



Clinical trial results:

Early vs. delayed EVERolimus in de novo HEART transplant recipients: optimization of the safety/efficacy profile (EVERHEART Study)

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2009-011008-43 |
| Trial protocol | IT |
| Global end of trial date | 31 December 2013 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 13 July 2016 |
| First version publication date | 02 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CRAD001AIT16 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01017029 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharmaceuticals |
| 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 | Final |
| Date of interim/final analysis | 31 December 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 December 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare the 6-month cumulative incidence of the safety composite endpoint of wound healing delay related to initial transplant surgery, pleural/pericardial effusions and occurrence of acute renal insufficiency, defined as an estimated glomerular filtration rate (eGFR) ≤ 30 mL/min/1.73 m², between the delayed everolimus arm and the immediate everolimus arm.

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 | 20 September 2009 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Italy: 181 |
| Worldwide total number of subjects | 181 |
| EEA total number of subjects | 181 |

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) | 167 |

| | |
|---------------------|----|
| From 65 to 84 years | 14 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eligible patients were randomized 1:1 ratio.

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 |
| Arm title | Immediate introduction of everolimus |

Arm description:

Everolimus within 144 hours (5 days) after graft reperfusion + cyclosporine microemulsion + steroids

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

Dosage and administration details:

Everolimus within 144 hours (5 days) after graft reperfusion + cyclosporine microemulsion + steroids

| | |
|------------------|------------------------------------|
| Arm title | Delayed introduction of everolimus |
|------------------|------------------------------------|

Arm description:

Mycophenolate mofetil (MMF) within 144 hours (5 days) after graft reperfusion + cyclosporine microemulsion + steroids. After 4 to 6 weeks since transplant, everolimus in place of MMF and dose of cyclosporine reduced.

| | |
|--|-----------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Mycophenolate mofetil (MMF) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

) within 144 hours (5 days) after graft reperfusion + cyclosporine microemulsion + steroids. After 4 to 6 weeks since transplant, everolimus in place of MMF and dose of cyclosporine reduced.

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

Dosage and administration details:

Mycophenolate mofetil (MMF) within 144 hours (5 days) after graft reperfusion + cyclosporine microemulsion + steroids. After 4 to 6 weeks since transplant, everolimus in place of MMF and dose of cyclosporine reduced.

| Number of subjects in period 1 | Immediate introduction of everolimus | Delayed introduction of everolimus |
|--------------------------------|--------------------------------------|------------------------------------|
| | | |
| Started | 89 | 92 |
| Completed | 85 | 90 |
| Not completed | 4 | 2 |
| Adverse event, serious fatal | 3 | 1 |
| Administrative problem | - | 1 |
| Lost to follow-up | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--|--------------------------------------|
| Reporting group title | Immediate introduction of everolimus |
| Reporting group description: | |
| Everolimus within 144 hours (5 days) after graft reperfusion + cyclosporine microemulsion + steroids | |
| Reporting group title | Delayed introduction of everolimus |
| Reporting group description: | |
| Mycophenolate mofetil (MMF) within 144 hours (5 days) after graft reperfusion + cyclosporine microemulsion + steroids. After 4 to 6 weeks since transplant, everolimus in place of MMF and dose of cyclosporine reduced. | |

| Reporting group values | Immediate introduction of everolimus | Delayed introduction of everolimus | Total |
|---|--------------------------------------|------------------------------------|-------|
| Number of subjects | 89 | 92 | 181 |
| Age categorical 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) | 82 | 85 | 167 |
| From 65-84 years | 7 | 7 | 14 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 52.69 | 52.95 | - |
| standard deviation | ± 10.15 | ± 10.19 | - |
| Gender, Male/Female Units: participants | | | |
| Female | 16 | 21 | 37 |
| Male | 73 | 71 | 144 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Caucasian | 88 | 88 | 176 |
| Black | 0 | 1 | 1 |
| Other | 1 | 3 | 4 |
| Study Specific Characteristic Units: kilograms | | | |
| arithmetic mean | 74.38 | 71.18 | - |
| standard deviation | ± 12.5 | ± 12.75 | - |
| Study Specific Characteristic Units: centimeters | | | |
| arithmetic mean | 170.8 | 170.1 | - |
| standard deviation | ± 7.69 | ± 8.03 | - |
| Study Specific Characteristic | | | |

| | | | |
|--------------------|--------|--------|---|
| Units: kg/m2* | | | |
| arithmetic mean | 25.44 | 24.48 | |
| standard deviation | ± 3.65 | ± 3.33 | - |

End points

End points reporting groups

| | |
|--|--------------------------------------|
| Reporting group title | Immediate introduction of everolimus |
| Reporting group description: | |
| Everolimus within 144 hours (5 days) after graft reperfusion + cyclosporine microemulsion + steroids | |
| Reporting group title | Delayed introduction of everolimus |
| Reporting group description: | |
| Mycophenolate mofetil (MMF) within 144 hours (5 days) after graft reperfusion + cyclosporine microemulsion + steroids. After 4 to 6 weeks since transplant, everolimus in place of MMF and dose of cyclosporine reduced. | |

Primary: Participants with at least one occurrence of safety composite endpoint after 6 months by treatment group

| | |
|---|--|
| End point title | Participants with at least one occurrence of safety composite endpoint after 6 months by treatment group |
| End point description: | |
| Comparison of 6-month cumulative incidence of safety composite endpoint (wound healing delay) related to initial transplant surgery, pleural/pericardial effusions and occurrence of acute renal insufficiency, defined as estimated glomerular filtration rate (eGFR) ≤ 30 mL/min/1.73 m ² , between delayed everolimus arm and immediate everolimus arm | |
| End point type | Primary |
| End point timeframe: | |
| 6 months | |

| End point values | Immediate introduction of everolimus | Delayed introduction of everolimus | | |
|------------------------------|--------------------------------------|------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 89 | 92 | | |
| Units: participants | | | | |
| number (confidence interval) | 40 (34.6 to 55.3) | 30 (23 to 42.2) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Safety endpoint by treatment group |
| Comparison groups | Immediate introduction of everolimus v Delayed introduction of everolimus |
| Number of subjects included in analysis | 181 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1043 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.482 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.922 |
| upper limit | 2.383 |

Secondary: Participants with at least one occurrence of each safety composite endpoint event after 6 months by treatment group

| | |
|-----------------|---|
| End point title | Participants with at least one occurrence of each safety composite endpoint event after 6 months by treatment group |
|-----------------|---|

End point description:

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

End point timeframe:

6 months

| End point values | Immediate introduction of everolimus | Delayed introduction of everolimus | | |
|------------------------------|--------------------------------------|------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 89 | 92 | | |
| Units: participants | | | | |
| number (confidence interval) | | | | |
| Wound healing complication | 10 (4.7 to 17.8) | 8 (2.9 to 14.5) | | |
| Pleural effusion | 1 (0 to 3.3) | 1 (0 to 3.2) | | |
| Pericardial effusion | 30 (23.9 to 43.5) | 18 (11.5 to 27.7) | | |
| eGFR ≤ 30 mL/min/1.73 m2 | 7 (2.3 to 13.5) | 8 (2.9 to 14.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Hazard Cox's model analysis of pericardial/pleural effusions

| | |
|-----------------|--|
| End point title | Hazard Cox's model analysis of pericardial/pleural effusions |
|-----------------|--|

End point description:

Pericardial effusions: any pericardial effusion defined as at least moderate (i.e. measuring at least 2.0 cm in diastole, in the point of largest distance between the pericardial leaflets), with or without signs of hemodynamic compromise, or leading to drainage or to prolonged hospitalization. Pleural effusions: need for surgical drainage tubes for longer than 7 days after surgery and subsequent pleural effusions leading to drainage. CI = confidence interval, HR = hazard ratio, MDRD = Modification of Diet in Renal Disease

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

End point timeframe:

6 months

| End point values | Immediate introduction of everolimus | Delayed introduction of everolimus | | |
|-----------------------------|--------------------------------------|------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 89 | 87 | | |
| Units: participants | 30 | 18 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute and percent frequencies of patients with LDL \geq 100 mg/mL at 1, 3 and 6 months, by treatment group

| | |
|-------------------------------|---|
| End point title | Absolute and percent frequencies of patients with LDL \geq 100 mg/mL at 1, 3 and 6 months, by treatment group |
| End point description: | |
| LDL = low density lipoprotein | |
| End point type | Secondary |
| End point timeframe: | |
| 6 months | |

| End point values | Immediate introduction of everolimus | Delayed introduction of everolimus | | |
|------------------------------|--------------------------------------|------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 89 | 92 | | |
| Units: participants | | | | |
| number (confidence interval) | | | | |
| Month 1 | 41 (35.7 to 56.4) | 38 (31.6 to 51.9) | | |
| Month 3 | 37 (32.6 to 53.5) | 37 (30.2 to 50.2) | | |
| Month 6 | 34 (28.1 to 48.3) | 36 (29.2 to 49.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with CMV infection and CMV syndrome/disease after 6 months by treatment group

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|-----------------|--|
| End point title | Participants with CMV infection and CMV syndrome/disease after 6 months by treatment group |
|-----------------|--|

| | |
|---|-----------|
| End point description: | |
| CMV infection is defined as pp65 antigenemia or DNAemia | |
| End point type | Secondary |
| End point timeframe: | |
| 6 months | |

| End point values | Immediate introduction of everolimus | Delayed introduction of everolimus | | |
|------------------------------|--------------------------------------|------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 89 | 92 | | |
| Units: participants | | | | |
| number (confidence interval) | | | | |
| CMV infections | 46 (41.3 to 62.1) | 63 (59 to 78) | | |
| CMV syndrome/disease | 3 (0 to 7.1) | 6 (1.5 to 11.6) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with at least one occurrence of composite treatment failure events

| | |
|---|---|
| End point title | Participants with at least one occurrence of composite treatment failure events |
| End point description: | |
| Comparison of 6-months cumulative incidence of composite treatment failure events (BPAR \geq 2R, rejection with hemodynamic compromise, graft loss, or death) between delayed everolimus arm and immediate everolimus arm | |
| End point type | Secondary |
| End point timeframe: | |
| 6 months | |

| End point values | Immediate introduction of everolimus | Delayed introduction of everolimus | | |
|------------------------------|--------------------------------------|------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 89 | 92 | | |
| Units: participants | | | | |
| number (confidence interval) | 33 (27 to 47.1) | 26 (19.1 to 37.5) | | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

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|-----------------------|-------------|
| Reporting group title | EVE Delayed |
|-----------------------|-------------|

Reporting group description:

EVE Delayed

| | |
|-----------------------|---------------|
| Reporting group title | EVE Immediate |
|-----------------------|---------------|

Reporting group description:

EVE Immediate

| Serious adverse events | EVE Delayed | EVE Immediate | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 31 / 92 (33.70%) | 35 / 89 (39.33%) | |
| number of deaths (all causes) | 1 | 3 | |
| number of deaths resulting from adverse events | 1 | 1 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 2 / 89 (2.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral arterial stenosis | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral artery aneurysm | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 89 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Cardiac pacemaker insertion | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (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 | | | |
| Concomitant disease progression | | | |
| subjects affected / exposed | 2 / 92 (2.17%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Drug interaction | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 89 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Hyperpyrexia | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 89 (1.12%) | |
| 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 / 92 (0.00%) | 2 / 89 (2.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 1 / 89 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 89 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Transplant rejection | | | |
| subjects affected / exposed | 3 / 92 (3.26%) | 7 / 89 (7.87%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Reproductive system and breast disorders | | | |
| Epididymitis | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 89 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mediastinitis | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 2 / 89 (2.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 2 / 89 (2.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 4 / 89 (4.49%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 89 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary microemboli | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Escherichia test positive | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count increased | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 89 (1.12%) | |
| 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 | | | |
| Incision site complication | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound complication | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 3 / 89 (3.37%) | |
| occurrences causally related to treatment / all | 0 / 1 | 5 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (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 | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|------------------|--|
| Bradycardia | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 89 (1.12%) | |
| 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 / 92 (0.00%) | 1 / 89 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 89 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 4 / 92 (4.35%) | 12 / 89 (13.48%) | |
| occurrences causally related to treatment / all | 0 / 12 | 12 / 24 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sick sinus syndrome | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 89 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Convulsion | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 89 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 1 / 89 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspepsia | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 92 (2.17%) | 1 / 89 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis and cholelithiasis | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 2 / 89 (2.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 3 / 89 (3.37%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue | | | |

| | | | |
|---|----------------|----------------|--|
| disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 6 / 92 (6.52%) | 4 / 89 (4.49%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus syndrome | | | |
| subjects affected / exposed | 3 / 92 (3.26%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (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 / 92 (2.17%) | 1 / 89 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infections | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 2 / 89 (2.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 89 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 92 (0.00%) | 1 / 89 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic syndrome | | | |
| subjects affected / exposed | 1 / 92 (1.09%) | 0 / 89 (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 %

| Non-serious adverse events | EVE Delayed | EVE Immediate | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 62 / 92 (67.39%) | 71 / 89 (79.78%) | |
| Injury, poisoning and procedural complications | | | |
| Wound complication | | | |

| | | | |
|---|--|---|--|
| subjects affected / exposed occurrences (all) | 8 / 92 (8.70%) 11 | 8 / 89 (8.99%) 12 | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 11 / 92 (11.96%) 12 | 10 / 89 (11.24%) 12 | |
| Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all) Pericardial effusion subjects affected / exposed occurrences (all) | 3 / 92 (3.26%) 3 32 / 92 (34.78%) 115 | 5 / 89 (5.62%) 5 40 / 89 (44.94%) 160 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) | 9 / 92 (9.78%) 9 7 / 92 (7.61%) 7 | 9 / 89 (10.11%) 12 16 / 89 (17.98%) 21 | |
| General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) | 3 / 92 (3.26%) 5 6 / 92 (6.52%) 7 | 5 / 89 (5.62%) 5 2 / 89 (2.25%) 5 | |
| Immune system disorders Transplant rejection subjects affected / exposed occurrences (all) | 23 / 92 (25.00%) 42 | 28 / 89 (31.46%) 57 | |
| Respiratory, thoracic and mediastinal disorders Pleural effusion subjects affected / exposed occurrences (all) | 25 / 92 (27.17%) 47 | 18 / 89 (20.22%) 35 | |
| Renal and urinary disorders | | | |

| | | | |
|---|------------------------|---------------------|--|
| Renal failure subjects affected / exposed occurrences (all) | 5 / 92 (5.43%) 5 | 0 / 89 (0.00%) 0 | |
| Infections and infestations | | | |
| Cytomegalovirus infection subjects affected / exposed occurrences (all) | 6 / 92 (6.52%) 6 | 2 / 89 (2.25%) 2 | |
| Infection subjects affected / exposed occurrences (all) | 5 / 92 (5.43%) 7 | 2 / 89 (2.25%) 4 | |
| Urinary tract infections subjects affected / exposed occurrences (all) | 3 / 92 (3.26%) 3 | 6 / 89 (6.74%) 8 | |
| Metabolism and nutrition disorders | | | |
| Hypercholesterolaemia subjects affected / exposed occurrences (all) | 6 / 92 (6.52%) 6 | 4 / 89 (4.49%) 4 | |
| Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 10 / 92 (10.87%) 10 | 4 / 89 (4.49%) 4 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 17 January 2010 | The randomization time-frame was increased from 96 hours to 144 hours after graft reperfusion in order to improve safety in eligible patients with sub-optimal postoperative renal function. The following statement was added: After a screening evaluation to be performed within the day of transplant surgery (Day 0), eligible patients were considered for randomization between 24 and 144 hours after transplant (Day 1 to 5). |
| 17 January 2010 | Changes to inclusion and exclusion criteria One inclusion criterion was revised from Male or female cardiac recipients 18 to 65 years of age undergoing primary heart transplantation to Male or female cardiac recipients of at least 18 years of age undergoing primary heart transplantation. |
| 17 January 2010 | The following exclusion criterion was removed from the protocol: - Patients unable to take oral medication. |
| 17 January 2010 | The following exclusion criteria were revised from: Presence of Donor/Recipient serological mismatch for Hepatitis B or C Donor older than 60 years and/or with known donor heart disease at the time of transplantation to Presence of Donor/Recipient serological mismatch for Hepatitis C Donor with known donor heart disease at the time of transplantation. |
| 27 April 2011 | The "Concomitant medications" section was updated as follows to include additional detail regarding induction therapy based on Phase 3 study results. |
| 27 April 2011 | Induction therapy with anti-lymphocyte antibodies or anti-CD25 antibodies are allowed as per center clinical practice. |
| 02 August 2012 | The "Interim analysis" section was updated as follows to include details regarding a second interim analysis. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported