



## 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:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| 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.  $\leq$  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-naïve 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.

| <b>Number of subjects in period 1</b> | <b>HX575, safety population</b> |
|---------------------------------------|---------------------------------|
| 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<br>Units: Subjects    |                          |       |  |
| Adults (18-64 years)                  | 317                      | 317   |  |
| From 65-84 years                      | 98                       | 98    |  |
| 85 years and over                     | 2                        | 2     |  |
| Age continuous<br>Units: years        |                          |       |  |
| arithmetic mean                       | 52.3                     |       |  |
| standard deviation                    | ± 15.78                  | -     |  |
| Gender categorical<br>Units: Subjects |                          |       |  |
| Female                                | 218                      | 218   |  |
| Male                                  | 199                      | 199   |  |
| Height<br>Units: cm                   |                          |       |  |
| arithmetic mean                       | 166.9                    |       |  |
| standard deviation                    | ± 9.44                   | -     |  |
| Weight<br>Units: kg                   |                          |       |  |
| arithmetic mean                       | 70.6                     |       |  |
| standard deviation                    | ± 15.92                  | -     |  |
| BMI<br>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,<br>ESA naïve Patients | Safety Population,<br>ESA maintenance<br>Patients |  |
|-------------------------------------------------------------------------|------------------------------------------|---------------------------------------------------|--|
| Number of subjects                                                      | 250                                      | 166                                               |  |
| Age categorical<br>Units: Subjects                                      |                                          |                                                   |  |
| Adults (18-64 years)<br>From 65-84 years<br>85 years and over           |                                          |                                                   |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 51.7<br>± 15.58                          | 53.3<br>± 16.08                                   |  |
| Gender categorical<br>Units: Subjects                                   |                                          |                                                   |  |
| Female<br>Male                                                          | 108<br>142                               | 90<br>76                                          |  |
| Height<br>Units: cm<br>arithmetic mean<br>standard deviation            | 167.2<br>± 9.03                          | 166.5<br>± 10.02                                  |  |
| Weight<br>Units: kg<br>arithmetic mean<br>standard deviation            | 71<br>± 15.88                            | 69.9<br>± 16.01                                   |  |
| BMI<br>Units: kg/m2<br>arithmetic mean<br>standard deviation            | 25.34<br>± 5.133                         | 25.14<br>± 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-naïve 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 <sup>[1]</sup> |
|-----------------|------------------------------------|

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 and 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]).

|                                  |                          |  |  |  |
|----------------------------------|--------------------------|--|--|--|
| <b>End point values</b>          | HX575, safety population |  |  |  |
| Subject group type               | Reporting group          |  |  |  |
| Number of subjects analysed      | 416 <sup>[2]</sup>       |  |  |  |
| 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

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

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|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| 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).

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| 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 <sup>[3]</sup>       | 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.

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**Statistical analyses**

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

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

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

|                                                                        |                      |  |  |
|------------------------------------------------------------------------|----------------------|--|--|
| Hyperphosphataemia<br>subjects affected / exposed<br>occurrences (all) | 6 / 416 (1.44%)<br>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