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 m2, 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: Partcipants with at least one occurrence of each safety composite endpoint event after 6 months by treatment group

End point title	Partcipants 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 ≥ 100 mg/mL at 1, 3 and 6 months, by treatment group

End point title	Absolute and percent frequencies of patients with LDL ≥ 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

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 ≥ 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

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

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

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