Clinical trial results:
A Randomized Controlled, Single-Blind, Proof-of-Concept-Study to Investigate the Protective Effects of Early Treatment With C.E.R.A. in Patients With Chronic Kidney Disease on Renal Disease Progression

Summary

EudraCT number	2009-015114-22
Trial protocol	DE
Global end of trial date	30 March 2015

Results information

Result version number	v1 (current)
This version publication date	09 April 2016
First version publication date	09 April 2016

Trial information

Trial identification

Sponsor protocol code	ML22916

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01194154
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Roche Pharma AG
Sponsor organisation address	Emil-Barell-Str. 1, D-79639, Grenzach-Wyhlen, Germany, 79639
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.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	11 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate if treatment with Mircera or Continuous Erythropoietin Receptor Activator (C.E.R.A.) has a protective effect on the kidney of CKD stage III participants.

Protection of trial subjects:

The study was designed, conducted, and evaluated according to the study protocol and in compliance with the International Conference of Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) E6 and the Declaration of Helsinki, as well as with local legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 August 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 241
Worldwide total number of subjects	241
EEA total number of subjects	241

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)	114
From 65 to 84 years	123
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total 241 participants were randomized, 2 participants in the Mircera group and 4 participants in the placebo group did not receive medication.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Mircera

Arm description:

Methoxy polyethylene glycol-epoetin beta 30 microgram (mcg) subcutaneous injection once monthly up to 24 months with sequential dose adjustments to 50 mcg or 75 mcg depending on change of hemoglobin values of more than 1.0 gram (g)/ deciliter (dL).

Arm type	Experimental
Investigational medicinal product name	Mircera
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Methoxy polyethylene glycol-epoetin beta 30 microgram (mcg) subcutaneous injection once monthly up to 24 months.

Arm title	Placebo

Arm description:

Placebo matching to methoxy polyethylene glycol-epoetin beta subcutaneous injection once monthly up to 24 months.

Arm type	Placebo
Investigational medicinal product name	NA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo matching to methoxy polyethylene glycol-epoetin beta, administered as subcutaneous injection.

Number of subjects in period 1	Mircera	Placebo
Started	117	124
Completed	68	91
Not completed	49	33
Adverse event, serious fatal	3	2
Hemoglobin decrease	-	1
Consent withdrawn by subject	5	6
Blood pressure increase	5	3
Adverse event, non-fatal	9	5
Hemoglobin increase	12	3
Treatment with prohibited medication	4	5
Skipping of CERA treatment at two visits	3	-
Unspecified	4	-
Lost to follow-up	2	3
Did not receive study medication	2	4
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Mircera
Reporting group description:	
Methoxy polyethylene glycol-epoetin beta 30 microgram (mcg) subcutaneous injection once monthly up to 24 months with sequential dose adjustments to 50 mcg or 75 mcg depending on change of hemoglobin values of more than 1.0 gram (g)/ deciliter (dL).	
Reporting group title	Placebo
Reporting group description:	
Placebo matching to methoxy polyethylene glycol-epoetin beta subcutaneous injection once monthly up to 24 months.	

Reporting group values	Mircera	Placebo	Total
Number of subjects	117	124	241
Age categorical			
Units: Subjects			

Age continuous			
N (number of participants analyzed) = 235			
Units: years			
arithmetic mean	63.37	62.97	
standard deviation	± 12.26	± 14.3	-
Gender categorical			
Units: Subjects			
Female	44	44	88
Male	71	76	147
Missing	2	4	6

End points

End points reporting groups

Reporting group title	Mircera
Reporting group description:	
Methoxy polyethylene glycol-epoetin beta 30 microgram (mcg) subcutaneous injection once monthly up to 24 months with sequential dose adjustments to 50 mcg or 75 mcg depending on change of hemoglobin values of more than 1.0 gram (g)/ deciliter (dL).	
Reporting group title	Placebo
Reporting group description:	
Placebo matching to methoxy polyethylene glycol-epoetin beta subcutaneous injection once monthly up to 24 months.	

Primary: Yearly Reduction Rate of Estimated Glomerular Filtration Rate (eGFR) Calculated by Modification of Diet in Renal Disease With 4 Variables (MDRD-4)

End point title	Yearly Reduction Rate of Estimated Glomerular Filtration Rate (eGFR) Calculated by Modification of Diet in Renal Disease With 4 Variables (MDRD-4)
End point description:	
The yearly reduction in eGFR was calculated using the MDRD-4 formula. This formula is based on age, sex, and serum creatinine and eGFR values are calculated as follows: GFR in ml/min per 1.73 m^2 = 175 x Serum Cr^-1.154 x age^-0.203 x 0.742 (if female). The yearly reduction rate (mL/min/1.73m^2 / Year) is defined as –365.25 multiplied by Beta, where Beta is the slope parameter derived for each participants separately by simple linear regression of the change from baseline in participant's eGFR measurements (from Baseline to Visit 24) on the actual day of measurement. FAS included all randomized participants who received at least one dose of the study medication and provided any successive eGFR measurement.	
End point type	Primary
End point timeframe:	
24 months	

End point values	Mircera	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	120		
Units: eGFR/year				
least squares mean (confidence interval 95%)	3.04 (1.2 to 4.87)	0.82 (-0.96 to 2.61)		

Statistical analyses

Statistical analysis title	Yearly Reduction Rate of eGFR
Statistical analysis description:	
An analysis of covariance (ANCOVA) model with adjustment for baseline eGFR was used to obtain an estimate of the treatment difference.	
Comparison groups	Mircera v Placebo

Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.657
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	treatment effect
Point estimate	2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	4.78

Secondary: Yearly Reduction Rate of Estimated Glomerular Filtration Rate (eGFR) Calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

End point title	Yearly Reduction Rate of Estimated Glomerular Filtration Rate (eGFR) Calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

End point description:

The eGFR value calculated using the CKD-EPI equation. The formula used is based on age, sex, ethnicity, and serum creatinine and eGFR values are calculated as follows: GFR in milliliter(mL)/min per 1.73 m^2 = 141 x min(SerumCr/k; 1)^a x max(SerumCr/k; 1)^(-1.209) x 0.993^age x F x B, where k=0.7 for female (else=0.9); a=-0.329 for female (else=-0.411), F=1.018 for female (else=1), B=1.159 for black (else=1), min/max=minimum/maximum of listed values. The Yearly Reduction Rate (mL/min/1.73m^2 / Year) is defined as –365.25 * Beta, where Beta is the slope parameter derived for each participant separately by simple linear regression of the change from baseline in participant's eGFR measurements (from Baseline to Visit 24) on the actual day of measurement.
FAS included all randomized participants who received at least one dose of the study medication and provided any successive eGFR measurement.

End point type	Secondary

End point timeframe:

24 months

End point values	Mircera	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	120		
Units: eGFR/year				
least squares mean (confidence interval 95%)	3.02 (1.03 to 5)	0.78 (-1.16 to 2.72)		

Statistical analyses

Statistical analysis title	Yearly Reduction Rate of eGFR

Statistical analysis description:

ANCOVA model with adjustment for baseline eGFR was used to obtain an estimate of the treatment difference.

Comparison groups	Mircera v Placebo

Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.709
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	treatment effect
Point estimate	2.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	5.01

Secondary: Change From Baseline in Calculated Creatinine Clearance (Cockcroft-Gault Equation) at Month 24

End point title	Change From Baseline in Calculated Creatinine Clearance (Cockcroft-Gault Equation) at Month 24

End point description:

Creatinine clearance was calculated according to the Cockcroft and Gault Formula. It measures rate creatinine (substance formed from metabolism of creatine) is cleared from blood by kidneys. Normal adult creatinine clearance is greater than or equal to (>=) 90 mL/min/1.73m^2. Change from baseline=CC at Week X minus CC at baseline where higher scores represented improved renal function. FAS included all randomized participants who received at least one dose of the study medication and provided any successive eGFR measurement. n=number of participants evaluable for each category.

End point type	Secondary

End point timeframe:

Baseline, Month 24

End point values	Mircera	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	120		
Units: ml/min]				
arithmetic mean (standard deviation)				
Baseline (n=115, 120)	53.18 (± 15.95)	52.48 (± 16.04)		
Change at Month 24 (n=67, 91)	-2.97 (± 10.52)	-2.08 (± 9.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Creatinine Concentration at Month 24

End point title	Change From Baseline in Serum Creatinine Concentration at Month 24

End point description:

Serum creatinine is an indicator of kidney function. Creatinine is a substance formed from the metabolism of creatine, commonly found in blood, urine, and muscle tissue. It is removed from the blood by the kidneys and excreted in urine. Normal adult blood levels of creatinine=45 to 90 micromoles per liter (mcmol/L) for females, 60 to 110 mcmol/L for males, however normal values are age-dependent.
FAS included all randomized participants who received at least one dose of the study medication and provided any successive eGFR measurement. n=number of participants evaluable for each category.

End point type	Secondary

End point timeframe:

Baseline, Month 24

End point values	Mircera	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	120		
Units: mcmol/L				
arithmetic mean (standard deviation)				
Baseline (n=115, 120)	147.8 (± 31.71)	149.3 (± 35.67)		
Change at Month 24 (n=68, 91)	7.04 (± 27.23)	4.04 (± 30.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Urinary Albumin Creatinine Ratio (UACR) at Month 24

End point title	Change From Baseline in Urinary Albumin Creatinine Ratio (UACR) at Month 24

End point description:

UACR is defined as the ratio: milligram of albumin per gram of creatinine. The presence of albumin in the urine (macroalbuminuria) is a marker of kidney disease. Albumin and creatinine concentrations were obtained from spot urine samples.
FAS included all randomized participants who received at least one dose of the study medication and provided any successive eGFR measurement. Number of Participants Analyzed (N) = number of participants evaluable and available with valid data for this outcome measure. n=number of participants evaluable for each category.

End point type	Secondary

End point timeframe:

Baseline, Month 24

End point values	Mircera	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	107		
Units: mg/g				
arithmetic mean (standard deviation)				

Baseline (n=110, 107)	261.1 (± 564)	237.3 (± 699.6)		
Change at Month 24 (n=43, 53)	173.8 (± 573.3)	70.59 (± 546.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Serum Cystatin C Concentration at Month 24

End point title	Change From Baseline in Serum Cystatin C Concentration at Month 24

End point description:

Cystatin C is a protein which is mainly used as a biomarker of kidney function. If kidney function and GFR decline, the blood levels of cystatin C rise.
FAS included all randomized participants who received at least one dose of the study medication and provided any successive eGFR measurement. n=number of participants evaluable for each category.

End point type	Secondary

End point timeframe:

Baseline, Month 24

End point values	Mircera	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	120		
Units: mg/L				
arithmetic mean (standard deviation)				
Baseline (n=115, 120)	1.79 (± 0.39)	1.76 (± 0.46)		
Change at Month 24 (n=67, 91)	0.1 (± 0.29)	0.02 (± 0.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability or incapacity; and congenital anomaly. Percentage of participants with AEs included participants affected with both SAEs and non-SAEs.
The Safety Analysis Set (SAF) included all participants who received at least one dose of the study medication. Analysis for SAF was performed according to the study medication actually received ('as treated' population).

End point type	Secondary

End point timeframe:
24 months

End point values	Mircera	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115[1]	120[2]		
Units: percentage of participants				
number (not applicable)				
SAEs	35.6	41		
AEs	84.7	86.3		

Notes:
[1] - N=117 (as treated population) were evaluable for this outcome measure.
[2] - N=118 (as treated population) participants evaluable for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 months

Adverse event reporting additional description:

The Safety Analysis Set (SAF) included all participants who received at least one dose of study medication. Analysis for SAF was performed according to the study medication actually received (as treated population).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo matching to Methoxy polyethylene glycol-epoetin beta subcutaneous injection once monthly up to 24 months.

Reporting group title	Mircera

Reporting group description:

Methoxy polyethylene glycol-epoetin beta 30 microgram (mcg) subcutaneous injection once monthly up to 24 months with sequential dose adjustments to 50 mcg or 75 mcg depending on change of hemoglobin values of more than 1.0 gram (g)/ deciliter (dL).

Serious adverse events	Placebo	Mircera	
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 117 (41.03%)	42 / 118 (35.59%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thyroid cancer			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip neoplasm malignant stage unspecified			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipoma			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmacytoma			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
alternative assessment type: Systematic			

subjects affected / exposed	3 / 117 (2.56%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Aortic anastomosis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (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			
Chest pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
General physical health deterioration			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Transplant rejection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
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			
Chronic obstructive pulmonary disease			
alternative assessment type:			

Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	4 / 118 (3.39%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive airways disorder			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Haemoglobin decreased			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 117 (0.85%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Humerus fracture			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus lesion			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic brain injury			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Tibial torsion			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 117 (1.71%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arrhythmia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (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			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (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			
Cerebrovascular accident			
alternative assessment type: Systematic			

subjects affected / exposed	2 / 117 (1.71%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular disorder			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myelopathy			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient global amnesia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Normochromic normocytic anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Ectropion			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			

alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lens dislocation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 117 (2.56%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 117 (1.71%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gastroparesis			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reflux oesophagitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Liver disorder			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 117 (1.71%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (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 prerenal failure			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 117 (1.71%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postrenal failure			

alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 117 (1.71%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 117 (0.85%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia primary atypical			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Placebo	Mircera	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	99 / 117 (84.62%)	95 / 118 (80.51%)	
Vascular disorders			
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	14 / 117 (11.97%)	11 / 118 (9.32%)	
occurrences (all)	16	12	
General disorders and administration site conditions			
Oedema peripheral			
alternative assessment type: Systematic			
subjects affected / exposed	10 / 117 (8.55%)	11 / 118 (9.32%)	
occurrences (all)	12	12	

Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	13 / 117 (11.11%)	11 / 118 (9.32%)	
occurrences (all)	15	12	
Nausea			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 117 (6.84%)	0 / 118 (0.00%)	
occurrences (all)	12	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative assessment type: Systematic			
subjects affected / exposed	10 / 117 (8.55%)	13 / 118 (11.02%)	
occurrences (all)	10	13	
Musculoskeletal and connective tissue disorders			
Back pain			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 117 (6.84%)	0 / 118 (0.00%)	
occurrences (all)	9	0	
Osteoarthritis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 117 (0.00%)	6 / 118 (5.08%)	
occurrences (all)	0	6	
Pain in extremity			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 117 (5.13%)	0 / 118 (0.00%)	
occurrences (all)	6	0	
Infections and infestations			
Bronchitis			
alternative assessment type: Systematic			
subjects affected / exposed	9 / 117 (7.69%)	0 / 118 (0.00%)	
occurrences (all)	9	0	
Influenza			
alternative assessment type: Systematic			

subjects affected / exposed	9 / 117 (7.69%)	9 / 118 (7.63%)	
occurrences (all)	15	10	
Nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	24 / 117 (20.51%)	29 / 118 (24.58%)	
occurrences (all)	33	40	
Urinary tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	7 / 117 (5.98%)	12 / 118 (10.17%)	
occurrences (all)	14	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 December 2010	Version 1: Protocol was amended to clarify the inclusion criteria (UACR, creatinine and total protein values needed for inclusion in the study) and exclusion criteria (an additional organ transplant, other than kidney and participants with myelofibrosis or a diagnosed hematologic disease were excluded). Acute transplant rejection and pregnancy were included as withdrawal criteria and erythropoietin-stimulating agent (ESAs) were included as prohibited concomitant medication. Visit 2 was defined to be the time point for starting possible dose adjustments of C.E.R.A.
16 August 2011	Version 2: UACR, creatinine and total protein values needed for inclusion in the study were changed. Increases and decreases in hemoglobin values of more than 1.5 g/dl now had to be present in combination with a current value of >14,0 g/dl or <10 g/dl respectively to allow for treatment discontinuation or premature withdrawal of the participant.
04 June 2012	Version 3: Due to temporarily stopped manufacturing of C.E.R.A., enrollment of new participants into the study was halted. To avoid any recruitment problems and any further extension of the duration of the study, the sample size calculation, total participant numbers as well as recruitment timelines were adapted. To avoid any recruitment problems and any further extension of the duration of the study, the sample size calculation, total participant numbers as well as recruitment timelines were adapted. The reporting time lines for possible SAE and pregnancies were specified in more detail.
06 May 2014	Version 4: As most of the participants had already had their EoS visit after the recruitment stop of the study, an interim analysis was no longer scheduled as originally planned. Change in eGFR over time calculated additionally by CKD-EPI equation (based on the same variables as MDRD) was included as a secondary efficacy parameter.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported