Sponsor

Novartis Pharmaceuticals Corporation

Generic Drug Name

Everolimus

Trial Indication(s)

Heart Transplantation

Protocol Number

CRAD001AB253E3

Protocol Title

A 2-year follow-up study to collect selected outcome measures among de novo heart transplant recipients who discontinued study medication prematurely in Study RAD001AB253

Clinical Trial Phase

Phase III

Study Start/End Dates

18-Oct-2005 to 25-Apr-07

Reason for Termination (If applicable)

Early termination date: 26-Sep-2006

Study Design/Methodology

This study was conducted as either a retrospective or prospective chart review to determine relevant patient and graft outcomes in patients who discontinued study medication or discontinued the study and did not complete the Month 48 visit. Prospective follow-up information was recorded annually for 1 year from the date of signature for informed consent in

the extension protocol. The final visit was conducted as an interview or retrospective chart review to determine the relevant patient and graft outcomes.

Centers

27 centers in 10 countries: US (12), Canada (3), Spain (3), Belgium (2), Germany (2), UK (1), Norway (1), Denmark (1), Austria (1), and Poland (1)

Objectives:

Primary objective(s)

Primary Objective: Study RAD001 B253E3 was designed to collect limited follow-up data on patient and graft outcomes in those patients who discontinued study medication prematurely during the first 4 years post randomization. These patients did not complete the Month 48 visit while enrolled in the RAD001 B253 study. Data was collected by retrospective chart review or by direct contact, e.g., telephone contact with follow-up evaluations for survival status and MACE history to occur up to one year from the date of signature obtained for informed consent in the extension protocol.

Secondary objective(s)

Not applicable

Test Product (s), Dose(s), and Mode(s) of Administration

No treatment was provided or specified in this extension study, patient immunosuppression was as per local practice.

Statistical Methods

Efficacy: KM estimates and KM plots were provided on the ITT population (from B253 Core study) for the following efficacy events using all data collected in B253E1, B253E2 and B253E3:
• Any MACE, graft loss or death
• Graft loss or death

Safety: All other data (demography, renal function, immunosuppressive drugs and non-fatal MACE) collected in B253E3 population were summarized using descriptive statistics: n (%) for binary data and mean/median/SD/min/max for continuous data (such as serum creatinine).

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:
Patients had given written informed consent to participate in the study. Patients were eligible to enter the RAD001 B253E3 study if they had discontinued study medication or withdrawn prematurely from the B253 core study or extension prior to the Month 48 visit.

Exclusion criteria:
Not applicable

Participant Flow Table

149 patients were enrolled in the E3 study, out of the 300 patients who were eligible for E3

RAD 1.5mg N=45	RAD 3mg N=58	AZA N=46

Baseline Characteristics

Patient demography B253E3 population - 48 month follow-up analysis

Demographic Variable	RAD 1.5mg N=45	RAD 3mg N=58	AZA N=46
Male	36 (80.0%)	43 (74.1%)	41 (89.1%)
Female	9 (20.0%)	15 (25.9%)	5 (10.9%)
Race			
Caucasian	39 (86.7%)	54 (93.1%)	43 (93.5%)
Black	6 (13.3%)	1 (1.7%)	2 (4.3%)
Oriental	0	1 (1.7%)	1 (2.2%)
Other	0	2 (3.4%)	0
Age at baseline (yr)			
n	45	58	46
Mean	51.5	52.6	51.2
SD	12.06	9.39	12.86
Weight (kg)			
n	45	58	46
Mean	74.4	76.5	77.5
SD	16.29	14.05	13.56

Summary of Efficacy

Primary Outcome Result(s)

Non-fatal MACE B253 ITT population - 48 month follow-up analysis

	RAD 1.5mg N=209 n	(%)	RAD 3mg N=211 n	(%)	AZA N=214 n	(%)
Any non-fatal MACE	55	(26.3)	52	(24.6)	63	(29.4)
By each type of non-fatal MACE						
Acute myocardial infarction	11	(5.3)	9	(4.3)	13	(6.1)
Congestive heart failure	12	(5.7)	17	(8.1)	13	(6.1)
Percutaneous cardiac intervention	6	(2.9)	4	(1.9)	4	(1.9)
Coronary artery bypass grafting	0		1	(0.5)	0	
Automated implanted cardiac defibrilat	3	(1.4)	3	(1.4)	2	(0.9)
Cerebral vascular accident	7	(3.3)	5	(2.4)	8	(3.7)
Peripheral vascular disease	7	(3.3)	6	(2.8)	9	(4.2)
Ventricular tachycardia	6	(2.9)	1	(0.5)	7	(3.3)
Ventricular fibrillation	1	(0.5)	1	(0.5)	1	(0.5)
Angiographic coronary artery disease	4	(1.9)	4	(1.9)	3	(1.4)
Other coronary heart disease	6	(2.9)	4	(1.9)	11	(5.1)
Allograft vascular disease	5	(2.4)	4	(1.9)	8	(3.7)

Log-rank test of the Kaplan-Meier estimates of an event comparing RAD and AZA treatment group B253 ITT population - 48 month follow-up analysis

Efficacy endpoint (*)	p-value for the Log-Rank test (RAD 1.5mg vs AZA) (RAD 3mg vs AZA)
MACE, graft loss or death	0.5745 0.6928
Graft loss or death	0.4683 0.5648

Secondary Outcome Result(s) (Only Key Secondary outcome measures not all)

Not Applicable

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

Not applicable

Other Adverse Events by System Organ Class

Not applicable

Date of Clinical Trial Report

2 Nov 2007

Date of Inclusion in the Novartis Trial Results Database

8 March 2016