



## Clinical trial results:

**A 2-arm, prospective, randomized, controlled, open-label, 12 month Phase III trial to evaluate the efficacy regarding renal function of everolimus in combination with a centre specific standard immunosuppressive regimen consisting of CNI, purinantagonists and steroids versus a standard triple immunosuppressive regimen in lung transplant recipients.**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2011-001539-21  |
| Trial protocol           | DE              |
| Global end of trial date | 05 January 2017 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 31 December 2017 |
| First version publication date | 31 December 2017 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CRAD001ADE36 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01404325 |
| 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:

## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Interim         |
| Date of interim/final analysis                       | 05 January 2017 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 05 January 2017 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate that an everolimus-based, quadruple immunosuppressive regimen had superior efficacy on renal function compared with a calcineurin inhibitor (CNI)-based triple immunosuppressive regimen as measured by calculated GFR (cGFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) at 12 months after randomization in lung transplant recipients.

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.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 01 February 2012 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Germany: 130 |
| Worldwide total number of subjects   | 130          |
| EEA total number of subjects         | 130          |

Notes:

### Subjects enrolled per age group

|                                           |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 121 |
| From 65 to 84 years                       | 9   |

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

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

232 patients who were de novo lung transplant recipients were planned for enrolling into the study. A total of 130 patients were actually randomized with 67 patients randomized to the quadruple low-level treatment arm and 63 patients randomized to the center-specific triple treatment arm.

### 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>             | Quadruple low level IS regimen |

Arm description:

quadruple immunosuppressive (IS) regimen consisting of everolimus, CNI, MPA and steroids

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

Dosage and administration details:

Everolimus (0.25mg, 0.5mg, 0.75mg or 1.0mg) oral tablets or (0.1mg) oral dispersible tablets administered as a suspension daily dosing according to blood levels serum trough level: 4 +/- 1 ng/mL

|                                        |                    |
|----------------------------------------|--------------------|
| Investigational medicinal product name | Cyclosporine A     |
| Investigational medicinal product code |                    |
| Other name                             | Sandimmun® Optoral |
| Pharmaceutical forms                   | Capsule            |
| Routes of administration               | Oral use           |

Dosage and administration details:

Cyclosporine A (10 mg, 25 mg, 50 mg or 100 mg) oral capsules daily dosing according to blood levels serum trough level: 50 +/- 25 ng/mL

|                                        |            |
|----------------------------------------|------------|
| Investigational medicinal product name | Tacrolimus |
| Investigational medicinal product code |            |
| Other name                             |            |
| Pharmaceutical forms                   | Capsule    |
| Routes of administration               | Oral use   |

Dosage and administration details:

Tacrolimus (0.5 mg, 1 mg or 5 mg,) oral capsules as a suspension daily dosing according to blood levels serum trough level: 3-5 ng/mL

|                                        |                             |
|----------------------------------------|-----------------------------|
| Investigational medicinal product name | Mycophenolate mofetil (MMF) |
| Investigational medicinal product code |                             |
| Other name                             | CellCept                    |
| Pharmaceutical forms                   | Tablet, Capsule             |
| Routes of administration               | Oral use                    |

|                                                                                                                                          |                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Dosage and administration details:                                                                                                       |                                                                      |
| Mycophenolate mofetil 250mg oral capsule or 500mg oral tablets daily dosing max 2000 mg/day                                              |                                                                      |
| Investigational medicinal product name                                                                                                   | Mycophenolic acid                                                    |
| Investigational medicinal product code                                                                                                   |                                                                      |
| Other name                                                                                                                               | Myfortic                                                             |
| Pharmaceutical forms                                                                                                                     | Tablet                                                               |
| Routes of administration                                                                                                                 | Oral use                                                             |
| Dosage and administration details:                                                                                                       |                                                                      |
| Mycophenolic acid 180mg or 360mg oral tablets daily dosing max 1440 mg/day                                                               |                                                                      |
| Investigational medicinal product name                                                                                                   | Azathioprine                                                         |
| Investigational medicinal product code                                                                                                   |                                                                      |
| Other name                                                                                                                               | Imurek                                                               |
| Pharmaceutical forms                                                                                                                     | Tablet, Powder and solvent for concentrate for solution for infusion |
| Routes of administration                                                                                                                 | Oral use                                                             |
| Dosage and administration details:                                                                                                       |                                                                      |
| Azathioprine 25mg or 50mg oral tablets daily or 50mg powder for infusion dosing max 2mg/kg/day                                           |                                                                      |
| Investigational medicinal product name                                                                                                   | Prednisone                                                           |
| Investigational medicinal product code                                                                                                   |                                                                      |
| Other name                                                                                                                               |                                                                      |
| Pharmaceutical forms                                                                                                                     | Tablet                                                               |
| Routes of administration                                                                                                                 | Oral use                                                             |
| Dosage and administration details:                                                                                                       |                                                                      |
| Prednisone oral tablets daily dosing $\leq 0.15$ mg/kg                                                                                   |                                                                      |
| <b>Arm title</b>                                                                                                                         | Centre specific triple IS regimen                                    |
| Arm description:                                                                                                                         |                                                                      |
| centre specific CNI-based triple drug immunosuppression (IS)                                                                             |                                                                      |
| Arm type                                                                                                                                 | Active comparator                                                    |
| Investigational medicinal product name                                                                                                   | Cyclosporine A                                                       |
| Investigational medicinal product code                                                                                                   |                                                                      |
| Other name                                                                                                                               | Sandimmun® Optoral                                                   |
| Pharmaceutical forms                                                                                                                     | Capsule                                                              |
| Routes of administration                                                                                                                 | Oral use                                                             |
| Dosage and administration details:                                                                                                       |                                                                      |
| Cyclosporine A (10 mg, 25 mg, 50 mg or 100 mg) oral capsules daily dosing according to blood levels serum trough level: $\geq 100$ ng/mL |                                                                      |
| Investigational medicinal product name                                                                                                   | Tacrolimus                                                           |
| Investigational medicinal product code                                                                                                   |                                                                      |
| Other name                                                                                                                               |                                                                      |
| Pharmaceutical forms                                                                                                                     | Capsule                                                              |
| Routes of administration                                                                                                                 | Oral use                                                             |
| Dosage and administration details:                                                                                                       |                                                                      |
| Tacrolimus (0.5 mg, 1 mg or 5 mg,) oral capsules as a suspension daily dosing according to blood levels serum trough level: $> 5$ ng/mL  |                                                                      |
| Investigational medicinal product name                                                                                                   | Mycophenolate mofetil (MMF)                                          |
| Investigational medicinal product code                                                                                                   |                                                                      |
| Other name                                                                                                                               | CellCept                                                             |
| Pharmaceutical forms                                                                                                                     | Capsule, Tablet                                                      |
| Routes of administration                                                                                                                 | Oral use                                                             |
| Dosage and administration details:                                                                                                       |                                                                      |
| Mycophenolate mofetil 250mg oral capsule or 500mg oral tablets daily dosing max 2000 mg/day dosage was center-specific                   |                                                                      |

|                                        |                   |
|----------------------------------------|-------------------|
| Investigational medicinal product name | Mycophenolic acid |
| Investigational medicinal product code |                   |
| Other name                             | Myfortic          |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

Mycophenolic acid 180mg or 360mg oral tablets daily dosing max 1440 mg/day dosage was center-specific

|                                        |                                                                      |
|----------------------------------------|----------------------------------------------------------------------|
| Investigational medicinal product name | Azathioprine                                                         |
| Investigational medicinal product code |                                                                      |
| Other name                             | Imurek                                                               |
| Pharmaceutical forms                   | Powder and solvent for concentrate for solution for infusion, Tablet |
| Routes of administration               | Oral use                                                             |

Dosage and administration details:

Azathioprine 25mg or 50mg oral tablets daily or 50mg powder for infusion dosing max 2mg/kg/day dosage was center-specific

|                                        |            |
|----------------------------------------|------------|
| Investigational medicinal product name | Prednisone |
| Investigational medicinal product code |            |
| Other name                             |            |
| Pharmaceutical forms                   | Tablet     |
| Routes of administration               | Oral use   |

