Clinical trial results:
Open label, single arm, multicenter study to evaluate the safety and immunogenicity of HX575 epoetin alfa in the treatment of anemia associated with chronic kidney disease in pre-dialysis and dialysis patients.

Summary

EudraCT number	2011-002871-40
Trial protocol	DE PL
Global end of trial date	05 June 2015

Results information

Result version number	v1 (current)
This version publication date	24 July 2016
First version publication date	24 July 2016

Trial information

Trial identification

Sponsor protocol code	HX575-308

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01576341
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hexal AG, a Sandoz company
Sponsor organisation address	Industriestrasse 25, Holzkirchen, Germany, 83607
Public contact	Sandoz, Strategic Planning Biopharma Clinical Development, 0049 80244760, biopharma.clinicaltrials@sandoz.com
Scientific contact	Sandoz, Strategic Planning Biopharma Clinical Development, 0049 80244760, biopharma.clinicaltrials@sandoz.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	27 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2014
Global end of trial reached?	Yes
Global end of trial date	05 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main objective was to demonstrate the lack of immunogenicity of HX575 administered s.c. in the treatment of anemia associated with CKD. The secondary objective was to assess the safety of HX575 administered s.c. and to demonstrate that administration at least once per week adequately corrects or maintains the correction of anemia associated with CKD. The study was designed as an open-label, single-arm, multicenter study with a 4-week screening period and a 52-week treatment period in patients with anemia associated with CKD with or without dialysis, and a safety follow-up of only those patients with newly developing anti-EPO antibodies for up to 6 month.

Protection of trial subjects:

This clinical study was designed, implemented and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki. Safety assessment included adverse events (AEs), vital signs, 12-lead ECG, clinical laboratory, immunogenicity, physical examination and other parameters considered relevant for the safety assessments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 April 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 47
Country: Number of subjects enrolled	Russian Federation: 107
Country: Number of subjects enrolled	Ukraine: 179
Country: Number of subjects enrolled	Turkey: 33
Country: Number of subjects enrolled	Romania: 41
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Germany: 5
Worldwide total number of subjects	417
EEA total number of subjects	98

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)	317
From 65 to 84 years	98
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Patients, suffering from anemia associated with CKD, were treated s.c. with HX575 at least once per week in order to achieve and maintain Hb concentration within the target range of 10.0 to 12.0 g/dL. 417 patients were enrolled, 416 patients were treated.

Pre-assignment

Screening details:

Male and female patients (ESA-naïve/on ESA-maintenance therapy, i.v./s.c.) aged 18 years/older, suffering from anemia assoc. with CKD, with/without dialysis treatment. Anemia: Mean Hb conc. <= 11.0 g/dL for ESA naïve, 9.0-12.0 g/dL for patients receiving ESA therapy. Main exclusion: History of PRCA/anti-EPO antibodies, lack of ESA therapy efficacy.

Period 1

Period 1 title	HX575, safety population (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Blinding was not applicable.

Arms

Arm title	HX575, safety population

Arm description:

In the single arm study, HX575 was tested as investigational medicinal product. The single arm includes ESA-naïve patients and patients on ESA-maintenance therapy. Primary endpoint was measured for the overall safety population, secondary endpoints were measured to compare per-protocol-ESA-naïve patients, per-protocol-ESA-maintenance patients, safety population-ESA-naive patients and safety population-ESA maintenance patients.

Arm type	Experimental
Investigational medicinal product name	HX575
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

HX575 was formulated as a sterile, clear, colorless solution for injection. Prefilled syringes containing different strengths of epoetin alfa. This study enrolled patients suffering from anemia associated with CKD, with or without dialysis treatment. During the treatment period, the dose was individually titrated to maintain Hb concentrations between 10.0 and 12.0 g/dL, and the dosing frequency was adjusted as required. For ESA-naïve patients the starting dose for correcting their anemia was 25 IU/kg of body weight 3 times per week or 75 IU/kg of body weight once per week from Analysis Week 1 to Analysis Week 5, afterwards dose adjustments were possible. Patients on maintenance treatment with short-acting ESA were converted to treatment with HX575 at a weekly dose equivalent to that received before entering the treatment period. It was preferable to keep the dosing frequency unchanged, but possible due to investigator decision.

Number of subjects in period 1	HX575, safety population
Started	417
Completed	324
Not completed	93
Adverse event, serious fatal	21
Consent withdrawn by subject	24
Physician decision	2
Kidney transplantation	10
Non specified	12
Adverse event, non-fatal	10
Administration of an ESA	6
Non-compliance	1
Lost to follow-up	2
Protocol deviation	5

Baseline characteristics

Reporting groups

Reporting group title	HX575, safety population

Reporting group description:

The Study was designed as single arm study with HX575 tested as investigational medicinal product. The safety population (SAF) consisted of all patients that received at least one dose of study drug. 417 patients enrolled, 416 treated. Group includes ESA-naïve patients and patients on ESA-maintenance therapy.

Reporting group values	HX575, safety population	Total	
Number of subjects	417	417	
Age categorical Units: Subjects			
Adults (18-64 years)	317	317	
From 65-84 years	98	98	
85 years and over	2	2	
Age continuous Units: years			
arithmetic mean	52.3		
standard deviation	± 15.78	-	
Gender categorical Units: Subjects			
Female	218	218	
Male	199	199	
Height Units: cm			
arithmetic mean	166.9		
standard deviation	± 9.44	-	
Weight Units: kg			
arithmetic mean	70.6		
standard deviation	± 15.92	-	
BMI Units: kg/m2			
arithmetic mean	25.26		
standard deviation	± 5.073	-	

Subject analysis sets

Subject analysis set title	Safety Population, ESA naïve Patients
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population (SAF) consisted of all patients that received at least one dose of study drug. For ESA-naïve patients (i.e., patients that had never received ESA treatment or who had not received ESA treatment within the last 2 months before their first screening visit), the starting dose for correcting their anemia was 25 IU/kg of body weight 3 times per week or 75 IU/kg of body weight once per week from Analysis Week 1 to Analysis Week 5. From Analysis Week 5 onwards dose adjustments were possible.

Subject analysis set title	Safety Population, ESA maintenance Patients
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population (SAF) consisted of all patients that received at least one dose of study drug. Patients on maintenance treatment with short-acting ESA were converted to treatment with HX575 at a weekly dose equivalent to that received before entering the treatment period. It was preferable to keep the dosing frequency unchanged. However, the frequency could be changed at the Investigator's discretion.

Reporting group values	Safety Population, ESA naïve Patients	Safety Population, ESA maintenance Patients	
Number of subjects	250	166	
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	51.7	53.3	
standard deviation	± 15.58	± 16.08	
Gender categorical Units: Subjects			
Female	108	90	
Male	142	76	
Height Units: cm			
arithmetic mean	167.2	166.5	
standard deviation	± 9.03	± 10.02	
Weight Units: kg			
arithmetic mean	71	69.9	
standard deviation	± 15.88	± 16.01	
BMI Units: kg/m2			
arithmetic mean	25.34	25.14	
standard deviation	± 5.133	± 4.995	

End points

End points reporting groups

Reporting group title	HX575, safety population

Reporting group description:

In the single arm study, HX575 was tested as investigational medicinal product. The single arm includes ESA-naïve patients and patients on ESA-maintenance therapy. Primary endpoint was measured for the overall safety population, secondary endpoints were measured to compare per-protocol-ESA-naïve patients, per-protocol-ESA-maintenance patients, safety population-ESA-naive patients and safety population-ESA maintenance patients.

Subject analysis set title	Safety Population, ESA naïve Patients
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population (SAF) consisted of all patients that received at least one dose of study drug. For ESA-naïve patients (i.e., patients that had never received ESA treatment or who had not received ESA treatment within the last 2 months before their first screening visit), the starting dose for correcting their anemia was 25 IU/kg of body weight 3 times per week or 75 IU/kg of body weight once per week from Analysis Week 1 to Analysis Week 5. From Analysis Week 5 onwards dose adjustments were possible.

Subject analysis set title	Safety Population, ESA maintenance Patients
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population (SAF) consisted of all patients that received at least one dose of study drug. Patients on maintenance treatment with short-acting ESA were converted to treatment with HX575 at a weekly dose equivalent to that received before entering the treatment period. It was preferable to keep the dosing frequency unchanged. However, the frequency could be changed at the Investigator's discretion.

Primary: Anti-EPO antibodies

End point title	Anti-EPO antibodies[1]

End point description:

End point type	Primary

End point timeframe:

Treatment period (ADA samples used for analysis of primary endpoint collected at visit 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to single arm study design und limitation of the system, statistical analysis could not be mentioned under section "Statistical analysis", but is included in End Point Value table. Statistical analysis is as follows: Exact 2-sided 95% CI (point estimate 1.7 [0.7 to 3.4]).

End point values	HX575, safety population			
Subject group type	Reporting group			
Number of subjects analysed	416[2]			
Units: Percentage				
number (confidence interval 95%)	1.7 (0.7 to 3.4)			

Notes:

[2] - 417 patients were enrolled, 416 were treated.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Hemoglobin at Visit 16 (End of Study)

End point title	Change from Baseline in Hemoglobin at Visit 16 (End of Study)

End point description:

End point type	Secondary

End point timeframe:

Hemoglobin levels were analysed over time and the change from baseline was measured. Shown here are the results of Visit 16 (End of Study).

End point values	HX575, safety population	Safety Population, ESA naïve Patients	Safety Population, ESA maintenance Patients	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	343[3]	250	166	
Units: g/dL				
arithmetic mean (standard deviation)	1.02 (± 1.606)	1.61 (± 1.601)	0.22 (± 1.223)	

Notes:

[3] - Patient-number shows patients with a valid hemoglobin assessment at Baseline and at Visit 16.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were reported from study start to study end. Once an AE was detected it was followed up until resolution or until judged to be permanent. Shown are all AE here, including Treatment-emergent and non-treatment-emergent AEs.

Adverse event reporting additional description:

Treatment-emergent AEs started on/after IMP admin., or AEs present before IMP admin. after signing ICF that worsened after receiving the study drug. All AEs reported during the study were listed, described and the onset, duration, intensity, relation to IMP, seriousness, device reaction, action taken with IMP, intervention and outcome was listed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	HX575, safety population

Reporting group description:

Study was designed as single arm study with HX575 tested as investigational medicinal product. Safety population includes ESA therapy naïve patients and ESA maintenance patients. Shown are all AEs including non-treatment related AEs.

Serious adverse events	HX575, safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	103 / 416 (24.76%)		
number of deaths (all causes)	25		
number of deaths resulting from adverse events	21		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cerebral haemangioma			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glioma			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Vascular disorders			
Hypertension			

subjects affected / exposed	5 / 416 (1.20%)		
occurrences causally related to treatment / all	3 / 5		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	2 / 416 (0.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Femoral artery occlusion			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Extremity necrosis			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Haematoma			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive emergency			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Calcinosis			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			

subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multi-organ failure			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	2 / 416 (0.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 416 (0.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pleurisy			

subjects affected / exposed	2 / 416 (0.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemothorax				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Idiopathic pulmonary fibrosis				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Pulmonary hypertension				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				

subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Sleep apnoea syndrome				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Arteriovenous fistula thrombosis				
subjects affected / exposed	3 / 416 (0.72%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Arteriovenous fistula site complication				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fibula fracture				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Shunt occlusion				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				

subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Myocardial infarction				
subjects affected / exposed	5 / 416 (1.20%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	2 / 2			
Acute coronary syndrome				
subjects affected / exposed	3 / 416 (0.72%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	2 / 2			
Angina pectoris				
subjects affected / exposed	3 / 416 (0.72%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Angina unstable				
subjects affected / exposed	2 / 416 (0.48%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	2 / 416 (0.48%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	2 / 416 (0.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				

subjects affected / exposed	2 / 416 (0.48%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Cardiovascular insufficiency				
subjects affected / exposed	2 / 416 (0.48%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 1			
Acute left ventricular failure				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arteriosclerosis coronary artery				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial tachycardia				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Cardiac failure chronic				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiomyopathy				

subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Carditis				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Congestive cardiomyopathy				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery stenosis				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocarditis				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	3 / 416 (0.72%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	3 / 3			
Transient ischaemic attack				
subjects affected / exposed	2 / 416 (0.48%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				

subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Extrapyramidal disorder			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic cerebral infarction			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Ischaemic stroke			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uraemic encephalopathy			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastritis erosive			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer haemorrhage			

subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic erosive gastritis				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal haemorrhage				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Intestinal obstruction				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal varices haemorrhage				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Oesophagitis				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Pancreatitis				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal haemorrhage				

subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure chronic			
subjects affected / exposed	21 / 416 (5.05%)		
occurrences causally related to treatment / all	0 / 25		
deaths causally related to treatment / all	3 / 3		
Azotaemia			
subjects affected / exposed	2 / 416 (0.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	2 / 416 (0.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diabetic nephropathy			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Glomerulonephritis chronic			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive nephropathy			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Nephropathy			

subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal cyst			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	2 / 416 (0.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Adrenal mass			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperparathyroidism			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteochondrosis			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 416 (1.44%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	5 / 416 (1.20%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	2 / 416 (0.48%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 1		
Bronchopneumonia			
subjects affected / exposed	2 / 416 (0.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intervertebral discitis			
subjects affected / exposed	2 / 416 (0.48%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute hepatitis B			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carbuncle			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			

subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endocarditis				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Laryngitis				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lobar pneumonia				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Orchitis				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis chronic				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Acidosis				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fluid retention				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypocalcaemia				
subjects affected / exposed	1 / 416 (0.24%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				

subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	HX575, safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	198 / 416 (47.60%)		
Investigations			
C-reactive protein increased			
subjects affected / exposed	6 / 416 (1.44%)		
occurrences (all)	6		
Blood potassium increased			
subjects affected / exposed	5 / 416 (1.20%)		
occurrences (all)	7		
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	5 / 416 (1.20%)		
occurrences (all)	5		
Arteriovenous fistula site complication			
subjects affected / exposed	4 / 416 (0.96%)		
occurrences (all)	4		
Vascular disorders			
Hypertension			
subjects affected / exposed	42 / 416 (10.10%)		
occurrences (all)	75		
Hypotension			
subjects affected / exposed	5 / 416 (1.20%)		
occurrences (all)	8		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 416 (1.92%)		
occurrences (all)	9		
General disorders and administration site conditions			

Oedema peripheral subjects affected / exposed occurrences (all)	9 / 416 (2.16%) 13		
Pyrexia subjects affected / exposed occurrences (all)	7 / 416 (1.68%) 8		
Asthenia subjects affected / exposed occurrences (all)	4 / 416 (0.96%) 6		
Chest pain subjects affected / exposed occurrences (all)	4 / 416 (0.96%) 4		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	9 / 416 (2.16%) 11		
Nausea subjects affected / exposed occurrences (all)	4 / 416 (0.96%) 4		
Gastritis subjects affected / exposed occurrences (all)	3 / 416 (0.72%) 3		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	5 / 416 (1.20%) 5		
Renal and urinary disorders Renal failure chronic subjects affected / exposed occurrences (all)	39 / 416 (9.38%) 42		
Endocrine disorders Hyperparathyroidism secondary subjects affected / exposed occurrences (all)	5 / 416 (1.20%) 5		
Hyperparathyroidism subjects affected / exposed occurrences (all)	4 / 416 (0.96%) 4		

Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	7 / 416 (1.68%)		
occurrences (all)	11		
Arthralgia			
subjects affected / exposed	4 / 416 (0.96%)		
occurrences (all)	4		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 416 (3.13%)		
occurrences (all)	15		
Pneumonia			
subjects affected / exposed	10 / 416 (2.40%)		
occurrences (all)	13		
Urinary tract infection			
subjects affected / exposed	9 / 416 (2.16%)		
occurrences (all)	11		
Respiratory tract infection viral			
subjects affected / exposed	5 / 416 (1.20%)		
occurrences (all)	5		
Influenza			
subjects affected / exposed	4 / 416 (0.96%)		
occurrences (all)	6		
Bronchitis			
subjects affected / exposed	4 / 416 (0.96%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	4 / 416 (0.96%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	19 / 416 (4.57%)		
occurrences (all)	25		
Hypocalcaemia			
subjects affected / exposed	8 / 416 (1.92%)		
occurrences (all)	13		

Hyperphosphataemia subjects affected / exposed occurrences (all)	6 / 416 (1.44%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2012	Protocol amendment 1 was issued following the recommendation of the German Health Authority to include a more detailed risk-benefit assessment and to introduce a stopping rule related to immunogenic adverse effects of HX575. Furthermore, a minor inconsistency in the protocol was corrected and references were added, which became available after protocol finalization.
14 August 2012	Protocol amendment 3 was issued to add clarifying information on the time point of sample collection for immunogenicity testing at Visit 1, to clarify the fasting status of patients, to add upper limits for serum ferritin and transferrin saturation to the inclusion criteria, to remove the lower hemoglobin threshold for ESA-naïve patients from the inclusion criteria, to add the Cockcroft-Gault formula for the calculation of the estimated glomerular filtration rate (eGFR), to make a correction in the wording of anemia and to change the unit regarding the threshold of reticulocytes applied to the case definition of suspected or proven anti-EPO antibody induced PRCA. At this occasion one typographical error was corrected and pharmacovigilance data was updated.
23 November 2012	Protocol amendment 4 has been issued to align the eligibility criteria with the current KDIGO guidelines by changing the lower limit for serum ferritin for patients not on dialysis, to allow the inclusion of patients who are pre-treated with ESAs via the i.v. route of administration and to allow the inclusion of patients receiving long-acting ESA therapy with an application frequency of less than once weekly. Further, to introduce a clearer wording for exclusion criterion no 9, to include hemoglobin values obtained by unscheduled visits during the screening period to the calculation of the mean value, to include the prolongation of the SAE reporting period as a safety follow-up measure for prematurely withdrawn patients, to align the study protocol with the local amendment requested by the Central Ethics Committee in Bari, Italy, to update the list of literature references, and to correct a typing error.
24 June 2014	Amendment 5 was issued by the sponsor on 24-June-2014, but was not submitted to any regulatory authorities. Therefore, changes to specific sections of the protocol implemented by amendment 5 are shown in the track changes version together with changes implemented by amendment 6. With the submission of amendment 6, amendment 5 gets formally incorporated, with the following rationale and changes: The purpose of this amendment is to implement safety follow-up measures after study completion or termination in patients who show confirmed positive results for binding anti-EPO antibodies in the RIP assay in order to monitor the evolution of such antibodies and ensure any potential case of a clinically relevant immunogenic reaction is detected. The duration of the follow-up will comprise between 6 and 12 months depending on the patient’s post-study ESA treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported