



## Clinical trial results:

### A PHASE II, OPEN LABEL, PARALLEL GROUP, MULTI-CENTER STUDY TO COMPARE THE PHARMACOKINETICS OF TACROLIMUS IN ADULT SUBJECTS UNDERGOING PRIMARY ALLOGRAFT TRANSPLANTATION RECEIVING AN ADVAGRAF OR PROGRAF BASED IMMUNOSUPPRESSIVE REGIMEN, INCLUDING A LONG-TERM FOLLOW-UP

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2010-019859-21   |
| Trial protocol           | AT GB IT BE      |
| Global end of trial date | 15 November 2013 |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 23 March 2016 |
| First version publication date | 28 May 2015   |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | PMR-EC-1501 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01332201 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Astellas Pharma Europe Ltd.  |
| Sponsor organisation address | 2000 Hillswood Drive, Chertsey, Surrey, United Kingdom, KT16 0RS                                   |
| Public contact               | Clinical Trial Disclosure, Astellas Pharma Europe Ltd.,<br>Astellas.resultsdisclosure@astellas.com |
| Scientific contact           | Clinical Trial Disclosure, Astellas Pharma Europe Ltd.,<br>Astellas.resultsdisclosure@astellas.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                       | 15 November 2013 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 15 November 2013 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 15 November 2013 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to compare the systemic exposure (AUC<sub>0-24h</sub>) of tacrolimus for Advagraf versus Prograf after the first dose and following repeated administration in patients undergoing primary heart, lung, pancreas (including simultaneous pancreas kidney (SPK)) transplantation.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH GCP Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy:

The Investigational Medicinal Products (IMP) Advagraf and Prograf were provided by the Sponsor. Antibodies (Anti-thymocyte globulin (ATG) was recommended), Mycophenolate Mofetil (MMF) and corticosteroids were not considered IMP in this study and were not provided by the Sponsor, but were provided by the local hospital pharmacy. Antibody Induction: the first dose of antibody induction therapy was to be given intravenously (IV) within 24 hours after skin closure. The initial dose and any later dose adjustments followed the routine practice of the center. The recommended dosing regimen for MMF was as follows: a loading dose of 1g of MMF given pre-operatively. The first post-operative dose of MMF administered within 72 hours following reperfusion. The daily dose of 2g given orally and split into two doses (equals 1g twice daily) for the first 14 days. Thereafter the daily dose was reduced to 1g given in two doses (equals 0.5g twice daily). From day 42 the dose of MMF was in accordance with the routine practice of the center. Corticosteroids: day -3 (500mg or less i.v. bolus pre, intra or post-operatively), day -2 (125mg i.v. bolus) for heart transplantation recipients. Day -1 (500mg or less i.v. bolus pre, intra or post-operatively), day 1 (125mg i.v. bolus) for lung/pancreas/SPK recipients. Prednisolone or equivalent: day -1 to 14 (20mg/day), day 15 to 28 (15mg/day), day 29 to 42 (10mg/day), Day 43 to 407 ( $\geq$  5mg/day) for heart transplantation recipients. Day 2 to 14 (20mg/day), day 15 to 28 (15mg/day), day 29 to 42 (10mg/day), Day 43 to 407 ( $\geq$  5mg/day) for lung/pancreas/SPK recipients.

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 23 July 2011 |
| Long term follow-up planned                               | Yes          |
| Long term follow-up rationale                             | Safety       |
| Long term follow-up duration                              | 1 Years      |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | Austria: 1        |
| Country: Number of subjects enrolled | France: 1         |

|                                      |           |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Italy: 9  |
| Country: Number of subjects enrolled | Taiwan: 5 |
| Worldwide total number of subjects   | 17        |
| EEA total number of subjects         | 12        |

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)                      | 17 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

This multinational, multicenter study was conducted at 6 contracted sites in a total of 5 countries: Austria, France Italy (2 sites), Taiwan and United Kingdom. Due to poor recruitment the study was terminated early.

### Pre-assignment

Screening details:

Eligibility took place baseline day -3 and day -2 prior to day 1/Visit 1 for heart transplant recipients and on day -1 for lung/pancreas/SPK recipients. Screening assessments: patient data, pregnancy test, donor/organ data, surgical details, physical examination (including body weight), vital signs and routine laboratory evaluations were performed.

### Period 1

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

Blinding implementation details:

Not applicable as this is an open label study.

### Arms

|                              |          |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes      |
| <b>Arm title</b>             | Advagraf |

Arm description:

Advagraf in strengths of 0.5mg, 1mg, 3mg and 5mg capsules for once daily oral administration.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | Advagraf   |
| Investigational medicinal product code | FK506E (MR4)   |
| Other name                             | MR4, Tacrolimus, Tacrolimus modified release, Tacrolimus prolonged release formulation |
| Pharmaceutical forms                   | Capsule, hard  |
| Routes of administration               | Oral use   |

Dosage and administration details:

Advagraf® was defined as study drug, considered IMP and provided by the Sponsor, available as hard gelatin capsules with 0.5 mg, 1 mg, 3 mg and 5 mg of tacrolimus. Dosing of Advagraf: heart transplant recipients: initial dose was 0.075mg/kg/day given orally (one dose), administered at 3 days (72 hours) post skin closure (Day 1) in the morning. Lung transplant recipients: initial dose was 0.075mg/kg/day given orally in one dose, administered in the morning following skin closure. Pancreas/SPK transplant recipients: initial dose was 0.2 mg/kg/day orally (one dose), administered in the morning following skin closure. Subsequent doses were taken orally once a day only in the morning. Advagraf was taken on an empty stomach or at least one hour before or 2 to 3 hours after meal. Dose adjustments were based on clinical evidence of efficacy/occurrence of adverse events (AEs)/observing the following recommended Tacrolimus blood trough levels: Day 1-42 10-20 ng/ml, Day 43-407 5-15 ng/ml.

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

Arm description:

Prograf in strengths of 0.5mg, 1mg and 5mg capsules for twice daily oral administration.

|  |  |
|--|--|
| Arm type                               | Active comparator                                    |
| Investigational medicinal product name | Prograf  |
| Investigational medicinal product code | FK506  |
| Other name                             | Tacrolimus, Tacrolimus immediate release formulation |
| Pharmaceutical forms                   | Capsule, hard  |
| Routes of administration               | Oral use   |

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**Dosage and administration details:**

Prograf® was defined as study drug, considered to be IMP and provided by the Sponsor, available as hard gelatin capsules with 0.5 mg, 1 mg and 5 mg of tacrolimus. Dosing of Prograf: heart transplant and lung recipients: initial total daily dose was 0.075mg/kg/day given orally (two doses) (equals 0.0375mg/kg) in the morning and the evening, first dose was to be administered 3 days (72 hours) post skin closure in the morning. Pancreas/SPK transplant recipients: initial dose was 0.2mg/kg/day given orally in two doses (equals 0.1mg/kg), first dose was to be administered in the morning following skin closure. Subsequent doses were taken orally twice a day in the morning and evening. Prograf was taken on an empty stomach or at least one hour before or 2 to 3 hours after the meal. Dose adjustments were based on clinical evidence of efficacy/occurrence of AE's/observing the following recommended Tacrolimus blood trough levels: Day 1-42 10-20 ng/ml, Day 43-407 5-15 ng/ml.

| <b>Number of subjects in period 1</b> | Advagraf | Prograf |
|---------------------------------------|----------|---------|
| Started                               | 8        | 9       |
| Completed                             | 6        | 8       |
| Not completed                         | 2        | 1       |
| Consent withdrawn by subject          | 1        | -       |
| Randomized but not treated            | 1        | -       |
| Lost to follow-up                     | -        | 1       |

## Baseline characteristics

### Reporting groups

|   |          |
|---|----------|
| Reporting group title   | Advagraf |
| Reporting group description:<br>Advagraf in strengths of 0.5mg, 1mg, 3mg and 5mg capsules for once daily oral administration. |          |
| Reporting group title   | Prograf  |
| Reporting group description:<br>Prograf in strengths of 0.5mg, 1mg and 5mg capsules for twice daily oral administration.      |          |

| Reporting group values   | Advagraf | Prograf | Total |
|--|----------|---------|-------|
| Number of subjects   | 8        | 9       | 17    |
| Age categorical  |          |         |       |
| Age values provided are for the total randomized population.   |          |         |       |
| Units: Subjects  |          |         |       |
| In utero   | 0        | 0       | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks)  | 0        | 0       | 0     |
| Newborns (0-27 days)   | 0        | 0       | 0     |
| Infants and toddlers (28 days-23 months)   | 0        | 0       | 0     |
| Children (2-11 years)  | 0        | 0       | 0     |
| Adolescents (12-17 years)  | 0        | 0       | 0     |
| Adults (18-64 years)   | 8        | 9       | 17    |
| From 65-84 years   | 0        | 0       | 0     |
| 85 years and over  | 0        | 0       | 0     |
| Gender categorical   |          |         |       |
| Gender values provided are for the Full Analysis Set (FAS) population. The FAS consisted of all patients transplanted and randomized who received at least one dose of study drug. |          |         |       |
| Units: Subjects  |          |         |       |
| Female   | 4        | 0       | 4     |
| Male   | 3        | 9       | 12    |
| Not recorded   | 1        | 0       | 1     |

## End points

### End points reporting groups

|   |          |
|---|----------|
| Reporting group title   | Advagraf |
| Reporting group description:<br>Advagraf in strengths of 0.5mg, 1mg, 3mg and 5mg capsules for once daily oral administration. |          |
| Reporting group title   | Prograf  |
| Reporting group description:<br>Prograf in strengths of 0.5mg, 1mg and 5mg capsules for twice daily oral administration.      |          |

### Primary: Systemic exposure area under the plasma concentration – time curve (AUC)0-24h of tacrolimus after first dose and under steady state conditions

|   |   |
|---|---|
| End point title   | Systemic exposure area under the plasma concentration – time curve (AUC)0-24h of tacrolimus after first dose and under steady state conditions <sup>[1]</sup> |
| End point description:<br>FAS population. AUC0-24h was calculated using the trapezoidal rule. N equals number of patients with pharmacokinetic data.      |   |
| End point type  | Primary   |
| End point timeframe:<br>Day 1, Day 3, Day 7 and Day 42. For Days 3, 7 and 42 profile was to be performed after a minimum of 3 days without a dose change. |   |

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: Since the enrollment for the study was terminated early due to poor recruitment, the data obtained are insufficient to make any meaningful comparison of systemic exposure of tacrolimus between the 2 treatment regimens.

| End point values                     | Advagraf          | Prograf           |  |  |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 7                 | 9                 |  |  |
| Units: ng/mL.h                       |                   |                   |  |  |
| arithmetic mean (standard deviation) |                   |                   |  |  |
| Day 1 [N=7,8]                        | 244.97 (± 214.59) | 339.91 (± 197.89) |  |  |
| Day 3 [N=7,9]                        | 439.55 (± 287.91) | 412.62 (± 233.45) |  |  |
| Day 7 [N=6,5]                        | 437.34 (± 222.87) | 231.47 (± 34.51)  |  |  |
| Day 42 [N=5,6]                       | 335.52 (± 41.7)   | 334.03 (± 140.87) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Safety as assessed by recording adverse events, laboratory assessments and vital signs

|                 |   |
|-----------------|---|
| End point title | Safety as assessed by recording adverse events, laboratory assessments and vital signs <sup>[2]</sup> |
|-----------------|---|

End point description:

Treatment-emergent Adverse Events (TEAEs) were AEs observed at the same time as or after starting administration of the study drug, and before the start of another treatment, if any. A treatment-related TEAE was defined as a TEAE whose relationship to study drug was assessed as "possible" or "probable" by the investigator, or whose relationship to study drug is missing. FAS population. Only one death occurred after patient was discontinued from the study but during serious adverse event 30 day follow-up window.

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

End point timeframe:

From the first dose of study drug until end of study. Treatment was a total of 58 weeks.

Notes:

[2] - 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: Since the enrollment for the study was terminated early due to poor recruitment, the data obtained are insufficient to make any meaningful comparison of systemic exposure of tacrolimus between the 2 treatment regimens.

| End point values                              | Advagraf        | Prograf         |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                            | Reporting group | Reporting group |  |  |
| Number of subjects analysed                   | 7               | 9               |  |  |
| Units: Participants                           |                 |                 |  |  |
| Any TEAE                                      | 7               | 9               |  |  |
| Drug-related TEAEs                            | 5               | 7               |  |  |
| Deaths  | 0               | 1               |  |  |
| Serious TEAEs                                 | 2               | 6               |  |  |
| Drug-related Serious TEAEs                    | 1               | 2               |  |  |
| TEAEs Leading to Discontinuation              | 0               | 0               |  |  |
| Drug-related TEAEs Leading to Discontinuation | 0               | 0               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Concentration (Cmax)

|                 |                              |
|-----------------|------------------------------|
| End point title | Maximum Concentration (Cmax) |
|-----------------|------------------------------|

End point description:

FAS population. N equals number of patients with pharmacokinetic data.

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

End point timeframe:

Day 1, Day 3, Day 7 and Day 42.

| End point values                     | Advagraf        | Prograf         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 7               | 9               |  |  |
| Units: ng/mL                         |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Day 1 [N=7,9]                        | 20.03 (± 15.77) | 20.45 (± 13.17) |  |  |
| Day 3 [N=7,9]                        | 29.46 (± 13.35) | 24.32 (± 13.67) |  |  |
| Day 7 [N=6,5]                        | 29.32 (± 15.41) | 16.97 (± 6.56)  |  |  |
| Day 42 [N=5,6]                       | 27.16 (± 5.85)  | 25.08 (± 11.25) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Attain Maximum Concentration (Tmax)

|  |   |
|--|---|
| End point title  | Time to Attain Maximum Concentration (Tmax) |
| End point description:   |   |
| FAS population. If Cmax occurred on more than one time point, the first time it occurred was considered for tmax. N equals number of patients with pharmacokinetic data. |   |
| End point type   | Secondary                                   |
| End point timeframe:   |   |
| Day 1, Day 3, Day 7 and Day 42.  |   |

| End point values              | Advagraf        | Prograf         |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 7               | 9               |  |  |
| Units: hours                  |                 |                 |  |  |
| median (full range (min-max)) |                 |                 |  |  |
| Day 1 [N=7,9]                 | 4 (1 to 6)      | 3 (0.5 to 4)    |  |  |
| Day 3 [N=7,9]                 | 2 (1 to 24)     | 2 (1 to 4)      |  |  |
| Day 7 [N=6,5]                 | 2.5 (1 to 8)    | 2 (1 to 3)      |  |  |
| Day 42 [N=5,6]                | 2 (1 to 4)      | 2 (1 to 4)      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Concentration prior to the morning dose C24 (24 hours after morning dose of once daily advagraf or 12 hours after evening dose of twice daily prograf)

|                 |   |
|-----------------|---|
| End point title | Concentration prior to the morning dose C24 (24 hours after morning dose of once daily advagraf or 12 hours after evening |
|-----------------|---|

dose of twice daily prograf)

End point description:

FAS population. N equals number of patients with pharmacokinetic data.

End point type Secondary

End point timeframe:

Day 1, Day 3, Day 7 and Day 42.

| End point values                     | Advagraf             | Prograf             |  |  |
|--------------------------------------|----------------------|---------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed          | 7                    | 9                   |  |  |
| Units: ng/mL                         |                      |                     |  |  |
| arithmetic mean (standard deviation) |                      |                     |  |  |
| Day 1 [N=7,8]                        | 6.91 ( $\pm$ 5.82)   | 13.6 ( $\pm$ 7.61)  |  |  |
| Day 3 [N=7,9]                        | 15.83 ( $\pm$ 13.09) | 14.72 ( $\pm$ 8.61) |  |  |
| Day 7 [N=6,5]                        | 13.63 ( $\pm$ 8.38)  | 7.69 ( $\pm$ 1.64)  |  |  |
| Day 42 [N=5,6]                       | 9.19 ( $\pm$ 1.8)    | 10.91 ( $\pm$ 4.56) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Rejection Episodes

End point title Rejection Episodes

End point description:

FAS population.

End point type Secondary

End point timeframe:

Up to 58 weeks.

| End point values                        | Advagraf        | Prograf         |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                      | Reporting group | Reporting group |  |  |
| Number of subjects analysed             | 7               | 9               |  |  |
| Units: Participants                     |                 |                 |  |  |
| Biopsy Confirmed Acute Rejection (BCAR) | 0               | 2               |  |  |
| Clinical Signs of Acute Rejection       | 1               | 0               |  |  |
| Clinical Diagnosis of Acute Rejection   | 0               | 1               |  |  |

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Subject survival**

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|                 |                  |
|-----------------|------------------|
| End point title | Subject survival |
|-----------------|------------------|

End point description:

FAS population. Only one death occurred in the study.

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

End point timeframe:

Up to 58 weeks.

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| End point values            | Advagraf        | Prograf         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 7               | 9               |  |  |
| Units: Participants         | 7               | 8               |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Graft survival**

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|                 |                |
|-----------------|----------------|
| End point title | Graft survival |
|-----------------|----------------|

End point description:

FAS population. Graft loss was defined as retransplantation, nephrectomy, death or dialysis ongoing at the End of Study or at discontinuation unless superseded by follow-up information.

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

End point timeframe:

Up to 58 weeks.

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| End point values            | Advagraf        | Prograf         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 7               | 9               |  |  |
| Units: Participants         | 7               | 8               |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug until end of study. TEAEs were AEs observed at the same time as or after starting study drug, and before the start of another treatment, if any. Treatment was a total of 58 weeks.

Adverse event reporting additional description:

An AE is defined as any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment. FAS population.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 11.1 |
|--------------------|------|

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | Advagraf |
|-----------------------|----------|

Reporting group description:

Advagraf in strengths of 0.5mg, 1mg, 3mg and 5mg capsules for once daily oral administration.

|                       |         |
|-----------------------|---------|
| Reporting group title | Prograf |
|-----------------------|---------|

Reporting group description:

Prograf in strengths of 0.5mg, 1mg and 5mg capsules for twice daily oral administration.

| Serious adverse events  | Advagraf       | Prograf        |  |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events                   |                |                |  |
| subjects affected / exposed   | 2 / 7 (28.57%) | 6 / 9 (66.67%) |  |
| number of deaths (all causes)                                       | 0              | 1              |  |
| number of deaths resulting from adverse events                      | 0              | 1              |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |                |  |
| Epstein-Barr virus associated lymphoproliferative disorder          |                |                |  |
| subjects affected / exposed   | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all                     | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications                      |                |                |  |
| Surgical procedure repeated   |                |                |  |
| subjects affected / exposed   | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Wound dehiscence  |                |                |  |

|  |                |                |  |
|--|----------------|----------------|--|
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Nervous system disorders                             |                |                |  |
| Syncope  |                |                |  |
| subjects affected / exposed                          | 1 / 7 (14.29%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Blood and lymphatic system disorders                 |                |                |  |
| Anaemia  |                |                |  |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General disorders and administration site conditions |                |                |  |
| General physical health deterioration                |                |                |  |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Immune system disorders                              |                |                |  |
| Heart transplant rejection                           |                |                |  |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Kidney transplant rejection                          |                |                |  |
| subjects affected / exposed                          | 1 / 7 (14.29%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Pancreas transplant rejection                        |                |                |  |
| subjects affected / exposed                          | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Gastrointestinal disorders                           |                |                |  |
| Intestinal obstruction                               |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 7 (14.29%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Pleural effusion                                |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pulmonary embolism                              |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| Respiratory failure                             |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| Renal and urinary disorders                     |                |                |  |
| Hydronephrosis                                  |                |                |  |
| subjects affected / exposed                     | 1 / 7 (14.29%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal artery thrombosis                         |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Renal impairment                                |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Infections and infestations                     |                |                |  |
| BK virus infection                              |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Bacteraemia                                     |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Bronchopulmonary aspergillosis                  |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          |  |
| Candida sepsis                                  |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| Cytomegalovirus infection                       |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Pyelonephritis acute                            |                |                |  |
| subjects affected / exposed                     | 1 / 7 (14.29%) | 0 / 9 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Respiratory tract infection bacterial           |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| Non-serious adverse events  | Advagraf        | Prograf         |  |
|---|-----------------|-----------------|--|
| Total subjects affected by non-serious adverse events               |                 |                 |  |
| subjects affected / exposed   | 7 / 7 (100.00%) | 9 / 9 (100.00%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |  |
| Thyroid neoplasm  |                 |                 |  |
| subjects affected / exposed   | 0 / 7 (0.00%)   | 1 / 9 (11.11%)  |  |
| occurrences (all)   | 0               | 1               |  |

|  |                             |                |                |  |
|--|-----------------------------|----------------|----------------|--|
| Vascular disorders                                   | Arterial occlusive disease  |                |                |  |
|  | subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
|  | occurrences (all)           | 0              | 1              |  |
|  | Circulatory collapse        |                |                |  |
|  | subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
|  | occurrences (all)           | 0              | 1              |  |
| Hot flush  | subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
|  | occurrences (all)           | 0              | 1              |  |
| Hypertension   | subjects affected / exposed | 2 / 7 (28.57%) | 1 / 9 (11.11%) |  |
|  | occurrences (all)           | 3              | 1              |  |
| Hypotension  | subjects affected / exposed | 1 / 7 (14.29%) | 0 / 9 (0.00%)  |  |
|  | occurrences (all)           | 1              | 0              |  |
| General disorders and administration site conditions |                             |                |                |  |
| Chest pain   | subjects affected / exposed | 1 / 7 (14.29%) | 1 / 9 (11.11%) |  |
|  | occurrences (all)           | 1              | 1              |  |
| Effusion   | subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
|  | occurrences (all)           | 0              | 1              |  |
| Oedema peripheral                                    | subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
|  | occurrences (all)           | 0              | 1              |  |
| Pyrexia  | subjects affected / exposed | 2 / 7 (28.57%) | 0 / 9 (0.00%)  |  |
|  | occurrences (all)           | 2              | 0              |  |
| Reproductive system and breast disorders             |                             |                |                |  |
| Benign prostatic hyperplasia                         | subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
|  | occurrences (all)           | 0              | 1              |  |
| Prostatism   | subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
|  | occurrences (all)           | 0              | 1              |  |

|   |                |                |  |
|---|----------------|----------------|--|
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| Bronchostenosis                                 |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Cough   |                |                |  |
| subjects affected / exposed                     | 2 / 7 (28.57%) | 3 / 9 (33.33%) |  |
| occurrences (all)                               | 3              | 3              |  |
| Dyspnoea  |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Dyspnoea exertional                             |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Lung disorder                                   |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Organising pneumonia                            |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 2              |  |
| Pneumothorax                                    |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Pulmonary hilum mass                            |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Upper respiratory tract inflammation            |                |                |  |
| subjects affected / exposed                     | 1 / 7 (14.29%) | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 1              | 1              |  |
| Psychiatric disorders                           |                |                |  |
| Insomnia  |                |                |  |
| subjects affected / exposed                     | 1 / 7 (14.29%) | 2 / 9 (22.22%) |  |
| occurrences (all)                               | 2              | 2              |  |
| Sleep disorder                                  |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Investigations                                  |                |                |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)          | 0 / 7 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Brain natriuretic peptide increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 7 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Drug level increased<br>subjects affected / exposed<br>occurrences (all)                | 0 / 7 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Electrocardiogram QT prolonged<br>subjects affected / exposed<br>occurrences (all)      | 1 / 7 (14.29%)<br>1 | 0 / 9 (0.00%)<br>0  |  |
| Electroencephalogram abnormal<br>subjects affected / exposed<br>occurrences (all)       | 1 / 7 (14.29%)<br>1 | 0 / 9 (0.00%)<br>0  |  |
| Plasma cells increased<br>subjects affected / exposed<br>occurrences (all)              | 0 / 7 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Tumour marker increased<br>subjects affected / exposed<br>occurrences (all)             | 0 / 7 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Weight increased<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 7 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Injury, poisoning and procedural complications  |                     |                     |  |
| Hand fracture<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 7 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Incisional hernia<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 7 (14.29%)<br>1 | 0 / 9 (0.00%)<br>0  |  |
| Skin laceration<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 7 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Wound dehiscence  |                     |                     |  |

|  |                     |                    |  |
|--|---------------------|--------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 7 (14.29%)<br>1 | 0 / 9 (0.00%)<br>0 |  |
| Cardiac disorders                                |                     |                    |  |
| Palpitations                                     |                     |                    |  |
| subjects affected / exposed                      | 0 / 7 (0.00%)       | 1 / 9 (11.11%)     |  |
| occurrences (all)                                | 0                   | 1                  |  |
| Tachycardia                                      |                     |                    |  |
| subjects affected / exposed                      | 0 / 7 (0.00%)       | 1 / 9 (11.11%)     |  |
| occurrences (all)                                | 0                   | 1                  |  |
| Nervous system disorders                         |                     |                    |  |
| Amnesia  |                     |                    |  |
| subjects affected / exposed                      | 0 / 7 (0.00%)       | 1 / 9 (11.11%)     |  |
| occurrences (all)                                | 0                   | 1                  |  |
| Headache   |                     |                    |  |
| subjects affected / exposed                      | 0 / 7 (0.00%)       | 2 / 9 (22.22%)     |  |
| occurrences (all)                                | 0                   | 2                  |  |
| Loss of consciousness                            |                     |                    |  |
| subjects affected / exposed                      | 0 / 7 (0.00%)       | 1 / 9 (11.11%)     |  |
| occurrences (all)                                | 0                   | 1                  |  |
| Syncope  |                     |                    |  |
| subjects affected / exposed                      | 0 / 7 (0.00%)       | 1 / 9 (11.11%)     |  |
| occurrences (all)                                | 0                   | 1                  |  |
| Tremor   |                     |                    |  |
| subjects affected / exposed                      | 1 / 7 (14.29%)      | 0 / 9 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                  |  |
| Blood and lymphatic system disorders             |                     |                    |  |
| Anaemia  |                     |                    |  |
| subjects affected / exposed                      | 3 / 7 (42.86%)      | 4 / 9 (44.44%)     |  |
| occurrences (all)                                | 5                   | 4                  |  |
| Iron deficiency anaemia                          |                     |                    |  |
| subjects affected / exposed                      | 1 / 7 (14.29%)      | 0 / 9 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                  |  |
| Leukopenia                                       |                     |                    |  |
| subjects affected / exposed                      | 2 / 7 (28.57%)      | 2 / 9 (22.22%)     |  |
| occurrences (all)                                | 3                   | 3                  |  |
| Lymphadenopathy                                  |                     |                    |  |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)           | 0              | 1              |  |
| Thrombocythaemia            |                |                |  |
| subjects affected / exposed | 2 / 7 (28.57%) | 0 / 9 (0.00%)  |  |
| occurrences (all)           | 3              | 0              |  |
| Thrombocytopenia            |                |                |  |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 9 (0.00%)  |  |
| occurrences (all)           | 1              | 0              |  |
| Eye disorders               |                |                |  |
| Ocular hyperaemia           |                |                |  |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)           | 0              | 1              |  |
| Visual impairment           |                |                |  |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 9 (0.00%)  |  |
| occurrences (all)           | 1              | 0              |  |
| Gastrointestinal disorders  |                |                |  |
| Abdominal pain upper        |                |                |  |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)           | 0              | 1              |  |
| Constipation                |                |                |  |
| subjects affected / exposed | 3 / 7 (42.86%) | 3 / 9 (33.33%) |  |
| occurrences (all)           | 4              | 3              |  |
| Diarrhoea                   |                |                |  |
| subjects affected / exposed | 2 / 7 (28.57%) | 3 / 9 (33.33%) |  |
| occurrences (all)           | 3              | 5              |  |
| Dyspepsia                   |                |                |  |
| subjects affected / exposed | 0 / 7 (0.00%)  | 2 / 9 (22.22%) |  |
| occurrences (all)           | 0              | 3              |  |
| Inguinal hernia             |                |                |  |
| subjects affected / exposed | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)           | 0              | 1              |  |
| Melaena                     |                |                |  |
| subjects affected / exposed | 1 / 7 (14.29%) | 0 / 9 (0.00%)  |  |
| occurrences (all)           | 1              | 0              |  |
| Nausea                      |                |                |  |

|  |                |                |  |
|--|----------------|----------------|--|
| subjects affected / exposed            | 0 / 7 (0.00%)  | 3 / 9 (33.33%) |  |
| occurrences (all)                      | 0              | 3              |  |
| Stomach discomfort                     |                |                |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Vomiting                               |                |                |  |
| subjects affected / exposed            | 1 / 7 (14.29%) | 1 / 9 (11.11%) |  |
| occurrences (all)                      | 1              | 1              |  |
| Hepatobiliary disorders                |                |                |  |
| Cholelithiasis                         |                |                |  |
| subjects affected / exposed            | 1 / 7 (14.29%) | 1 / 9 (11.11%) |  |
| occurrences (all)                      | 1              | 1              |  |
| Hepatic cyst                           |                |                |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Hepatic function abnormal              |                |                |  |
| subjects affected / exposed            | 1 / 7 (14.29%) | 0 / 9 (0.00%)  |  |
| occurrences (all)                      | 1              | 0              |  |
| Hepatic lesion                         |                |                |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Hypertransaminasaemia                  |                |                |  |
| subjects affected / exposed            | 1 / 7 (14.29%) | 0 / 9 (0.00%)  |  |
| occurrences (all)                      | 1              | 0              |  |
| Skin and subcutaneous tissue disorders |                |                |  |
| Keratosis pilaris                      |                |                |  |
| subjects affected / exposed            | 1 / 7 (14.29%) | 0 / 9 (0.00%)  |  |
| occurrences (all)                      | 1              | 0              |  |
| Rash                                   |                |                |  |
| subjects affected / exposed            | 1 / 7 (14.29%) | 0 / 9 (0.00%)  |  |
| occurrences (all)                      | 1              | 0              |  |
| Renal and urinary disorders            |                |                |  |
| Dysuria                                |                |                |  |
| subjects affected / exposed            | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Nocturia                               |                |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Oliguria  |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Proteinuria                                     |                |                |  |
| subjects affected / exposed                     | 1 / 7 (14.29%) | 0 / 9 (0.00%)  |  |
| occurrences (all)                               | 1              | 0              |  |
| Renal failure                                   |                |                |  |
| subjects affected / exposed                     | 1 / 7 (14.29%) | 0 / 9 (0.00%)  |  |
| occurrences (all)                               | 1              | 0              |  |
| Renal failure chronic                           |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Renal impairment                                |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Ureteric stenosis                               |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Urinary incontinence                            |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| Back pain                                       |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Muscle spasms                                   |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Myalgia   |                |                |  |
| subjects affected / exposed                     | 0 / 7 (0.00%)  | 1 / 9 (11.11%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Osteolysis                                      |                |                |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                                | 0 / 7 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)           | 1 / 7 (14.29%)<br>1 | 0 / 9 (0.00%)<br>0  |  |
| Spinal osteoarthritis<br>subjects affected / exposed<br>occurrences (all)       | 0 / 7 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Infections and infestations   |                     |                     |  |
| BK virus infection<br>subjects affected / exposed<br>occurrences (all)          | 0 / 7 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Cytomegalovirus infection<br>subjects affected / exposed<br>occurrences (all)   | 0 / 7 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Cytomegalovirus viraemia<br>subjects affected / exposed<br>occurrences (all)    | 0 / 7 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Localised infection<br>subjects affected / exposed<br>occurrences (all)         | 1 / 7 (14.29%)<br>1 | 0 / 9 (0.00%)<br>0  |  |
| Oral herpes<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 7 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 7 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 7 (0.00%)<br>0  | 2 / 9 (22.22%)<br>2 |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)     | 1 / 7 (14.29%)<br>2 | 0 / 9 (0.00%)<br>0  |  |
| Viral infection<br>subjects affected / exposed<br>occurrences (all)             | 1 / 7 (14.29%)<br>1 | 0 / 9 (0.00%)<br>0  |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| Vulvovaginal candidiasis<br>subjects affected / exposed<br>occurrences (all) | 1 / 7 (14.29%)<br>1 | 0 / 9 (0.00%)<br>0  |  |
| Metabolism and nutrition disorders   |                     |                     |  |
| Acidosis<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 7 (14.29%)<br>1 | 1 / 9 (11.11%)<br>1 |  |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all)    | 0 / 7 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |  |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)           | 2 / 7 (28.57%)<br>2 | 0 / 9 (0.00%)<br>0  |  |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)            | 3 / 7 (42.86%)<br>4 | 0 / 9 (0.00%)<br>0  |  |
| Hyperlipidaemia<br>subjects affected / exposed<br>occurrences (all)          | 1 / 7 (14.29%)<br>1 | 2 / 9 (22.22%)<br>2 |  |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)         | 1 / 7 (14.29%)<br>1 | 0 / 9 (0.00%)<br>0  |  |
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all)            | 3 / 7 (42.86%)<br>3 | 2 / 9 (22.22%)<br>2 |  |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)             | 1 / 7 (14.29%)<br>1 | 1 / 9 (11.11%)<br>1 |  |
| Hypomagnesaemia<br>subjects affected / exposed<br>occurrences (all)          | 1 / 7 (14.29%)<br>1 | 2 / 9 (22.22%)<br>2 |  |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all)            | 2 / 7 (28.57%)<br>3 | 0 / 9 (0.00%)<br>0  |  |
| Hypophosphataemia  |                     |                     |  |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 7 (14.29%) | 1 / 9 (11.11%) |  |
| occurrences (all)           | 1              | 1              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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| The study was terminated early due to poor recruitment. The data obtained are insufficient to draw firm conclusions from the results of this study. |
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Notes: