



## Clinical trial results:

### An Open-Label Study to Investigate the Efficacy and Safety of Peginesatide in the Treatment of Anemia Caused by Antibody-Mediated Pure Red Cell Aplasia in Patients With Chronic Kidney Disease.

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2005-004944-30  |
| Trial protocol           | GB DE           |
| Global end of trial date | 31 October 2016 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1               |
| This version publication date  | 20 November 2018 |
| First version publication date | 08 November 2017 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | AFX01-06 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00314795 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Takeda Development Centre Europe Ltd  |
| Sponsor organisation address | 61 Aldwych, London, United Kingdom, WC2B 4AE  |
| Public contact               | Medical Director, Clinical Science, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.com |
| Scientific contact           | Medical Director, Clinical Science, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.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                       | 31 October 2016 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 31 October 2016 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the ability of peginesatide (AF37702) to increase and maintain increased hemoglobin levels in participants with chronic kidney disease (CKD) (either not on dialysis, receiving regular hemodialysis or peritoneal dialysis, or following renal transplant) with confirmed antibody-mediated pure red cell aplasia (PRCA).

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 06 April 2006    |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Efficacy, Safety |
| Long term follow-up duration                              | 6 Years          |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | France: 6         |
| Country: Number of subjects enrolled | Germany: 8        |
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Worldwide total number of subjects   | 22                |
| EEA total number of subjects         | 22                |

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)                      | 6 |

|                     |    |
|---------------------|----|
| From 65 to 84 years | 12 |
| 85 years and over   | 4  |

## Subject disposition

### Recruitment

Recruitment details:

Participants took part in the study at 5 investigative sites in Europe from 06-Apr-2006 to 31-Oct-2016.

### Pre-assignment

Screening details:

Participants with a diagnosis of chronic renal failure (CRF) with confirmed antibody-mediated pure red cell aplasia (PRCA) were enrolled to receive peginesatide subcutaneous injection up to 0.3 mg/kg, once every 4 weeks for up to 60 months.

### Period 1

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

### Arms

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | Peginesatide |
|------------------|--------------|

Arm description:

Peginesatide 0.05 mg/kg injection, subcutaneously followed by peginesatide 0.1 mg/kg injection, subcutaneously once every 4 weeks for up to 60 months. Individual dose of peginesatide injection was modified based on hemoglobin levels. Dose adjustments were made in order to achieve and maintain hemoglobin in the target range of 10.0–12.0 g/dL.

|  |                                   |
|--|-----------------------------------|
| Arm type                               | Experimental                      |
| Investigational medicinal product name | Peginesatide                      |
| Investigational medicinal product code |                                   |
| Other name                             | AF37702                           |
| Pharmaceutical forms                   | Solution for injection            |
| Routes of administration               | Intramuscular and intravenous use |

Dosage and administration details:

Peginesatide injection

| Number of subjects in period 1 | Peginesatide |
|--------------------------------|--------------|
| Started                        | 22           |
| Completed                      | 2            |
| Not completed                  | 20           |
| Adverse event, serious fatal   | 4            |
| Renal Transplant               | 3            |
| Adverse event, non-fatal       | 8            |
| Participants Withdrew Consent  | 2            |
| Reason not Specified           | 3            |

## Baseline characteristics

### Reporting groups

|   |              |
|---|--------------|
| Reporting group title   | Peginesatide |
| Reporting group description:  |              |
| Peginesatide 0.05 mg/kg injection, subcutaneously followed by peginesatide 0.1 mg/kg injection, subcutaneously once every 4 weeks for up to 60 months. Individual dose of peginesatide injection was modified based on hemoglobin levels. Dose adjustments were made in order to achieve and maintain hemoglobin in the target range of 10.0–12.0 g/dL. |              |

| Reporting group values | Peginesatide | Total |  |
|------------------------|--------------|-------|--|
| Number of subjects     | 22           | 22    |  |
| Age categorical        |              |       |  |
| Units: Subjects        |              |       |  |

|  |         |    |  |
|--|---------|----|--|
| Age Continuous   |         |    |  |
| Units: years   |         |    |  |
| arithmetic mean  | 73.3    |    |  |
| standard deviation   | ± 13.65 | -  |  |
| Gender, Male/Female  |         |    |  |
| Units: Subjects  |         |    |  |
| Female   | 5       | 5  |  |
| Male   | 17      | 17 |  |
| Race/Ethnicity, Customized   |         |    |  |
| Units: Subjects  |         |    |  |
| Asian  | 4       | 4  |  |
| Caucasian  | 17      | 17 |  |
| Other  | 1       | 1  |  |
| Bone Marrow Evaluation   |         |    |  |
| Here Erythroblastopenia=EBP; Hypoplasia= HYP; Hypocellular=hpc; bone marrow=BM; Erythroid lineage=EL; diagnosis=dgn; reticulocyte=retic. |         |    |  |
| Units: Subjects  |         |    |  |
| Aplasia of Erythropoese  | 1       | 1  |  |
| Erythroblastopenia (EBP)   | 1       | 1  |  |
| EBP 0% normal values for other cell lineages   | 1       | 1  |  |
| Erythroid series absent  | 1       | 1  |  |
| Erythroid severe HYP no decrease in other lineages   | 1       | 1  |  |
| Erythropoietic hypoplasia  | 1       | 1  |  |
| Hpc BM with reduced EL consistent with dgn of pure   | 1       | 1  |  |
| HYP of erythropoiesis staining of iron in BM retic   | 1       | 1  |  |
| Normal   | 1       | 1  |  |
| PRCA   | 8       | 8  |  |
| PRCA / Bone Marrow Trephine  | 1       | 1  |  |
| Pure Red Cell Aplasia  | 2       | 2  |  |
| Red cell aplasia   | 1       | 1  |  |
| Red cell hypoplasia  | 1       | 1  |  |
| Region of Enrollment   |         |    |  |

|  |           |   |  |
|--|-----------|---|--|
| Units: Subjects  |           |   |  |
| France   | 6         | 6 |  |
| Germany  | 8         | 8 |  |
| United Kingdom   | 8         | 8 |  |
| Study Specific Characteristic   Height   |           |   |  |
| Data was available for 21 participants.  |           |   |  |
| Units: cm  |           |   |  |
| arithmetic mean  | 168.1     |   |  |
| standard deviation   | ± 9.66    | - |  |
| Study Specific Characteristic   Weight   |           |   |  |
| Units: kg  |           |   |  |
| arithmetic mean  | 67.6      |   |  |
| standard deviation   | ± 12.31   | - |  |
| Study Specific Characteristic   Body Mass Index (BMI)                              |           |   |  |
| Data was available for 21 participants.  |           |   |  |
| Units: kg/m <sup>2</sup>   |           |   |  |
| arithmetic mean  | 23.8      |   |  |
| standard deviation   | ± 2.41    | - |  |
| Study Specific Characteristic   Baseline Hemoglobin (Hgb)                          |           |   |  |
| Units: g/L   |           |   |  |
| arithmetic mean  | 96.5      |   |  |
| standard deviation   | ± 16.11   | - |  |
| Study Specific Characteristic   Baseline Ferritin                                  |           |   |  |
| Data was available for 21 participants.  |           |   |  |
| Units: ug/L  |           |   |  |
| arithmetic mean  | 2332.0    |   |  |
| standard deviation   | ± 1695.02 | - |  |
| Study Specific Characteristic   Baseline Transferrin Saturation                    |           |   |  |
| Data was available for 19 participants.  |           |   |  |
| Units: % transferrin   |           |   |  |
| arithmetic mean  | 79.2      |   |  |
| standard deviation   | ± 21.87   | - |  |
| Study Specific Characteristic   Baseline Anti-erythropoietin (EPO) Antibody Titers |           |   |  |
| Units: U/mL  |           |   |  |
| arithmetic mean  | 94.1      |   |  |
| standard deviation   | ± 217.08  | - |  |

## End points

### End points reporting groups

|   |              |
|---|--------------|
| Reporting group title   | Peginesatide |
| Reporting group description:<br>Peginesatide 0.05 mg/kg injection, subcutaneously followed by peginesatide 0.1 mg/kg injection, subcutaneously once every 4 weeks for up to 60 months. Individual dose of peginesatide injection was modified based on hemoglobin levels. Dose adjustments were made in order to achieve and maintain hemoglobin in the target range of 10.0–12.0 g/dL. |              |

### **Primary: Percentage of Participants who Experienced Increase and Maintain Hemoglobin Levels (two consecutive values) Greater Than or Equal to the Lower Limit of the Target Range in the Absence of Red Blood Cell Transfusion in the Previous 28 days by Week 24**

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants who Experienced Increase and Maintain Hemoglobin Levels (two consecutive values) Greater Than or Equal to the Lower Limit of the Target Range in the Absence of Red Blood Cell Transfusion in the Previous 28 days by Week 24 <sup>[1]</sup> |
|-----------------|---|

End point description:

Percentage of participants who experienced increase and maintain hemoglobin levels (two consecutive values) greater than or equal to the lower limit (11 g/dL) in the absence of red blood cell transfusion in the previous 28 days by week 24 were reported.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to Week 24

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: Only descriptive statistics were planned for this endpoint.

|                                   |                  |  |  |  |
|-----------------------------------|------------------|--|--|--|
| <b>End point values</b>           | Peginesatide     |  |  |  |
| Subject group type                | Reporting group  |  |  |  |
| Number of subjects analysed       | 0 <sup>[2]</sup> |  |  |  |
| Units: percentage of participants |                  |  |  |  |
| number (confidence interval 95%)  | ( to )           |  |  |  |

Notes:

[2] - This endpoint was not assessed at end of the study as the development of drug has been discontinued.

### Statistical analyses

No statistical analyses for this end point

### **Secondary: Number of Red Blood Cells (RBCs) Transfusions During the 26 Weeks Pre-treatment Period (prior to enrollment) and During 13- and 26 Weeks Intervals During the Study**

|                 |   |
|-----------------|---|
| End point title | Number of Red Blood Cells (RBCs) Transfusions During the 26 Weeks Pre-treatment Period (prior to enrollment) and During 13- and 26 Weeks Intervals During the Study |
|-----------------|---|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

26 weeks prior to enrollment up to end of study (up to 60 months)

|                             |                  |  |  |  |
|-----------------------------|------------------|--|--|--|
| <b>End point values</b>     | Peginesatide     |  |  |  |
| Subject group type          | Reporting group  |  |  |  |
| Number of subjects analysed | 0 <sup>[3]</sup> |  |  |  |
| Units: RBCs transfusion     |                  |  |  |  |

Notes:

[3] - This endpoint was not assessed at end of the study as the development of drug has been discontinued.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with RBC Transfusions During the 26-week Pre-treatment Period and During 13- and 26-week Intervals During the Study

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants with RBC Transfusions During the 26-week Pre-treatment Period and During 13- and 26-week Intervals During the Study |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

26 weeks prior to enrollment up to end of study (up to 60 months)

|                                   |                  |  |  |  |
|-----------------------------------|------------------|--|--|--|
| <b>End point values</b>           | Peginesatide     |  |  |  |
| Subject group type                | Reporting group  |  |  |  |
| Number of subjects analysed       | 0 <sup>[4]</sup> |  |  |  |
| Units: percentage of participants |                  |  |  |  |
| number (confidence interval 95%)  | ( to )           |  |  |  |

Notes:

[4] - This endpoint was not assessed at end of the study as the development of drug has been discontinued.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Initial Achievement of Hemoglobin (Hgb) Greater Than or Equal to the Lower Limit of the Target Range in the Absence of Red Blood Cell Transfusions in the Previous 28 Days

|                 |  |
|-----------------|--|
| End point title | Time to Initial Achievement of Hemoglobin (Hgb) Greater Than or Equal to the Lower Limit of the Target Range in the Absence of Red Blood Cell Transfusions in the Previous 28 Days |
|-----------------|--|

End point description:

The time between first dose administered and the initial achievement of a Hgb increase  $\geq 11$  g/dL for two consecutive visits was calculated for each participant as the number of days between the first dose administration date and the earlier of (1) the study termination date [i.e. censor date] and (2) the first



date of an Hgb increase  $\geq 11$  g/dL for two consecutive visits without whole blood or RBC transfusion during the previous 28 days. Time to initial Hgb increase  $\geq 11$  g/dL will be calculated for each participant as the minimum of censor date and increase date minus the first dose date plus 1.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to 60 months      |           |

|                               |                  |  |  |  |
|-------------------------------|------------------|--|--|--|
| <b>End point values</b>       | Peginesatide     |  |  |  |
| Subject group type            | Reporting group  |  |  |  |
| Number of subjects analysed   | 0 <sup>[5]</sup> |  |  |  |
| Units: days                   |                  |  |  |  |
| median (full range (min-max)) | ( to )           |  |  |  |

Notes:

[5] - This endpoint was not assessed at end of the study as the development of drug has been discontinued.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Adverse Events (AEs), Serious Adverse Events (SAEs), and AEs Leading to Treatment Discontinuation

|                 |   |
|-----------------|---|
| End point title | Number of Participants with Adverse Events (AEs), Serious Adverse Events (SAEs), and AEs Leading to Treatment Discontinuation |
|-----------------|---|

End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A Serious Adverse Event (SAE) is any experience that suggests a significant hazard, contraindication, side effect or precaution that: results in death, is life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant. A treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset that occurs after receiving study drug.

|  |           |
|--|-----------|
| End point type                                       | Secondary |
| End point timeframe:                                 |           |
| From signing of informed consent form up to Month 60 |           |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| <b>End point values</b>                   | Peginesatide    |  |  |  |
| Subject group type                        | Reporting group |  |  |  |
| Number of subjects analysed               | 22              |  |  |  |
| Units: participants                       |                 |  |  |  |
| AEs                                       | 22              |  |  |  |
| SAEs                                      | 17              |  |  |  |
| AEs Leading to Study Drug Discontinuation | 3               |  |  |  |

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From signing of informed consent form up to Month 60

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | Peginesatide |
|-----------------------|--------------|

Reporting group description:

Peginesatide 0.05 mg/kg injection, subcutaneously followed by peginesatide 0.1 mg/kg injection, subcutaneously once every 4 weeks for up to 60 months. Individual dose of peginesatide injection was modified based on hemoglobin levels. Dose adjustments were made in order to achieve and maintain hemoglobin in the target range of 10.0–12.0 g/dL.

| Serious adverse events  | Peginesatide  |  |  |
|---|---|--|--|
| Total subjects affected by serious adverse events                   |   |  |  |
| subjects affected / exposed   | 17 / 22 (77.27%)  |  |  |
| number of deaths (all causes)                                       | 9   |  |  |
| number of deaths resulting from adverse events                      |   |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |  |  |
| Gastrointestinal cancer metastatic                                  | Additional description: One treatment emergent death occurred and is related to the study drug. |  |  |
| subjects affected / exposed   | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all                     | 1 / 1   |  |  |
| deaths causally related to treatment / all                          | 1 / 1   |  |  |
| Metastases to bone  |   |  |  |
| subjects affected / exposed   | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 1   |  |  |
| deaths causally related to treatment / all                          | 0 / 0   |  |  |
| Prostate cancer recurrent   |   |  |  |
| subjects affected / exposed   | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 1   |  |  |
| deaths causally related to treatment / all                          | 0 / 0   |  |  |
| Vascular disorders  |   |  |  |

|  |  |  |  |
|--|--|--|--|
| Aortic stenosis                                      |  |  |  |
| subjects affected / exposed                          | 1 / 22 (4.55%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 1  |  |  |
| deaths causally related to treatment / all           | 0 / 0  |  |  |
| Blood pressure inadequately controlled               |  |  |  |
| subjects affected / exposed                          | 1 / 22 (4.55%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 1  |  |  |
| deaths causally related to treatment / all           | 0 / 0  |  |  |
| Femoral artery aneurysm                              |  |  |  |
| subjects affected / exposed                          | 1 / 22 (4.55%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 1  |  |  |
| deaths causally related to treatment / all           | 0 / 0  |  |  |
| General disorders and administration site conditions |  |  |  |
| Chest Pain   |  |  |  |
| subjects affected / exposed                          | 1 / 22 (4.55%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 1  |  |  |
| deaths causally related to treatment / all           | 0 / 0  |  |  |
| Death  | Additional description: Treatment-emergent death is not related to the study drug. |  |  |
| subjects affected / exposed                          | 1 / 22 (4.55%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 1  |  |  |
| deaths causally related to treatment / all           | 0 / 1  |  |  |
| Sudden death   | Additional description: Treatment-emergent death is not related to the study drug. |  |  |
| subjects affected / exposed                          | 1 / 22 (4.55%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 1  |  |  |
| deaths causally related to treatment / all           | 0 / 1  |  |  |
| Vascular stent restenosis                            |  |  |  |
| subjects affected / exposed                          | 1 / 22 (4.55%)   |  |  |
| occurrences causally related to treatment / all      | 0 / 1  |  |  |
| deaths causally related to treatment / all           | 0 / 0  |  |  |
| Respiratory, thoracic and mediastinal disorders      |  |  |  |
| Pleural effusion                                     |  |  |  |

|   |   |  |  |
|---|---|--|--|
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Pulmonary oedema                                |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Respiratory failure                             | Additional description: One treatment-emergent death occurred and is not related to the study drug. |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 1   |  |  |
| Investigations                                  |   |  |  |
| C-reactive protein increased                    |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 1   |  |  |
| Drug specific antibody present                  |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Haematocrit decreased                           | Additional description: One treatment-emergent death occurred and is not related to the study drug. |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 1   |  |  |
| Injury, poisoning and procedural complications  |   |  |  |
| Femur fracture                                  |   |  |  |
| subjects affected / exposed                     | 2 / 22 (9.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Coronary artery restenosis                      |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Peritoneal dialysis complication                |                 |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Shunt occlusion                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular pseudoaneurysm                         |                 |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Acute myocardial infarction                     |                 |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Angina pectoris                                 |                 |  |  |
| subjects affected / exposed                     | 2 / 22 (9.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrial fibrillation                             |                 |  |  |
| subjects affected / exposed                     | 3 / 22 (13.64%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrial flutter                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrioventricular block                          |                 |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrioventricular block complete                 |                 |  |  |

|   |   |  |  |
|---|---|--|--|
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Cardiac arrest                                  | Additional description: One treatment-emergent death occurred and is not related to the study drug. |  |  |
| subjects affected / exposed                     | 2 / 22 (9.09%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2   |  |  |
| deaths causally related to treatment / all      | 0 / 1   |  |  |
| Cardiac failure                                 | Additional description: One treatment-emergent death occurred and is not related to the study drug. |  |  |
| subjects affected / exposed                     | 3 / 22 (13.64%)   |  |  |
| occurrences causally related to treatment / all | 0 / 3   |  |  |
| deaths causally related to treatment / all      | 0 / 1   |  |  |
| Cardiac failure acute                           |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Myocardial infarction                           |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Nervous system disorders                        |   |  |  |
| Vascular dementia                               |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| 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 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 1 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Neutropenia                                     |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |

|   |   |  |  |
|---|---|--|--|
| Eye disorders                                   |   |  |  |
| Optic ischaemic neuropathy                      |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Gastrointestinal disorders                      |   |  |  |
| Anal prolapse                                   |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Gastrointestinal haemorrhage                    | Additional description: One treatment-emergent death occurred and is not related to the study drug. |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 1   |  |  |
| Renal and urinary disorders                     |   |  |  |
| Renal salt-wasting syndrome                     |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Infections and infestations                     |   |  |  |
| Cytomegalovirus infection                       |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Disseminated tuberculosis                       |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Endocarditis                                    |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Escherichia bacteraemia                         |   |  |  |



|   |   |  |  |
|---|---|--|--|
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Gangrene  |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 1 / 2   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Lower respiratory tract infection               |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Pneumocystis jirovecii pneumonia                |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Pneumonia                                       |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Urinary tract infection                         | Additional description: One treatment-emergent death occurred and is not related to the study drug. |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 3   |  |  |
| deaths causally related to treatment / all      | 0 / 1   |  |  |
| Urosepsis                                       |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Metabolism and nutrition disorders              |   |  |  |
| Fluid overload                                  |   |  |  |
| subjects affected / exposed                     | 1 / 22 (4.55%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1   |  |  |
| deaths causally related to treatment / all      | 0 / 0   |  |  |
| Hyperkalaemia                                   |   |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 22 (4.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| <b>Non-serious adverse events</b>                     | Peginesatide      |  |  |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 22 / 22 (100.00%) |  |  |
| Vascular disorders                                    |                   |  |  |
| Hypertension  |                   |  |  |
| subjects affected / exposed                           | 6 / 22 (27.27%)   |  |  |
| occurrences (all)                                     | 14                |  |  |
| Haematoma   |                   |  |  |
| subjects affected / exposed                           | 3 / 22 (13.64%)   |  |  |
| occurrences (all)                                     | 3                 |  |  |
| Hypotension   |                   |  |  |
| subjects affected / exposed                           | 3 / 22 (13.64%)   |  |  |
| occurrences (all)                                     | 3                 |  |  |
| General disorders and administration site conditions  |                   |  |  |
| Oedema peripheral                                     |                   |  |  |
| subjects affected / exposed                           | 7 / 22 (31.82%)   |  |  |
| occurrences (all)                                     | 10                |  |  |
| Asthenia  |                   |  |  |
| subjects affected / exposed                           | 6 / 22 (27.27%)   |  |  |
| occurrences (all)                                     | 7                 |  |  |
| Fatigue   |                   |  |  |
| subjects affected / exposed                           | 5 / 22 (22.73%)   |  |  |
| occurrences (all)                                     | 9                 |  |  |
| Non-cardiac chest pain                                |                   |  |  |
| subjects affected / exposed                           | 2 / 22 (9.09%)    |  |  |
| occurrences (all)                                     | 2                 |  |  |
| Pyrexia   |                   |  |  |
| subjects affected / exposed                           | 2 / 22 (9.09%)    |  |  |
| occurrences (all)                                     | 3                 |  |  |
| Immune system disorders                               |                   |  |  |

|  |                       |  |  |
|--|-----------------------|--|--|
| Drug hypersensitivity<br>subjects affected / exposed<br>occurrences (all)      | 3 / 22 (13.64%)<br>5  |  |  |
| Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)           | 2 / 22 (9.09%)<br>3   |  |  |
| Respiratory, thoracic and mediastinal disorders                                |                       |  |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                      | 5 / 22 (22.73%)<br>7  |  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 22 (13.64%)<br>5  |  |  |
| Rales<br>subjects affected / exposed<br>occurrences (all)                      | 3 / 22 (13.64%)<br>5  |  |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)         | 2 / 22 (9.09%)<br>2   |  |  |
| Pleural effusion<br>subjects affected / exposed<br>occurrences (all)           | 2 / 22 (9.09%)<br>2   |  |  |
| Investigations   |                       |  |  |
| Haemoglobin decreased<br>subjects affected / exposed<br>occurrences (all)      | 6 / 22 (27.27%)<br>11 |  |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)           | 4 / 22 (18.18%)<br>4  |  |  |
| Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)   | 3 / 22 (13.64%)<br>5  |  |  |
| Blood phosphorus increased<br>subjects affected / exposed<br>occurrences (all) | 2 / 22 (9.09%)<br>2   |  |  |
| Blood potassium increased  |                       |  |  |

|  |  |  |  |
|--|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Liver function test increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Platelet count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Reticulocyte count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>2 / 22 (9.09%)</p> <p>2</p> <p>2 / 22 (9.09%)</p> <p>2</p> <p>2 / 22 (9.09%)</p> <p>3</p> <p>2 / 22 (9.09%)</p> <p>4</p>                                  |  |  |
| <p>Injury, poisoning and procedural complications</p> <p>Fall</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Skin abrasion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Contusion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Heat exhaustion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Procedural hypotension</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>8 / 22 (36.36%)</p> <p>9</p> <p>5 / 22 (22.73%)</p> <p>8</p> <p>2 / 22 (9.09%)</p> <p>9</p> <p>2 / 22 (9.09%)</p> <p>2</p> <p>2 / 22 (9.09%)</p> <p>3</p> |  |  |
| <p>Cardiac disorders</p> <p>Palpitations</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>2 / 22 (9.09%)</p> <p>4</p>   |  |  |
| <p>Nervous system disorders</p> <p>Dizziness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Headache</p>   | <p>3 / 22 (13.64%)</p> <p>3</p>  |  |  |

|   |  |  |  |
|---|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Restless legs syndrome</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sciatica</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>2 / 22 (9.09%)</p> <p>5</p> <p>2 / 22 (9.09%)</p> <p>3</p> <p>2 / 22 (9.09%)</p> <p>2</p>   |  |  |
| <p>Ear and labyrinth disorders</p> <p>Tinnitus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>2 / 22 (9.09%)</p> <p>2</p>   |  |  |
| <p>Eye disorders</p> <p>Cataract</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>4 / 22 (18.18%)</p> <p>4</p>  |  |  |
| <p>Gastrointestinal disorders</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Toothache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>10 / 22 (45.45%)</p> <p>11</p> <p>3 / 22 (13.64%)</p> <p>5</p> <p>3 / 22 (13.64%)</p> <p>4</p> <p>3 / 22 (13.64%)</p> <p>4</p> <p>2 / 22 (9.09%)</p> <p>3</p> |  |  |
| <p>Hepatobiliary disorders</p> <p>Hepatomegaly</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>2 / 22 (9.09%)</p> <p>2</p>   |  |  |
| <p>Skin and subcutaneous tissue disorders</p>   |  |  |  |

|   |                        |  |  |
|---|------------------------|--|--|
| Eczema<br>subjects affected / exposed<br>occurrences (all)  | 4 / 22 (18.18%)<br>4   |  |  |
| Pruritus Generalised<br>subjects affected / exposed<br>occurrences (all)  | 2 / 22 (9.09%)<br>3    |  |  |
| Renal and urinary disorders<br>Haematuria<br>subjects affected / exposed<br>occurrences (all)                     | 4 / 22 (18.18%)<br>4   |  |  |
| Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all)  | 2 / 22 (9.09%)<br>2    |  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 5 / 22 (22.73%)<br>6   |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 5 / 22 (22.73%)<br>6   |  |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)   | 5 / 22 (22.73%)<br>5   |  |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)  | 2 / 22 (9.09%)<br>2    |  |  |
| Osteoarthritis<br>subjects affected / exposed<br>occurrences (all)  | 2 / 22 (9.09%)<br>2    |  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)   | 2 / 22 (9.09%)<br>2    |  |  |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                | 10 / 22 (45.45%)<br>20 |  |  |

|                                    |                 |  |  |
|------------------------------------|-----------------|--|--|
| Bronchitis                         |                 |  |  |
| subjects affected / exposed        | 6 / 22 (27.27%) |  |  |
| occurrences (all)                  | 9               |  |  |
| Urinary tract infection            |                 |  |  |
| subjects affected / exposed        | 6 / 22 (27.27%) |  |  |
| occurrences (all)                  | 14              |  |  |
| Upper respiratory tract infection  |                 |  |  |
| subjects affected / exposed        | 3 / 22 (13.64%) |  |  |
| occurrences (all)                  | 4               |  |  |
| Cystitis                           |                 |  |  |
| subjects affected / exposed        | 2 / 22 (9.09%)  |  |  |
| occurrences (all)                  | 2               |  |  |
| Cytomegalovirus infection          |                 |  |  |
| subjects affected / exposed        | 2 / 22 (9.09%)  |  |  |
| occurrences (all)                  | 3               |  |  |
| Lower respiratory tract infection  |                 |  |  |
| subjects affected / exposed        | 2 / 22 (9.09%)  |  |  |
| occurrences (all)                  | 2               |  |  |
| Respiratory tract infection        |                 |  |  |
| subjects affected / exposed        | 2 / 22 (9.09%)  |  |  |
| occurrences (all)                  | 2               |  |  |
| Metabolism and nutrition disorders |                 |  |  |
| Decreased appetite                 |                 |  |  |
| subjects affected / exposed        | 4 / 22 (18.18%) |  |  |
| occurrences (all)                  | 4               |  |  |
| Fluid overload                     |                 |  |  |
| subjects affected / exposed        | 2 / 22 (9.09%)  |  |  |
| occurrences (all)                  | 2               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 07 July 2006     | Changed the study design for starting dose, dose escalation, maximum dose, and dose reduction criteria, extended dosing from 6 months to 24 months and updated inclusion criteria.   |
| 15 November 2007 | Increased continuation of treatment duration to up to 60 months and revised individual patient peginesatide dose adjustment guidelines due to safety concerns associated with elevated haemoglobin (Hgb) values on erythropoiesis-stimulating agent use. |
| 07 June 2010     | Increased continuation of treatment duration to up to 70 months.   |
| 15 April 2011    | Changed study design for starting dose, maximum dose, and Hgb target range, provided details for study endpoints and increased continuation of treatment duration to up to 108 months.   |
| 23 April 2013    | Sponsor changed from Affymax to Takeda   |
| 04 April 2014    | Extended continuation of treatment duration to 30 September 2015 and added vials with concentration of 6 mg/0.5 ml.  |
| 09 July 2014     | Changed frequency of sample collection for peginesatide-specific and anti-erythropoietin antibodies.   |
| 16 June 2015     | Extended continuation of treatment duration to approximately 30 September 2016.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date             | Interruption   | Restart date |
|------------------|--|--------------|
| 23 February 2013 | Following post-marketing reports of serious hypersensitivity reactions, enrolment of new subjects into the study was halted (due to risk of hypersensitivity after first injection) and subjects already in the study were informed and reconsented, (ie, were given the option to stop or continue treatment), so study treatment was not halted (subjects with PRCA in the study had been receiving treatment for between approximately 1 and up to 7 years and their benefit:risk remained positive). | -            |

Notes:

### Limitations and caveats

None reported