Dosage and administration details:

Prednisone oral tablets daily dosing  $\leq 0.2$  mg/kg

| <b>Number of subjects in period 1</b> | Quadruple low level IS regimen | Centre specific triple IS regimen |
|---------------------------------------|--------------------------------|-----------------------------------|
| Started                               | 67                             | 63                                |
| Completed                             | 63                             | 61                                |
| Not completed                         | 4                              | 2                                 |
| Adverse event, serious fatal          | 2                              | -                                 |
| non-specified reason                  | -                              | 2                                 |
| Graft loss/Retransplantation          | 1                              | -                                 |
| Lost to follow-up                     | 1                              | -                                 |

## Baseline characteristics

### Reporting groups

|                                                                                                                          |                                   |
|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Reporting group title                                                                                                    | Quadruple low level IS regimen    |
| Reporting group description:<br>quadruple immunosuppressive (IS) regimen consisting of everolimus, CNI, MPA and steroids |                                   |
| Reporting group title                                                                                                    | Centre specific triple IS regimen |
| Reporting group description:<br>centre specific CNI-based triple drug immunosuppression (IS)                             |                                   |

| Reporting group values                             | Quadruple low level IS regimen | Centre specific triple IS regimen | Total |
|----------------------------------------------------|--------------------------------|-----------------------------------|-------|
| Number of subjects                                 | 67                             | 63                                | 130   |
| 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)                               | 64                             | 57                                | 121   |
| From 65-84 years                                   | 3                              | 6                                 | 9     |
| 85 years and over                                  | 0                              | 0                                 | 0     |
| Age Continuous<br>Units: years                     |                                |                                   |       |
| arithmetic mean                                    | 53.9                           | 54.2                              |       |
| standard deviation                                 | ± 9.5                          | ± 9.2                             | -     |
| Gender, Male/Female<br>Units: Subjects             |                                |                                   |       |
| Female                                             | 27                             | 22                                | 49    |
| Male                                               | 40                             | 41                                | 81    |

## End points

### End points reporting groups

|                              |                                                                                          |
|------------------------------|------------------------------------------------------------------------------------------|
| Reporting group title        | Quadruple low level IS regimen                                                           |
| Reporting group description: | quadruple immunosuppressive (IS) regimen consisting of everolimus, CNI, MPA and steroids |
| Reporting group title        | Centre specific triple IS regimen                                                        |
| Reporting group description: | centre specific CNI-based triple drug immunosuppression (IS)                             |

### Primary: Calculated Glomerular Filtration Rate (cGFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) at 12 months

|                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Calculated Glomerular Filtration Rate (cGFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) at 12 months                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| End point description: | Calculated Glomerular Filtration Rate (cGFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) at 12 months The CKD-EPI equation, expressed as a single equation, is $GFR = 141 \times \min(Scr/\kappa, 1)^a \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female) $\times 1.159$ (if black), where Scr is serum creatinine, $\kappa$ is 0.7 for females and 0.9 for males, $a$ is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/ $\kappa$ or 1, and max indicates the maximum of Scr/ $\kappa$ or 1 |
| End point type         | Primary                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| End point timeframe:   | Month 12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| End point values                             | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|----------------------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type                           | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed                  | 67                             | 63                                |  |  |
| Units: mL/min                                |                                |                                   |  |  |
| least squares mean (confidence interval 95%) | 64.5 (59.4 to 69.6)            | 54.6 (49.5 to 59.7)               |  |  |

### Statistical analyses

|                                         |                                                                    |
|-----------------------------------------|--------------------------------------------------------------------|
| Statistical analysis title              | cGFR according to CKD EPI at 12 months                             |
| Comparison groups                       | Centre specific triple IS regimen v Quadruple low level IS regimen |
| Number of subjects included in analysis | 130                                                                |
| Analysis specification                  | Pre-specified                                                      |
| Analysis type                           | superiority                                                        |
| P-value                                 | < 0.0001                                                           |
| Method                                  | ANCOVA                                                             |

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**Secondary: Calculated Glomerular Filtration Rate (cGFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) at Month 1, 3, 6, 9, 12**

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|                 |                                                                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Calculated Glomerular Filtration Rate (cGFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) at Month 1, 3, 6, 9, 12 |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Calculated Glomerular Filtration Rate (cGFR) according to Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) at Month 1, 3, 6, 9 and 12. The CKD-EPI equation, expressed as a single equation, is  $GFR = 141 \times \min(Scr/\kappa, 1)^\alpha \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$  (if female)  $\times 1.159$  (if black), where Scr is serum creatinine,  $\kappa$  is 0.7 for females and 0.9 for males,  $\alpha$  is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/ $\kappa$  or 1, and max indicates the maximum of Scr/ $\kappa$  or 1

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

End point timeframe:

Month 1, 3, 6, 9, 12

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| End point values                     | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|--------------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type                   | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed          | 67                             | 63                                |  |  |
| Units: mL/min                        |                                |                                   |  |  |
| arithmetic mean (standard deviation) |                                |                                   |  |  |
| Month 1                              | 73.5 (± 13.9)                  | 67.1 (± 12.4)                     |  |  |
| Month 3                              | 70.4 (± 13.3)                  | 64.3 (± 12.7)                     |  |  |
| Month 6                              | 69.2 (± 15.5)                  | 63.1 (± 15.0)                     |  |  |
| Month 9                              | 69.0 (± 16.3)                  | 62.3 (± 14.8)                     |  |  |
| Month 12                             | 68.3 (± 16.3)                  | 61.2 (± 14.3)                     |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Calculated Glomerular Filtration Rate (cGFR) according to Cystatin C-based Hoek's formula at Month 1, 3, 6, 9, 12**

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|                 |                                                                                                                   |
|-----------------|-------------------------------------------------------------------------------------------------------------------|
| End point title | Calculated Glomerular Filtration Rate (cGFR) according to Cystatin C-based Hoek's formula at Month 1, 3, 6, 9, 12 |
|-----------------|-------------------------------------------------------------------------------------------------------------------|

End point description:

Calculated Glomerular Filtration Rate (cGFR) according to Cystatin C-based Hoek's formula at Month 1, 3, 6, 9, 12

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

End point timeframe:

Month 1, 3, 6, 9, 12

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| End point values                     | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|--------------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type                   | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed          | 67                             | 63                                |  |  |
| Units: mL/min                        |                                |                                   |  |  |
| arithmetic mean (standard deviation) |                                |                                   |  |  |
| Month 1                              | 68.5 (± 14.6)                  | 61.8 (± 12.8)                     |  |  |
| Month 3                              | 65.7 (± 15.2)                  | 60.3 (± 10.6)                     |  |  |
| Month 6                              | 63.0 (± 15.1)                  | 58.7 (± 12.2)                     |  |  |
| Month 9                              | 61.8 (± 14.1)                  | 57.7 (± 12.8)                     |  |  |
| Month 12                             | 60.8 (± 14.2)                  | 57.5 (± 14.1)                     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Calculated Glomerular Filtration Rate (cGFR) Using Modification of Diet in Renal Disease (MDRD) Formula at Month 1, 3, 6, 9, 12

|                 |                                                                                                                                 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|
| End point title | Calculated Glomerular Filtration Rate (cGFR) Using Modification of Diet in Renal Disease (MDRD) Formula at Month 1, 3, 6, 9, 12 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|

End point description:

Calculated Glomerular Filtration Rate (cGFR) Using Modification of Diet in Renal Disease (MDRD) Formula at Month 1, 3, 6, 9, 12 cGFR (in mL/min/1.73 m<sup>2</sup>) = 186.3\*(C-1.154)\*(A-0.203)\*G\*R where C = the serum concentration of creatinine (mg/dL), A = age (years), G = 0.742 when gender is female, otherwise G = 1, R = 1.21 when race is black, otherwise R = 1.

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

End point timeframe:

Month 1, 3, 6, 9, 12

| End point values                     | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|--------------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type                   | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed          | 67                             | 63                                |  |  |
| Units: mL/min                        |                                |                                   |  |  |
| arithmetic mean (standard deviation) |                                |                                   |  |  |
| Month 1                              | 72.0 (± 13.5)                  | 65.8 (± 11.8)                     |  |  |
| Month 3                              | 68.7 (± 12.2)                  | 63.3 (± 12.3)                     |  |  |
| Month 6                              | 67.6 (± 14.1)                  | 62.3 (± 15.0)                     |  |  |
| Month 9                              | 67.4 (± 14.9)                  | 61.7 (± 15.1)                     |  |  |
| Month 12                             | 67.0 (± 14.8)                  | 60.5 (± 14.4)                     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Calculated Glomerular Filtration Rate (cGFR) according to Cockcroft-Gault at Month 1, 3, 6, 9, 12

|                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                  | Calculated Glomerular Filtration Rate (cGFR) according to Cockcroft-Gault at Month 1, 3, 6, 9, 12 |
| End point description:<br>Calculated Glomerular Filtration Rate (cGFR) according to Cockcroft-Gault at Month 1, 3, 6, 9, 12 For men: $GFR = (140 - \text{Age}) \times \text{Body weight [kg]} / 72 \times \text{Serum Creatinine [mg/dl]}$ For women: $GFR = 0.85 (140 - \text{Age}) \times \text{Body weight [kg]} / 72 \times \text{Serum Creatinine [mg/dl]}$ |                                                                                                   |
| End point type                                                                                                                                                                                                                                                                                                                                                   | Secondary                                                                                         |
| End point timeframe:<br>Month 1, 3, 6, 9, 12                                                                                                                                                                                                                                                                                                                     |                                                                                                   |

| End point values                     | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|--------------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type                   | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed          | 67                             | 63                                |  |  |
| Units: mL/min                        |                                |                                   |  |  |
| arithmetic mean (standard deviation) |                                |                                   |  |  |
| Month 1                              | 78.6 (± 19.2)                  | 72.1 (± 14.9)                     |  |  |
| Month 3                              | 76.1 (± 17.6)                  | 70.1 (± 16.0)                     |  |  |
| Month 6                              | 76.2 (± 19.3)                  | 69.1 (± 17.5)                     |  |  |
| Month 9                              | 76.2 (± 20.1)                  | 69.0 (± 18.2)                     |  |  |
| Month 12                             | 76.2 (± 20.6)                  | 68.4 (± 17.8)                     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of patients experiencing a decline in GFR of < 10, 10-15, 15-20, 20-25 and > 25 mL/min from Baseline to Month 6 and 12.

|                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                 | Incidence of patients experiencing a decline in GFR of < 10, 10-15, 15-20, 20-25 and > 25 mL/min from Baseline to Month 6 and 12. |
| End point description:<br>Incidence of patients experiencing a decline in GFR of < 10, 10-15, 15-20, 20-25 and > 25 mL/min from Baseline to Month 6 and 12 calculated by the CKD-EPI method. Participants are counted in each decline level observed for that participant; this means participants may be counted in more than 1 decline level. |                                                                                                                                   |
| End point type                                                                                                                                                                                                                                                                                                                                  | Secondary                                                                                                                         |

End point timeframe:

Baseline, Month 6, Month 12

| End point values                 | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|----------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type               | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed      | 67                             | 63                                |  |  |
| Units: count of incidences       |                                |                                   |  |  |
| Up to Month 6: < 10 mL/min       | 28                             | 44                                |  |  |
| Up to Month 6: 10 - < 15 mL/min  | 9                              | 18                                |  |  |
| Up to Month 6: 15 - < 20 mL/min  | 6                              | 11                                |  |  |
| Up to Month 6: 20 - < 25 mL/min  | 2                              | 7                                 |  |  |
| Up to Month 6: > 25 mL/min       | 3                              | 7                                 |  |  |
| Up to Month 12: < 10 mL/min      | 36                             | 53                                |  |  |
| Up to Month 12: 10 - < 15 mL/min | 10                             | 27                                |  |  |
| Up to Month 12: 15 - < 20 mL/min | 8                              | 18                                |  |  |
| Up to Month 12: 20 - < 25 mL/min | 8                              | 9                                 |  |  |
| Up to Month 12: > 25 mL/min      | 7                              | 9                                 |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of renal replacement therapy at Month 6 and Month 12

|                 |                                                                |
|-----------------|----------------------------------------------------------------|
| End point title | Incidence of renal replacement therapy at Month 6 and Month 12 |
|-----------------|----------------------------------------------------------------|

End point description:

Incidence of renal replacement therapy at Month 6 and Month 12: There were no incidences in either group where renal replacement therapy was required

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

End point timeframe:

Month 6, Month 12

| End point values            | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|-----------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type          | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed | 67                             | 63                                |  |  |
| Units: count of incidences  |                                |                                   |  |  |
| up to Month 6               | 0                              | 0                                 |  |  |
| up to Month 12              | 0                              | 0                                 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to renal replacement therapy at Month 6 and Month 12

|                 |                                                           |
|-----------------|-----------------------------------------------------------|
| End point title | Time to renal replacement therapy at Month 6 and Month 12 |
|-----------------|-----------------------------------------------------------|

End point description:

Time to renal replacement therapy at Month 6 and Month 12: There were no incidences in either group where renal replacement therapy was required

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

End point timeframe:

Month 6, Month 12

| End point values            | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|-----------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type          | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed | 0 <sup>[1]</sup>               | 0 <sup>[2]</sup>                  |  |  |
| Units: days                 |                                |                                   |  |  |

Notes:

[1] - There were no incidences in either group where renal replacement therapy was required

[2] - There were no incidences in either group where renal replacement therapy was required

## Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of acute rejection episodes at Month 6 and Month 12

|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| End point title | Incidence of acute rejection episodes at Month 6 and Month 12 |
|-----------------|---------------------------------------------------------------|

End point description:

Incidence of acute rejection episodes at Month 6 and Month 12. This table counts multiple occurrences of rejection in the same patient as different incidents. Every incident is associated with both an A and a B classification.

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

End point timeframe:

Month 6, Month 12

| End point values                 | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|----------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type               | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed      | 67                             | 63                                |  |  |
| Units: count of incidences       |                                |                                   |  |  |
| Up to 6 months: Classification A | 11                             | 13                                |  |  |
| Up to 6 months: Classification B | 11                             | 13                                |  |  |
| 6 to 12 months: Classification A | 10                             | 9                                 |  |  |
| 6 to 12 months: Classification B | 10                             | 9                                 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of graft loss/re-transplantation at Month 6 and Month 12

|                 |                                                                    |
|-----------------|--------------------------------------------------------------------|
| End point title | Incidence of graft loss/re-transplantation at Month 6 and Month 12 |
|-----------------|--------------------------------------------------------------------|

End point description:

Incidence of graft loss/re-transplantation at Month 6 and Month 12

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

End point timeframe:

Month 6, Month 12

| End point values            | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|-----------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type          | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed | 67                             | 63                                |  |  |
| Units: count of incidences  |                                |                                   |  |  |
| Month 6                     | 0                              | 0                                 |  |  |
| Month 12                    | 1                              | 1                                 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of Bronchiolitis obliterans syndrome (BOS) at Month 6 and Month 12

|                 |                                                                              |
|-----------------|------------------------------------------------------------------------------|
| End point title | Incidence of Bronchiolitis obliterans syndrome (BOS) at Month 6 and Month 12 |
|-----------------|------------------------------------------------------------------------------|

End point description:

Incidence of Bronchiolitis obliterans syndrome (BOS) at Month 6 and Month 12

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

End point timeframe:

Month 6, Month 12

| End point values              | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|-------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type            | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed   | 67                             | 63                                |  |  |
| Units: count of incidences    |                                |                                   |  |  |
| Month 6 - Total (all grades)  | 66                             | 61                                |  |  |
| Month 12 - Total (all grades) | 66                             | 61                                |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of death at Month 6 and Month 12

|                        |                                            |
|------------------------|--------------------------------------------|
| End point title        | Incidence of death at Month 6 and Month 12 |
| End point description: | Incidence of death at Month 6 and Month 12 |
| End point type         | Secondary                                  |
| End point timeframe:   | Month 6, Month 12                          |

| End point values            | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|-----------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type          | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed | 67                             | 63                                |  |  |
| Units: number of events     |                                |                                   |  |  |
| Month 6                     | 0                              | 0                                 |  |  |
| Month 12                    | 3                              | 1                                 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Quality of Life (QoL, SF36) at Month 6 and Month 12

|                        |                                                                                                                                                    |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Quality of Life (QoL, SF36) at Month 6 and Month 12                                                                                                |
| End point description: | Quality of Life (QoL, SF36) at Month 6 and Month 12 Scores can range from a minimum of 0 (maximum disability) to a maximum of 100 (no disability). |
| End point type         | Secondary                                                                                                                                          |
| End point timeframe:   | Month 6, Month 12                                                                                                                                  |

| <b>End point values</b>                    | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|--------------------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type                         | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed                | 67                             | 63                                |  |  |
| Units: score                               |                                |                                   |  |  |
| arithmetic mean (standard deviation)       |                                |                                   |  |  |
| Month 6: Physical component summary score  | 46.9 (± 7.6)                   | 48.9 (± 7.3)                      |  |  |
| Month 6: Mental component summary score    | 51.5 (± 10.8)                  | 52.6 (± 8.1)                      |  |  |
| Month 6: Physical functioning              | 78.8 (± 20.9)                  | 84.1 (± 16.8)                     |  |  |
| Month 6: Role-Physical                     | 71.1 (± 23.2)                  | 77.1 (± 24.2)                     |  |  |
| Month 6: Bodily pain                       | 76.4 (± 27.9)                  | 81.3 (± 23.4)                     |  |  |
| Month 6: General health perception         | 65.4 (± 19.2)                  | 70.6 (± 19.9)                     |  |  |
| Month 6: Vitality                          | 67.4 (± 18.0)                  | 70.0 (± 14.6)                     |  |  |
| Month 6: Social functioning                | 84.1 (± 22.6)                  | 88.9 (± 17.6)                     |  |  |
| Month 6: Role-Emotional                    | 84.7 (± 22.4)                  | 84.8 (± 17.9)                     |  |  |
| Month 6: Mental health                     | 78.5 (± 17.2)                  | 81.0 (± 12.8)                     |  |  |
| Month 12: Physical component summary score | 47.2 (± 8.8)                   | 47.7 (± 7.1)                      |  |  |
| Month 12: Mental component summary score   | 49.7 (± 11.8)                  | 53.8 (± 9.1)                      |  |  |
| Month 12: Physical functioning             | 77.4 (± 21.8)                  | 82.5 (± 20.0)                     |  |  |
| Month 12: Role-Physical                    | 68.3 (± 26.8)                  | 78.0 (± 22.9)                     |  |  |
| Month 12: Bodily Pain                      | 76.8 (± 27.0)                  | 80.1 (± 22.7)                     |  |  |
| Month 12: General health perception        | 66.7 (± 17.3)                  | 65.8 (± 20.3)                     |  |  |
| Month 12: Vitality                         | 65.7 (± 19.4)                  | 69.9 (± 17.5)                     |  |  |
| Month 12: Social functioning               | 82.3 (± 23.0)                  | 90.5 (± 16.1)                     |  |  |
| Month 12: Role-Emotional                   | 79.4 (± 27.3)                  | 86.2 (± 20.5)                     |  |  |
| Month 12: Mental health                    | 75.4 (± 18.2)                  | 81.8 (± 14.8)                     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Exercise capacity 6-Minute walk test(6MWT) at Month 6 and Month 12

|                 |                                                                    |
|-----------------|--------------------------------------------------------------------|
| End point title | Exercise capacity 6-Minute walk test(6MWT) at Month 6 and Month 12 |
|-----------------|--------------------------------------------------------------------|

End point description:

Exercise capacity (6MWT) at Month 6 and Month 12 The higher the Borg score implies increased shortness of breath and/or increased fatigue.

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

End point timeframe:

Month 6, Month 12

| End point values                           | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|--------------------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type                         | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed                | 67                             | 63                                |  |  |
| Units: Score                               |                                |                                   |  |  |
| arithmetic mean (standard deviation)       |                                |                                   |  |  |
| Month 6-Borg score - Before start of test  | 0.47 (± 0.78)                  | 0.39 (± 0.77)                     |  |  |
| Month 6-Borg score - At end of test        | 1.75 (± 1.58)                  | 1.64 (± 1.31)                     |  |  |
| Month 12-Borg score - Before start of test | 0.38 (± 0.94)                  | 0.42 (± 0.79)                     |  |  |
| Month 12-Borg score - At end of test       | 2.08 (± 1.58)                  | 2.06 (± 1.85)                     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of treated arterial hypertension up to Month 12

|                        |                                                              |
|------------------------|--------------------------------------------------------------|
| End point title        | Incidence of treated arterial hypertension up to Month 12    |
| End point description: | Incidence of treated of arterial hypertension up to Month 12 |
| End point type         | Secondary                                                    |
| End point timeframe:   | up to Month 12                                               |

| End point values            | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|-----------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type          | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed | 67                             | 63                                |  |  |
| Units: number of event      |                                |                                   |  |  |
| Month 1                     | 2                              | 1                                 |  |  |
| Month 3                     | 2                              | 1                                 |  |  |
| Month 6                     | 2                              | 1                                 |  |  |
| Month 9                     | 3                              | 1                                 |  |  |
| Month 12                    | 4                              | 1                                 |  |  |

### Statistical analyses

No statistical analyses for this end point

**Secondary: Incidence of Diabetes Mellitus up to Month 12**

|                 |                                               |
|-----------------|-----------------------------------------------|
| End point title | Incidence of Diabetes Mellitus up to Month 12 |
|-----------------|-----------------------------------------------|

End point description:

Incidence of Diabetes Mellitus up to Month 12

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

End point timeframe:

up to Month 12

| End point values            | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|-----------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type          | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed | 67                             | 63                                |  |  |
| Units: number of events     |                                |                                   |  |  |
| Month 1                     | 0                              | 0                                 |  |  |
| Month 3                     | 0                              | 0                                 |  |  |
| Month 6                     | 0                              | 1                                 |  |  |
| Month 9                     | 1                              | 1                                 |  |  |
| Month 12                    | 1                              | 1                                 |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Trough levels of everolimus at Month 1, 3, 6, 9, 12**

|                 |                                                                    |
|-----------------|--------------------------------------------------------------------|
| End point title | Trough levels of everolimus at Month 1, 3, 6, 9, 12 <sup>[3]</sup> |
|-----------------|--------------------------------------------------------------------|

End point description:

Trough levels of everolimus at Month 1, 3, 6, 9, 12

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

End point timeframe:

Month 1, 3, 6, 9, 12

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This Endpoint is on everolimus levels only

| End point values                     | Quadruple low level IS regimen |  |  |  |
|--------------------------------------|--------------------------------|--|--|--|
| Subject group type                   | Reporting group                |  |  |  |
| Number of subjects analysed          | 67                             |  |  |  |
| Units: ng/mL                         |                                |  |  |  |
| arithmetic mean (standard deviation) |                                |  |  |  |
| Month 1 n=66                         | 4.2 (± 1.4)                    |  |  |  |
| Month 3 n=61                         | 4.4 (± 1.2)                    |  |  |  |
| Month 6 n=58                         | 4.1 (± 1.2)                    |  |  |  |
| Month 9 n=52                         | 4.5 (± 1.6)                    |  |  |  |

|               |                  |  |  |  |
|---------------|------------------|--|--|--|
| Month 12 n=50 | 4.3 ( $\pm$ 1.1) |  |  |  |
|---------------|------------------|--|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Adherence to target ranges of everolimus at Month 1, 3, 6, 9, 12

|                 |                                                                                 |
|-----------------|---------------------------------------------------------------------------------|
| End point title | Adherence to target ranges of everolimus at Month 1, 3, 6, 9, 12 <sup>[4]</sup> |
|-----------------|---------------------------------------------------------------------------------|

End point description:

Adherence to target ranges of everolimus at Month 1, 3, 6, 9, 12

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

End point timeframe:

Month 1, 3, 6, 9, 12

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: This Endpoint is on everolimus levels only

| End point values             | Quadruple low level IS regimen |  |  |  |
|------------------------------|--------------------------------|--|--|--|
| Subject group type           | Reporting group                |  |  |  |
| Number of subjects analysed  | 67                             |  |  |  |
| Units: participant adherence |                                |  |  |  |
| Month 1 Below Target Range   | 10                             |  |  |  |
| Month 1 Within Target Range  | 42                             |  |  |  |
| Month 1 Above Target Range   | 14                             |  |  |  |
| Month 3 Below Target Range   | 5                              |  |  |  |
| Month 3 Within Target Range  | 41                             |  |  |  |
| Month 3 Above Target Range   | 15                             |  |  |  |
| Month 6 Below Target Range   | 7                              |  |  |  |
| Month 6 Within Target Range  | 39                             |  |  |  |
| Month 6 Above Target Range   | 12                             |  |  |  |
| Month 9 Below Target Range   | 5                              |  |  |  |
| Month 9 Within Target Range  | 34                             |  |  |  |
| Month 9 Above Target Range   | 13                             |  |  |  |
| Month 12 Below Target Range  | 3                              |  |  |  |
| Month 12 Within Target Range | 38                             |  |  |  |
| Month 12 Above Target Range  | 9                              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Trough levels of Cyclosporine A (CsA) at Month 1, 3, 6, 9, 12

|                                                                                         |                                                               |
|-----------------------------------------------------------------------------------------|---------------------------------------------------------------|
| End point title                                                                         | Trough levels of Cyclosporine A (CsA) at Month 1, 3, 6, 9, 12 |
| End point description:<br>Trough levels of Cyclosporine A (CsA) at Month 1, 3, 6, 9, 12 |                                                               |
| End point type                                                                          | Secondary                                                     |
| End point timeframe:<br>Month 1, 3, 6, 9, 12                                            |                                                               |

| End point values                     | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|--------------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type                   | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed          | 67                             | 63                                |  |  |
| Units: ng/mL                         |                                |                                   |  |  |
| arithmetic mean (standard deviation) |                                |                                   |  |  |
| Month 1 n=21, 16                     | 61 (± 21.83)                   | 106 (± 21.25)                     |  |  |
| Month 3 n=20, 14                     | 59.65 (± 20.43)                | 109 (± 24.95)                     |  |  |
| Month 6 n= 20, 14                    | 58.50 (± 12.84)                | 103 (± 32.95)                     |  |  |
| Month 9 n=17, 13                     | 57.59 (± 23.26)                | 107 (± 29.13)                     |  |  |
| Month 12 n=21, 13                    | 69.33 (± 48.41)                | 108 (± 27.82)                     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Adherence to target ranges of Cyclosporine A (CsA) at Month 1, 3, 6, 9, 12

|                                                                                                      |                                                                            |
|------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| End point title                                                                                      | Adherence to target ranges of Cyclosporine A (CsA) at Month 1, 3, 6, 9, 12 |
| End point description:<br>Adherence to target ranges of Cyclosporine A (CsA) at Month 1, 3, 6, 9, 12 |                                                                            |
| End point type                                                                                       | Secondary                                                                  |
| End point timeframe:<br>Month 1, 3, 6, 9, 12                                                         |                                                                            |

| End point values             | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type           | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed  | 67                             | 63                                |  |  |
| Units: participant adherence |                                |                                   |  |  |
| Month 1 Below Target Range   | 0                              | 8                                 |  |  |
| Month 1 Within Target Range  | 18                             | 8                                 |  |  |

|                              |    |    |  |  |
|------------------------------|----|----|--|--|
| Month 1 Above Target Range   | 3  | 0  |  |  |
| Month 3 Below Target Range   | 0  | 4  |  |  |
| Month 3 Within Target Range  | 18 | 10 |  |  |
| Month 3 Above Target Range   | 2  | 0  |  |  |
| Month 6 Below Target Range   | 0  | 6  |  |  |
| Month 6 Within Target Range  | 18 | 8  |  |  |
| Month 6 Above Target Range   | 2  | 0  |  |  |
| Month 9 Below Target Range   | 0  | 4  |  |  |
| Month 9 Within Target Range  | 16 | 9  |  |  |
| Month 9 Above Target Range   | 1  | 0  |  |  |
| Month 12 Below Target Range  | 0  | 3  |  |  |
| Month 12 Within Target Range | 16 | 10 |  |  |
| Month 12 Above Target Range  | 5  | 0  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Trough levels of Tacrolimus at Month 1, 3, 6, 9, 12

|                        |                                                     |
|------------------------|-----------------------------------------------------|
| End point title        | Trough levels of Tacrolimus at Month 1, 3, 6, 9, 12 |
| End point description: | Trough levels of Tacrolimus at Month 1, 3, 6, 9, 12 |
| End point type         | Secondary                                           |
| End point timeframe:   | Month 1, 3, 6, 9, 12                                |

| End point values                     | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|--------------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type                   | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed          | 67                             | 63                                |  |  |
| Units: ng/mL                         |                                |                                   |  |  |
| arithmetic mean (standard deviation) |                                |                                   |  |  |
| Month 1 n=44, 45                     | 5.07 (± 1.80)                  | 10.44 (± 2.73)                    |  |  |
| Month 3 n=44, 47                     | 5.18 (± 2.02)                  | 10.53 (± 2.88)                    |  |  |
| Month 6 n= 40, 46                    | 4.70 (± 1.98)                  | 10.09 (± 3.37)                    |  |  |
| Month 9 n=38, 46                     | 5.78 (± 4.18)                  | 10.67 (± 3.44)                    |  |  |
| Month 12 n=41, 47                    | 5.19 (± 2.36)                  | 9.66 (± 3.01)                     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Adherence to target ranges of Tacrolimus at Month 1, 3, 6, 9, 12

|                                                                                            |                                                                  |
|--------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| End point title                                                                            | Adherence to target ranges of Tacrolimus at Month 1, 3, 6, 9, 12 |
| End point description:<br>Adherence to target ranges of Tacrolimus at Month 1, 3, 6, 9, 12 |                                                                  |
| End point type                                                                             | Secondary                                                        |
| End point timeframe:<br>Month 1, 3, 6, 9, 12                                               |                                                                  |

| End point values             | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type           | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed  | 67                             | 63                                |  |  |
| Units: participant adherence |                                |                                   |  |  |
| Month 1 Below Target Range   | 3                              | 0                                 |  |  |
| Month 1 Within Target Range  | 24                             | 45                                |  |  |
| Month 1 Above Target Range   | 17                             | 0                                 |  |  |
| Month 3 Below Target Range   | 3                              | 0                                 |  |  |
| Month 3 Within Target Range  | 23                             | 47                                |  |  |
| Month 3 Above Target Range   | 18                             | 0                                 |  |  |
| Month 6 Below Target Range   | 5                              | 1                                 |  |  |
| Month 6 Within Target Range  | 23                             | 45                                |  |  |
| Month 6 Above Target Range   | 12                             | 0                                 |  |  |
| Month 9 Below Target Range   | 2                              | 0                                 |  |  |
| Month 9 Within Target Range  | 18                             | 46                                |  |  |
| Month 9 Above Target Range   | 18                             | 0                                 |  |  |
| Month 12 Below Target Range  | 3                              | 0                                 |  |  |
| Month 12 Within Target Range | 23                             | 47                                |  |  |
| Month 12 Above Target Range  | 15                             | 0                                 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Incidence of bacterial, viral, and fungal infections at Month 12

|                                                                                            |                                                                  |
|--------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| End point title                                                                            | Incidence of bacterial, viral, and fungal infections at Month 12 |
| End point description:<br>Incidence of bacterial, viral, and fungal infections at Month 12 |                                                                  |
| End point type                                                                             | Secondary                                                        |
| End point timeframe:<br>Month 12                                                           |                                                                  |

| End point values            | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|-----------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type          | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed | 67                             | 63                                |  |  |
| Units: number of incidences |                                |                                   |  |  |
| Bacterial infections        | 3                              | 4                                 |  |  |
| Viral infections            | 14                             | 20                                |  |  |
| Fungal infections           | 3                              | 0                                 |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Triglyceride levels at Month 1, 3, 6, 9, 12

|                        |                                             |
|------------------------|---------------------------------------------|
| End point title        | Triglyceride levels at Month 1, 3, 6, 9, 12 |
| End point description: | Triglyceride levels at Month 1, 3, 6, 9, 12 |
| End point type         | Secondary                                   |
| End point timeframe:   | Month 1, 3, 6, 9, 12                        |

| End point values                     | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|--------------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type                   | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed          | 67                             | 63                                |  |  |
| Units: mmol/L                        |                                |                                   |  |  |
| arithmetic mean (standard deviation) |                                |                                   |  |  |
| Month 1 (n=66, 60)                   | 2.6 (± 1.4)                    | 2.0 (± 0.9)                       |  |  |
| Month 3 (n=65, 60)                   | 2.7 (± 1.3)                    | 2.1 (± 1.0)                       |  |  |
| Month 6 (n=60, 60)                   | 2.6 (± 1.2)                    | 2.0 (± 1.1)                       |  |  |
| Month 9 (n=55, 59)                   | 2.7 (± 1.3)                    | 2.0 (± 1.0)                       |  |  |
| Month 12 (n=63, 60)                  | 2.7 (± 1.5)                    | 2.1 (± 0.9)                       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Total Cholesterol levels at Month 1, 3, 6, 9, 12

|                        |                                                  |
|------------------------|--------------------------------------------------|
| End point title        | Total Cholesterol levels at Month 1, 3, 6, 9, 12 |
| End point description: | Total Cholesterol levels at Month 1, 3, 6, 9, 12 |
| End point type         | Secondary                                        |

End point timeframe:

Month 1, 3, 6, 9, 12

| End point values                     | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|--------------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type                   | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed          | 67                             | 63                                |  |  |
| Units: mmol/L                        |                                |                                   |  |  |
| arithmetic mean (standard deviation) |                                |                                   |  |  |
| Month 1 (n=64, 60)                   | 0.8 (± 0.8)                    | -0.2 (± 0.7)                      |  |  |
| Month 3 (n=63, 60)                   | 1.0 (± 0.8)                    | -0.1 (± 0.9)                      |  |  |
| Month 6 (n=59, 60)                   | 1.1 (± 0.9)                    | -0.2 (± 0.8)                      |  |  |
| Month 9 (n=54, 59)                   | 1.1 (± 0.9)                    | -0.1 (± 0.9)                      |  |  |
| Month 12 (n=61, 60)                  | 0.8 (± 1.1)                    | -0.1 (± 0.8)                      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Low-Density Lipoprotein (LDL)Cholesterol levels at Month 1, 3, 6, 9, 12

|                        |                                                                         |
|------------------------|-------------------------------------------------------------------------|
| End point title        | Low-Density Lipoprotein (LDL)Cholesterol levels at Month 1, 3, 6, 9, 12 |
| End point description: | LDL Cholesterol levels at Month 1, 3, 6, 9, 12                          |
| End point type         | Secondary                                                               |
| End point timeframe:   | Month 1, 3, 6, 9, 12                                                    |

| End point values                     | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|--------------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type                   | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed          | 67                             | 63                                |  |  |
| Units: mmol/L                        |                                |                                   |  |  |
| arithmetic mean (standard deviation) |                                |                                   |  |  |
| Month 1 (n=63, 57)                   | 0.4 (± 0.8)                    | 0.0 (± 0.5)                       |  |  |
| Month 3 (n=62, 58)                   | 0.6 (± 0.7)                    | -0.0 (± 0.6)                      |  |  |
| Month 6 (n=58, 57)                   | 0.7 (± 0.8)                    | -0.0 (± 0.6)                      |  |  |
| Month 9 (n=53, 56)                   | 0.8 (± 0.8)                    | 0.1 (± 0.7)                       |  |  |
| Month 12 (n=57, 57)                  | 0.5 (± 0.9)                    | 0.1 (± 0.6)                       |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: High-Density Lipoprotein (HDL)Cholesterol levels at Month 1, 3, 6, 9, 12

|                                                                          |                                                                          |
|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| End point title                                                          | High-Density Lipoprotein (HDL)Cholesterol levels at Month 1, 3, 6, 9, 12 |
| End point description:<br>HDL Cholesterol levels at Month 1, 3, 6, 9, 12 |                                                                          |
| End point type                                                           | Secondary                                                                |
| End point timeframe:<br>Month 1, 3, 6, 9, 12                             |                                                                          |

| End point values                     | Quadruple low level IS regimen | Centre specific triple IS regimen |  |  |
|--------------------------------------|--------------------------------|-----------------------------------|--|--|
| Subject group type                   | Reporting group                | Reporting group                   |  |  |
| Number of subjects analysed          | 67                             | 63                                |  |  |
| Units: mmol/L                        |                                |                                   |  |  |
| arithmetic mean (standard deviation) |                                |                                   |  |  |
| Month 1 (n=65, 59)                   | 0.1 (± 0.3)                    | -0.1 (± 0.3)                      |  |  |
| Month 3 (n=64, 59)                   | 0.1 (± 0.3)                    | -0.0 (± 0.4)                      |  |  |
| Month 6 (n=60, 59)                   | 0.1 (± 0.4)                    | -0.0 (± 0.4)                      |  |  |
| Month 9 (n=55, 58)                   | 0.0 (± 0.4)                    | -0.0 (± 0.4)                      |  |  |
| Month 12 (n=59, 59)                  | 0.0 (± 0.5)                    | -0.0 (± 0.4)                      |  |  |

## 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

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20.0   |

### Reporting groups

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Center specific triple IS |
|-----------------------|---------------------------|

Reporting group description:

Center specific triple IS

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Quadruple low level IS |
|-----------------------|------------------------|

Reporting group description:

Quadruple low level IS

| Serious adverse events                                              | Center specific triple IS | Quadruple low level IS |  |
|---------------------------------------------------------------------|---------------------------|------------------------|--|
| Total subjects affected by serious adverse events                   |                           |                        |  |
| subjects affected / exposed                                         | 22 / 63 (34.92%)          | 29 / 67 (43.28%)       |  |
| number of deaths (all causes)                                       | 0                         | 0                      |  |
| number of deaths resulting from adverse events                      | 0                         | 0                      |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                           |                        |  |
| BLADDER TRANSITIONAL CELL CARCINOMA                                 |                           |                        |  |
| subjects affected / exposed                                         | 0 / 63 (0.00%)            | 1 / 67 (1.49%)         |  |
| occurrences causally related to treatment / all                     | 0 / 0                     | 1 / 1                  |  |
| deaths causally related to treatment / all                          | 0 / 0                     | 0 / 0                  |  |
| SQUAMOUS CELL CARCINOMA                                             |                           |                        |  |
| subjects affected / exposed                                         | 0 / 63 (0.00%)            | 1 / 67 (1.49%)         |  |
| occurrences causally related to treatment / all                     | 0 / 0                     | 0 / 1                  |  |
| deaths causally related to treatment / all                          | 0 / 0                     | 0 / 0                  |  |
| Vascular disorders                                                  |                           |                        |  |
| DEEP VEIN THROMBOSIS                                                |                           |                        |  |
| subjects affected / exposed                                         | 0 / 63 (0.00%)            | 1 / 67 (1.49%)         |  |
| occurrences causally related to treatment / all                     | 0 / 0                     | 0 / 1                  |  |
| deaths causally related to treatment / all                          | 0 / 0                     | 0 / 0                  |  |

|                                                      |                |                |  |
|------------------------------------------------------|----------------|----------------|--|
| LYMPHOCELE                                           |                |                |  |
| subjects affected / exposed                          | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| LYMPHORRHOEA                                         |                |                |  |
| subjects affected / exposed                          | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| PERIPHERAL VENOUS DISEASE                            |                |                |  |
| subjects affected / exposed                          | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| Pregnancy, puerperium and perinatal conditions       |                |                |  |
| ABORTION SPONTANEOUS                                 |                |                |  |
| subjects affected / exposed                          | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| General disorders and administration site conditions |                |                |  |
| CHEST PAIN                                           |                |                |  |
| subjects affected / exposed                          | 0 / 63 (0.00%) | 3 / 67 (4.48%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 3          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| CHILLS                                               |                |                |  |
| subjects affected / exposed                          | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| HERNIA                                               |                |                |  |
| subjects affected / exposed                          | 2 / 63 (3.17%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          |  |
| INFLAMMATION                                         |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| LOCAL SWELLING                                  |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| LOCALISED OEDEMA                                |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| OEDEMA PERIPHERAL                               |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 3 / 67 (4.48%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| PERIPHERAL SWELLING                             |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| PYREXIA                                         |                |                |  |
| subjects affected / exposed                     | 3 / 63 (4.76%) | 4 / 67 (5.97%) |  |
| occurrences causally related to treatment / all | 2 / 3          | 1 / 5          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Immune system disorders                         |                |                |  |
| LUNG TRANSPLANT REJECTION                       |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 5 / 67 (7.46%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 4 / 5          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Reproductive system and breast disorders        |                |                |  |
| BENIGN PROSTATIC HYPERPLASIA                    |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 2 / 67 (2.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Respiratory, thoracic and mediastinal disorders |                |                |  |
| BRONCHOSTENOSIS                                 |                |                |  |
| subjects affected / exposed                     | 2 / 63 (3.17%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| DYSпноEA                                        |                |                |  |
| subjects affected / exposed                     | 4 / 63 (6.35%) | 3 / 67 (4.48%) |  |
| occurrences causally related to treatment / all | 1 / 5          | 1 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| DYSпноEA EXERTIONAL                             |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| EPISTAXIS                                       |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| HAEMOPTYSIS                                     |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| IDIOPATHIC PULMONARY FIBROSIS                   |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| LUNG DISORDER                                   |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| LUNG INFILTRATION                               |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 3 / 67 (4.48%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| OBLITERATIVE BRONCHIOLITIS                      |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 3 / 67 (4.48%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 1 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| ORGANISING PNEUMONIA                            |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| PAINFUL RESPIRATION                             |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 2 / 67 (2.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| PLEURAL EFFUSION                                |                |                |  |
| subjects affected / exposed                     | 2 / 63 (3.17%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| PULMONARY EMBOLISM                              |                |                |  |
| subjects affected / exposed                     | 2 / 63 (3.17%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 1 / 2          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| SLEEP APNOEA SYNDROME                           |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Investigations                                  |                |                |  |
| BLOOD CREATINE PHOSPHOKINASE INCREASED          |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| C-REACTIVE PROTEIN INCREASED                    |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| FORCED EXPIRATORY VOLUME DECREASED              |                |                 |  |
| subjects affected / exposed                     | 5 / 63 (7.94%) | 9 / 67 (13.43%) |  |
| occurrences causally related to treatment / all | 4 / 8          | 0 / 12          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| IMMUNOSUPPRESSANT DRUG LEVEL INCREASED          |                |                 |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| PULMONARY FUNCTION TEST DECREASED               |                |                 |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| WEIGHT DECREASED                                |                |                 |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                |                 |  |
| COMPLICATIONS OF TRANSPLANTED LUNG              |                |                 |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| MATERNAL EXPOSURE DURING PREGNANCY              |                |                 |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| PELVIC FRACTURE                                 |                |                 |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Congenital, familial and genetic disorders      |                |                 |  |
| HYDROCELE                                       |                |                 |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Cardiac disorders                               |                |                |  |
| ACUTE CORONARY SYNDROME                         |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| ACUTE MYOCARDIAL INFARCTION                     |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| ATRIAL FLUTTER                                  |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| CARDIAC FAILURE CONGESTIVE                      |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| COR PULMONALE                                   |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| CORONARY ARTERY DISEASE                         |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| RIGHT VENTRICULAR FAILURE                       |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 2 / 67 (2.99%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 3          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| SINUS TACHYCARDIA                               |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Nervous system disorders</b>                 |                |                |  |
| <b>HEADACHE</b>                                 |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>PARAPARESIS</b>                              |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>SCIATICA</b>                                 |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>TREMOR</b>                                   |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Blood and lymphatic system disorders</b>     |                |                |  |
| <b>LEUKOPENIA</b>                               |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>Eye disorders</b>                            |                |                |  |
| <b>RETINAL DETACHMENT</b>                       |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| <b>RETINAL VEIN OCCLUSION</b>                   |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| Gastrointestinal disorders                      |                |                |  |
| ABDOMINAL PAIN UPPER                            |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| DIARRHOEA                                       |                |                |  |
| subjects affected / exposed                     | 2 / 63 (3.17%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| DUODENAL ULCER HAEMORRHAGE                      |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| GASTRIC ULCER                                   |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| GASTROINTESTINAL HAEMORRHAGE                    |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| GASTROOESOPHAGEAL REFLUX DISEASE                |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| HAEMORRHAGIC EROSIVE GASTRITIS                  |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| INGUINAL HERNIA                                 |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

|                                                                                                                                                                                                   |                                  |                                  |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|----------------------------------|--|
| Skin and subcutaneous tissue disorders<br>NIGHT SWEATS<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all            | 0 / 63 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 67 (1.49%)<br>0 / 1<br>0 / 0 |  |
| Renal and urinary disorders<br>ACUTE KIDNEY INJURY<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                | 1 / 63 (1.59%)<br>0 / 1<br>0 / 0 | 1 / 67 (1.49%)<br>1 / 2<br>0 / 0 |  |
| URGE INCONTINENCE<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                                 | 0 / 63 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 67 (1.49%)<br>0 / 1<br>0 / 0 |  |
| Musculoskeletal and connective tissue disorders<br>PSEUDARTHROSIS<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 0 / 63 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 67 (1.49%)<br>0 / 1<br>0 / 0 |  |
| Infections and infestations<br>ATYPICAL PNEUMONIA<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                 | 1 / 63 (1.59%)<br>1 / 1<br>0 / 0 | 0 / 67 (0.00%)<br>0 / 0<br>0 / 0 |  |
| BRONCHITIS<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                                        | 1 / 63 (1.59%)<br>0 / 1<br>0 / 0 | 2 / 67 (2.99%)<br>2 / 4<br>0 / 0 |  |
| BRONCHITIS BACTERIAL<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                              | 0 / 63 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 67 (1.49%)<br>1 / 1<br>0 / 0 |  |
| BRONCHITIS VIRAL                                                                                                                                                                                  |                                  |                                  |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (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                     | 4 / 63 (6.35%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 3 / 4          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| GASTROENTERITIS                                 |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| GASTROINTESTINAL INFECTION                      |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| INFECTION                                       |                |                |  |
| subjects affected / exposed                     | 2 / 63 (3.17%) | 3 / 67 (4.48%) |  |
| occurrences causally related to treatment / all | 1 / 2          | 6 / 6          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| LUNG INFECTION                                  |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| PNEUMONIA                                       |                |                |  |
| subjects affected / exposed                     | 3 / 63 (4.76%) | 3 / 67 (4.48%) |  |
| occurrences causally related to treatment / all | 0 / 3          | 6 / 6          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| PNEUMONIA VIRAL                                 |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| PYELONEPHRITIS                                  |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| RESPIRATORY SYNCYTIAL VIRUS INFECTION           |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| RESPIRATORY TRACT INFECTION                     |                |                |  |
| subjects affected / exposed                     | 3 / 63 (4.76%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 3 / 3          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| SUPERINFECTION BACTERIAL                        |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| TRACHEOBRONCHITIS                               |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| URINARY TRACT INFECTION                         |                |                |  |
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| UROSEPSIS                                       |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Metabolism and nutrition disorders              |                |                |  |
| DEHYDRATION                                     |                |                |  |
| subjects affected / exposed                     | 0 / 63 (0.00%) | 1 / 67 (1.49%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| HYPERKALAEMIA                                   |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 63 (1.59%) | 0 / 67 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| 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>                     | Center specific triple IS | Quadruple low level IS |  |
|-------------------------------------------------------|---------------------------|------------------------|--|
| Total subjects affected by non-serious adverse events |                           |                        |  |
| subjects affected / exposed                           | 58 / 63 (92.06%)          | 62 / 67 (92.54%)       |  |
| Investigations                                        |                           |                        |  |
| BRONCHOALVEOLAR LAVAGE ABNORMAL                       |                           |                        |  |
| subjects affected / exposed                           | 6 / 63 (9.52%)            | 3 / 67 (4.48%)         |  |
| occurrences (all)                                     | 6                         | 3                      |  |
| C-REACTIVE PROTEIN INCREASED                          |                           |                        |  |
| subjects affected / exposed                           | 4 / 63 (6.35%)            | 2 / 67 (2.99%)         |  |
| occurrences (all)                                     | 4                         | 3                      |  |
| FORCED EXPIRATORY VOLUME DECREASED                    |                           |                        |  |
| subjects affected / exposed                           | 8 / 63 (12.70%)           | 7 / 67 (10.45%)        |  |
| occurrences (all)                                     | 8                         | 7                      |  |
| PULMONARY FUNCTION TEST DECREASED                     |                           |                        |  |
| subjects affected / exposed                           | 3 / 63 (4.76%)            | 6 / 67 (8.96%)         |  |
| occurrences (all)                                     | 4                         | 7                      |  |
| Injury, poisoning and procedural complications        |                           |                        |  |
| COMPLICATIONS OF TRANSPLANTED LUNG                    |                           |                        |  |
| subjects affected / exposed                           | 4 / 63 (6.35%)            | 0 / 67 (0.00%)         |  |
| occurrences (all)                                     | 4                         | 0                      |  |
| Vascular disorders                                    |                           |                        |  |
| HYPERTENSION                                          |                           |                        |  |
| subjects affected / exposed                           | 4 / 63 (6.35%)            | 7 / 67 (10.45%)        |  |
| occurrences (all)                                     | 4                         | 7                      |  |
| Nervous system disorders                              |                           |                        |  |
| HEADACHE                                              |                           |                        |  |
| subjects affected / exposed                           | 9 / 63 (14.29%)           | 8 / 67 (11.94%)        |  |
| occurrences (all)                                     | 11                        | 8                      |  |

|                                                                                                                        |                        |                        |  |
|------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|--|
| MIGRAINE<br>subjects affected / exposed<br>occurrences (all)                                                           | 4 / 63 (6.35%)<br>7    | 3 / 67 (4.48%)<br>4    |  |
| Blood and lymphatic system disorders<br>ANAEMIA<br>subjects affected / exposed<br>occurrences (all)                    | 3 / 63 (4.76%)<br>3    | 6 / 67 (8.96%)<br>6    |  |
| LEUKOPENIA<br>subjects affected / exposed<br>occurrences (all)                                                         | 19 / 63 (30.16%)<br>25 | 15 / 67 (22.39%)<br>18 |  |
| General disorders and administration site conditions<br>CHEST PAIN<br>subjects affected / exposed<br>occurrences (all) | 5 / 63 (7.94%)<br>5    | 2 / 67 (2.99%)<br>2    |  |
| OEDEMA PERIPHERAL<br>subjects affected / exposed<br>occurrences (all)                                                  | 10 / 63 (15.87%)<br>11 | 19 / 67 (28.36%)<br>20 |  |
| PYREXIA<br>subjects affected / exposed<br>occurrences (all)                                                            | 5 / 63 (7.94%)<br>5    | 1 / 67 (1.49%)<br>1    |  |
| Gastrointestinal disorders<br>DIARRHOEA<br>subjects affected / exposed<br>occurrences (all)                            | 10 / 63 (15.87%)<br>12 | 9 / 67 (13.43%)<br>10  |  |
| NAUSEA<br>subjects affected / exposed<br>occurrences (all)                                                             | 10 / 63 (15.87%)<br>14 | 9 / 67 (13.43%)<br>10  |  |
| VOMITING<br>subjects affected / exposed<br>occurrences (all)                                                           | 4 / 63 (6.35%)<br>8    | 5 / 67 (7.46%)<br>5    |  |
| Respiratory, thoracic and mediastinal disorders<br>COUGH<br>subjects affected / exposed<br>occurrences (all)           | 7 / 63 (11.11%)<br>7   | 10 / 67 (14.93%)<br>11 |  |
| OROPHARYNGEAL PAIN                                                                                                     |                        |                        |  |

|                                                                                                                   |                        |                        |  |
|-------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                  | 4 / 63 (6.35%)<br>4    | 4 / 67 (5.97%)<br>4    |  |
| PRODUCTIVE COUGH<br>subjects affected / exposed<br>occurrences (all)                                              | 5 / 63 (7.94%)<br>5    | 1 / 67 (1.49%)<br>1    |  |
| Skin and subcutaneous tissue disorders<br>ACNE<br>subjects affected / exposed<br>occurrences (all)                | 1 / 63 (1.59%)<br>1    | 12 / 67 (17.91%)<br>14 |  |
| Musculoskeletal and connective tissue disorders<br>ARTHRALGIA<br>subjects affected / exposed<br>occurrences (all) | 5 / 63 (7.94%)<br>5    | 2 / 67 (2.99%)<br>2    |  |
| BACK PAIN<br>subjects affected / exposed<br>occurrences (all)                                                     | 5 / 63 (7.94%)<br>5    | 2 / 67 (2.99%)<br>3    |  |
| PAIN IN EXTREMITY<br>subjects affected / exposed<br>occurrences (all)                                             | 5 / 63 (7.94%)<br>5    | 8 / 67 (11.94%)<br>8   |  |
| Infections and infestations<br>CYTOMEGALOVIRUS INFECTION<br>subjects affected / exposed<br>occurrences (all)      | 11 / 63 (17.46%)<br>16 | 10 / 67 (14.93%)<br>14 |  |
| LOWER RESPIRATORY TRACT INFECTION<br>subjects affected / exposed<br>occurrences (all)                             | 4 / 63 (6.35%)<br>5    | 2 / 67 (2.99%)<br>2    |  |
| NASOPHARYNGITIS<br>subjects affected / exposed<br>occurrences (all)                                               | 17 / 63 (26.98%)<br>21 | 17 / 67 (25.37%)<br>20 |  |
| RESPIRATORY TRACT INFECTION<br>subjects affected / exposed<br>occurrences (all)                                   | 7 / 63 (11.11%)<br>10  | 8 / 67 (11.94%)<br>10  |  |
| URINARY TRACT INFECTION<br>subjects affected / exposed<br>occurrences (all)                                       | 2 / 63 (3.17%)<br>3    | 4 / 67 (5.97%)<br>4    |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 15 November 2011 | Amendment 1: (prior to study start), introduced the following change:<br>Clarification of the involvement of a CRO.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 01 August 2012   | Amendment 2: introduced the following changes:<br>1) Clarified that 1 measurement of the GFR by CKD EPI prior to screening and baseline visit was sufficient, rather than 2 measurements.<br>2) Tablets for preparation of a suspension, containing 0.1 mg everolimus, were allowed as study medication.<br>3) 1 spirometry assessment could be skipped at either screening or baseline visit when the visits occurred within 5 days of each other.                                                                                                                                                                                                                                                                                                          |
| 30 January 2015  | Amendment 3: introduced the following changes:<br>1) Out of 3 scheduled GFR measurements (CKD-EPI), i.e. 1 prior screening (d-42 to d-1 before screening) 1 at screening (d -42 to d-1) and 1 at baseline (d1), all of these 3 measurements needed to be $\geq 40$ mL/min and $\leq 100$ mL/min/1.73 m <sup>2</sup> ; however, 1 measurement out of these 3 with at least $\geq 50$ mL/min/1.73 m <sup>2</sup> and $\leq 90$ mL/min/1.73m <sup>2</sup> was sufficient to qualify for eligibility with respect to this criterion<br>2) Allowance of CsA trough level reduction once patients reached 2 years post-transplant<br>3) Trade names of 'other immunosuppressive drugs' were changed to generic names<br>4) Corrections of typos for clarification. |
| 25 November 2015 | Amendment 4: introduced the following change:<br>Enrollment was to be terminated by 31-Dec-2015 due to slow recruitment.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported