



## Clinical trial results:

**A 3-month, multicenter, randomized, open label study to evaluate the impact of early vs. delayed introduction of everolimus on wound healing in de novo kidney transplant recipients with a follow-up evaluation at 12 months after transplant (NEVERWOUND)**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2011-002866-19   |
| Trial protocol           | IT               |
| Global end of trial date | 10 December 2015 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1               |
| This version publication date  | 07 December 2016 |
| First version publication date | 07 December 2016 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CRAD001AIT25 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01410448 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Novartis Pharma, AG  |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                   |
| Public contact               | Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, |

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:

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**Results analysis stage**

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|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 10 December 2015 |
| Is this the analysis of the primary completion data? | No               |

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|                                  |                  |
|----------------------------------|------------------|
| Global end of trial reached?     | Yes              |
| Global end of trial date         | 10 December 2015 |
| Was the trial ended prematurely? | No               |

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Notes:

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**General information about the trial**

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Main objective of the trial:

The primary objective was to compare the incidence of surgical wound complications (lymphorrhea, fluid collection, incisional hernia, wound dehiscence, wound infections) in the first three months following renal transplant between patients treated with everolimus immediately after transplantation (IE) with those treated 28 ± 4 days later (delayed everolimus - DE).

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Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

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Background therapy: -

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Evidence for comparator: -

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|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 04 November 2011 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Italy: 383 |
| Worldwide total number of subjects   | 383        |
| EEA total number of subjects         | 383        |

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Notes:

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**Subjects enrolled per age group**

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|   |     |
|---|-----|
| 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)                      | 328 |
| From 65 to 84 years                       | 55  |

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|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

This study included a 3 month treatment period followed by an observational follow-up period. Participants were treated as per local practice during follow-up and a follow-up evaluation was performed at 12 months.

### Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio to one of the 2 treatment groups.

### Period 1

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

### Arms

|                              |                           |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes                       |
| <b>Arm title</b>             | Immediate Everolimus (IE) |

Arm description:

Everolimus was started within 48 hours after graft reperfusion at a starting dose of 0.75 mg twice daily in combination with low-dose cyclosporine and steroids for 3 months.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Everolimus   |
| Investigational medicinal product code | RAD001       |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Everolimus was started within 48 hours after graft reperfusion at a starting dose of 0.75 mg twice daily in combination with low-dose cyclosporine and steroids for 3 months.

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Delayed Everolimus (DE) |
|------------------|-------------------------|

Arm description:

The standard dose of mycophenolate sodium was administered within 48 hours after graft reperfusion in combination with a full dose of cyclosporine and steroids. After 28 +/- 4 days of treatment, mycophenolate sodium was discontinued and everolimus was introduced at a starting dose of 0.75 mg twice daily for 3 months.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Everolimus   |
| Investigational medicinal product code | RAD001       |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

The standard dose of mycophenolate sodium was administered within 48 hours after graft reperfusion in combination with a full dose of cyclosporine and steroids. After 28 +/- 4 days of treatment, mycophenolate sodium was discontinued and everolimus was introduced at a starting dose of 0.75 mg twice daily for 3 months.

| <b>Number of subjects in period 1</b> | <b>Immediate Everolimus (IE)</b> | <b>Delayed Everolimus (DE)</b> |
|---------------------------------------|----------------------------------|--------------------------------|
| Started                               | 193                              | 190                            |
| Intent-to treat (ITT) analysis set    | 193                              | 190                            |
| modified ITT analysis set             | 161 <sup>[1]</sup>               | 149 <sup>[2]</sup>             |
| Completed                             | 181                              | 155                            |
| Not completed                         | 12                               | 35                             |
| Adverse event, serious fatal          | 2                                | 3                              |
| Consent withdrawn by subject          | 3                                | 2                              |
| Graft loss                            | 4                                | 1                              |
| Administrative issues                 | 2                                | 1                              |
| No conversion to everolimus           | -                                | 24                             |
| Lost to follow-up                     | 1                                | -                              |
| Protocol deviation                    | -                                | 4                              |

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Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects is correct.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects is correct.

## Baseline characteristics

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Immediate Everolimus (IE) |
|-----------------------|---------------------------|

Reporting group description:

Everolimus was started within 48 hours after graft reperfusion at a starting dose of 0.75 mg twice daily in combination with low-dose cyclosporine and steroids for 3 months.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Delayed Everolimus (DE) |
|-----------------------|-------------------------|

Reporting group description:

The standard dose of mycophenolate sodium was administered within 48 hours after graft reperfusion in combination with a full dose of cyclosporine and steroids. After 28 +/- 4 days of treatment, mycophenolate sodium was discontinued and everolimus was introduced at a starting dose of 0.75 mg twice daily for 3 months.

| Reporting group values                             | Immediate Everolimus (IE) | Delayed Everolimus (DE) | Total |
|--|---------------------------|-------------------------|-------|
| Number of subjects                                 | 193                       | 190                     | 383   |
| Age categorical<br>Units: Subjects                 |                           |                         |       |
| In utero   | 0                         | 0                       | 0     |
| Preterm newborn infants (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)                               | 165                       | 163                     | 328   |
| From 65-84 years                                   | 28                        | 27                      | 55    |
| 85 years and over                                  | 0                         | 0                       | 0     |
| Age Continuous<br>Units: Years                     |                           |                         |       |
| arithmetic mean                                    | 51.46                     | 51.19                   |       |
| standard deviation                                 | ± 11.37                   | ± 12.29                 | -     |
| Gender, Male/Female<br>Units: Subjects             |                           |                         |       |
| Female   | 59                        | 58                      | 117   |
| Male   | 134                       | 132                     | 266   |

## End points

### End points reporting groups

|  |                           |
|--|---------------------------|
| Reporting group title  | Immediate Everolimus (IE) |
| Reporting group description:<br>Everolimus was started within 48 hours after graft reperfusion at a starting dose of 0.75 mg twice daily in combination with low-dose cyclosporine and steroids for 3 months.  |                           |
| Reporting group title  | Delayed Everolimus (DE)   |
| Reporting group description:<br>The standard dose of mycophenolate sodium was administered within 48 hours after graft reperfusion in combination with a full dose of cyclosporine and steroids. After 28 +/- 4 days of treatment, mycophenolate sodium was discontinued and everolimus was introduced at a starting dose of 0.75 mg twice daily for 3 months. |                           |

### Primary: Percentage of participants without wound healing complications - Worst-case scenario

|  |  |
|--|--|
| End point title  | Percentage of participants without wound healing complications - Worst-case scenario |
| End point description:<br>The percentage of participants with at least one wound healing complication was assessed. Wound healing complications consisted of lymphorrhea, fluid collections, wound dehiscence, wound infections and incisional hernia. In the worst-case scenario, failure, i.e. at least one healing complication occurrence, was identified in one of the following cases: wound complication occurrence, missing information about wound complication occurrence, or study discontinuation due to any reason. |  |
| End point type   | Primary  |
| End point timeframe:<br>3 months   |  |

| End point values                  | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|-----------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed       | 193                       | 190                     |  |  |
| Units: Percentage of participants |                           |                         |  |  |
| number (not applicable)           | 68.39                     | 61.58                   |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Complication-free wound healing                     |
| Comparison groups                       | Delayed Everolimus (DE) v Immediate Everolimus (IE) |
| Number of subjects included in analysis | 383   |
| Analysis specification                  | Pre-specified                                       |
| Analysis type                           |   |
| P-value                                 | = 0.0921  |
| Method                                  | Regression, Logistic                                |

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**Secondary: Percentage of participants without wound healing complications - Worst-case scenario**

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|                 |  |
|-----------------|--|
| End point title | Percentage of participants without wound healing complications - Worst-case scenario |
|-----------------|--|

End point description:

The percentage of participants with at least one wound healing complication was assessed. Wound healing complications consisted of lymphorrhea, fluid collections, wound dehiscence, wound infections and incisional hernia. In the worst-case scenario, failure, i.e. at least one healing complication occurrence, was identified in one of the following cases: wound complication occurrence, missing information about wound complication occurrence or study discontinuation due to any reason for participants who did not complete the 12 month follow-up visit.

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

End point timeframe:

12 months

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| End point values                  | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|-----------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed       | 193                       | 190                     |  |  |
| Units: Percentage of participants |                           |                         |  |  |
| number (not applicable)           | 65.8                      | 59.47                   |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Percentage of participants who experienced treatment failure - Worst-case scenario**

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|                 |  |
|-----------------|--|
| End point title | Percentage of participants who experienced treatment failure - Worst-case scenario |
|-----------------|--|

End point description:

The percentage of participants who experienced treatment failure was assessed. Treatment failure was defined as the occurrence of at least one failure event among death, graft loss or biopsy-proven acute rejection (BPAR). In the worst-case scenario, treatment failure was identified in one of the following cases: occurrence of at least one treatment failure event or study discontinuation due to any reason.

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

End point timeframe:

3 months

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| End point values                  | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|-----------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed       | 193                       | 190                     |  |  |
| Units: Percentage of participants |                           |                         |  |  |
| number (not applicable)           | 11.4                      | 21.05                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patient survival rate: percentage of deaths - Worst-case scenario

|   |   |
|---|---|
| End point title   | Patient survival rate: percentage of deaths - Worst-case scenario |
| End point description:  |   |
| The percentage of deaths was assessed. In the worst-case scenario, failure, i.e. death, was identified in one of the following cases: participant's death or study discontinuation due to any reason. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| 3 Months, 12 months   |   |

| End point values                  | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|-----------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed       | 193                       | 190                     |  |  |
| Units: Percentage of participants |                           |                         |  |  |
| number (not applicable)           | 6.22                      | 18.42                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Participant/graft survival rate: percentage of participants with failure events of death or graft loss - Worst-case scenario

|   |  |
|---|--|
| End point title   | Participant/graft survival rate: percentage of participants with failure events of death or graft loss - Worst-case scenario |
| End point description:  |  |
| The percentage of participants who experienced death or graft loss was assessed. In the worst-case scenario, failure, i.e. participants death or graft loss, was identified in one of the following cases: occurrence of at least one failure event or study discontinuation due to any reason. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| 3 months  |  |

| <b>End point values</b>           | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|-----------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed       | 193                       | 190                     |  |  |
| Units: Percentage of participants |                           |                         |  |  |
| number (not applicable)           | 6.74                      | 18.42                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Graft survival rate: percentage of participants with graft loss - Worst-case scenario

|  |   |
|--|---|
| End point title  | Graft survival rate: percentage of participants with graft loss - Worst-case scenario |
| End point description:<br>The percentage of participants who experienced graft loss was assessed. In the worst-case scenario, failure, i.e. graft loss, was identified in one of the following cases: occurrence of graft loss or discontinuation due to any reason. |   |
| End point type   | Secondary   |
| End point timeframe:<br>3 months, 12 months  |   |

| <b>End point values</b>           | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|-----------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed       | 193                       | 190                     |  |  |
| Units: Percentage of participants |                           |                         |  |  |
| number (not applicable)           |                           |                         |  |  |
| 3 months                          | 6.74                      | 18.42                   |  |  |
| 12 months                         | 7.25                      | 19.47                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants with BPAR - Worst-case scenario

|   |  |
|---|--|
| End point title   | Percentage of participants with BPAR - Worst-case scenario |
| End point description:<br>A biopsy-proven acute rejection was defined as a biopsy graded IA, IB, IIA, IIB or III. In the worst-case scenario, failure, i.e. BPAR, was identified in one of the following cases: occurrence of BPAR or study |  |

discontinuation due to any reason.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 3 Months, 12 months  |           |

| End point values                  | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|-----------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed       | 193                       | 190                     |  |  |
| Units: Percentage of participants |                           |                         |  |  |
| number (not applicable)           | 11.4                      | 21.05                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants with delayed graft function (DGF) -

|   |  |
|---|--|
| End point title   | Percentage of participants with delayed graft function (DGF) - |
| End point description:  |  |
| DGF was defined as the need for dialysis in the first week after transplant, excluding Renal Replacement Therapy within the first 24 hours after transplantation. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| 3 Months  |  |

| End point values                  | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|-----------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed       | 193                       | 190                     |  |  |
| Units: Percentage of participants |                           |                         |  |  |
| number (not applicable)           | 23.83                     | 31.58                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of DGF

|   |                 |
|---|-----------------|
| End point title   | Duration of DGF |
| End point description:  |                 |
| The duration of DGF was defined as the elapsed time from first to last day of post-transplant dialysis. |                 |

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 3 months             |           |

| End point values              | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|-------------------------------|---------------------------|-------------------------|--|--|
| Subject group type            | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed   | 46                        | 60                      |  |  |
| Units: Days                   |                           |                         |  |  |
| median (full range (min-max)) | 8.5 (1 to 93)             | 5.5 (1 to 76)           |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in estimated glomerular filtration rate (eGFR) (calculated with modified diet in renal disease (MDRD)-4 formula - ITT

|                 |  |
|-----------------|--|
| End point title | Change from baseline in estimated glomerular filtration rate (eGFR) (calculated with modified diet in renal disease (MDRD)-4 formula - ITT |
|-----------------|--|

End point description:

Renal function was assessed by measuring serum creatinine and serum urea and by calculating creatinine clearance using the MDRD-4 formula.  $eGFR = 186.3 * (\text{serum creatinine [mg/dL]})^{-1.154} * (\text{age at screening})^{-0.203} * (0.742 \text{ if female}) * (1.21 \text{ if African American})$ . A positive change from baseline indicates improvement.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| baseline, 3 Months   |           |

| End point values                     | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|--------------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                   | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed          | 187                       | 183                     |  |  |
| Units: mL/min                        |                           |                         |  |  |
| arithmetic mean (standard deviation) | 38.64 (± 22.45)           | 39.13 (± 21.46)         |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in estimated glomerular filtration rate (eGFR)

**(calculated with modified diet in renal disease (MDRD)-4 formula - modified ITT**

|   |   |
|---|---|
| End point title   | Change from baseline in estimated glomerular filtration rate (eGFR) (calculated with modified diet in renal disease (MDRD)-4 formula - modified ITT |
| End point description:<br>Renal function was assessed by measuring serum creatinine and serum urea and by calculating creatinine clearance using the MDRD-4 formula. $eGFR = 186.3 * (\text{serum creatinine [mg/dL]})^{-1.154} * (\text{age at screening})^{-0.203} * (0.742 \text{ if female}) * (1.21 \text{ if African American})$ . A positive change from baseline indicates improvement. |   |
| End point type  | Secondary   |
| End point timeframe:<br>baseline, 12 months   |   |

| End point values                     | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|--------------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                   | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed          | 151                       | 142                     |  |  |
| Units: mL/min                        |                           |                         |  |  |
| arithmetic mean (standard deviation) | 41.26 ( $\pm$ 18.69)      | 41.56 ( $\pm$ 19.9)     |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change from baseline in serum creatinine - ITT**

|  |  |
|--|--|
| End point title  | Change from baseline in serum creatinine - ITT |
| End point description:<br>Blood samples were collected to assess serum creatinine measurements. A negative change from baseline indicates improvement. |  |
| End point type   | Secondary                                      |
| End point timeframe:<br>baseline, 3 months   |  |

| End point values                     | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|--------------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                   | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed          | 187                       | 183                     |  |  |
| Units: mg/dL                         |                           |                         |  |  |
| arithmetic mean (standard deviation) | -4.79 ( $\pm$ 2.74)       | -5.13 ( $\pm$ 2.32)     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in serum creatinine - modified ITT

|                 |   |
|-----------------|---|
| End point title | Change from baseline in serum creatinine - modified ITT |
|-----------------|---|

End point description:

Blood samples were collected to assess serum creatinine measurements. A negative change from baseline indicates improvement.

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

End point timeframe:

baseline, 12 months

| End point values                     | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|--------------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                   | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed          | 150                       | 141                     |  |  |
| Units: mg/dL                         |                           |                         |  |  |
| arithmetic mean (standard deviation) | -4.96 (± 2.48)            | -5.22 (± 2.24)          |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants with proteinuria

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with proteinuria |
|-----------------|---|

End point description:

Incidence of proteinuria (>1,000 mg/day in urine collected in 24 hours or > 1.0 if measured on the urine protein/creatinine concentration ratio in a spot urine sample) was assessed.

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

End point timeframe:

3 months

| End point values                  | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|-----------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed       | 193                       | 190                     |  |  |
| Units: Percentage of participants |                           |                         |  |  |
| number (not applicable)           |                           |                         |  |  |
| Yes                               | 4.15                      | 4.21                    |  |  |
| No                                | 68.91                     | 68.42                   |  |  |
| Missing                           | 26.94                     | 27.37                   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants with acute rejection (AR)

|                 |  |
|-----------------|--|
| End point title | Percentage of participants with acute rejection (AR) |
|-----------------|--|

End point description:

AR was defined as an episode of increased serum creatinine >30% that was clinically diagnosed as an acute rejection but was not biopsy proven.

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

End point timeframe:

12 months

| End point values                  | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|-----------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed       | 193                       | 190                     |  |  |
| Units: Percentage of participants |                           |                         |  |  |
| number (not applicable)           | 12.44                     | 10.53                   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants with a new onset of malignancy

|                 |   |
|-----------------|---|
| End point title | Percentage of participants with a new onset of malignancy |
|-----------------|---|

End point description:

The percentage of participants with a new onset of malignancy was assessed.

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

End point timeframe:

12 months

| End point values                  | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|-----------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed       | 159                       | 147                     |  |  |
| Units: Percentage of participants |                           |                         |  |  |
| number (not applicable)           | 0                         | 0.68                    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants with a new onset of diabetes

|   |   |
|---|---|
| End point title   | Percentage of participants with a new onset of diabetes |
| End point description:<br>The percentage of participants with a new onset of diabetes was assessed. |   |
| End point type  | Secondary   |
| End point timeframe:<br>12 months   |   |

| End point values                  | Immediate Everolimus (IE) | Delayed Everolimus (DE) |  |  |
|-----------------------------------|---------------------------|-------------------------|--|--|
| Subject group type                | Reporting group           | Reporting group         |  |  |
| Number of subjects analysed       | 159                       | 148                     |  |  |
| Units: Percentage of participants |                           |                         |  |  |
| number (not applicable)           | 3.14                      | 4.05                    |  |  |

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 17.1   |

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Immediate Everolimus |
|-----------------------|----------------------|

Reporting group description:

Immediate Everolimus

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Delayed Everolimus |
|-----------------------|--------------------|

Reporting group description:

Delayed Everolimus

| Serious adverse events  | Immediate Everolimus | Delayed Everolimus |  |
|---|----------------------|--------------------|--|
| Total subjects affected by serious adverse events                   |                      |                    |  |
| subjects affected / exposed   | 73 / 193 (37.82%)    | 61 / 190 (32.11%)  |  |
| number of deaths (all causes)                                       | 2                    | 3                  |  |
| number of deaths resulting from adverse events                      | 0                    | 0                  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                      |                    |  |
| Renal cancer  |                      |                    |  |
| subjects affected / exposed   | 0 / 193 (0.00%)      | 1 / 190 (0.53%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0                | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0                | 0 / 0              |  |
| Vascular disorders  |                      |                    |  |
| Arterial thrombosis   |                      |                    |  |
| subjects affected / exposed   | 0 / 193 (0.00%)      | 1 / 190 (0.53%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0                | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0                | 0 / 0              |  |
| Circulatory collapse  |                      |                    |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Haematoma                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 193 (1.55%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhage                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypotension                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymphocele                                      |                 |                 |  |
| subjects affected / exposed                     | 7 / 193 (3.63%) | 7 / 190 (3.68%) |  |
| occurrences causally related to treatment / all | 5 / 8           | 1 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lymphorrhoea                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 2 / 190 (1.05%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Shock   |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Shock haemorrhagic                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombophlebitis                                |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Thrombosis   |                 |                 |  |
| subjects affected / exposed                          | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Venous thrombosis                                    |                 |                 |  |
| subjects affected / exposed                          | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                      |                 |                 |  |
| Bladder catheter replacement                         |                 |                 |  |
| subjects affected / exposed                          | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Lymphocele marsupialisation                          |                 |                 |  |
| subjects affected / exposed                          | 1 / 193 (0.52%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 2 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Hyperpyrexia   |                 |                 |  |
| subjects affected / exposed                          | 1 / 193 (0.52%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Impaired healing                                     |                 |                 |  |
| subjects affected / exposed                          | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Multi-organ failure                                  |                 |                 |  |
| subjects affected / exposed                          | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| Oedema  |                  |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%)  | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Oedema peripheral                               |                  |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%)  | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pyrexia   |                  |                 |  |
| subjects affected / exposed                     | 3 / 193 (1.55%)  | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Immune system disorders                         |                  |                 |  |
| Autoimmune disorder                             |                  |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%)  | 1 / 190 (0.53%) |  |
| 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                     | 11 / 193 (5.70%) | 4 / 190 (2.11%) |  |
| occurrences causally related to treatment / all | 4 / 11           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Transplant rejection                            |                  |                 |  |
| subjects affected / exposed                     | 3 / 193 (1.55%)  | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 1 / 3            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                  |                 |  |
| Pleural effusion                                |                  |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%)  | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pneumonitis                                     |                  |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%)  | 1 / 190 (0.53%) |  |
| 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 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Blood creatinine increased                      |                 |                 |  |
| subjects affected / exposed                     | 4 / 193 (2.07%) | 5 / 190 (2.63%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Platelet count decreased                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Complications of transplanted kidney            |                 |                 |  |
| subjects affected / exposed                     | 2 / 193 (1.04%) | 3 / 190 (1.58%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Expired product administered                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femur fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Graft loss                                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 193 (1.55%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Graft thrombosis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 2 / 190 (1.05%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Incisional hernia                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Perinephric collection                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Perirenal haematoma                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 193 (1.04%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural haemorrhage                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal haematoma                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal transplant failure                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subcutaneous haematoma                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Toxicity to various agents                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ureteric anastomosis complication               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound dehiscence                                |                 |                 |  |
| subjects affected / exposed                     | 2 / 193 (1.04%) | 2 / 190 (1.05%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Congenital, familial and genetic disorders      |                 |                 |  |
| Protein S deficiency                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 193 (1.04%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cardiac arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cardiomyopathy                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Myocardial ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Nervous system disorders                        |                 |                 |  |
| Ataxia  |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Coma  |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic stroke                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tremor  |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (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                     | 3 / 193 (1.55%) | 2 / 190 (1.05%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemolytic anaemia                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Leukopenia                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 193 (1.04%) | 3 / 190 (1.58%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Thrombocytopenia                                |                 |                 |  |
| subjects affected / exposed                     | 3 / 193 (1.55%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ascites   |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intra-abdominal haemorrhage                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 193 (1.04%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Localised intraabdominal fluid collection       |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Retroperitoneal haemorrhage                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 193 (1.04%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Hepatobiliary disorders                         |                 |                 |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hydrocholecystitis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Liver disorder                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Dysuria   |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hydronephrosis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oliguria  |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Perinephric effusion                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Proteinuria                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 2 / 190 (1.05%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal artery stenosis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (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 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure acute                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 2 / 190 (1.05%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal impairment                                |                 |                 |  |
| subjects affected / exposed                     | 3 / 193 (1.55%) | 2 / 190 (1.05%) |  |
| occurrences causally related to treatment / all | 2 / 4           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal ischaemia                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal tubular necrosis                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal vein thrombosis                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tubulointerstitial nephritis                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary fistula                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary retention                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinoma   |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 2 / 190 (1.05%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pelvic deformity                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Abscess   |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Bronchopneumonia                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystitis  |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cytomegalovirus infection                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 3 / 190 (1.58%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related infection                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterobacter infection                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia infection                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infected lymphocele                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Klebsiella infection                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infection                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Retroperitoneal abscess                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Septic shock                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 8 / 193 (4.15%) | 7 / 190 (3.68%) |  |
| occurrences causally related to treatment / all | 2 / 9           | 5 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urosepsis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 2 / 190 (1.05%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection                                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 193 (1.55%) | 2 / 190 (1.05%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyslipidaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 193 (0.00%) | 1 / 190 (0.53%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fluid overload                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 193 (1.04%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypercreatininaemia                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 193 (0.52%) | 0 / 190 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolic disorder                              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 193 (0.00%) | 2 / 190 (1.05%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Immediate Everolimus | Delayed Everolimus |  |
|---|----------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                      |                    |  |
| subjects affected / exposed                           | 155 / 193 (80.31%)   | 156 / 190 (82.11%) |  |
| Injury, poisoning and procedural complications        |                      |                    |  |
| Complications of transplanted kidney                  |                      |                    |  |
| subjects affected / exposed                           | 26 / 193 (13.47%)    | 23 / 190 (12.11%)  |  |
| occurrences (all)                                     | 26                   | 23                 |  |
| Vascular disorders                                    |                      |                    |  |
| Haematoma   |                      |                    |  |
| subjects affected / exposed                           | 12 / 193 (6.22%)     | 6 / 190 (3.16%)    |  |
| occurrences (all)                                     | 12                   | 7                  |  |
| Hypertension  |                      |                    |  |
| subjects affected / exposed                           | 34 / 193 (17.62%)    | 30 / 190 (15.79%)  |  |
| occurrences (all)                                     | 36                   | 30                 |  |
| Lymphocele  |                      |                    |  |
| subjects affected / exposed                           | 25 / 193 (12.95%)    | 33 / 190 (17.37%)  |  |
| occurrences (all)                                     | 28                   | 35                 |  |
| Lymphorrhoea  |                      |                    |  |
| subjects affected / exposed                           | 6 / 193 (3.11%)      | 11 / 190 (5.79%)   |  |
| occurrences (all)                                     | 6                    | 11                 |  |
| Blood and lymphatic system disorders                  |                      |                    |  |
| Anaemia   |                      |                    |  |
| subjects affected / exposed                           | 67 / 193 (34.72%)    | 58 / 190 (30.53%)  |  |
| occurrences (all)                                     | 67                   | 60                 |  |
| Leukopenia  |                      |                    |  |
| subjects affected / exposed                           | 8 / 193 (4.15%)      | 14 / 190 (7.37%)   |  |
| occurrences (all)                                     | 9                    | 14                 |  |
| General disorders and administration site conditions  |                      |                    |  |



|   |                         |                         |  |
|---|-------------------------|-------------------------|--|
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)         | 17 / 193 (8.81%)<br>17  | 14 / 190 (7.37%)<br>14  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                   | 16 / 193 (8.29%)<br>19  | 14 / 190 (7.37%)<br>14  |  |
| Gastrointestinal disorders  |                         |                         |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)            | 14 / 193 (7.25%)<br>14  | 15 / 190 (7.89%)<br>17  |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)              | 12 / 193 (6.22%)<br>12  | 13 / 190 (6.84%)<br>13  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                    | 4 / 193 (2.07%)<br>5    | 14 / 190 (7.37%)<br>14  |  |
| Renal and urinary disorders   |                         |                         |  |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)                | 14 / 193 (7.25%)<br>14  | 3 / 190 (1.58%)<br>3    |  |
| Infections and infestations   |                         |                         |  |
| Cytomegalovirus infection<br>subjects affected / exposed<br>occurrences (all) | 13 / 193 (6.74%)<br>14  | 16 / 190 (8.42%)<br>16  |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)   | 34 / 193 (17.62%)<br>45 | 34 / 190 (17.89%)<br>40 |  |
| Metabolism and nutrition disorders  |                         |                         |  |
| Dyslipidaemia<br>subjects affected / exposed<br>occurrences (all)             | 28 / 193 (14.51%)<br>28 | 24 / 190 (12.63%)<br>24 |  |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all)     | 20 / 193 (10.36%)<br>20 | 9 / 190 (4.74%)<br>9    |  |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)             | 10 / 193 (5.18%)<br>10  | 18 / 190 (9.47%)<br>18  |  |

|                             |                   |                   |  |
|-----------------------------|-------------------|-------------------|--|
| Hyperlipidaemia             |                   |                   |  |
| subjects affected / exposed | 6 / 193 (3.11%)   | 10 / 190 (5.26%)  |  |
| occurrences (all)           | 6                 | 10                |  |
| Hyperphosphataemia          |                   |                   |  |
| subjects affected / exposed | 20 / 193 (10.36%) | 13 / 190 (6.84%)  |  |
| occurrences (all)           | 20                | 14                |  |
| Hypertriglyceridaemia       |                   |                   |  |
| subjects affected / exposed | 14 / 193 (7.25%)  | 9 / 190 (4.74%)   |  |
| occurrences (all)           | 14                | 9                 |  |
| Hyperuricaemia              |                   |                   |  |
| subjects affected / exposed | 21 / 193 (10.88%) | 25 / 190 (13.16%) |  |
| occurrences (all)           | 21                | 25                |  |
| Hypocalcaemia               |                   |                   |  |
| subjects affected / exposed | 24 / 193 (12.44%) | 30 / 190 (15.79%) |  |
| occurrences (all)           | 24                | 30                |  |
| Hypokalaemia                |                   |                   |  |
| subjects affected / exposed | 26 / 193 (13.47%) | 24 / 190 (12.63%) |  |
| occurrences (all)           | 26                | 24                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 29 January 2013 | <p>Results from the CALLISTO study, a 12-month, randomized, multicenter study comparing de novo everolimus versus de novo MPA, were presented. The CALLISTO study investigated whether the delayed administration of everolimus reduced the incidence of DGF and wound-healing events without compromising efficacy in transplant patients at protocol-specified DGF risk during a 3-month period and then at 1 year post- transplant. After 4 weeks from kidney transplant, the incidence of wound-healing disorders was 24.6% (16/65) and 33.8% (25/74) in the immediate everolimus and delayed everolimus groups respectively (<math>p=0.267</math>). At 3 months and at 1 year, consistent results and similar differences in the incidences of wound-healing complications between treatment groups were observed. Based on these results (about 10% difference), but considering the small population of the</p> <p>CALLISTO study and sample size estimation calculated not only on wound-healing complication (the primary objective was a composite endpoint including DGF and wound- healing complications), it was decided to maintain the superiority design but to revise the limit. The expected difference between groups was changed from 20% to 15% since it was considered more adequate as a clinically significant difference in the proportion of patients without wound-healing complications in each group at 3 months after transplant. Consequently, the total number of patients to be enrolled increased from 214 to 396 (i.e. 198 patients in each treatment group). In addition, it was decided to collect more data on long-term wound-healing complications in the two groups. For this reason, an additional follow-up visit at 12 months after transplant was added to the study period stated in the original protocol. At this visit, the safety profile and immunosuppressive therapy used from the end of the study to 12 months after transplantation was to be described as well.</p> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported