (minimum of 52 weeks, maximum up to approximately 4 years), except if a subject required <20 mg TIW (i.e., <60 mg per week) to maintain Hb levels.	
Reporting group title	Epoetin Alfa
Reporting group description:	
Epoetin alfa was supplied to the study site from commercial sources. Within the U.S., sites obtained commercially available epoetin alfa; outside of the U.S., FibroGen provided commercially available epoetin alfa for use by the sites. Epoetin alfa was stored according to the USPI or SmPC.	

Reporting group values	Roxadustat	Epoetin Alfa	Total
Number of subjects	522	521	1043
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	381	391	772
From 65 to 74	100	94	194
75 and older	41	36	77
Age continuous			
Age			
Units: years			
arithmetic mean	53.8	54.3	
standard deviation	± 14.74	± 14.55	-
Gender categorical			
Gender			
Units: Subjects			
Female	213	214	427
Male	309	307	616
Ethnicity			
Ethnicity			
Units: Subjects			
Non-Hispanic/Non-Latino	423	444	867
Hispanic/Latino	99	77	176
Race			
Race			
Units: Subjects			
White	415	400	815
Black/African American	44	50	94
Asian	43	51	94
Other	19	16	35

American Indian/Alaskan Native	1	4	5
Region			
Region			
Units: Subjects			
Ex-U.S.	395	396	791
U.S.	127	125	252
ESA			
ESA (erythropoiesis-stimulating agent) naïve was defined as never having received ESA or not having received ESA within 12 weeks prior to randomization. Limited ESA use was defined as limited (≤3 weeks) ESA use to prior to screening.			
Units: Subjects			
ESA Naïve	489	489	978
ESA Limited	33	32	65
Hemoglobin Group Units: Subjects			
≤8.0 g/dL	166	157	323
>8.0 g/dL	356	364	720
CRP			
C-reactive protein			
Units: Subjects			
≤ULN	289	289	578
>ULN	228	226	454
Not recorded	5	6	11
Ferritin Group Units: Subjects			
<100 ng/mL	30	36	66
100 to <400 ng/mL	266	255	521
≥400 ng/mL	226	230	456
TSAT Group Units: Subjects			
<20%	99	89	188
≥20% to <40%	347	388	735
≥40%	49	44	93
Not reported	27	0	27
Iron Repletion Status Units: Subjects			
Ferritin ≥100 ng/mL and TSAT ≥20%	406	406	812
Ferritin <100 ng/mL or TSAT <20%	116	115	231
History of Cardiovascular, Cerebrovascular, or Thromboembolic Disease Risk Factors as randomization Units: Subjects			
Yes	219	224	443
No	303	297	600
Cardiovascular, Cerebrovascular Cardiovascular Disease (Excluding Hypertension) Units: Subjects			
Cardiovascular	141	149	290
Cerebrovascular	77	79	156
Not reported	304	293	597
Diabetes			

Units: Subjects			
Type 1	22	25	47
Type 2	183	179	362
Not reported	317	317	634
Dialysis Modality Units: Subjects			
Hemodialysis	469	462	931
Peritonaeal Dialysis	53	58	111
Missing	0	1	1
Height			
Height			
Units: cm			
arithmetic mean	168.43	168.25	
standard deviation	± 9.487	± 9.805	-
BMI			
Body Mass Index			
Units: kg/m2			
arithmetic mean	26.73	27.01	
standard deviation	± 5.835	± 6.026	-
Hemoglobin			
Hb baseline was defined as the mean of up to 4 of the last central laboratory values prior to the first dose.			
Units: g/dL			
arithmetic mean	8.43	8.46	
standard deviation	± 1.044	± 0.964	-
Prior Duration on Dialysis (weeks) Units: weeks			
arithmetic mean	10.13	10.16	
standard deviation	± 3.906	± 3.621	-
TSAT			
TSAT = transferrin saturation (%). TSAT baselines are defined as the mean of values obtained within 6 weeks prior to the first dose.			
Units: percent			
arithmetic mean	27.02	27.56	
standard deviation	± 9.265	± 8.910	-
Ferritin Units: ng/mL			
arithmetic mean	441.38	437.42	
standard deviation	± 337.016	± 311.359	-
Weight			
Body weight			
Units: kg			
arithmetic mean	76.01	76.70	
standard deviation	± 18.499	± 19.087	-

End points

End points reporting groups

Reporting group title	Roxadustat

Reporting group description:

Roxadustat was dosed orally 3 times weekly (TIW) throughout the Treatment Period (minimum of 52 weeks, maximum up to approximately 4 years), except if a subject required <20 mg TIW (i.e., <60 mg per week) to maintain Hb levels.

Reporting group title	Epoetin Alfa

Reporting group description:

Epoetin alfa was supplied to the study site from commercial sources. Within the U.S., sites obtained commercially available epoetin alfa; outside of the U.S., FibroGen provided commercially available epoetin alfa for use by the sites. Epoetin alfa was stored according to the USPI or SmPC.

Primary: Primary Endpoint Analysis-U.S. Submission

End point title	Primary Endpoint Analysis-U.S. Submission

End point description:

The primary efficacy endpoint for the U.S. submission was defined as the Hb change from baseline to the average level from Week 28 until Week 52, regardless of rescue therapy, in the ITT population. (ANCOVA with Multiple Imputation)

End point type	Primary

End point timeframe:

The treatment period is from week 1 up to Week 52. The endpoint is the average of values measured over weeks 28 to 52.

End point values	Roxadustat	Epoetin Alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	522	521		
Units: g/dL				
least squares mean (confidence interval 95%)	2.38 (2.298 to 2.461)	2.20 (2.115 to 2.278)		

Statistical analyses

Statistical analysis title	HB change from baseline averaged over w. 28 to 52

Statistical analysis description:

The primary non-inferiority hypothesis tested for the primary efficacy analysis was:
- H0: Hb mean change from baseline to the average level from Week 28 to Week 52 in the roxadustat arm ≤Hb mean change from baseline in the epoetin alfa arm minus 0.75 g/dL

versus
- H1: Hb mean change from baseline to the average level of Week 28 to Week 52 in the roxadustat arm >Hb mean change from baseline in the epoetin alfa arm minus 0.75 g/dL

Comparison groups	Epoetin Alfa v Roxadustat

Number of subjects included in analysis	1043
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.0005
Method	MI ANCOVA
Parameter estimate	Least Square Means Difference
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.079
upper limit	0.287
Variability estimate	Standard error of the mean
Dispersion value	0.053

Notes:

[1] - Baseline Hb is defined the mean of up to four last central lab values prior to the first dose of study treatment. A multiple imputation analysis of covariance (MI ANCOVA) model approach was used to analyze the primary endpoint. The method first imputed all intermediate missing values using Markov Chain Monte Carlo (MCMC). The complete observed plus imputed data were analyzed using the analysis of covariance (ANCOVA) model.

Primary: Primary Endpoint Analysis—Ex-U.S. Submission

End point title	Primary Endpoint Analysis—Ex-U.S. Submission

End point description:

The primary efficacy endpoint for the Ex-U.S. submission was defined as the proportion of subjects who achieved an Hb response at 2 consecutive visits during the first 24 weeks of treatment, censoring for rescue therapy. (PPS population)
A Hb response was defined, using central laboratory values, as: Hb ≥11.0 g/dL and a Hb increase from baseline by ≥1.0 g/dL in subjects whose baseline Hb >8.0 g/dL, or Increase in Hb ≥2.0 g/dL in subjects whose baseline Hb ≤8.0 g/dL.

End point type	Primary

End point timeframe:

First 24 weeks of treatment

End point values	Roxadustat	Epoetin Alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	490	468		
Units: subjects	432	395		

Statistical analyses

Statistical analysis title	proportion of subjects who achieved an Hb response

Statistical analysis description:

A two-sided 95% CI for the difference of 2 responder rates (roxadustat minus epoetin alfa) based on the Miettinen & Nurminen approach adjusting for treatment and other stratification factors was calculated and non-inferiority is reached if the lower bound of the 95% CI is greater than -15%

Comparison groups	Roxadustat v Epoetin Alfa

Number of subjects included in analysis	958
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	difference in proportions (%)
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	7.7

Notes:

[2] - To preserve the overall alpha level, the multiple comparison was performed using the fixed sequence testing procedure at a 2-sided significance level of 0.05

Secondary: The mean Hb (g/dL) change from baseline to the average level during the Evaluation Period, defined as Week 28 until Week 52 for Ex-U.S.

End point title	The mean Hb (g/dL) change from baseline to the average level during the Evaluation Period, defined as Week 28 until Week 52 for Ex-U.S.

End point description:

The mean Hb (g/dL) change from baseline to the average level during the Evaluation Period, defined as Week 28 until Week 52 for Ex-U.S. (in PPS population).

To preserve the overall alpha level, the multiple comparison was performed using the fixed sequence testing procedure at a 2-sided significance level of 0.05.

End point type	Secondary

End point timeframe:

Week 28 until Week 52

End point values	Roxadustat	Epoetin Alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	490	468		
Units: g/dL				
least squares mean (confidence interval 95%)	2.49 (2.391 to 2.582)	2.32 (2.225 to 2.419)		

Statistical analyses

Statistical analysis title	The mean Hb (g/dL) change from baseline

Statistical analysis description:

MMRM model which included baseline Hb as covariates and treatment group, visit (a class variable, up to Week 52), interaction of treatment group and visit, and stratification factors as fixed effects. The treatment difference was calculated from an estimate statement based on LSMeans of visits Week 28 to 52 from the MMRM model.

Comparison groups	Roxadustat v Epoetin Alfa

Number of subjects included in analysis	958
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Method	MMRM Model
Parameter estimate	Least Square Means Difference
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.032
upper limit	0.296

Notes:

[3] - Non-inferiority of roxadustat versus Epoetin alfa.
Non-inferiority was declared when the lower bound of the 95% CI was above -0.75 g/dL.

Secondary: LDL cholesterol (mg/dL) change from BL to the average of weeks 12 to 24

End point title	LDL cholesterol (mg/dL) change from BL to the average of weeks 12 to 24

End point description:

LDL cholesterol (mg/dL) change from BL to the average of weeks 12 to 24 (in FAS population)

End point type	Secondary

End point timeframe:

over weeks 12 to 24

End point values	Roxadustat	Epoetin Alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	522	513		
Units: mg/dL				
least squares mean (confidence interval 95%)	-25.76 (-28.152 to -23.362)	-7.42 (-9.828 to -5.007)		

Statistical analyses

Statistical analysis title	Mean change from baseline in LDL cholesterol

Statistical analysis description:

The LDL cholesterol averaged over Weeks 12 to 24 was compared between the 2 treatment groups using the MMRM model with baseline LDL cholesterol as a covariate, treatment group, visit, interaction of visit and treatment group baseline LDL cholesterol measurement, and stratification factors of CV/cerebrovascular/thromboembolic medical history (yes versus no) and geographic region (U.S. versus Ex-U.S.) as fixed effects.

Comparison groups	Roxadustat v Epoetin Alfa

Number of subjects included in analysis	1035
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001
Method	MMRM Model
Parameter estimate	Least Square Means Difference
Point estimate	-18.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.448
upper limit	-15.232
Variability estimate	Standard error of the mean
Dispersion value	1.584

Notes:

[4] - Superiority of roxadustat versus EPO when p<0.05

Secondary: Mean change from baseline in Hb (g/dL) levels between Weeks 18 to 24 in patients whose baseline CRP> ULN

End point title	Mean change from baseline in Hb (g/dL) levels between Weeks 18 to 24 in patients whose baseline CRP> ULN

End point description:

Mean change from baseline in Hb (g/dL) levels between Weeks 18 to 24 in patients whose baseline CRP> ULN (in PPS population).

End point type	Secondary

End point timeframe:

over weeks 18 to 24

End point values	Roxadustat	Epoetin Alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	212	201		
Units: mg/dL				
least squares mean (confidence interval 95%)	2.33 (2.168 to 2.477)	2.33 (2.175 to 2.482)		

Statistical analyses

Statistical analysis title	Mean Change in Hemoglobin Levels

Statistical analysis description:

Mean change from baseline in Hb (g/dL) levels between Weeks 18 to 24 in patients whose baseline CRP> ULN.

Comparison groups	Roxadustat v Epoetin Alfa

Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Method	MI ANCOVA
Parameter estimate	Least Square Means Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.194
upper limit	0.201

Notes:

[5] - Non-inferiority was declared when the lower bound of the 95% CI was above -0.75 g/dL.

Secondary: Monthly IV iron (mg per Patient-exposure-month) use per subject during weeks 28 to 52

End point title	Monthly IV iron (mg per Patient-exposure-month) use per subject during weeks 28 to 52

End point description:

Monthly IV iron (mg per Patient-exposure-month) use per subject during weeks 28 to 52 (in FAS population).

End point type	Secondary

End point timeframe:

Weeks 28 to 52

End point values	Roxadustat	Epoetin Alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	438		
Units: mg per patient-exposure-month				
arithmetic mean (standard deviation)	59.09 (± 145.179)	63.99 (± 98.771)		

Statistical analyses

Statistical analysis title	Monthly IV iron use
Comparison groups	Roxadustat v Epoetin Alfa
Number of subjects included in analysis	875
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.00028
Method	non-parametric rank ANCOVA

Notes:

[6] - Superiority of roxadustat versus EPO when $p<0.05$

Secondary: Time to first RBC transfusion during the treatment

End point title	Time to first RBC transfusion during the treatment

End point description:

Time to first RBC transfusion during the treatment (in PPS population).

End point type	Secondary

End point timeframe:

Treatment period.

End point values	Roxadustat	Epoetin Alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	490	468		
Units: events per patient-exposure-year				
number (not applicable)	4.2	3.1		

Statistical analyses

Statistical analysis title	Time to first RBC transfusion

Statistical analysis description:

Cox proportional hazard regression model.

Comparison groups	Roxadustat v Epoetin Alfa
Number of subjects included in analysis	958
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.871
upper limit	2.335

Notes:

[7] - Non-inferiority of roxadustat versus EPO with Non-inferiority margin of 1.8 for the hazard ratio. Non-inferiority was declared when the upper bound of the 95% CI for the hazard ratio was below 1.8. The endpoint did not met the non-inferiority criteria, and the fixed sequence testing stopped.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 through 28 days after last dose.

Adverse event reporting additional description:

Table "Serious adverse events": all fatal and serious adverse events in ≥1% of subjects; table "Non-serious adverse events": both serious and non-serious adverse events in ≥%5 of subjects in either treatment group.
One TESAE of transplant rejection in the epoetin alfa arm was found retrospectively, and therefore was not included in the tables.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Epoetin Alfa
Reporting group description: -	
Reporting group title	Roxadustat

Reporting group description: -

Serious adverse events	Epoetin Alfa	Roxadustat	
Total subjects affected by serious adverse events			
subjects affected / exposed	218 / 517 (42.17%)	234 / 522 (44.83%)	
number of deaths (all causes)	59	63	
number of deaths resulting from adverse events	59	63	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	0 / 517 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Glioblastoma			
subjects affected / exposed	0 / 517 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 517 (0.58%)	7 / 522 (1.34%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypertensive crisis			
subjects affected / exposed	12 / 517 (2.32%)	9 / 522 (1.72%)	
occurrences causally related to treatment / all	1 / 14	2 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	3 / 517 (0.58%)	6 / 522 (1.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic rupture			
subjects affected / exposed	1 / 517 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	4 / 517 (0.77%)	7 / 522 (1.34%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 4	0 / 7	
Death			
subjects affected / exposed	7 / 517 (1.35%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 7	0 / 2	
General physical health deterioration			
subjects affected / exposed	0 / 517 (0.00%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden cardiac death			
subjects affected / exposed	2 / 517 (0.39%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 517 (0.00%)	3 / 522 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	

Social circumstances			
Refusal of treatment by patient			
subjects affected / exposed	0 / 517 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	6 / 517 (1.16%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	2 / 517 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 517 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 517 (0.77%)	3 / 522 (0.57%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Pulmonary oedema			
subjects affected / exposed	5 / 517 (0.97%)	5 / 522 (0.96%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory failure			
subjects affected / exposed	4 / 517 (0.77%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Investigations			
Coagulation time prolonged			

subjects affected / exposed	0 / 517 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	21 / 517 (4.06%)	39 / 522 (7.47%)	
occurrences causally related to treatment / all	2 / 27	5 / 28	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbon monoxide poisoning			
subjects affected / exposed	0 / 517 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Craniocerebral injury			
subjects affected / exposed	2 / 517 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 517 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory fume inhalation disorder			
subjects affected / exposed	0 / 517 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriovenous fistula site complication			
subjects affected / exposed	2 / 517 (0.39%)	5 / 522 (0.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 517 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			

Cardiac failure congestive			
subjects affected / exposed	7 / 517 (1.35%)	5 / 522 (0.96%)	
occurrences causally related to treatment / all	0 / 9	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	11 / 517 (2.13%)	6 / 522 (1.15%)	
occurrences causally related to treatment / all	0 / 11	0 / 9	
deaths causally related to treatment / all	0 / 2	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	2 / 517 (0.39%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac arrest			
subjects affected / exposed	5 / 517 (0.97%)	3 / 522 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 5	0 / 3	
Cardiac failure			
subjects affected / exposed	1 / 517 (0.19%)	3 / 522 (0.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cardiac failure acute			
subjects affected / exposed	3 / 517 (0.58%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 517 (0.19%)	4 / 522 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cardiopulmonary failure			
subjects affected / exposed	0 / 517 (0.00%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Coronary artery insufficiency			

subjects affected / exposed	0 / 517 (0.00%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Myocardial ischaemia			
subjects affected / exposed	1 / 517 (0.19%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial infarction			
subjects affected / exposed	2 / 517 (0.39%)	5 / 522 (0.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 3	
Angina unstable			
subjects affected / exposed	5 / 517 (0.97%)	3 / 522 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	5 / 517 (0.97%)	4 / 522 (0.77%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hemorrhagic stroke			
subjects affected / exposed	6 / 517 (1.16%)	3 / 522 (0.57%)	
occurrences causally related to treatment / all	2 / 6	0 / 3	
deaths causally related to treatment / all	0 / 4	0 / 0	
Basal ganglia haemorrhage			
subjects affected / exposed	1 / 517 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain injury			
subjects affected / exposed	1 / 517 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain stem infarction			

subjects affected / exposed	1 / 517 (0.19%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral haemorrhage			
subjects affected / exposed	1 / 517 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	3 / 517 (0.58%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	0 / 517 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic stroke			
subjects affected / exposed	2 / 517 (0.39%)	5 / 522 (0.96%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Gastric ulcer perforation			
subjects affected / exposed	1 / 517 (0.19%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal haemorrhage			
subjects affected / exposed	5 / 517 (0.97%)	4 / 522 (0.77%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal ulcer haemorrhage			
subjects affected / exposed	2 / 517 (0.39%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal obstruction			

subjects affected / exposed	2 / 517 (0.39%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Gallbladder necrosis			
subjects affected / exposed	0 / 517 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	2 / 517 (0.39%)	3 / 522 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Infections and infestations			
Peritonitis			
subjects affected / exposed	12 / 517 (2.32%)	12 / 522 (2.30%)	
occurrences causally related to treatment / all	0 / 14	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	26 / 517 (5.03%)	30 / 522 (5.75%)	
occurrences causally related to treatment / all	0 / 30	0 / 30	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	8 / 517 (1.55%)	13 / 522 (2.49%)	
occurrences causally related to treatment / all	0 / 8	0 / 14	
deaths causally related to treatment / all	0 / 4	0 / 6	
Device related infection			
subjects affected / exposed	3 / 517 (0.58%)	9 / 522 (1.72%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gangrene			
subjects affected / exposed	6 / 517 (1.16%)	6 / 522 (1.15%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Septic shock			
subjects affected / exposed	4 / 517 (0.77%)	7 / 522 (1.34%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 5	
Device related sepsis			
subjects affected / exposed	2 / 517 (0.39%)	7 / 522 (1.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	4 / 517 (0.77%)	6 / 522 (1.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetic gangrene			
subjects affected / exposed	0 / 517 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal wall abscess			
subjects affected / exposed	0 / 517 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gallbladder empyema			
subjects affected / exposed	0 / 517 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung infection			
subjects affected / exposed	0 / 517 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Meningitis			
subjects affected / exposed	1 / 517 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Osteomyelitis			

subjects affected / exposed	4 / 517 (0.77%)	4 / 522 (0.77%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 517 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Toxic shock syndrome			
subjects affected / exposed	0 / 517 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subcutaneous abscess			
subjects affected / exposed	0 / 517 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	5 / 517 (0.97%)	4 / 522 (0.77%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 517 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	12 / 517 (2.32%)	9 / 522 (1.72%)	
occurrences causally related to treatment / all	0 / 15	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalemia			
subjects affected / exposed	6 / 517 (1.16%)	3 / 522 (0.57%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			

subjects affected / exposed	1 / 517 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Epoetin Alfa	Roxadustat	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	441 / 517 (85.30%)	450 / 522 (86.21%)	
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	46 / 517 (8.90%)	59 / 522 (11.30%)	
occurrences (all)	69	80	
Arteriovenous fistula site complication			
subjects affected / exposed	43 / 517 (8.32%)	31 / 522 (5.94%)	
occurrences (all)	79	40	
Procedural hypotension			
subjects affected / exposed	31 / 517 (6.00%)	26 / 522 (4.98%)	
occurrences (all)	49	35	
Vascular disorders			
Hypertension			
subjects affected / exposed	88 / 517 (17.02%)	99 / 522 (18.97%)	
occurrences (all)	134	165	
Hypotension			
subjects affected / exposed	35 / 517 (6.77%)	54 / 522 (10.34%)	
occurrences (all)	51	104	
Nervous system disorders			
Headache			
subjects affected / exposed	44 / 517 (8.51%)	57 / 522 (10.92%)	
occurrences (all)	66	88	
Dizziness			
subjects affected / exposed	24 / 517 (4.64%)	28 / 522 (5.36%)	
occurrences (all)	32	39	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	30 / 517 (5.80%)	45 / 522 (8.62%)	
occurrences (all)	33	57	
Diarrhoea			
subjects affected / exposed	38 / 517 (7.35%)	72 / 522 (13.79%)	
occurrences (all)	56	112	
Constipation			
subjects affected / exposed	23 / 517 (4.45%)	35 / 522 (6.70%)	
occurrences (all)	24	40	
Vomiting			
subjects affected / exposed	17 / 517 (3.29%)	32 / 522 (6.13%)	
occurrences (all)	23	45	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	21 / 517 (4.06%)	28 / 522 (5.36%)	
occurrences (all)	22	35	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	22 / 517 (4.26%)	30 / 522 (5.75%)	
occurrences (all)	26	36	
Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	27 / 517 (5.22%)	25 / 522 (4.79%)	
occurrences (all)	32	26	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	27 / 517 (5.22%)	18 / 522 (3.45%)	
occurrences (all)	28	21	
Muscle spasms			
subjects affected / exposed	39 / 517 (7.54%)	60 / 522 (11.49%)	
occurrences (all)	65	106	
Infections and infestations			
Pneumonia			
subjects affected / exposed	40 / 517 (7.74%)	42 / 522 (8.05%)	
occurrences (all)	46	48	
Viral upper respiratory tract infection			

subjects affected / exposed	25 / 517 (4.84%)	26 / 522 (4.98%)	
occurrences (all)	42	52	
Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	35 / 517 (6.77%)	52 / 522 (9.96%)	
occurrences (all)	39	57	
Fluid overload			
subjects affected / exposed	28 / 517 (5.42%)	29 / 522 (5.56%)	
occurrences (all)	39	42	
Hyperkalaemia			
subjects affected / exposed	36 / 517 (6.96%)	26 / 522 (4.98%)	
occurrences (all)	47	37	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2014	Amendment 1 was dated as 20 October 2014 and included the following key changes: • Changed the compound name from FG 4592 to roxadustat. • Increased the total sample size and number of sites to reflect the needs of the global program. • Implemented roxadustat dosing, adjustments to the starting dose, and dose adjustment rules to provide a more conservative dosing and to simplify the dose adjustment rules globally. • Clarified dosing with epoetin alfa: specified use of prefilled syringes in countries other than USA; allowed local standard-of-care EPO dosing for subjects on PD. • Added recommendations for the concomitant use of phosphate binders and statins. • Added more specific instructions, to better standardize supplemental IV iron use. • Modified the language regarding ESA rescue criteria for subjects receiving roxadustat, to allow 1 round of ESA rescue on study. • Clarified that chronic use of paracetamol was prohibited. • Modified eligibility criteria for ferritin, TSAT, and IV iron restrictions, to meet the need of subjects being iron-replete at baseline; modified eligibility to allow for investigator discretion in the exclusion of subjects who had abnormal laboratory parameters that could have posed a safety risk. • Reduced the frequency of the visit schedule without impacting the assessment of safety and efficacy. • Added follow-up requirements for subjects who terminated participation in the study early, until overall study end. • Added additional reasons for subject discontinuation. • Added the following tests and assessments: added creatinine phosphokinase (CPK) at the time of liver function test (LFT) assessment, pregnancy testing every 12 weeks, and weight and ECG every 24 weeks, and changed the Week 28 QOL to Week 36. • Stipulated that archival samples were provided on a voluntary basis. • .....
24 November 2015	Amendment 2 was implemented in the U.S. only, was dated as 24 November 2015, and included the following key changes: • Changed Exclusion Criterion #1 to allow the total duration of prior effective ESA use to be ≤3 weeks within the preceding 12 weeks at the time of informed consent. • Increased the number of planned subjects from 1000 to 1200. • Increased the number of planned study centers from 300 to 400.

12 August 2016	Amendment 3 was implemented in the U.S. only, was dated as 12 August 2016, and included the following key changes: • Modified Inclusion Criterion #5 to reduce the number of values from 3 to 2 and the number of days between sample collection from 4 to 2 days; this change was implemented to improve participation of incident dialysis patients with severe anemia by streamlining eligibility assessments without changing the Hb requirement for participation. • Modified Exclusion Criterion #1 language related to CERA dosing guidance to align with the current standard of dosing based on the package insert. • Added text to allow for the participation of subjects receiving HHD and clarified that the administration of epoetin alfa would be according to USPI, SmPC, or local standard of care. • Revised the timeline for reassessment of TSAT and ferritin values after the last dose of IV iron to align with the current clinical practice. • Aligned the Adverse Event Reporting Period with GCP/ICH guidelines for AE reporting. • Added the definition of baseline Hb for subjects in the U.S. who were enrolled under Protocol Amendment 3. • Added guidance for epoetin alfa administration to subjects requiring ultra-low dose therapy.
20 September 2017	Amendment 4 was dated as 20 September 2017 and included the following key changes: • Allowed the participation of subjects who had restarted dialysis recently after a failed kidney transplant. • Revised the TSAT, ferritin, vitamin B12, folate screening criteria to improve the screening success rate without altering the patient population. • Modified and clarified several exclusion criteria to allow more incident subjects to be eligible for participation, to retain a representative sample of real-life incident dialysis patients. • Updated the duration of the Treatment Period to allow for less than 52 weeks of participation for subjects who were enrolled towards the end of the overall study completion. • Modified the protocol to align it with new standard operating procedures (SOPs) for the handling of incorrectly enrolled subjects, contraception, protocol deviations, and disease progression. • Added instructions for the handling of excessive hematopoiesis, to include the scenario of prolonged dose-hold, and dosing of ultra-low doses. • Loosened IV iron use restrictions. • Clarified that inadvertent administration of ESA therapy or ESA administration as part of standard-of-care did not qualify as ESA rescue. • Reduced screening visits/procedures. • Increased the visit windows to avoid unnecessary protocol deviations. • Added instruction that a central laboratory measurement of Hb was to be performed any time a HemoCue®/CritLine® or other local laboratory Hb measurement was obtained. • Clarified action taken with study drug for AE reporting. • Clarified the reporting requirements in case of pregnancy. • Modified the BP and heart rate measurement guidelines to allow for flexibility with standard clinical practice. • Clarified the sample size determination with regard to the European Medicines Agency (EMA) primary endpoint. • Removed the EMA potential interim analysis. • Clarified and corrected descriptions of the analysis model. .....

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported