U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-628/000 (tablet: 0.25, 0.50, 0.75, 1.0 mg) 21-631/000 (dispersible tablet: 0.10, 0.25 mg) For administration purposes, the original NDA was separated by indication into four NDA numbers. NDAs 21-560 (tablet) and 21-561 (dispersible tablet) were assigned for the kidney indication and will be reviewed separately.
Drug Name:	Certican™ (everolimus) 1.5 and 3.0 mg
Indication(s):	Prophylaxis of organ rejection in allogeneic kidney and heart transplantation.
Applicant:	Novartis Pharmaceuticals Corporation
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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This review focuses on the prophylaxis of organ rejection in allogenic heart transplantation indication only. The indication for prophylaxis of organ rejection in allogenic renal transplantation will be discussed in a separate review.

Study B253 showed that fixed doses (1.5 mg/day and 3.0 mg/day) of Certican™ (everolimus, RAD, SDZ RAD, RAD001), administered to *de novo* heart transplant patients in combination with Neoral (CsA) and corticosteroids, were superior to azathioprine (AZA) at 6 months (primary endpoint) and at 12 and 24 months (secondary endpoints) in preventing the incidence of the primary composite endpoint (graft loss, biopsy-proven acute rejection of grade ≥ 3A, acute rejection associated with hemodynamic compromise, death, or loss to follow-up). These differences were mainly due to the incidence rate of acute rejection of grade ≥ 3A, which was statistically lower in both everolimus groups compared to AZA. No statistically significant differences were shown in the incidence of graft loss, death or acute rejection due to hemodynamic compromise.

Although shown to be superior to azathioprine in reducing the incidence of acute rejection, both everolimus doses but were found to be unsafe due to unacceptable renal toxicity. Statistically and clinically significant elevations in creatinine and decreases in creatinine clearance were observed as early as three months following therapy initiation and persisted up through twenty-four months. Treatment unblinding and therapeutic drug monitoring of everolimus in combination with CsA did not result in a statistically relevant improvement in renal function. Additionally, there were higher numbers of bacterial infections, particularly pneumonias, and a lower incidence of viral infections, primarily cytomegalovirus (CMV) infections, in both everolimus groups compared to AZA.

This single Phase 3 study does not provide adequate information to determine a safe and efficacious everolimus dose or regimen, combined with CsA, for organ rejection prophylaxis in *de novo* heart transplant patients. Pharmacokinetic and pharmacodynamic analyses to determine a suitable everolimus regimen followed by a confirmatory Phase 3, randomized, well-controlled, double-blind, comparative study is recommended. This additional Phase 3 study should compare the safety and efficacy of an appropriate everolimus regimen, administered in combination with appropriate doses (full or reduced dose) of CsA and corticosteroids, with an approved comparator such as mycophenolate mofetil (MMF). A suitable primary efficacy endpoint would be a composite endpoint comprised of biopsy-proven acute rejection, acute rejection due to hemodynamic compromise, death, graft loss, and loss-to-follow-up measured at 6 months following treatment initiation. Appropriate sensitivity analyses to include treatment discontinuation and biopsy non-compliance in the composite endpoint should also be performed. To fully measure safety, follow-up data on this new regimen should be collected for at least 24 months. Additionally, this study should consider a cyclosporine sparring regimen if appropriate with selected everolimus dose or concentration.

1.2 Brief Overview of Clinical Studies

1.2.1 Study in heart transplant patients

The sponsor conducted one Phase 3 study, B253, to evaluate the safety and efficacy of everolimus as

prophylaxis for organ rejection in allogenic heart transplant patients. This study assessed the safety and efficacy of two fixed doses of everolimus versus azathioprine as part of a triple therapy immunosuppressive regimen in new heart transplant patients. Study B253 enrolled 634 male or female cardiac patients, between the ages of 16 and 65, who were undergoing primary heart transplant with a donor heart having a cold ischemia time of less than 8 hours. Patients were randomized to 1.5 mg/day of everolimus, 3.0 mg/day of everolimus (given as 0.75 or 1.5 mg twice daily respectively), or 1.0-3.0 mg/kg/day of azathioprine in conjunction with CsA and corticosteroids. Fifty-two clinical sites across the United States, Canada, and Europe participated in this study. The primary objective of this study was to evaluate the efficacy of everolimus versus AZA as measured by the incidence of efficacy failure (composite endpoint consisting of: death, graft loss, biopsy-proven acute rejection, acute rejection associated with hemodynamic compromise, or lost to follow-up). The study was powered to test for superiority of both everolimus doses over azathioprine.

1.2.2 Studies in kidney transplant patients

The sponsor conducted two phase 3 studies, B201 and B251 to evaluate the safety and efficacy of everolimus as prophylaxis for organ rejection in renal transplant patients. Both studies were 1-year (with a one-year open label extension) double-blind, double-dummy, randomized, multicenter, parallel-group, comparing the efficacy and safety of everolimus (1.5 mg/day and 3.0 mg/day) versus MMF (2g/day) in combination with CsA and corticosteriods. Studies B201 and B251 enrolled 588 and 583 patients respectively. The primary objectives of each study was to show that at least one dose of everolimus was clinically equivalent (pre-specified delta of 10%) to MMF in efficacy failure at 6 months and in incidence of graft loss, death or loss to follow-up at 12 months (co-primary endpoint).

Review of these studies and the indication of prophylaxis for organ rejection in kidney transplantation will be presented in a separate statistical review and will not be discussed further in this review.

1.3 Statistical Issues and Findings

The primary efficacy variable of study B253 was a composite endpoint of graft loss (GL), biopsy-proven acute rejection (BPAR) of grade ≥ 3A, acute rejection (AR) associated with hemodynamic compromise (HDC), death, or loss to follow-up (LTF) at 6 months. The sponsor demonstrated that everolimus given orally (1.5 mg/day and 3.0 mg/day), in combination with CsA and corticosteriods, to *de novo* heart transplant patients, is superior over azathioprine 1.0-3.0 mg/kg/day at 6 months post-transplant as measured by the incidence of the primary efficacy variable. Superiority of everolimus over AZA was also demonstrated at months 12 and 24 as secondary endpoints. Results of the primary and secondary analyses of this endpoint are provided in Table 1.1 below.

Table 1.1: Endpoints at months 6 (primary), 12 and 24 (secondary)

	everolimus 1.5 mg	everolimus 3.0 mg	AZA 1-3 mg/kg/day	p-value	95% CI	97.5% CI
Month 6	76/209 (36.4%)	57/211 (27.0%)	100/214 (46.7%)	0.031[a] <0.001[b]	(-19.6, -.1*)[a] (-28.7, -11.0)[b]	(-21.0, 0.4)[a] (-30.0, -9.4)[b]
Month 12	87/209 (41.6%)	68/211 (32.2%)	113/214 (52.8%)	0.020[a] <0.001[b]	(-20.7, -1.7)[a] (-29.8, -11.0)[b]	(-22.0, -0.4)[a] (-31.1, -10)[b]
Month 24**	96/209 (45.9%)	76/211 (36.0%)	123/214 (57.5%)	0.016[a] <0.001[b]	(-21.1, -2.1)[a] (-30.8, -12.0)[b]	(-22.4, -0.8)[a] (-32.1, -11)[b]

** Sponsor reports an upper bound of -1.0 on page 50 of Clinical Study Report of 12-month analysis. Reviewer calculates an upper bound of -.10 (typo likely)*
*** Assigned treatments were unblinded after month 12 prior to the month 24 analyses. This should be considered when interpreting the month 24 results.*
Both 95% and 97.5% confidence intervals are presented since adjustments for multiplicity were made using the Hochberg method.
Cut-off days for 6, 12, and 24-month efficacy analyses were 194, 381, and 810 respectively
[a] everolimus1.5 mg vs. AZA, [b] everolimus 3 mg vs. AZA (P-values and CI's calculated using the Z-test statistic)

Individual response rates for GL, BPAR of grade ≥ 3A, AR associated with HDC, death, or LTF were measured as secondary endpoints (Table 3.5). At month 6, 12, and 24 (unblinded treatment), there were significantly more (pair-wise z-test) episodes of BPAR of grade ≥ 3A observed in the AZA arm compared with both everolimus groups. No statistically significant between-group differences were observed in numbers of GL, AR associated with HDC, death, or LTF at months 6, 12, and 24.

At month 12, the incidence of death was greater in the everolimus 3.0 mg group (n=24) as compared to both the everolimus 1.5 mg group (n=18) and the AZA group (n=17). This difference was not statistically significant nor was there a notable difference in causes of death among the treatment arms. Similarly, at month 24, the death rates were 10% (n=21), 13.7% (n=29), and 11.2% (n=24) for everolimus 1.5, everolimus 3.0 and AZA respectively and again not statistically different. Patients experiencing graft loss at month 12 were 7, 11, and 10 and at month 24 were 10, 14, and 13 for everolimus 1.5, everolimus 3.0 and AZA respectively with no observed statistical differences. None of these patients received a re-transplant following graft loss and consequently all died.

An additional secondary analysis sought to compare the change from baseline in coronary vessel intimal thickness as measured by intravascular ultrasound (IVUS). This analysis studied a subset of patients (n=211, 33%) who were selected based on having successfully (i.e. no graft-loss, death, premature treatment discontinuation or lost to follow-up) completed at least 12 months of treatment and who had sufficient renal function to allow for proper use of radiological contrast material. Impaired renal function was the primary reason for not performing IVUS at scheduled 12 and 24 months assessments. At 12 months, 16, 12, and 4 patients and at 24 months, 16, 24, and 12 patients in the everolimus 1.5, everolimus 3.0, and AZA groups respectively did not have an IVUS measurement due to renal dysfunction. The selection of patients for IVUS based on the ability to tolerate study drug, coupled with the inability to perform IVUS in patients with renal impairment potentially biases these results.

Of clinical and statistical significance are large increases in plasma creatinine levels and decreases in creatinine clearance values, observed in both everolimus groups. There were significantly more patients who dropped below 50% of baseline creatinine clearance levels, indicative of renal impairment, in both everolimus groups compared with AZA. These changes were observed by the third month following heart transplantation and continued until the end of the study in most patients. Additionally, there were more cases of pneumonia, cardiac tamponade, and pericardial effusion in the everolimus groups compared to AZA and more cases of viral infection in the AZA group compared to both everolimus groups.

There were three major amendments to protocol B253. Of statistical concern is amendment 3, dated 10/29/01, which allowed for treatment unblinding and therapeutic drug monitoring of everolimus and CsA. The rationale for these changes was to minimize nephrotoxicity, which is a believed to be due to combining everolimus and full-dose CsA. Unblinding occurred with the implementation of the amendment at which time all patients had completed one year of double-blind treatment. The amendment specified that for patients with satisfactory renal function and allograft status, everolimus patients were to remain on their current doses of immunosuppressants. For those patients with renal dysfunction, the amendment allowed for adjustment of everolimus doses to achieve a trough level > 3 ng/mL prior to any significant CsA reduction. These changes indicate that fixed everolimus doses of 1.5 mg/day or 3.0 mg/day in combination with CsA and corticosteriods were unsafe. Since this amendment resulted in changes to the original randomized everolimus treatments, a safe and efficacious dose of everolimus can not be determined from this study.

Premature treatment discontinuation, primarily due to adverse events, was frequent and significantly higher in the everolimus 3.0 mg group compared to the AZA group. In this subset of patients who prematurely discontinued study treatment, protocol schedule surveillance biopsies and most safety information were not collected (as per-protocol, adverse events recorded more than 8 days following treatment discontinuation were not included in the sponsor's safety analyses). Comparisons of safety and the intent-to-treat efficacy analyses may be biased due to shorter observation times for events while on study treatment and the fact that more patients in the everolimus 3.0 group received alternative therapy after prematurely discontinuing study treatment. Additionally, it is possible that events of BPAR, particularly in the everolimus 3.0 mg, were missed due the fact that surveillance biopsies were not performed after treatment discontinuation.

2 INTRODUCTION

2.1 Overview

Certican™ is a derivative of rapamycin being studied as a new immunosuppressive agent as prophylaxis of organ rejection in heart or kidney transplant recipients. The Phase 3 clinical program for everolimus consists of two Phase 3 studies (B251 and B201), two supportive studies (B156 and B157) and one pediatric study (B351) for the renal indication and one Phase 3 study (B253) for the heart indication. The sponsor conducted two additional studies in renal transplant, A2306 and A2307, which were not submitted in full in this NDA. This review will focus on only the indication of immunosuppression in heart transplant recipients and therefore will focus on study B253. Everolimus indicated for immunosuppression in kidney transplant recipients will be reviewed separately.

Clinical study B253 was a prospective, randomized, 1-year with a 1-year open label extension, multi-center, active control, parallel-group, double-blind, double-dummy study in *de novo* heart transplant recipients. A total of 634 patients were enrolled in approximately 40 clinical sites located in the United States, Canada and Europe.

Study B253 assessed the safety and efficacy of two fixed doses of everolimus compared to azathioprine as part of an immunosuppressive regimen of CsA and corticosteroids in *de novo* heart transplant recipients. Patients were randomized to either everolimus 1. 5 mg, everolimus 3.0 mg or AZA 1.0-3.0 mg/kg in a 1:1:1 fashion.

The primary objective of study B253 was to compare the efficacy of each dose of everolimus against AZA as measured by the incidence of death, graft loss, biopsy-proven acute rejection episode of grade ≥3A or any clinically suspected acute rejection episode associated with hemodynamic compromise within the first 6 months post-transplant. Secondary endpoints were to compare the efficacy of everolimus against AZA as measured by the incidence of the primary efficacy endpoint, its single components, and the incidence of chronic rejection as measured by IVUS at 12 and 24 months post-transplant. Safety outcomes and population pharmacokinetics of everolimus were also evaluated as part of the secondary analysis.

2.2 Data Sources

The sponsor provided electronic study reports and datasets for the Phase 3 study B253. The following files available within the FDA Electronic Document Room were utilized during this review:

12-month analysis study report
24-month analysis study report
\\Cdsesub1\N21560\N_000\2002-12-19\clinstat

Integrated summary of efficacy and safety
\\Cdsesub1\N21560\N_000\2002-12-19\clinstat\ises

12-month data files
\\Cdsesub1\N21560\N_000\2002-12-19\crt\datasets\253\derived

24-month data files
\\Cdsesub1\N21560\N_000\2002-12-19\crt\datasets\253\der24m

Reviewer requested data files
\\Cdsesub1\N21560\N_000\2003-07-18\CRT\Datasets\heart\derived
\\Cdsesub1\N21560\N_000\2003-08-06\CRT\Datasets\Heart\derived
\\Cdsesub1\N21560\N_000\2003-08-07\CRT\Datasets\heart\derived
\\Cdsesub1\n21561\N_000\2003-09-26\clinstat
\\CDSESUB1\N21560\N_000\2003-10-03

120-Day Safety Update
\\CDSESUB1\N21560\N_000\2003-05-02

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study B253 is a 1-year double-blind, double-dummy, with a 1-year open label extension, randomized, multicenter, active controlled study. Randomized patients received everolimus 1.5 mg/day (three 0.25 mg everolimus tablets taken b.i.d.), everolimus 3.0 mg/day (three 0.50 mg everolimus tablets taken b.i.d.) or AZA 1-3 mg/kg/day (1-6 AZA capsules q.d.) in conjunction with CsA and corticosteriods (prednisone) as part of a triple immunosuppressive therapy. To maintain blinding, patients randomized to everolimus also took 1-6 capsules of AZA placebo q.d. and patients randomized to AZA took three everolimus placebo tables bid. Study medication was initiated with CsA within 72 hours following heart transplantation.

Entry criteria consisted of male and female patients 16-65 years of age in North America and 18-65 year of age in Europe who were undergoing primary heart transplantation with a donor heart ischemia time of less than 8 hours. A functional graft at the time of randomization was required for entry. Treatment assignment remained double-blinded during the first 12 months following transplantation and then was unblinded for the remaining 12 months (amendment 3). Regardless of treatment status, all patients who did not withdraw consent, become lost to follow-up, or expire remained in the study for 24 months.

The primary endpoint was the incidence of efficacy failure, which was defined as the first occurrence of death, graft loss, biopsy-proven acute rejection of grade ≥3A, clinically suspected acute rejection associated with hemodynamic compromise or loss to follow-up during the first 6 months following heart transplant.

Secondary endpoints were the incidence of the primary composite endpoint at 12 and 24 months, incidence of simple endpoints at 6, 12, and 24 months, incidence of chronic rejection (allograft vasculopathy) as measured by IVUS at 12 and 24 months, electrocardiography measured heart function differences between the two everolimus doses and AZA at 6, 12, and 24 months, and the safety of the two everolimus doses and AZA at 6, 12, and 24 months. Additionally, this study collected quality of life information during the first 12 and 24 months post transplant and assessed the population pharmacokinetics of everolimus during steady-state administration of CsA for selected subjects. Neither of these two later secondary endpoints will be discussed in this statistical review.

The study protocol states that patients who prematurely discontinue study medication will be contacted to determine the status of acute rejection, hemodynamic compromise, immunosuppressive therapy, biopsy result, graft loss, and death. All post-treatment follow-up information will be analyzed and attributed to the randomized study medication for each patient. The protocol did not require for protocol scheduled biopsies to be performed in patients who prematurely discontinued study medication. Results from any locally performed (not part of the protocol scheduled biopsy requirement) biopsies were documented in patient case report forms and included in the final analyses.

3.1.2 Statistical Methods

The sponsor's Master Analysis Plan for everolimus is located in the Integrated Safety and Efficacy Summary (\\Cdsesub1\N21560\N_000\2002-12-19\clinstat\ises). More detailed statistical methods are located in Appendix 5.1 of the Clinical Study Report for study B253 (\\Cdsesub1\N21560\N_000\2002-12-19\clinstat).

The intent-to-treat population was defined as all patients who were randomized into the study. The safety population was defined as all patients randomized into the study and who received at least one dose of

study medication followed by at least one safety assessment. The safety population was the same as the ITT population in this study since all randomized patients received at least one dose of study drug and had one follow-up visit. The primary efficacy analysis compared the incidence, using the Z-test, of efficacy failure at month 6 between groups in the intent-to-treat population. Approximate 95% and 97.5% confidence intervals were constructed based on Z-test statistics. The statistical null hypotheses tested were: $H_{O,1.5mg}$: rate (everolimus 1.5 mg/day) = rate (AZA) versus the alternative $H_{A,1.5mg}$: rate(everolimus 1.5mg/day) ≠ rate (AZA), and $H_{O,3.0mg}$: rate (everolimus 3.0 mg/day) = rate (AZA) versus the alternative $H_{A,3.0mg}$: rate (everolimus 3.0mg/day) ≠ rate (AZA).

The sponsor proposed the Hochberg method to adjust α for the two comparisons, which rejects both null hypotheses if and only if the largest p-value obtained is less than or equal to α=0.05 (two-sided). Otherwise, the smallest p-value obtained must be less than or equal to 0.025 (α/2) to be considered significant under the respective null hypothesis.

Time to efficacy failure functions for composite and simple events, at months 6, 12, and 24, were calculated using Kaplan-Meier (KM) methodology and compared using the log-rank test. Between-group comparisons of simple event rates were also performed using the Cochran-Mantel-Haenszel (CMH) test, stratifying by study center. Interactions between treatment and center were tested using the Breslow-Day test. Secondary endpoints were compared using the Z-test for superiority and survival function testing using the log-rank test. Safety analyses were performed on events or assessments which occurred while on treatment in the safety population. Safety events were compared using descriptive statistics.

3.1.3 Demographics and Patient Disposition

A total of 634 patients were randomized across 52 centers located throughout the United States, Canada, and Europe. Demographic characteristics (Table 3.1) were similar among the three treatment groups with no statistically significant differences. On average, patients were at least 40 years of age and heart donor ages averaged between 32 and 34 years of age. Over 79% of all patients were men and over 86% were Caucasian. Although reasons for heart transplant varied, the major causes were idiopathic cardiomyopathy and coronary artery disease (CAD). Although not statistically significant, there were approximately 5% more patients in the everolimus 3.0 mg group compared to the other two groups with negative cytomegalovirus (CMV) status receiving a graft from a CMV + donor. Although this population is considered clinically as a high-risk population for developing CMV infection post-transplant the incidence of CMV infection at months 6, 12, and 24 in the everolimus 3.0 mg/day group was no different than in the everolimus 1.5 mg/day group. Cold ischemia time was statistically significantly different (p=0.009) between the everolimus 1.5 mg and the everolimus 3.0 mg groups.

Table 3.1: Baseline demographics and background characteristics

	everolimus 1.5 mg (N=209)	everolimus 3.0 mg (N=211)	AZA (N=214)
Heart Recipient Age (yrs)			
Mean (±SD)	51.2 (11.2)	42.1 (10.8)	50.5 (11.5)
Range	(18-68)	(16-69)	(18-69)
Donor Age, mean yrs (SD)	32.5 (12.5)	34.1 (12.9)	33.6 (13.2)
Age group, n (%)			
< 50 years	81 (38.8)	73 (34.6)	78 (36.4)
≥ 50 years	128 (61.2)	138 (65.4)	136 (63.6)
Recipient Sex, n (%)			
Male	166 (79.4)	171 (81.0)	182 (85.0)
Female	43 (20.6)	40 (19.0)	32 (15.0)
Donor Sex, n (%)			
Male	138 (66.0)	138 (65.4)	147 (68.7)
Female	69 (33.0)	73 (34.6)	66 (30.8)
Unknown	2 (1.0)	0	1 (0.5)
Recipient Race, n (%)			
Caucasian	181 (86.6)	192 (91.0)	193 (90.2)
Black	21 (10.0)	11 (5.2)	13 (6.1)
Asian	2 (1.0)	3 (1.4)	3 (1.4)
Other	5 (2.4)	5 (2.4)	5 (2.3)
Primary Disease for Tx, n (%)			
Idiopathic cardiomyopathy	100 (47.8)	98 (46.4)	115 (53.7)
CAD	78 (37.3)	84 (39.8)	68 (31.8)
Congenital Heart Disease	3 (1.4)	1 (0.5)	7 (3.3)
Myocarditis	3 (1.4)	2 (0.9)	3 (1.4)
Valvular heart disease	6 (2.9)	8 (3.8)	6 (2.8)
Others	19 (9.1)	18 (8.5)	15 (7.0)
CMV Status, n (%)			
Donor +/recipient-	36 (17.2)	48 (22.7)	37 (17.3)
Donor +/recipient +	75 (35.9)	80 (37.9)	83 (38.8)
Cold Ischemia Time (hrs), mean (SD)	2.9 (1.1)	3.2 (1.1)*	3.0 (1.1)

** Statistically significantly different from everolimus 1.5 mg group, p=0.009*

Patient disposition at the 6, 12 and 24-month analyses are presented below in Table 3.2, Table 3.3 and Table 3.4 respectively. By month 12, 29.7%, 39.8%, and 28.5% of patients in the everolimus 1.5 mg/day, everolimus 3.0 mg/day, and AZA groups respectively discontinued treatment, resulting in a significant difference between everolimus 3.0 mg and AZA. Adverse events were the primary reasons for treatment discontinuations. Approximately twenty more patients (10%) discontinued treatment, in each treatment group, by 24 months. The majority of patients, 45%, 39%, and 49% in the everolimus 1.5, everolimus 3.0, and AZA groups, who prematurely discontinued study treatment, switched to mycophenolate mofetil therapy.

Study discontinuations averaged around 7% by month 6, 10% by month 12 and around 13.7% by month 24 with the primary cause being death. Although not statistically significant, there were more deaths in the everolimus 3.0 mg/day groups compared with the other groups at months 12 and 24. Cardiac and vascular disorders and infections were the major causes of death reported.

Table 3.2: Patient disposition up to month 6 (225 day safety cut-off)

	everolimus 1.5 mg (n=209)	everolimus 3 mg (n=211)	AZA (n=214
Discontinued treatment up to 6 months	46 (22.0%)	62 (29.4%) [a]	44 (20.6%)
Adverse Event(s)	22 (10.5%)	36 (17.1%) [b]	18 (8.4%)
Abnormal Lab Value(s)	2 (1%)	10 (4.7%)	7 (3.3%)
Abnormal test procedure results	0	0	0
Unsatisfactory therapeutic effect	12 (5.7%)	2 (1%)	12 (5.6%)
Death	4 (1.9%)	5 (2.4%)	4 (1.9%)
Withdrawn Consent	5 (2.4%)	7 (3.3%)	1 (0.5%)
Lost to follow-up	0	0	1 (0.5%)
Protocol Violation	1 (0.5%)	2 (1%)	1 (0.5%)
Discontinued study up to 6 months	15 (7.2%)	16 (7.6%)	14 (6.5%)
Death	15 (7.2%)	16 (7.6%)	12 (5.6%)
Withdrawn Consent	0	0	1 (0.5%)
Lost to follow-up	0	0	1 (0.5%)

[a.] *everolimus 3.0 mg/day vs. AZA: p=0.036, 95% CI (0.6, 17.0), Z-test statistic*
[b.] *everolimus 3.0 mg/day vs. AZA: p=0.007, 95% CI (2.4, 15.2), Z-test statistic*

Table 3.3: Patient disposition up to month 12 (450 days safety cut-off)

	everolimus 1.5 mg (n=209)	everolimus 3 mg (n=211)	AZA (n=214
Discontinued treatment up to 12 months	62 (29.7%)	84 (39.8%) [a]	61 (28.5%)
Adverse Event(s)	33 (15.8%)	46 (21.8%) [b]	28 (13.1%)
Abnormal Lab Value(s)	4 (1.9%)	14 (6.6%)	8 (3.7%)
Abnormal test procedure results	0	1 (0.5%)	0
Unsatisfactory therapeutic effect	14 (6.7%)	2 (0.9%)	15 (7.0%)
Death	5 (2.4%)	8 (3.8%)	5 (2.3%)
Withdrawn Consent	5 (2.4%)	9 (4.3%)	2 (0.9%)
Lost to follow-up	0	0	1 (0.5%)
Protocol Violation	1 (0.5%)	4 (1.9%)	2 (0.9%)
Discontinued study prior to 12 months	19 (9.1%)	24 (11.4%)	21 (9.8%)
Death	19 (9.1%)	24 (11.4%)	18 (8.4%)
Withdrawn Consent	0	0	2 (0.9%)
Lost to follow-up	0	0	1 (0.5%)

[a.] *everolimus 3.0 mg/day vs. AZA: p=0.014, 95% CI (2.3, 20.2), Z-test statistic*
[b.] *everolimus 3.0 mg/day vs. AZA: p=0.018, 95% CI (1.5, 16.0), Z-test statistic*

Table 3.4: Patient disposition up to month 24 (820 day safety cut-off)

	everolimus 1.5 mg (n=209)	everolimus 3 mg (n=211)	AZA (n=214)
Discontinued treatment up to 24 months	82 (39.2%)	104 (49.3%) [a]	83 (38.8%)
Adverse Event(s)	43 (20.6%)	58 (27.5%) [b]	40 (18.7%)
Abnormal Lab Value(s)	9 (4.3%)	18 (8.5%)	10 (4.7%)
Unsatisfactory therapeutic effect	15 (7.2%)	3 (1.4%)	18 (8.4%)
Death	7 (3.3%)	9 (4.3%)	7 (3.3%)
Withdrawn Consent	6 (2.9%)	11 (5.2%)	3 (1.4%)
Lost to follow-up	0	1 (0.5%)	2 (0.9%)
Protocol Violation	2 (1.0%)	4 (1.9%)	2 (0.9%)
Administration Problems	0	0	1 (0.5%)
Drug taken after study drug discontinuation			
azathioprine	17 (21%)	29 (28%)	5 (6%)
mycophenolate mofetil	37 (45%)	41 (39%)	41 (49%)
Discontinued study prior to 24 months	23 (11.0%)	33 (15.6%)	31 (14.5%)
Death	21 (10.0%)	29 (13.7%)	24 (11.2%)
Withdrawn Consent	2 (1.0%)	3 (1.4%)	5 (2.3%)
Lost to follow-up	0	1 (0.5%)	2 (0.9%)

[a.] *everolimus 3.0 mg/day vs. AZA: p=0.029, 95% CI (1.1, 19.7), Z-test statistic*
[b.] *everolimus 3.0 mg/day vs. AZA: p=0.031, 95% CI (.79, 16.8), Z-test statistic*

3.1.4 Sponsor's Analysis

3.1.4.1 Primary Efficacy Analysis

The primary objective of study B253 was to compare the efficacy of everolimus 1.5 mg/day, everolimus 3.0 mg/day and azathioprine 1.0-3.0 mg/kg/day measured by the incidence of the composite endpoint comprised of death, graft loss, biopsy-proven acute rejection, acute rejection due to hemodynamic compromise, or lost to follow-up. The composite endpoint was measured at 6 months (primary endpoint), and at 12 and 24 months (secondary endpoints) following transplantation. The incidence of the primary composite endpoint was statistically greater in the AZA group compared to both everolimus groups. This overall difference was significant due to the greater number of biopsy proven acute rejections observed in the AZA group. The incidences of death, graft loss, acute rejection due to hemodynamic compromise, or loss to follow-up were not statistically different between everolimus and AZA at 6, 12, and 24 months. Results are presented below in Table 3.5.

Reviewer's Comment: Since treatment unblinding occurred after month 12, the 24 month results should be interpreted differently when examining the safety and efficacy of the randomized fixed everolimus doses.

Table 3.5: Incidence of Composite and Simple Events at 6, 12, and 24 months

Month 6 (up to day 194)	everolimus 1.5 mg (n=209)	everolimus 3 mg (n=211)	AZA (n=214)	95.0% CI	97.5% CI
Primary composite endpoint: (BPAR of grade ≥3A, AR assoc. with HDC, GL, death, or LTFU)	76 (36.5%) p=0.031 [a]	57 (27.0%) p<0.001 [b]	100(46.7%)	(-19.6,-1.0) [a] (-28.5,-10.6) [b]	(-20.9.0,0.4) [a] (-29.7,-9.3) [b]
• BPAR of grade ≥3A	58 (27.8%) p=0.003 [a]	40 (19.0%) p<0.001 [b]	89 (41.6%)	(-22.7,-4.8) [a] (-30.8,-13.8) [b]	(-23.9,-3.5) [a] (-32.0,-12.6) [b]
• AR associated with HDC	14 (6.7%) p=0.755 [a]	11 (5.2%) p=0.339 [b]	16 (7.5%)	(-5.89, 4.32) [a] (-7.20, 2.51) [b]	(-6.69, 5.12) [a] (-7.99, 3.26) [b]
• Graft loss	4 (1.9%) p=0.547 [a]	8 (3.8%) p=0.568 [b]	6 (2.8%)	(-4.31, 2.36) [a] (-2.68, 4.84) [b]	(-4.94, 2.96) [a] (-3.31, 5.52) [b]
• Death	13 (6.2%) p=0.789 [a]	14 (6.6%) p=0.659 [b]	12 (5.6%)	(-4.09, 5.40) [a] (-3.71, 5.88) [b]	(-4.84, 6.18) [a] (-4.47, 6.66) [b]
• Loss-to-follow-up	0 p=0.323 [a]	0 p=0.320 [b]	1 (0.5%)	(-2.60, 1.34) [a] (-2.60, 1.33) [b]	(-3.14, 1.89) [a] (-3.14, 1.86) [b]

Month 12 (up to day 381)	everolimus 1.5 mg (n=209)	everolimus 3 mg (n=211)	AZA (n=214)	95.0% CI	97.5% CI
Primary composite endpoint: (BPAR of grade ≥3A, AR assoc. with HDC, GL, death, or LTFU)	87 (41.6%) p=0.020 [a]	68 (32.2%) p<0.001 [b]	113 (52.8%)	(-20.7,-1.7) [a] (-29.8,-11) [b]	(-22.0,-0.4) [a] (-31.1,-10) [b]
• BPAR of grade ≥3A	64 (30.6%) p=0.001 [a]	45 (21.3%) p<0.001 [b]	98 (45.8%)	(-24.3,-6.1) [a] (-33.2,-16) [b]	(-25.7,-4.7) [a] (-34.4,-15) [b]
• AR associated with HDC	17 (8.1%) p=0.359 [a]	14 (6.6%) p=0.812 [b]	23 (10.7%)	(-8.2, 3.0) [a] (-9.4, 1.2) [b]	(-9.0, 3.8) [a] (-10.2, 2.0) [b]
• Graft loss*	7 (3.3%) p=0.462 [a]	11 (5.2%) p=0.221 [b]	10 (4.7%)	(-5.1, 2.3) [a] (-3.6, 4.6) [b]	(-5.7, 2.9) [a] (-4.2, 5.2) [b]
• Death*	18 (8.6%) p=0.794 [a]	24 (11.4%) p=0.221 [b]	17 (7.9%)	(-4.5, 5.9) [a] (-2.1, 9.1) [b]	(-5.3, 6.7) [a] (-2.9, 9.9) [b]
• Loss-to-follow-up	0 p=0.163 [a]	0 p=0.163 [b]	2 (0.9%)	(-2.2, 0.4) [a] (-2.2, 0.4) [b]	(-2.3, 0.5) [a] (-2.3, 0.5) [b]

Month 24 (up to day 810)	everolimus 1.5 mg (n=209)	everolimus 3 mg (n=211)	AZA (n=214)	95.0% CI	97.5% CI
Primary composite efficacy variable: (BPAR of grade ≥3A, AR assoc. w/HDC, GL, death, or LTFU)	96 (45.9%) p=0.016 [a]	76 (36.0%) p<0.001 [b]	123 (57.5%)	(-21.1,-2.1) [a] (-30.8,-12) [b]	(-22.4,-0.8) [a] (-32.1,-11) [b]
• BPAR of grade ≥3A	73 (34.9%) p=0.005 [a]	48 (22.7%) p<0.001 [b]	103 (48.1%)	(-22.4,-3.9) [a] (-34.2,-17) [b]	(-23.8,-2.6) [a] (-35.4,-15) [b]
• AR associated with HDC	19 (9.1%) p=0.189 [a]	17 (8.1%) p=0.093 [b]	28 (13.1%)	(-10.0, 2.0) [a] (-10.8, 0.8) [b]	(-10.8,-2.8) [a] (-11.7,1.7) [b]
• Graft loss*	10 (4.8%) p=0.556 [a]	14 (6.6%) p=0.833 [b]	13 (6.1%)	(-5.6,3.0) [a] (-4.1, 5.1) [b]	(-6.2,3.6) [a] (-4.8,5.8) [b]
• Death*	21 (10.0%) p=0.688 [a]	29 (13.7%) p=0.435 [b]	24 (11.2%)	(-7.1,4.7) [a] (-3.8,8.8) [b]	(-7.9,5.5) [a] (-4.7,9.7) [b]
• Loss-to-follow-up	0 p=0.163 [a]	0 p=0.163 [b]	2 (0.9%)	(-2.2, 0.4) [a] (-2.2, 0.4) [b]	(-2.3, 0.5) [a] (-2.3, 0.5) [b]

Source: Table 9-1 (b253-12-month.pdf) and Table 2 (b253-34-month.pdf). Values verified by reviewer.
AR=acute rejection, BPAR=biopsy-proven acute rejection, HDC=hemodynamic compromise, GL=graft loss, LTFU=lost to follow-up
[a] everolimus 1.5 mg vs. AZA, [b] everolimus 3 mg vs. AZA (Sponsor's analyses)
Pair-wise comparisons, at month 6, 12, and 24, between everolimus 1.5 mg and everolimus 3.0 mg resulted in p-values <0.05 for the overall primary endpoint (composite endpoint) and for the incidence of BPAR of grade ≥3A. This comparison was not defined as a primary comparison in the study protocol.
Both 95% and 97.5% confidence intervals presented since adjustments for multiplicity were considered where α =0.025 when largest p-value>0.05.
**Discussed further in section 3.1.6*

As a secondary analysis of the primary endpoint, the sponsor performed a survival analysis at month 12 censoring data on day 381. Results (Table 3.6 and Figure 3.1) showed an overall longer (p<0.001) time to endpoint in both everolimus groups compared to AZA.

Table 3.6: Kaplan-Meier Mean Time Estimates of Composite Endpoint at Month 12

	N	Composite Endpoint	Mean time (days) to endpoint	P-value everolimus 1.5 v. AZA everolimus 3.0 v. AZA
everolimus 1.5 mg	209	87	255	0.029
everolimus 3.0 mg	211	68	285	<0.001
AZA	214	113	219	

P-values calculated using the log rank test
Data censored on day 381
Source: Survival curves generated by reviewer and verified against sponsor's data (figure 9-1, page 51 and PTT 9.1-3 of b253-12-month.pdf)

Survival analyses were also performed on month 24 data, censoring data on day 810, resulting in similar results to the month 12 data. Results of this analysis are provided in below in Figure 3.1 and Table 3.7.

Figure 3.1: KM Survival Curves of Composite Efficacy Endpoint at Month 24

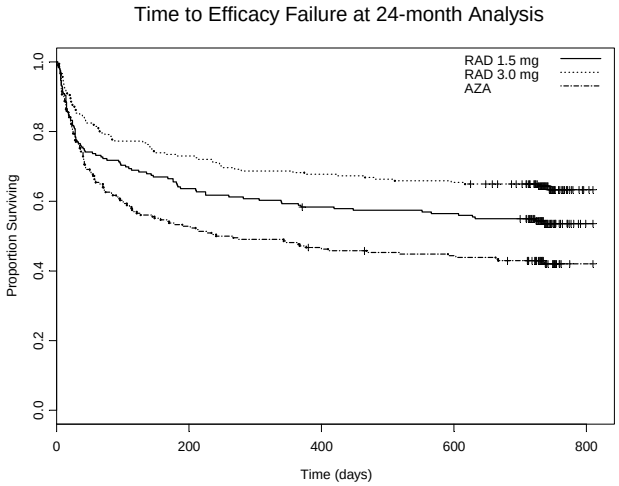


Table 3.7: Kaplan-Meier Mean Time Estimates of Composite Endpoint at month 24

	N	Composite Endpoint	Mean time (days) to endpoint	P-value everolimus 1.5 v. AZA everolimus 3.0 v. AZA
everolimus 1.5 mg	209	96	496	0.0205
everolimus 3.0 mg	211	76	567	<0.0001
AZA	214	123	407	

P-values calculated using the log rank test
Data censored on day 810
Source: Survival curves generated by reviewer and verified against sponsor's data (figure 9-1, page 51 and PTT 9.1-3 of b253-24-month.pdf)

3.1.4.2 Intravenous Ultrasound (IVUS) Sub-Study

An intravenous ultrasound sub-study was conducted on 211 patients to assess coronary artery intimal proliferation. Patients who were continuing treatment, or just discontinued treatment before the month 12 assessment and who had a successful baseline IVUS measurement were selected. The sponsor's rational for selection of patients after completion of 12 months of therapy was to allow for sufficient exposure to randomized treatment.

The primary IVUS efficacy variable was the change, at month 12, in average maximum intimal thickness from baseline, and the incidence of allograft vasculopathy, which was defined as an increase of at least >0.5 mm in maximum intimal thickness from baseline. Per the study protocol, baseline IVUS was required within 6 weeks following heart transplant. The sponsor reports a greater increase in change in intimal thickness and a higher incidence of allograft vasculopathy in the AZA sub-group as compared to both everolimus sub-groups. The sponsor's results are in Table 3.8.

Table 3.8: IVUS Results

	everolimus 1. 5 mg (n=70)	everolimus 3.0 mg (n=69)	AZA (n=72)
Change (mm) in average maximum intimal thickness from baseline to month 12			
mean	0.04 p=0.014	0.03 p=0.003	0.10
range	(-0.36, 0.27)	(-0.20, 0.25)	(-0.44,0.74)
Allograft vasculopathy			
≥0.5 mm	25 (35.7%) p=0.045	21 (30.4%) p=0.010	38 (52.8%)
<0.5 mm	45 (64.3%)	48 (69.6%)	34 (47.2%)

P-values represent pair-wise comparison against AZA
Wilcoxon's Rank Sum test used to compare change in average intimal thickness
Fisher's Exact Test Use to compare incidence of allograft vasculopathy

Although these results suggest a benefit of everolimus in reducing intimal thickening, the method of patient selection for IVUS potentially biased these results. Renal impairment, likely due to treatment assignment as suggested by significant changes in creatinine in the everolimus groups, prevented some patients from participating due to the inability to utilize contrast dye necessary for IVUS reading. Baseline IVUS, required within 6 weeks following transplant, occurred on average, one month following study treatment initiation. Additionally, events which occurred after randomization, particularly coronary arteriopathy, may have influenced the baseline and month 12 test, omitting some patients due to technical difficulties. Since only patients who tolerated at least 12 months of treatment and who had sufficient renal function to allow for a baseline and matching month 12 measurement were included in the IVUS analysis, the results are potentially biased and difficult to fully interpret. IVUS patient selection at the time of randomization, IVUS baseline measured prior to treatment initiation, and an approach for handling drop-outs due to drug discontinuation or medical conditions preventing measurement would yield more interpretable IVUS results.

3.1.5 Reviewer's Analyses

3.1.5.1 Biopsy Compliance

Protocol surveillance endomyocardial biopsies were scheduled at days 7, 14 and 28 and months 2, 3, 6, 9, 12, 18 and 24 and at the time of any suspected rejection episode. The protocol states that patients who prematurely discontinued study medication are to be contacted at 3, 6, 12 and 24 months after the first dose of study drug to obtain follow-up information regarding rejection episodes, graft loss, malignancies, opportunistic infections, survival and immunosuppressive therapy. The protocol does not state the requirement to obtain protocol scheduled biopsies. Biopsy non-compliance (Table 3.9), due to missed visit or premature treatment discontinuation was approximately 20% at month 9 and steadily increased up until month 24. There were more missed biopsies in the everolimus 3.0 mg group, which was likely related to the corresponding high number of premature treatment discontinuations. The fact that protocol biopsies were not required following premature treatment discontinuation raises concern regarding the

sponsor's intent-to-treat analysis. Although biopsies were performed as part of the patient's regular follow-up, these biopsies likely did not follow the same schedule and uniformity as specified in the protocol. This concern prompted a request by the Division to the Sponsor requesting an additional analysis including missed biopsy as an event within the primary composite endpoint. This analysis treated any missed biopsy, either on or off treatment as an event. The results of this additional analysis (Table 3.10) are supportive of the overall efficacy findings of the study but yield less significant results.

Table 3.9: Missed Protocol Biopsies

		Day			Month						
		7	**14**	**28**	**2**	**3**	**6**	**9**	**12**	**18**	**24**
No. eligible*	RAD 1.5mg	19	12	12	16	13	21	40	42	57	71
patients with		(9.1)	(5.9)	(5.9)	(8.0)	(6.6)	(10.7)	(20.6)	(21.9)	(30.0)	(37.8)
missed biopsy (%)	RAD 3mg	17	14	12	24	25	35	44	48	72	82
		(8.1)	(6.2)	(5.7)	(11.8)	(12.4)	(17.5)	(22.6)	(25.3)	(38.5)	(45.3)
	AZA	32	11	11	19	13	22	34	37	54	72
		(15.0)	(5.2)	(5.2)	(9.1)	(6.3)	(10.9)	(17.0)	(18.7)	(27.6)	(38.7)
Reason											
No. D/C study	RAD 1.5mg	1	3	6	10	11	18	29	35	44	50
med. (%)		(0.5)	(1.5)	(2.9)	(5.0)	(5.6)	(9.1)	(14.9)	(18.2)	(23.2)	(26.6)
	RAD 3mg	4	7	8	16	23	33	39	44	53	66
		(1.9)	(3.3)	(3.8)	(7.8)	(11.4)	(16.5)	(20.0)	(23.2)	(28.3)	(36.5)
	AZA	2	4	6	8	11	18	25	26	37	44
		(0.9)	(1.9)	(2.8)	(3.8)	(5.4)	(9.0)	(12.5)	(13.1)	(19.3)	(23.7)
	Average %	**1.1**	**2.2**	**3.2**	**5.6**	**7.4**	**11.5**	**15.8**	**18.2**	**23.6**	**28.9**
Missed Study	RAD 1.5 mg	18	9	6	6	2	3	11	7	13	21
Visit		(8.7)	(4.4)	(2.9)	(3.0)	(1.0)	(1.5)	(5.7)	(3.6)	(6.8)	(11.2)
(%)	RAD 3mg	13	6	4	8	2	2	5	4	19	16
		(6.2)	(2.8)	(1.9)	(3.9)	(1.0)	(1.0)	(2.6)	(2.1)	(10.2)	(8.8)
	AZA	30	7	5	11	2	4	9	11	16	28
		(14.1)	(3.3)	(2.4)	(5.3)	(1.0)	(2.0)	(4.5)	(5.6)	(8.3)	(15.1)
	Average %	**9.6**	**3.5**	**2.4**	**4.1**	**1.0**	**1.5**	**4.2**	**3.8**	**8.4**	**11.7**

** Eligible patients who missed protocol scheduled biopsy include all patients who had not died, had a graft loss, discontinued the study, or became lost-to-follow-up to this time point (patients who had scheduled biopsy are excluded)*
Data source: Sponsor provided data table in 08/07/03 submission to NDA

Table 3.10: Primary Endpoint Containing Missed Biopsy

	everolimus 1.5 mg (n=209)	everolimus 3.0 mg (n=211)	AZA (n=214)
No. of Events (%)*	114 (54.5)	110 (52.1)	134 (62.6)
Difference in Rates (everolimus-AZA)	-8.1%	-10.5%	
95% CI (everolimus –AZA)	(-17.5, 1.3)	(-19.9, -1.1)	
Z-test p-value vs. AZA, 95% CI	0.090	0.028	
Log-rank p-value vs. AZA	0.079	0.013	

Data source: \\Cdsesub1\n21561\N_000\2003-09-26\clinstat
Incidence (%) of the first occurrence of acute rejection of grade ≥3A, acute rejection associated with HDC, graft loss, death, lost-to-follow-up, or* ***missed protocol surveillance biopsy (on or off treatment)*

3.1.5.2 Treatment Discontinuations

Due to the high number of treatment discontinuations, additional analyses were performed to compare the incidence of treatment discontinuation at months 6, 12 and 24. The purpose of these analyses was to study any possible treatment effect on drug compliance between everolimus and azathioprine.

At month 6 (efficacy cut-off of 194 days), the incidence of treatment discontinuation in the everolimus low, high, and AZA groups were 42, 59 and 42 respectively resulting in a significant difference between everolimus 3.0 and AZA with a Z-test p-value=0.04 [95% CI (.24, 16.4)]. At month 12 (efficacy cut-off of 381 days), the incidence was 60, 80, and 60 for everolimus 1.5 mg/day, everolimus 3.0 mg/day and AZA respectively resulting in a p-value=0.030 [95% CI (0.9, 18.6)] when comparing everolimus 3.0 vs. AZA. Additionally, at month 24 (cut-off of 810 days), there were 81, 105, and 83 treatment discontinuations in everolimus 1.5 mg/day, everolimus 3.0 mg/day and AZA respectively resulting in a pair-wise p-value between the high dose everolimus group and AZA of 0.023 [95% CI (0.2, 20.2)].

A survival analysis (Table 3.11) suggested that at 6, 12 and 24 months post-transplant (data censored on days, 194, 381 and 810 respectively) the time to treatment discontinuation was significantly shorter in the everolimus 3.0 mg/day group as compared to the azathioprine group.

Table 3.11: Time to treatment discontinuation (simple event) at months 12 and 24

	everolimus 1.5 mg (n=209)	**everolimus 3.0 mg (n=211)**	**AZA (n=214)**
d/c trt at month 6	42	59	42
d/c trt at month 12	60	80	60
d/c trt at month 24	81	105	83
mean days to trt d/c at mo. 6	66	73	57
mean days to trt d/c at mo. 12	308	286 [a]	310
mean days to trt d/c at mo. 24	595	528 [b]	598

[a.] *everolimus 3.0 vs. AZA, p=0.034 (log rank test)*
[b.] *everolimus 3.0 vs. AZA, p=0.021 (log rank test)*

3.1.5.3 Incidence of Treatment Failure

Treatment discontinuation treated as an event within the efficacy composite endpoint, hereafter referred to as **treatment failure**, is the sponsor's composite endpoint including treatment discontinuation, i.e. it consists of BPAR of grade ≥3A, AR associated with HDC, graft loss, death, lost-to-follow-up, or premature treatment discontinuation. This analysis (Table 3.12) showed that at the month 12 there were statistically more events of treatment failure in the AZA group compared to both everolimus groups, mainly due to the significant number of BPARs of ≥grade 3A. This difference was not observed at the month 24 analyses however, which is likely due to the increased number of treatment discontinuations in the everolimus groups.

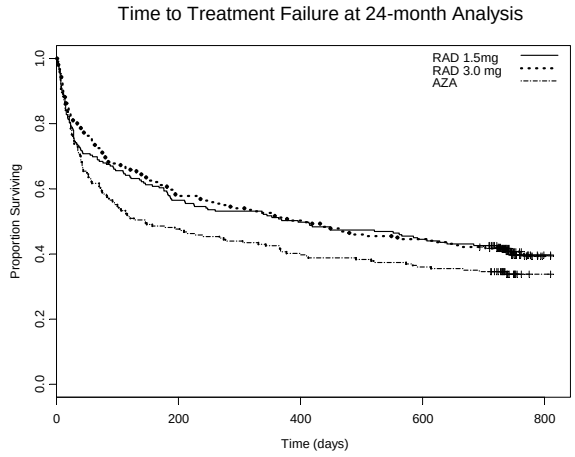
Table 3.12: Incidence of treatment failure*

	everolimus 1.5 mg (n=209)	everolimus 3 mg (n=211)	AZA (n=214)	p-value (95% CI) everolimus 1.5 vs. AZA everolimus 3.0 vs. AZA	Log rank p-value everolimus 1.5 vs. AZA everolimus 3.0 vs. AZA
Month 6	91 (43.5%)	86 (40.8%)	112 (52.3%)	p=0.070 (-18.2,.73) p=0.017 (-20.9,-2.1)	p=0.078 p=0.012
Month 12	104 (49.8%)	105 (49.8%)	128 (59.8%)	p=0.038 (-20.6,0.8) p=0.038 -20.6,0.8)	p=0.045 p=0.019
Month 24	124 (59.3%)	125 (59.2%)	141 (65.9%)	p= 0.163 (-17.0,4.0) p=0.157 (-17.0,3.9)	p=0.103 p=0.053

** Treatment Failure (TF) is defined as the first occurrence of acute rejection of grade ≥3A, acute rejection associated with HDC, graft loss, death, lost-to-follow-up, or* ***treatment discontinuation (reviewer's analysis)***

A Kaplan-Meier survival analysis of time to treatment failure at month 6 resulted in a significant difference in mean time between everolimus 3.0 mg and AZA. At month 12 both everolimus groups had a significantly longer time to failure when compared to AZA. The survival curves up to month 24 are shown in Figure 3.2.

Figure 3.2: Time to treatment failure at month 24



3.1.6 Death and Graft Loss

At the month 12 efficacy analysis, there were 18 deaths (average time to death=177.4 days), 24 deaths (average time to death=223.9 days), and 17 deaths (average time to death=201.8 days) in the everolimus 1.5 mg, everolimus 3.0 mg and AZA groups respectively. Similarly at the 24 month analysis, there were 3 (21 total deaths, average time to death=160.0 days), 5 (29 total deaths, average time to death=232.8 days) and 7 (24 total deaths, average time to death=245.3 days) additional deaths in the everolimus 1.5 mg, everolimus 3.0 mg, and AZA groups respectively. One year survival rates (Table 3.13) are consistent with heart transplant registry data[4] survival rate of 84% and although the incidence of death was higher in

the everolimus 3.0 mg group, a Z-test of proportions and a log-rank test of time to event yielded no statistically significant differences.

Table 3.13: Months 6, 12, and 24 Death Rates

	everolimus 1.5 mg (n=209)	everolimus 3.0 mg (n=211)	AZA (n=214)
Deaths (%) at 6 mos. (day 194)	13 (6.2)	14 (6.6)	12 (5.6)
% Survival at 6 mos.	**93.8**	**93.4**	**94.4**
Deaths (%) at 12 mos. (day 381)	18 (8.6)	24 (11.4)	17 (7.9)
% Survival at 12 mos.	**91.4**	**88.6**	**92.1**
Deaths (%) at 24 mos. (day 810)	21 (10.0)	29 (13.7)	24 (11.2)
% Survival at 24 mos.	**90**	**86.3**	**88.8**

As shown in Table 3.5, there were 7 (average time to GL=199.0 days), 11 (average time to GL=133.6 days), and 10 (average time to GL=152.7 days) graft losses at month 12 and 10 (average time to GL=235.2 days), 14 (average time to GL=237.1 days) and 13 (average time to GL=230.7 days) graft losses at 24 months in the everolimus 1.5 mg, everolimus 3.0 mg, and AZA groups respectively. None of these patients who developed a graft loss received a re-transplant and all expired during the study.

3.2 Evaluation of Safety

At month 24, there were notably more events of pericardial effusion, cardiac tamponade, pneumonia, renal impairment, and thrombotic microangiopathy in both everolimus groups compared to AZA (Table 3.14). The incidence of viral infections was significantly higher in the AZA group compared to both everolimus groups. Conversely, there were significantly more bacterial infections observed in both everolimus groups compared to AZA. Cholesterol and triglycerides increased in all treatment groups but changes from baseline were significantly greater in both everolimus groups compared to AZA. Renal function was significantly impaired in both everolimus groups by month 3 and did not improve during the study. At the recommendation of FDA medical reviewers, additional analyses were performed on changes in renal function and are presented in section 3.2.1. Per the study protocol, adverse events observed while on study treatment or no later than 8 days following treatment discontinuation were included in the safety analyses. Comparisons of incidence rates may be biased since more patients discontinued treatment, and treatment discontinuation occurred earlier on average, in the everolimus 3.0 mg group compared to the other groups. Since the total number randomized was used as the denominator value of the proportion of events to number of patients in treatment group, the incidence rates in the everolimus 3.0 mg may be underestimated. Generally, there is a dose relationship in the everolimus groups in the frequency of events. This trend is reversed for certain adverse events such as pneumonia and hyperlipidemia, which is likely due to more premature discontinuations occurring in the everolimus 3.0 mg group than in the everolimus 1.5 mg group.

Table 3.14: Incidence rates of AEs/infections at month 24 with relevant differences

	everolimus 1.5 mg (n=209)	everolimus 3 mg (n=211)	AZA (n=214)	p-value* (95% CI) everolimus 1.5 vs. AZA everolimus 3.0 vs. AZA
Anemia NOS	70 (33.5%)	93 (44%)	58 (27%)	0.15 (-2.4, 15.1) <0.01 (7.9, 25.8)
Leukopenia NOS	43 (21%)	44 (21%)	63 (29%)	0.04 (-17.0, -.61) 0.04 (-16.8, -.34)
Neutropenia	1(0.5%)	5(2%)	10(5%)	0.01 (-8.2, -1.5) 0.25 (-6.5, 1.3)
Thrombocytopenia	21 (10%)	37 (17.5%)	16(7.5%)	0.39 (-3.2, 8.1) <0.01 (3.6, 16.4)
TMA [1]	5 (2%)	6 (3%)	0%	0.02 (.61, 5.5) 0.01 (1.1, 6.1)
Pericardial effusion	48 (23%)	49 (23%)	36 (17%)	0.11 (-1.5, 13.8) 0.10 (-1.2, 14.0)
Cardiac tamponade	6 (3%)	10 (5%)	3 (1%)	0.30 (-1.5, 4.9) 0.05 (0.1, 7.3)
CMV infection	15 (7%)	15 (7%)	45 (21%)	<0.01 (-20.5, -7.4) <0.01 (-20.6, -7.5)
Pneumonia NOS	29 (14%)	20 (9.5%)	6 (3%)	<0.01 (6.1, 16.7) <0.01 (2.3, 11.7)
Renal impairment NOS	61 (29 %)	65 (31%)	40 (19%)	0.01 (2.4, 18.6) <0.01 (3.9, 20.2)
Blood creatinine increased	24 (11.5%)	18 (8.5%)	10 (5%)	0.01 (1.7, 12.4) 0.11 (-0.9,8.9)
Hyperlipidaemia NOS	38 (18%)	29 (14%)	13 (6%)	<0.01 (6.1, 18.5) <0.01 (2.1, 13.6)
Hypercholesterolemia [2]	27 (13%)	25 (12%)	20 (9%)	0.24 (-2.5, 9.8) 0.40 (-3.4, 8.5)
Hypertriglyceridemia [3]	13 (6%)	21 (10%)	11(5%)	0.63 (-3.5, 5.8) 0.06 (-0.21, 10.2)
Total Lipid Abnormalities	78(37%)	75(35.5%)	44(20.5%)	<0.01 (8.2, 25.2) <0.01 (6.5, 23.3)
Bacterial infection	78 (37%)	85 (40%)	55 (26%)	0.01 (2.8, 20.3) <0.01 (5.7, 23.3)
Fungal infection	18 (9%)	27 (13%)	19 (9%)	0.92 (-5.8, 5.3) 0.19 (-2.0, 10.0)
Viral infection	34 (16%)	39 (18.5%)	69 (32%)	<0.01 (-24.0, -7.9) <0.01 (-21.9, -5.5)
GI hemorrhage NOS	2 (1.0%)	9 (4.3%)	3 (1.4%)	0.67 (-3.2, 2.2) 0.07 (-0.3, 6.7)
New onset post-tx DM [4]	7/174 (4%)	17/162 (10.5%)	7/178 (4%)	0.97 (-4.4, 4.6) 0.02 (1.2, 12.7)

[1] TMA (thrombotic microangiopathy) including HUS (haemolytic uraemic syndrome) and TTP (thrombotic thrombocytopenic purpura) are consumptive coagulopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia

[2] Includes blood cholesterol increased and hypercholesterolemia aggravated

[3] Includes blood triglycerides increased and V blood triglycerides abnormal

[4] DM=diabetes mellitus, excludes patients with diabetes mellitus at baseline

**Fisher's Exact Test*

At month 12, more frequent [p=0.01, 95% CI: (3.1, 21.8)] serious adverse events were reported in the high everolimus group (61.6%) compared to AZA (49.1%). At month 24, the incidence of SAEs was 60.8% 64.9% and 54.7% [p=0.03, 95% CI (.9, 19), everolimus high dose vs. AZA] in the everolimus low, high and AZA groups respectively. SAEs with relevant rates of incidences are reported in the following table.

Table 3.15: Incidence rate of SAEs/infections at month 24 with relevant differences between groups

System Organ Classification or Preferred Term	everolimus 1.5mg (n=209)	everolimus 3.0 mg (n=211)	AZA (n=214)	P-value* (95% CI) everolimus 1.5-AZA everolimus 3.0-AZA
Any SAE	127(61%)	137(65%)	117(55%)	0.21 (-3.3,15.4) 0.03 (0.93, 19.4)
Infections and infestations	30 (14%)	44 (21%)	25 (12%)	0.41 (-3.8, 9.2) 0.01 (2.2, 16.3)
All types of pneumonia*	13(6%)	21(10%)	4(2%)	0.02 (0.60, 8.7) <0.01 (3.3, 13.1)
Renal impairment NOS	13(6%)	12(6%)	4(2%)	0.02 (0.60, 8.7) 0.04 (0.18, 8.1)
Pericardial effusion	12(6%)	11(5%)	6(3%)	0.14 (-1.0, 7.3) 0.22 (-1.5, 6.5)
Cardiac tamponade	3(1.4%)	5(2.4%)	2(1%)	0.74 (-2.1, 3.3) 0.27 (-1.3, 4.6)
Leukopenia NOS	5(2%)	5(2%)	11(5%)	0.15 (-6.9, 0.99) 0.14 (-6.9, 0.98)
CMV infections including: CMV infection, CMV hepatitis, Encephalitis CMV	1(0.5%)	4(2%)	5(2%)	0.13 (-4.9, 0.62) 0.83 (-3.7, 2.7)
Gastric hemorrhage/Gastrointestinal hemorrhage NOS	3(1%)	5(2 %)	1(0.5%)	0.36 (-1.3, 3.7) 0.12 (-0.54, 5.0)
Dyslipedimia including: Hyperlipidaemia NOS, Hypercholesterolemia, Blood cholesterol increased, Hypercholesterolemia aggravated Hypertriglyceridemia, increased blood triglycerides	5(2%)	9(4%)	2(1%)	0.27 (-1.2, 4.7) 0.03 (0.30, 7.1)

**Including: Pneumonia Pneumonia nos, Bronchopneumonia nos, Interstitial pneumonia, Pneumonia cytomegaloviral, Lobar pneumonia nos, Enterobacter pneumonia, Pneumocystis carinii pneumonia, Pneumonia aspergillus, Pneumonia chlamydial, Pneumonia Escherichia, Pneumonia haemophilus, Pneumonia legionella, Pneumonia pneumococcal, Pneumonia staphylococcal*
Data obtained from Post-text Table 10.1-4 (Page 2 of 22), Incidence Rates of Severe Adverse Events/Infections by System Organ Classification and Preferred Term (Safety Population - 24 Month Analysis)
** Fisher's Exact Test*

Suspected drug related adverse events occurred more frequently [p-value=0.01, 95%; (3.1, 21.1)] (not necessarily mutually exclusive from serious adverse events) in the everolimus 3.0 mg/day (70.6%) compared to AZA (58.4%) at month 12 and similarly at month 24, rates were 69.9%, 73%, and 63.1% [p=0.03, 95% CI (1.0, 18.6), everolimus high dose vs. AZA].

The main safety concerns associated with the Certican plus CsA regimen are renal impairment, pneumonia, bacterial infections, gastrointestinal hemorrhage, pericardial effusion and cardiac tamponade, lipid abnormalities, new onset of diabetes mellitus, anemia and thrombocytopenia.

It should also be noted that given the high number of premature treatment discontinuations, especially in the everolimus 3.0 mg group, events which may have occurred following treatment discontinuation (≥8 days after discontinuation) were not included in the overall safety analyses. The proportions presented were calculated using the randomized number as the denominator value, which may have underestimated or overestimated the incidence rate based on the number of patients on treatment at the specified time point.

3.2.1 Renal Function

Based on the unsatisfactory renal toxicities observed in both everolimus groups prompting amendment 3 additional safety analyses on renal laboratory parameters were performed. Serum creatinine (Crt) and serum creatinine clearance (CrCL) were chosen as specific parameters for additional analysis at the recommendation of the medical reviewers. Sponsor provided creatinine clearance values, or glomerular filtration rate, were calculated using the Cockcroft-Gault formula [1]. Changes from baseline and mean values at measured time points in both everolimus groups were analyzed and compared against values in the AZA group. There were significant differences observed between both everolimus groups and AZA in mean Crt, CrCL, change from baseline in Crt, and change from baseline in CrCL (Table 3.16-Table 3.19, Figure 3.3 and Figure 3.4). These differences were noted as early as month 3 following transplantation and continued throughout the study.

Figure 3.3: Mean Creatinine Clearance Plots

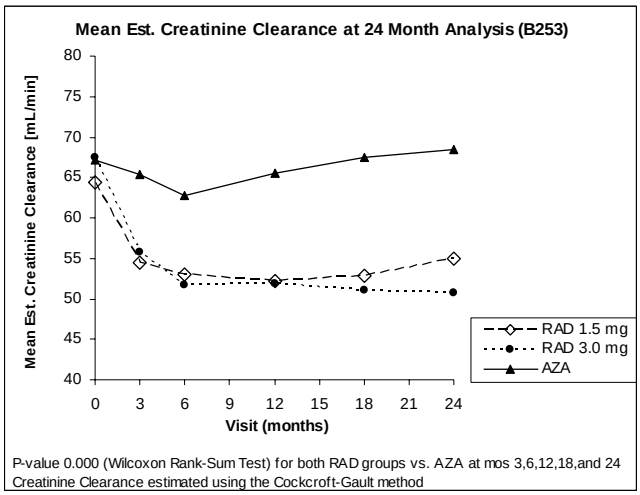


Table 3.16: Mean Serum Creatinine Clearance (mL/min) by Treatment Month

	everolimus 1.5 mg (N=209)	everolimus 3.0 mg (N=211)	AZA (N=214)	p-value everolimus 1.5 vs. AZA everolimus 3.0 vs. AZA
Baseline	64.38(n=204) (m=5)	67.5(n=209) (m=2)	67.18 (n=210) (m=4)	0.2610 0.9053
Month 3	54.59 (n=170) (m=28) (gl/death=11)	55.56 (n=155) (m=46) (gl/death=10)	65.23 (n=168) (m=35) (gl/death=11)	<0.0001 0.0007
Month 6	53.00 (n=158) (m=38) (gl/death=13)	51.75 (n=155) (m=43) (gl/death=13)	62.68 (n=168) (m=34) (gl/death=12)	0.0001 <0.0001
Month 9	52.17 (n=144) (m=50) (gl/death=15)	53.11 (n=121) (m=70) (gl/death=20)	61.73 (n=145) (m=55) (gl/death=14)	0.0002 0.0032
Month 12	52.03 (n=146) (m=47) (gl/death=16)	52.95 (n=137) (m=50) (gl/death=24)	64.83 (n=156) (m=40) (gl/death=18)	<0.0001 0.0001
Month 18	52.64 (n=125) (m=65) (gl/death=19)	51.00 (n=105) (m=80) (gl/death=26)	67.15 (n=130) (m=63) (gl/death=21)	<0.0001 0.0000
Month 24	54.46 (n=162) (m=27) (gl/death=20)	53.95 (n=164) (m=19) (gl/death=28)	67.41 (n=169) (m=22) (gl/death=23)	<0.0001 <0.0001

n=number of patients with assessments at time point
m=missed assessment not due to graft loss or death
gl/death=missed assessments due to graft loss or death
Pair-wise comparisons of treatment groups using Wilcoxon's Rank Sum test
CrCL calculated using the Cockcroft-Gault formula
Data description: All on and off-treatment creatinine measurements (ITT) in safety population.
Data source: Reviewer analyses of additional data requested from sponsor. Sponsor provided dataset located in NDA file \\Cdsesub1\N21560\N_000\2003-08-06\CRT\Datasets\Heart\derived\crt_b253.xpt. Findings consistent with NDA post-text table 10.7-28d.

Figure 3.4: Mean Creatinine Plots

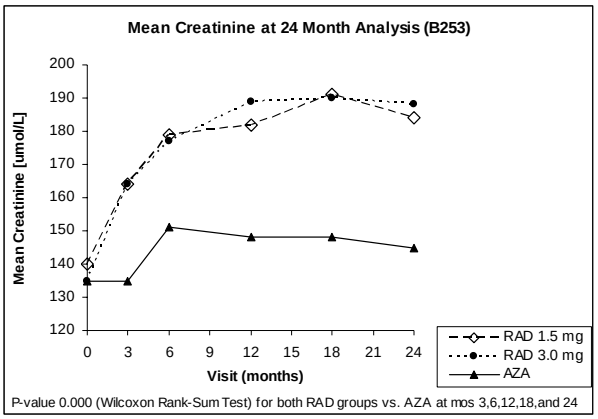


Table 3.17: Mean Serum Creatinine (µmol/L) by Treatment Month

	everolimus 1.5 mg (N=209)	everolimus 3.0 mg (N=211)	AZA (N=214)	p-value everolimus 1.5 vs. AZA everolimus 3.0 vs. AZA
Baseline	139.52 (n=204) (m=5)	135.12 (n=209) (m=2)	134.84 (n=210) (m=4)	0.3868 0.9547
Month 3	163.39 (n=170) (m=28) (gl/death=11)	163.18 (n=155) (m=46) (gl/death=10)	134.24 (n=168) (m=35) (gl/death=11)	<0.0001 <0.0001
Month 6	176.60 (n=158) (m=38) (gl/death=13)	176.30 (n=155) (m=43) (gl/death=13)	149.11 (n=168) (m=34) (gl/death=12)	0.0001 <0.0001
Month 9	189.77 (n=144) (m=50) (gl/death=15)	180.32 (n=121) (m=70) (gl/death=20)	151.67 (n=145) (m=55) (gl/death=14)	<0.0001 0.0001
Month 12	182.03 (n=146) (m=47) (gl/death=16)	185.84 (n=137) (m=50) (gl/death=24)	147.91 (n=156) (m=40) (gl/death=18)	<0.0001 <0.0001
Month 18	186.31 (n=125) (m=65) (gl/death=19)	186.73 (n=105) (m=80) (gl/death=26)	147.05 (n=130) (m=63) (gl/death=21)	0.0001 <0.0001
Month 24	179.69 (n=162) (m=27) (gl/death=20)	179.52 (n=164) (m=19) (gl/death=28)	147.57 (n=169) (m=22) (gl/death=23)	<0.0001 <0.0001

n=number of patients with assessments at time point
m=missed assessment not due to graft loss or death
gl/death=missed assessments due to graft loss or death
Amendment 3 added serum creatinine at time of discontinuation and at 3 and 6 months after discontinuation
Pair-wise comparisons of treatment groups using Wilcoxon's Rank Sum test
Data description: All on and off-treatment creatinine measurements (ITT) in safety population.
Data source: Reviewer analyses of additional data requested from sponsor. Sponsor provided dataset located in NDA file \\Cdsesub1\N21560\N_000\2003-08-06\CRT\Datasets\Heart\derived\crt_b253.xpt.

Table 3.18: Mean Change from Baseline in Creatinine (µmol/L)

	everolimus 1.5 mg (n=209)	everolimus 3.0 mg (n=211)	AZA (n=214)
Month 3	25 (n=165)	28 (n=151)	2 (n=163)
Month 6	40 (n=152)	47 (n=151)	17 (n=163)
Month 9	55 (n=134)	49 (n=118)	18 (n=140)
Month 12	46 (n=137)	58 (n=131)	14 (n=149)
Month 18	54 (n=118)	57 (n=101)	14 (n=124)
Month 24	51 (n=115)	56 (n=99)	8 (n=120)

P<0.0001 for all everolimus pair-wise comparisons (Wilcoxon's Rank Sum test) against AZA at all time points

Only patients with matched assessments at baseline and corresponding follow-up visit are included.
On and off-treatment assessments (ITT) included from safety population.
Data source: Post-text table 10.3-1a (page 56-57)

Table 3.19: Mean Change from Baseline in Creatinine Clearance (mL/min)

	everolimus 1.5 mg (n=209)	everolimus 3.0 mg (n=211)	AZA (n=214)
Month 3	-10.9 (n=158)	-12.8 (n=149)	-2.3 (n=159)
Month 6	-12.7 (n=146)	-19.3 (n=149)	-4.8 (n=159)
Month 9	-14.2 (n=129)	-18.4 (n=116)	-5.2 (n=136)
Month 12	-14.7 (n=132)	-18.7 (n=129)	-2.8 (n=145)
Month 18	-13.7 (n=113)	-19.0 (n=99)	0.0 (n=121)
Month 24	-13.4 (n=109)	-17.4 (n=98)	1.2 (n=118)

P<0.0001 for all everolimus pair-wise comparisons (Wilcoxon's Rank Sum test) against AZA at all time points
Creatinine Clearance calculated using the Cockcroft-Gault formula
Only patients with matched assessments at baseline and corresponding follow-up visit are included. On and off-treatment assessments (ITT) included from safety population.
Data source: Post-text table 10.3-1a (page 59-60)

The number of patients dropping to or below a clinically relevant threshold of 50% (defined as postoperative acute renal failure)[2,3] of individual baseline was significantly higher in both everolimus groups as compared to AZA at months 3, 6, 9, 18 and 24 (Table 3.20) . At month 12, only the everolimus 3.0 mg/day group had significantly more patients dropping below this threshold compared to AZA. Both on and off study treatment values are presented in this table.

Table 3.20: Patients with Creatinine Clearance ≤ 50% of Baseline Value

	everolimus 1.5 mg (n=209)	everolimus 3.0 mg (n=211)	AZA (n=214)	p-value everolimus 1.5 vs. AZA everolimus 3.0 vs. AZA
Month 3	13/159 (.08)	15/151 (.10)	4/161 (.025)	0.020 0.005
Month 6	15/146 (.10)	23/151 (.15)	7/160 (.044)	0.050 0.001
Month 9	20/133 (.15)	16/118 (.14)	8/137 (.058)	0.010 0.035
Month 12	14/136 (.10)	26/133 (.20)	7/148 (.047)	0.070 <0.001
Month 18	13/116 (.11)	17/102 (.17)	5/125 (.04)	0.033 0.001
Month 24	21/150 (.14)	26/160 (.16)	10/164 (.061)	0.019 0.004

P-values obtained using the chi-square test
Creatinine clearance calculated using the Cockcroft-Gault Formula

Data description: All on and off-treatment creatinine measurements (ITT) in safety population.
Data source: Reviewer analyses of additional data requested from sponsor. Sponsor provided dataset located in NDA file \\Cdsesub1\N21560\N_000\2003-08-06\CRT\Datasets\Heart\derived\crt_b253.xpt

The UNOS/IHLT Thoracic Registry Information (US April 1994-December 1999)[4] reports that approximately 7.8% of transplant patients have a serum creatinine ≥2.5 mg/dL one year following transplantation. Similar to registry data, approximately 8% of patients in the AZA group had serum creatinine values ≥2.5 mg/dL at month 12 and an overall range of 3-11%. Rates (Table 3.21) in the everolimus groups were 2-3 times larger (range: 14-27%) than registry data, with an average 14% by month 3 and 20% by month 6. Rates in both everolimus groups were statistically higher than rates in the AZA group by month 3 and remained higher through month 24.

Table 3.21: Patients with serum creatinine ≥ 2.5 mg/dL (221 μmol/L)

	everolimus 1.5 mg (n=209)	everolimus 3.0 mg (n=211)	AZA (n=214)	p-value everolimus 1.5 vs. AZA everolimus 3.0 vs. AZA
Baseline	21/202 (.10)	14/209 (.07)	9/214 (.07)	p=0.180 p=1.000
Month 3	24/170 (.14)	22/155 (.14)	5/168 (.03)	p<0.001 p<0.001
Month 6	32/156 (.21)	33/155 (.21)	14/168 (.08)	p=0.002 p=0.001
Month 9	39/142 (.27)	25/121 (.21)	16/145 (.11)	p<0.001 p=0.030
Month 12	36/144 (.25)	37/137 (.27)	12/156 (.08)	p<0.001 p<0.001
Month 18	27/123 (.22)	23/105 (.22)	10/130 (.08)	p=0.001 p=0.002
Month 24	29/150 (.19)	36/164 (.22)	12/169 (.07)	p=0.011 p<0.001

P-values obtained using the chi-square test
Data description: All on and off-treatment creatinine measurements (ITT) in safety population.
Data source: Reviewer analyses of additional data requested from sponsor. Sponsor provided dataset located in NDA file \\Cdsesub1\N21560\N_000\2003-08-06\CRT\Datasets\Heart\derived\crt_b253.xpt

Histograms in Appendix I illustrate the frequency of percent changes in CrCL from baseline by treatment group. The x-axis represents the percent change of mean CrCL from baseline at specified time point. Values less than 1 indicate a decrease in mean CrCL and values greater than 1 indicate an increase in CrCL. An increase in CrCL correlates to an increase in creatinine excretion and hence an improvement in renal function.

3.2.1.1 Renal Function during Open-Label Phase (year 2)

To address the issue of renal toxicity in both everolimus groups, the sponsor implemented amendment 3 (at month 12), which allowed for treatment unblinding and everolimus dose adjustments based on target concentration followed by CsA reductions in patients with renal dysfunction. This amendment also required collection of blood samples for serum creatinine, blood urea nitrogen, CsA trough levels and everolimus trough levels at baseline, months 1, 2, 3, and 6 of the open-label period in patients with renal dysfunction and at months 3 and 6 in patients not having renal dysfunction.

A total of 170 (58, 51, 61 in everolimus 1.5, 3.0 and AZA respectively) patients entered the open-label phase requiring adjustments to everolimus treatment. The sponsor concluded that there was an improvement in renal function when comparing baseline (of amendment phase or month 12 of original protocol) creatinine against month 6 (month 18 of the original protocol). Although these results (Table 3.22) suggest an improvement in median renal function following dose adjustments, the number of patients studied is small and the change in mean creatinine suggests otherwise. Several patients were omitted from this analysis due to missed baseline and month 6 creatinine measurements during the open-label phase. Furthermore, this analysis omits those patients who previously experienced renal toxicity but discontinued study treatment prior to amendment 3. The selection of patients studied in this open-label phase is biased toward patients who tolerated study treatment long enough to switch to a concentration based regimen. Prospective data collected on patients randomized at study entry to appropriate treatment regimens is needed to fully evaluate the effects of concentration based everolimus on renal function.

Table 3.22: Creatinine values in patients with post-amendment 3 values

		Mean (umol/L)		Median (umol/L)	
	N	**Baseline**	**Month 6**	**Baseline**	**Month 6**
everolimus 1.5	**38**	164.4	162.9	167.0	157.5
everolimus 3.0	**27**	182.7	189.5	185.6	160.0
AZA	**24**	138.0	135.2	123.3	127.0

Month 6 following of amendment phase
Only patients with baseline and month 6 (open-label phase of the study) are included
Data source: \\CDSESUB1\N21560\N_000\2003-05-02, PTT 20.3-6

3.2.2 120-Day Safety Follow-up

At the 120 day safety follow-up an additional sixteen deaths were reported (4 in each everolimus group and 8 in the AZA group). One death in each everolimus group was suspected to be drug related (graft failure in the high everolimus and epithelioma in the low everolimus group). Additionally, there were 6, 5, and 5 reported rejections in the everolimus 1.5, 3.0 and AZA groups respectively along with one life threatening infection in both the everolimus 3.0 and the AZA group. Additional information on renal function provided in this update is summarized in section 3.2.1.1 of this review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Analysis of the primary endpoint by gender resulted in similar results for both genders (Table 4.1). Superiority of both everolimus groups was demonstrated against AZA in male subjects while superiority was only demonstrated for everolimus 3.0 mg versus AZA in female subjects. When interpreting these results one must take into account that the majority of patients (82%) were men.

Comparing mean creatinine by treatment group in men and women resulted in similar results showing that by month 3, both everolimus groups had significantly higher mean creatinine values compared to the AZA group. These results (Table 4.2) are consistent with the overall comparisons of creatinine discussed in section 3.2.1.

Table 4.1: Incidence of primary endpoint at month 12 by recipient gender

	Males			Females		
	everolimus 1.5 (n=166)	**everolimus 3.0 (n=171)**	**AZA (n=182)**	**everolimus 1. 5 (n=43)**	**everolimus 3.0 (n=40)**	**AZA (n=32)**
Primary Event at month 12	64 (38.6%)	58 (33.9%)	92 (50.5%)	23 (53.5%)	10 (25.0%)	21 (65.6%)
p-value (everolimus-AZA)	0.025	0.001		0.286	<0.001	
95% CI (everolimus-AZA)	(-22.3, -1.5)	(-25.8, -6.4)		(-34.3, 10.1)	(-61.8, -19)	
97.5% (everolimus-AZA)	(-23.8, -0.0)	(-28.2, -5.0)		(-37.5, 13.3)	(-64.9, -16)	

Data source: \\Cdsesub1\N21560\N_000\2002-12-19\clinstat, PTT 9.3-1 (page 1 of 1)

Table 4.2: Creatinine (umol/L) by Gender and Treatment

	Males			Females		
	everolimus 1.5 (n=166)	**everolimus 3.0 (n=171)**	**AZA (n=182)**	**everolimus 1. 5 (n=43)**	**everolimus 3.0 (n=40)**	**AZA (n=32)**
Baseline	145.9 (m=5)	140.4 (m=2)	138.0 (m=4)	114.4 (m=2)	112.8 (m=0)	117.4 (m=0)
Month 3	162.6* (m=27)	167.5* (m=46)	138.6 (m =40)	166.8* (m=12)	145.3* (m=10)	110.4 (m=6)
Month 12	183.7 * (m=48)	188.1 * (m=65)	152.3 (m=48)	174.3* (m=17)	178.2* (m=9)	121.2 m=(10)
Month 24	186.9* (m=33)	187.2* (m=42)	151.7 (m=35)	143.8 (m=16)	151.3* (m=5)	120.1 (m=10)

**p<0.05, Student's T-test*

Over 89% of the study population was Caucasian. No sub-analysis based on race is feasible.

The sponsor provided a sub-analysis of the primary endpoint and simple event of BPAR stratifying by age (< 60 years and ≥ 60 years). Efficacy failure rates were similar by treatment arm in each age strata (Table 4.3). Pair-wise comparisons between everolimus and AZA were similar to those observed in the primary analyses with no evidence of an age effect.

Table 4.3: Efficacy sub-analysis by Recipient Age

	Primary Efficacy Endpoint		BPAR Simple Event	
	< 60 years	**≥ 60 years**	**< 60 years**	**≥ 60 years**
everolimus 1.5	67/155 (43.2%)	22/54 (40.7%)	53/155 (34.2%)	13/54 (24.1%)
everolimus 3.0	47/151 (31.1%)	22/60 (36.7%)	31/151 (20.5%)	15/60 (25.0%)
AZA	92/166 (55.4%)	24/48 (50.0%)	82/166 (49.4%)	18/48 (37.5%)

Given the Division's concern regarding renal toxicity with fixed dose everolimus, the sponsor submitted additional analyses on September 30, 2003 evaluating patient age as a risk factor for decreased creatinine

clearance value. These analyses showed a statistically significant increase in the number of patients receiving everolimus 3.0 mg/day with clinically relevant decreases in creatinine clearance (Table 4.4) who were at least 60 years of age. These results suggest that age is a risk factor when treating with everolimus but these results do not take into consideration other risk factors, which may have contributed to acute rejection. More conclusive data from prospective data is needed to fully determine if there is an age effect with this drug.

Table 4.4: Patients Experiencing CrCL < 35 mL/min at Month 12

	Patient Age		P-value (95% CI)
	< 60 years	**≥ 60 years**	<60 v. ≥60
everolimus 1.5	16/153 (10.5%)	9/54 (16.7%)	0.229 (-19.0, 3.5)
everolimus 3.0	19/151 (12.6%)	18/60 (30.0%)	0.003 (-30.8, -5.6)
AZA	11/166 (6.6%)	2/48 (4.2%)	0.530 (-7.7, 8.4)

4.2 Other Special/Subgroup Populations

Subgroup analyses of efficacy failure by donor age (<50 years and ≥50 years) showed no noticeable differences from the overall efficacy analysis but it should be noted that the sample size for patient receiving a heart from a donor ≥50 years was quite small (27, 32, 35 for everolimus 1.5, 3.0, and AZA respectively). Subgroup analysis according to donor gender and race yielded no notable differences.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary statistical issue with study B253 is the change in everolimus treatment from a fixed dose to a concentration based dose at month 12 due to unacceptable renal toxicity. This change, although clinically appropriate, invalidates the overall safety and efficacy conclusions and prevents correct identification of a safe and efficacious everolimus regimen when combined with full dose CsA and corticosteriods. The randomized doses assigned at study entry led to unacceptable toxicity and therefore are not appropriate when given in combination with full dose CsA and corticosteriods for the target indication. Additionally, results reported from month 12 through month 24 of therapeutic drug monitoring with everolimus and CsA are inconclusive as they only contain those patients who tolerated treatment long enough to enter the open-label phase of the study and omits patients who prematurely discontinued study medication due to renal toxicity.

A secondary statistical concern is the high number of premature treatment discontinuations, which were more frequent in the everolimus 3.0 mg/day group compared to the other two treatment groups. The primary reason for treatment discontinuation was adverse events, which raises additional concern regarding the safety of fixed dose everolimus in combination with full dose CsA.

An additional statistical issue is the method of patient selection used in the IVUS sub-study. Only patients tolerating at least 12 months of treatment, who had a successful baseline measurement, and who had no clinical condition preventing accurate IVUS measurement at months 12 and 24, were eligible for this sub-study. This method is potentially biased since it selected only those subjects who could tolerate assigned treatment without notable renal toxicity. Patients who were enrolled in the IVUS sub-study but who

prematurely discontinued treatment before the 12 or 24-month assessment were excluded from the 12 or 24-month analyses respectively. A more statistically appropriate method would have been to randomly select a subset of patients for IVUS at study randomization and account for premature treatment discontinuations and IVUS assessment non-compliance in the analyses.

Superiority (Table 5.1) of fixed dose everolimus at 1.5 mg/day and 3.0 mg/day over azathioprine in combination with full-dose CsA and corticosteroids, as demonstrated by the reduction in biopsy proven acute rejections of grade ≥3A, was demonstrated at 6 months following transplant. At month 6, there were 58 (27.8%), 40 (19.0%) and 89 (41.6%) episodes of BPAR of grade ≥3A in the everolimus 1.5 mg, everolimus 3.0 mg and AZA groups respectively, resulting in a z-test p-value of 0.003, 95% CI [-22.7, -4.8] for everolimus 1.5mg – AZA and p<0.001, 95% CI [-30.8, -13.8] for everolimus 3.0 - AZA. No statistically significant differences were observed in the rates of acute rejection due to hemodynamic compromise, death, graft loss, or lost to follow-up between groups. At month 12, the difference in rate of BPAR of grade ≥3A continued to be significant between both everolimus groups and AZA. The analysis at month 24 showed similar trends, however these results must be interpreted differently since treatment unblinding occurred following the month 12 analysis and before the month 24 analysis resulting in changes in everolimus concentrations for patients experiencing renal toxicity on fixed everolimus doses. These results are fairly robust in sensitivity analyses accounting for missed biopsies and premature treatment discontinuation.

Table 5.1: Collective efficacy findings

	everolimus 1.5 mg (n=209)	**everolimus 3 mg (n=211)**	**AZA (n=214)**	**95.0% CI**	**97.5% CI**
Month 6 (up to day 194)					
Primary composite endpoint: (BPAR of grade ≥3A, AR assoc. with HDC, GL, death, or LTFU)	76 (36.5%) p=0.031 [a]	57 (27.0%) p<0.001 [b]	100(46.7%)	(-19.6,-1.0) [a] (-28.5,-10.6) [b]	(-20.9.0,0.4) [a] (-29.7,-9.3) [b]
• BPAR of grade ≥3A	58 (27.8%) p=0.003 [a]	40 (19.0%) p<0.001 [b]	89 (41.6%)	(-22.7,-4.8) [a] (-30.8,-13.8) [b]	(-23.9,-3.5) [a] (-32.0,-12.6) [b]
Month 12 (up to day 381)					
Primary composite endpoint: (BPAR of grade ≥3A, AR assoc. with HDC, GL, death, or LTFU)	87 (41.6%) p=0.020 [a]	68 (32.2%) p<0.001 [b]	113 (52.8%)	(-20.7,-1.7) [a] (-29.8,-11) [b]	(-22.0,-0.4) [a] (-31.1,-10) [b]
• BPAR of grade ≥3A	64 (30.6%) p=0.001 [a]	45 (21.3%) p<0.001 [b]	98 (45.8%)	(-24.3,-6.1) [a] (-33.2,-16) [b]	(-25.7,-4.7) [a] (-34.4,-15) [b]
Month 24 (up to day 810)*					
Primary composite endpoint: (BPAR of grade ≥3A, AR assoc. with HDC, GL, death, or LTFU)	96 (45.9%) p=0.016 a	76 (36.0%) p<0.001 b	123 (57.5%)	(-21.1,-2.1) a (-30.8,-12) b	(-22.4,-0.8) a (-32.1,-11) b
• BPAR of grade ≥3A	73 (34.9%) p=0.005 a	48 (22.7%) p<0.001 b	103 (48.1%)	(-22.4,-3.9) a (-34.2,-17) b	(-23.8,-2.6) a (-35.4,-15) b

** Treatment unblinded prior to analyses to allow for dose adjustments based on concentration in the everolimus groups. Treatment received from month 12-24 may vary from originally assigned randomized dose in the everolimus groups.*

Unacceptable renal toxicity was observed in both everolimus groups by month 3 and persisted until month 12. Patients still on study treatment and experiencing renal dysfunction at month 12 were enrolled

into an amendment phase of the study. Results from this amendment phase suggest an improvement in median (mean values do not suggest an improvement) renal function but these results are inconclusive. The number of patients observed was small (38, 27, and 24 for everolimus 1.5, 3.0 and AZA respectively) consisting of only patients with amendment baseline values and amendment month 6 (month 18 of total study) values. Although efforts were made to reduce renal toxicity, by implementing therapeutic drug monitoring, no conclusions regarding efficacy and safety of a modified regimen can be made from this study. There were statistically more premature treatment discontinuations in the everolimus 3.0 mg group compared to the AZA and statistically more due to adverse events. There were statistically more bacterial infections, particularly pneumonias reported in the everolimus groups compared to the AZA group. The converse is true for the incidence of viral infections where the rate of CMV infection was statistically higher in the AZA group.

After a thorough risk-benefit analyses of fixed dose everolimus, it is apparent that there is a need for additional prospective data to study a safer yet effective everolimus treatment regimen combined with appropriate doses of CsA.

5.2 Conclusions and Recommendations

Study B253 showed that fixed doses (1.5 mg/day and 3.0 mg/day) of Certican™ (everolimus, RAD, SDZ RAD, RAD001), administered to *de novo* heart transplant patients in combination with Neoral (CsA) and corticosteroids, were superior to azathioprine (AZA) at 6 months (primary endpoint) and at 12 and 24 months (secondary endpoints) in preventing the incidence of the primary composite endpoint (graft loss, biopsy-proven acute rejection of grade ≥ 3A, acute rejection associated with hemodynamic compromise, death, or loss to follow-up). These differences were mainly due to the incidence rate of acute rejection of grade ≥ 3A, which was statistically lower in both everolimus groups compared to AZA. No statistically significant differences were shown in the incidence of graft loss, death or acute rejection due to hemodynamic compromise.

Although shown to be superior to azathioprine in reducing the incidence of acute rejection, both everolimus doses but were found to be unsafe due to unacceptable renal toxicity. Statistically and clinically significant elevations in creatinine and decreases in creatinine clearance were observed as early as three months following therapy initiation and persisted up through twenty-four months. Treatment unblinding and therapeutic drug monitoring of everolimus in combination with CsA did not result in a statistically relevant improvement in renal function. Additionally, there were higher numbers of bacterial infections, particularly pneumonias, and a lower incidence of viral infections, primarily cytomegalovirus (CMV) infections, in both everolimus groups compared to AZA.

This single Phase 3 study does not provide adequate information to determine a safe and efficacious everolimus dose or regimen, combined with CsA, for organ rejection prophylaxis in *de novo* heart transplant patients. Pharmacokinetic and pharmacodynamic analyses to determine a suitable everolimus regimen followed by a confirmatory Phase 3, randomized, well-controlled, double-blind, comparative study is recommended. This additional Phase 3 study should compare the safety and efficacy of an appropriate everolimus regimen, administered in combination with appropriate doses (full or reduced dose) of CsA and corticosteroids, with an approved comparator such as mycophenolate mofetil (MMF). A suitable primary efficacy endpoint would be a composite endpoint comprised of biopsy-proven acute rejection, acute rejection due to hemodynamic compromise, death, graft loss, and loss-to-follow-up measured at 6 months following treatment initiation. Appropriate sensitivity analyses to include treatment discontinuation and biopsy non-compliance in the composite endpoint should also be performed. To fully measure safety, follow-up data on this new regimen should be collected for at least

24 months. Additionally, this study should consider a cyclosporine sparring regimen if appropriate with selected everolimus dose or concentration.

Appendix I: Creatinine Clearance Histograms

Figures 1-6 below represent the ratio of creatinine clearance at specified time point to baseline. Ratios greater than 1 indicate improved renal function. From months 3-24, there were significant more ratios <1 observed in both everolimus groups compared to AZA.

Figure 1: Month 3/baseline Creatinine Clearance

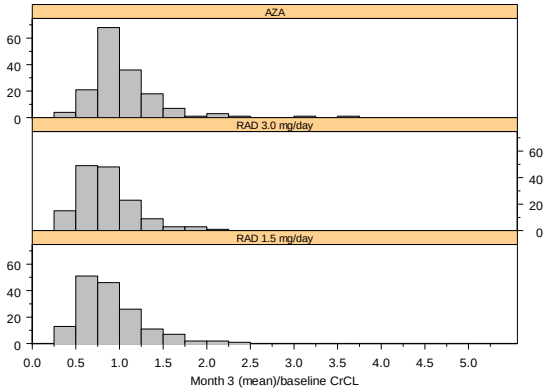


Figure 2: Month 6/baseline Creatinine Clearance

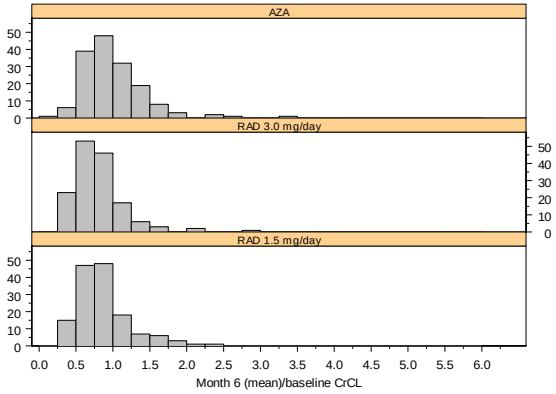


Figure 3: Month 9/baseline Creatinine Clearance

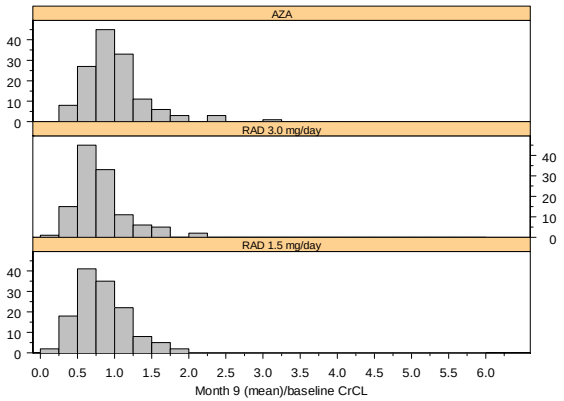


Figure 4: Month 12/baseline Creatinine Clearance

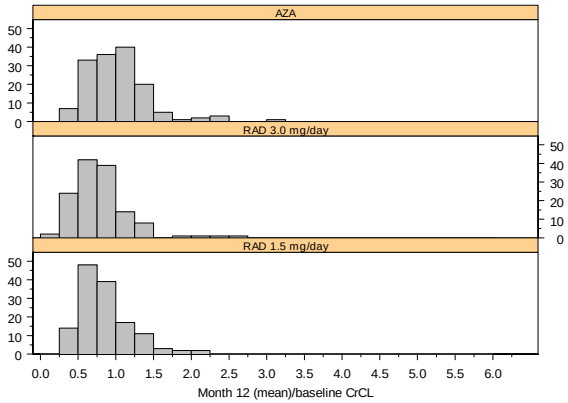


Figure 5: Month 18/baseline Creatinine Clearance

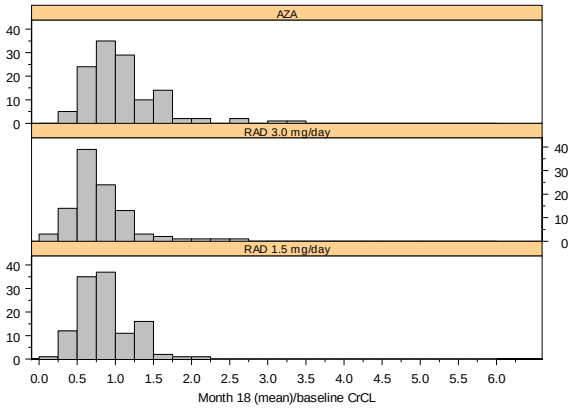
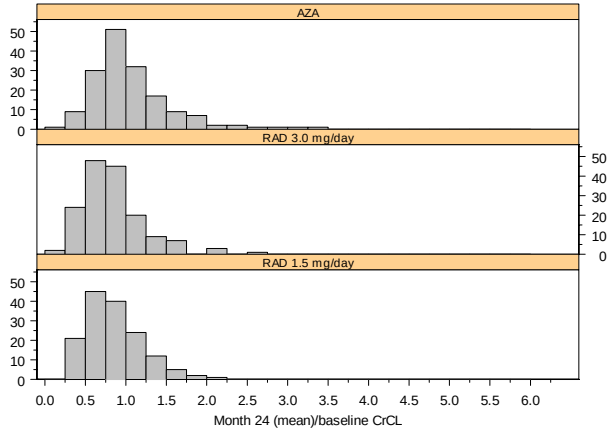


Figure 6: Month 24/baseline Creatinine Clearance



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