

MEDICAL OFFICER REVIEW

NDA 21-628 (Adult tablets – Heart transplantation)

NDA 21-631 (Tablets for oral suspension – Heart transplantation)

Certican® (everolimus) Tablets and Tablets for Oral Suspension for the Prophylaxis of Organ Rejection in Allogeneic Heart Transplantation

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Review completed: October 17, 2003

Sponsor: Novartis Pharmaceuticals Corporation

Name of Drug: Certican® (everolimus) Tablets

Indication: Certican® (everolimus) for the prophylaxis of organ rejection in allogeneic kidney and heart transplantation.

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Note: This review is abstracted from the original NDA review for everolimus. Sections relevant only to the use of everolimus for renal transplantation are not included in this document. A separate document is attached which summarizes the safety of everolimus observed in the phase 3 studies for renal transplantation.

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1. LIST OF ABBREVIATIONS

AC	Active controlled,
ADOs	Adverse dropouts
AE	Adverse Events, Adverse reaction
ANCOVA	Analysis of covariance
AR	Acute rejection
ATG	Anti-thymocyte globulin
ATN	Acute tubular necrosis
AZA	Azathioprine
BCI	Blood Creatinine Increased
BPAR	Biopsy Proved Acute Rejection
bid	Twice daily
BSA	Body surface area
CAD	Coronary Artery Disease
CsA	Cyclosporine
CI	Confidence interval
CIT	Cold Ischemia Time
CI _{inh}	Calcineurin Inhibitor
CMH	Cochran-Mantel-Haenszel test
CMV	Cytomegalovirus
CR	Chronic Rejection = allograft vasculopathy
CrCl	Creatinine Clearance
CsA	Cyclosporine
CV	Cardiovascular
DB	Double blind,
DD	Double dummy,
DGF	Delayed graft function
DAE	Adverse Event Leading to Discontinuation from Study Medication.
ECG	Electrocardiogram
ECHO	Echocardiography
E	Efficacy
ESHD	End Stage Heart Disease
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GFR	Glomerular filtration rate
HDL	High-density lipoprotein
HLA	Human leukocyte antigen
HDC	Hemodynamic compromise
HUS	Hemolytic uremic syndrome
IVUS	intravascular ultrasound
ISHLT	International Society of Heart and Lung Transplantation
ITT	Intent-to-treat
LDH	Lactate dehydrogenase

LDL	Low-density lipoprotein
LH	Luteinizing hormone
KM	Kaplan-Meier
MC	Multicenter
MD	Multiple dose
MMF	Mycophenolate mofetil
NDA	New Drug Application
NCEP-ATPIII	National Cholesterol Education Program - Adult Treatment Panel III
NHLBI	National Heart, Lung and Blood Institute
NSAEs	Non-Fatal Serious AEs
OKT3	Orthoclone, A murine monoclonal antibody specific to the human CD3 complex
OL	Open label
PTLD	Posttransplantation lymphoproliferative disorder
PK	Pharmacokinetics
PWR	Pediatric Written Request
RAD	Everolimus, Certican [®]
RAD1.5	Certican [®] 1.5 mg dose group (given as 0.75mg twice daily [bid])
RAD3	Certican [®] 3 mg dose group (given as 1.5 mg twice daily [bid])
R	Randomized
S-	Study, e.g., S-B253
SCr	Serum Creatinine.
SEM	Standard error of the mean.
SGOT/AST	Serum glutamic oxaloacetic transaminase/aspartate aminotransferase
SGPT/ALT	Serum glutamate pyruvate transaminase/alanine aminotransferase
T	Tolerability
TEAE	Treatment-emergent adverse event
TEP	Treatment End Point = Last Observation Carried Forward
TMA	Thrombotic Microangiopathy (HUS and TTP)
TMFAS	Table Modified from Applicant's Submission
TTP	Thrombotic thrombocytopenic purpura
WBC	White Blood Cells

2. DEFINITIONS

Everolimus	(40-O-[2-hydroxyethyl]-rapamycin), SDZ-RAD, RAD or RAD001: a Rapamycin derivative known also as Certican [®] . RAD is used primarily in this review but all terms are used synonymously.
Acute Rejection Episodes	International Society of Heart and Lung Transplantation (ISHLT) classification.
Antibody treated acute rejection	Only <i>suspected</i> rejections (treated with antibodies) where <i>final clinical diagnosis = acute rejection</i> will be considered <i>antibody treated acute rejections</i> . <i>Antibody treated acute rejections</i> are thus a subset of <i>clinically confirmed acute rejections</i> .
Chronic Rejection	Also referred as allograft vasculopathy.
Clinically confirmed acute rejection episodes	Includes biopsy-proven acute rejection episodes (without regard to anti-rejection treatment) plus suspected/presumed acute rejection episodes (i.e., those episodes for which the investigator indicates acute rejection as the final clinical diagnosis and for which anti-rejection treatment was given). Subclinical rejections were not included as part of the clinically confirmed acute rejection endpoint.
Clinically confirmed chronic rejection	<i>Rejections diagnosed as chronic on clinical grounds. Do not include biopsy-proven chronic rejection.</i>
DAE	Adverse Event Leading to Discontinuation from Study Medication
Efficacy failure in study B253	Defined as the incidence of the composite efficacy endpoint (death, graft loss/re-transplant, biopsy-proven acute rejection episode International Society of Heart and Lung Transplantation (ISHLT) \geq grade 3A or any clinically suspected acute rejection episode associated with hemodynamic compromise [HDC]).
HDC (Hemodynamic compromise)	Defined as having one or more of the following conditions: ejection fraction \leq 30%, or \geq 25% lower than baseline, fractional shortening \leq 20%, or \geq 25% lower than baseline, and/or the use of inotropic treatment.
Hypogonadism (Laboratory-defined)	Low (age adjusted) testosterone level and LH $>$ 15 IU/L in an adult male.
Non-significant, was not significant, etc.	Used to denote "not statistically significant"

Notable events	Includes Deaths, NSAEs (Non-Fatal Serious AEs) and ADOs (Adverse dropouts). ADOs were patients with primary discontinuation reasons, e.g., AEs, abnormal laboratory values or abnormal test procedure result.
Safety Population	The safety population is defined as all randomized patients who receive at least one dose of study drug and have at least one safety assessment
Significantly	We use the term significantly to imply a statistically significant difference
Sponsor	In the review we will use the words "sponsor", "applicant" and "Novartis" interchangeably
Testosterone levels	Low testosterone levels <10 nmol/l for males less than 50 years old; <7 nmol/l for males 50 years of age or older
Thrombotic Microangiopathy (TMA)	Including HUS (Hemolytic uremic syndrome) and TTP (Thrombotic thrombocytopenic purpura) are consumptive coagulopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia.
Treatment Endpoint (TEP) was used as a synonym of the last observation carried forward (LOCF)	Used as a synonym of the last observation carried forward (LOCF)

3. EXECUTIVE SUMMARY

Everolimus (RAD) is a macrolide immunosuppressant derived from rapamycin that binds to FK binding protein (FKBP). The RAD-FKBP complex binds and inhibits the action of the mammalian target of Rapamycin (mTOR), suppressing cytokine-driven (IL-2, 4, 7 and 15) T-cell proliferation. This action inhibits the progression from phase G1 to S in the cell cycle of different cell lines, including but not restricted to T cells.

Novartis Pharmaceuticals Corporation submitted an original NDA for the prophylaxis of organ rejection in allogeneic kidney and heart transplant patients¹ by a proposed regimen of Certican[®] used concurrently with Neoral (cyclosporine) and corticosteroids. To support this application, the applicant conducted two key phase 3 *de novo* renal allograft trials (B201 and B251) for the kidney indication and one key *de novo* heart study (B253) for the heart indication. This review focuses only on the prophylaxis of organ rejection for heart transplant patients.

Key Heart Study: Study B253 was the only study presented to support the proposed heart indication. This study was designed to assess the safety and efficacy of two fixed doses of RAD compared to Azathioprine in *de novo* heart transplant recipients.

In this two year randomized, multicenter study, RAD 1.5 mg/day and RAD 3 mg/day, were compared to Azathioprine (AZA), 1-3 mg/kg/d. The three arms received standard doses of Neoral and corticosteroids. Efficacy was measured by the incidence of the composite endpoint² in the first 6 months post-transplant.

The applicant has also proposed that RAD antiproliferative effects would be beneficial in preventing chronic rejection or cardiac vasculopathy; the incidence of chronic rejection was a secondary endpoint evaluated by intravascular ultrasound (IVUS) to determine the degree of intimal thickening in the LAD coronary artery. The population for this secondary efficacy analysis included a non-randomized subset of patients. As will be discussed, the patient selection for IVUS was potentially biased and therefore does not accurately reflect the effect of RAD on arterial intimal thickening and chronic allograft rejection.

The primary composite endpoint for RAD 1.5 and RAD 3 was superiority to AZA. However, RAD fixed dose regimens were demonstrated to be unsafe due to marked nephrotoxicity. In an attempt to decrease nephrotoxicity while maintaining efficacy, the applicant implemented amendment # 3.

¹ This review focuses almost exclusively on the heart transplant indication; however, two phase 3 studies were submitted in support of prophylaxis of organ rejection for *de novo* renal allograft transplant (Studies B201 and B251). In these studies, everolimus (RAD) at 1.5 mg/day and 3 mg/day fixed doses in combination with full dose Neoral[®], and corticosteroids was compared with MMF plus full dose Neoral[®] and corticosteroids. The primary composite endpoint for the key renal studies was the incidence of efficacy failure at 6 months. A separate attachment to this document reviews the safety information from the two renal transplantation studies.

² Composite endpoint Key Heart Study: Death, graft loss/re-transplant, biopsy-proven acute rejection episode (BPAR) \geq Grade 3A, or any clinically suspected acute rejection episode associated with hemodynamic compromise (HDC)

Protocol Amendment #3 provided for very important modifications in study design and the RAD arms therapeutic regimen. It provided for conversion from a double blind to an open label design, from RAD fixed dose to a therapeutic drug monitoring (TDM) dosing regimen targeting patients with decreased renal function.

The original studies were designed to have the strength to meet specific objectives. After amendment modifications, the strength of randomization was lost and the potential for bias increased. This intervention disqualified the study from reaching conclusions based on fixed dose regimens after the amendments were enacted.

The therapeutic regimen was modified from fixed doses to target blood concentration for both RAD and CsA. A sub-population of patient with renal dysfunction was specifically targeted in the RAD arms to modify the immunosuppressive regimen according to RAD blood levels and to decrease the Neoral[®] dose.

In general, the pivotal trials for kidney and heart were extensively amended, with important changes in the original study design and dose regimen at one year. These changes introduced the potential for bias and made the safety and efficacy review a serious challenge for the Agency. The absence of a consistent, concurrent control group throughout the duration of the study make any conclusion based on these data unreliable.

Results of fixed dose RAD regimen and full dose Neoral[®] and concentration controlled regimen of RAD and reduced CsA exposure: The original regimens proposed for the prevention of allograft rejection in heart and kidney proved to be effective with respect to the primary endpoints.³ However, RAD fixed dose regimens were demonstrated to be unsafe due to marked nephrotoxicity. In an attempt to decrease nephrotoxicity while maintaining efficacy, the applicant implemented amendment #3 at 12 months post-transplantation in both Key Heart and Key Renal studies. The studies were unblinded and the RAD fixed dose regimens changed to RAD TDM (> 3 ng/mL). The full dose Neoral[®] regimen was changed to CsA minimization to improve renal function, and the TDM for CsA was also modified from C0 trough levels to C2 (concentration 2 hours after dosing). Dose adjustments implemented by amendment #3 at 12 months had a limited effect in improving renal function and failed to reverse chronic renal deterioration in both heart and renal key studies.

Studies A2306 and A2307 addressed the use of concentration-controlled RAD in combination with reduced CsA exposure (by C₂ monitoring) and corticosteroids either without Simulect (A2306) or with Simulect (A2307). These studies were open-label using historical controls and full reports are still pending.

³ Kidney studies primary endpoint: Composite of Biopsy-proven acute rejection, graft loss, death or loss to follow-up. Heart study primary endpoint: Composite of death, graft loss / re-transplant, BPAR, □ Grade 3A or any clinically suspected acute rejection episode associated with HDC in the first 6 months post-transplant.

4. STATEMENT OF CONCLUSIONS

The information provided in this NDA supports the conclusion that the combination of RAD, Neoral®, and steroids is effective for the prophylaxis of acute rejection in Heart and Renal allograft recipients.

The originally proposed regimens for the prevention of allograft rejection in heart and kidney proved to be effective with respect to the primary endpoints. However, we can recommend neither a fixed dose regimen nor a TDM regimen. The fixed dose regimen proved to be unsafe due to unacceptable nephrotoxicity. On the other hand we cannot recommend TDM regimen based on the open label phase of the key heart and renal studies that tested a TDM regimen in a subset of selected patients during maintenance phase after transplantation.

Preliminary reports of renal studies A2307 and A2306 are encouraging. However, the use of historical controls for these open label studies presents important difficulties due to differences in study design, regimens, CsA target concentration levels, and method used for dose adjustments. Furthermore, extrapolation of efficacy data from these renal studies to the heart indication is not adequate.

Therapeutic drug monitoring is a promising approach to optimize efficacy and improve safety. However, we have been unable to identify an appropriate TDM regimen for the heart and kidney indication that will allow us to maintain efficacy while minimizing toxicity in both early period post-transplantation and during the maintenance phase. Furthermore, the adequate timing for CsA minimization has not been well characterized and tested in a prospective, well controlled trial.

5. RISKS/BENEFITS ASSESSMENT

The toxic effects of the immunosuppressants may be acceptable in order to decrease rejection rates and improve patient and graft survival. However, toxicity is not acceptable if it exceeds the supposed benefits, i.e., rejection free patient and graft survival.

The information provided in these NDAs supports that the combination of RAD, Neoral®, and steroids is effective for the prophylaxis of acute rejection in heart and renal allograft recipients. The originally proposed fixed dose regimens for the prevention of allograft rejection in heart and kidney transplantation proved to be effective with respect to the primary endpoints. However, the RAD fixed dose regimens were demonstrated to be unsafe due to marked nephrotoxicity. The 12-month analysis of the Key Heart and Renal Studies showed progressive renal function deterioration in the RAD arms when compared with the control arm.

The enhanced CsA nephrotoxicity in the RAD and CsA combination proved to be unacceptable, leading to protocol amendments #3. By these amendments, patients with renal dysfunction in the RAD arms were identified, and every necessary treatment adjustment was made to improve renal function. However, no evidence of reversibility was observed in both key renal studies and heart studies. The sub-optimal response to Neoral dose reduction with no satisfactory explanation for the creatinine elevation persistence, i.e., ongoing or recent acute rejection, suggests irreversible kidney damage.

In both RAD arms and across Key Heart and Renal Studies, common characteristics were present. Higher rates of discontinuation from study medication were observed in the Certican® plus CsA regimens mainly due to renal dysfunction/creatinine increased adverse events. Anemia NOS, thrombocytopenia, TMA,⁴ higher incidence and degree of lipid abnormalities and lymphocele were complications more frequently observed in the both RAD arms and in both key renal and heart studies. On the other hand, leucopenia was more frequently observed in the AZA and MMF groups compared to the RAD groups in the Key Heart and Key Renal studies, respectively.

In the key heart study and the European renal study B201, CMV infection was three times higher in control groups compared with RAD arms. These results were not consistent with the American study B251, in which the incidence of CMV infection was similar across arms.

The Key Heart and Renal studies were not designed to demonstrate rate differences in CMV infection, CMV syndrome, or tissue invasive CMV and the incidence of cytomegalovirus infection or disease was not a prospectively defined endpoint or efficacy variable, and the studies did not include any precautions to avoid bias in the collection of CMV related information.

⁴ TMA (thrombotic microangiopathy), which includes HUS (hemolytic uremic syndrome) and TTP (thrombotic thrombocytopenic purpura), are consumptive coagulopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia.

We were not able to attribute any anti-CMV effects to RAD and the presence of many confounding factors do not allow us to draw valid conclusions based on a retrospective finding. Finally, the observed differences in cytomegalovirus infections was due to mild to moderate cases. These differences may not be clinically relevant, given that only a few cases were severe and none of these cases led to discontinuation or deaths.

Both Key Renal Studies consistently showed higher rates of adverse events blood creatinine increased/renal dysfunction, hyperlipidemia, pneumonias, hemolytic uremic syndrome, lymphocele, peripheral edema, deep venous thrombosis and proteinuria in both RAD arms compared with MMF.

Hypertension and diabetes mellitus (DM) occur as a common comorbidity recognized among transplant patients. Clinically relevant differences were not observed in the occurrence of this comorbidity across arms in the pivotal heart and kidney trials. However, when they are associated to other pathologies their long term consequences may become more drastic.

Hyperlipidemia, proteinuria, hypertension and DM are conditions that are known to correlate with the progression of renal dysfunction. The coexistence of these morbidities (i.e., more than one of these conditions in the same individual) was more frequently observed in both RAD arms across both key renal studies. This fact correlates with the higher incidence of clinically-confirmed chronic rejection at 36 months in both RAD groups compared with the MMF group, in both key renal studies.

In the Key Heart Study, renal dysfunction was also the issue of most concern. Clinical experience has demonstrated that chronic administration of CsA in heart allograft recipients commonly produces a dose related progressive nephropathy that frequently leads to HD. The enhanced nephrotoxic effect in the RAD plus CsA combination may not be acceptable in the risk/benefit equation.

Organ specific complications that were more commonly observed in both RAD arms were pericardial effusion and tamponade which are clinically relevant for the potential fatal consequences. The higher incidence of pneumonia, GI hemorrhage, and new onset diabetes mellitus are also a major concern.

The Certican[®] plus Neoral combination in the key studies has clearly demonstrated an unacceptable degree of nephrotoxicity and pneumonia without improvement in graft or patient survival, which clearly indicates that the gain in decreasing acute rejection is paid of by the increase in toxicities.

A late reduction in the dose of CsA appears to have limited beneficial effect in improving renal function and this poor response is probably related to irreversible changes in the kidneys. The drop in GFR is significant, non-reversible and may potentially lead to chronic renal dysfunction. Progressive renal function impairment in the presence of well known co-morbidities increases place these patients at a greater risk for severe renal failure which has been associated with increased mortality.

6. APPROVABILITY

We have completed the review of the new proposed indication for Certican[®] for the prophylaxis of organ rejection in *de novo* allogeneic kidney and heart transplantation and recommend an approvable letter for this application.

We have concluded that adequate information has been presented to demonstrate that the combination Certican[®], Neoral[®] and corticosteroids is effective to prevent allograft rejection in heart and kidney transplantation. However, unacceptable safety profiles were observed in the original fixed dose regimens studied in the key heart and renal trials.

We believe that therapeutic drug monitoring is a promising approach. The use of everolimus plus CsA minimization strategy may optimize efficacy and improve safety. However, we were not able to identify an appropriate TDM regimen for the heart or kidney indications that will allow maintaining efficacy while minimizing toxicity in both early and maintenance periods after transplantation.

7. RECOMMENDATIONS

The information provided suggests that Certican[®] has the potential to improve the care of renal transplant patients. However, renal toxicity is evident early after RAD plus CsA exposure and subsequent chronic renal changes are not entirely reversible. It appears that CsA minimization strategy should be implemented at early stage post-transplantation. We were unable to identify a CsA minimization/sparing strategy that would minimize toxicity without compromising efficacy in both heart and kidney transplant patients.

Exposure-efficacy and exposure-safety analyses provided data to delineate a potential TDM range that in conjunction with CsA dose minimization may show a more acceptable safety profile. However, such concentration-controlled regimens would be expected to demonstrate a better safety profile while maintaining efficacy in a prospective, well-controlled clinical trial. Such trial should demonstrate that the regimen is feasible, well tolerated, and produces the desired improvement in renal function.

We recommend that this study defines prospective target concentration ranges over time for both Certican and CsA and demonstrate them to be safe and effective in both, early stages post-transplantation and during the maintenance phase.

Primary analyses at 6 months post transplantation could support a resubmission of the NDA for these indication, providing that there is a commitment to provide follow-up outcome and safety data at 12, 24 and 36 months.

If the regimen would require doses and concentrations of Everolimus that are higher than those observed in the pivotal trial, additional safety data (duration and number of subjects) might be needed to support approval of the regimen.

Other approaches that may support the definition for safe and effective regimen could be discussed with the Division.

8. BACKGROUND

Everolimus (40-O-[2-hydroxyethyl]-rapamycin, SDZ RAD or RAD001) is a macrolide immunosuppressant derived from rapamycin. Everolimus forms a complex with FKBP that inhibits the action of mTOR, suppressing cytokine-driven (IL-2, 4, 7 and 15) T-cell proliferation, inhibiting the progression from phase G1 to S in the cell cycle of different cell lines including but not restricted to T cell and smooth muscle cells.

Novartis Pharmaceuticals Corporation submitted the original IND 52,003 application for everolimus Tablets on November 15, 1996⁵. Novartis' rationale for developing RAD was based on a novel mechanism of action which could aid in preventing acute and chronic rejection and act in synergy with Neoral, thereby potentially decreasing the dose of Neoral and its side effects.

Three pre-NDA meetings were held for this product, (December 3, 1999; February 6, 2001 and March 25, 2002) before the final NDA was submitted.

The initial proposed indication for Certican (first pre-NDA meeting, December 3, 1999) was limited to kidney transplantation and was supported by two randomized, double-blind, double-dummy, multicenter trials (Key Renal Studies B201 and B251). The study design of this trial was drastically modified by amendment #3, converting the double-blind, double dummy design to open label at 12 months post randomization. These drastic changes resulted from the interim analyses that indicated RAD001 was worse in terms of creatinine clearance compared to MMF. The DSMB did not recommend any changes to the study protocols for B201 and B251, but Novartis was concerned enough to convene a panel of nephrologists and other experts in late September to review the issue.

In a teleconference on October 20, 2000, the FDA discussed with the applicant the proposed modifications to the RAD001/Neoral/corticosteroids regimen that would be implemented for the open-label conversion of studies B201 and B251. By that time, the European study had already been unblinded. (See teleconference minutes October 20, 2000.)

In the second pre-NDA meeting, held on February 6, 2001, Novartis planned to pursue the indication of RAD in combination with Neoral[®] and corticosteroids for prophylaxis of rejection in allogeneic adult kidney transplantation. Additionally, Novartis wanted to file for the indication in pediatric kidney transplant patients. The heart indication was not considered by the applicant at this point in time.

The data presented at this meeting showed worse renal function and higher lipid levels in the fixed dose RAD arms (1.5mg and 3 mg) compared to the MMF-treated patients (Key Renal Studies). Amendment #3 provided for lower CsA trough blood levels (50 – 75 ng/mL); Novartis'

⁵ In order to keep uniformity, all dates in the background document are the actual "letter dates", "meeting dates", or "teleconference date". The actual submitted documents were received around the same dates as the "letter dates".

hope was that this change would help alleviate the nephrotoxicity associated with the RAD plus Neoral[®] combination.

The immunosuppressive regimen and study design changes in the presence of worse renal function in the RAD arms raised important concerns for the Agency.

Reviewers Comments:

- ***Key studies converted from double blind to open label design.***
- ***Difficulties in determining the reversibility of nephrotoxicity observed and the long-term consequences of maintaining patients on a RAD plus Neoral based regimen.***
- ***Lack of data from well-controlled trials supporting the newly proposed regimen of RAD (blood trough levels ≥ 3 ng/mL) and Neoral[®] (CsA trough level 50 to 75ng/mL) when given in combination. (FDA did not agree with these recommendations: see minutes from Pre-NDA Meeting/Type B, February 6, 2001.)***
- ***Lack of data on how well the new regimen would perform at early stages post-transplantation.***

As a consequence of these concerns FDA was seriously considering the option of taking this application to an Advisory Committee for its consideration. However, the planed submission for April, 2000 was postponed.

The third and last Pre-NDA meeting was held on March 25, 2002. On this occasion, Novartis proposed NDAs for heart and renal transplantation indications. The indication for heart and the use of IVUS as a surrogate marker to demonstrate the RAD benefits on chronic rejection were new characteristics to be included in the NDA. To be filed.

During this meeting Novartis presented the latest data from their pivotal renal studies (B201 and B251) and heart trial (B253).

During this meeting, the agency clearly stated the following concerns:

- The extensively amended pivotal trials would be a serious review challenge for both the safety and efficacy (See amendment # 3). It was stated that, "*Without a consistent, concurrent control group present throughout the duration of the study, any conclusion based on these data would be difficult to defend*".
- The difficulty to determine if those patients treated under the amendments for studies B201 and B251 were fairly representative of the original population.
- The parameters for creatinine clearance improvement were not predefined before analysis.
- The criteria used to select a subset of patients for IVUS analysis was not prospectively defined in the original protocol for S-B253
- Regarding the two ongoing *de novo* renal studies A2306 and A2307, the agency pointed out that incomplete reports would not be considered for review⁶. Furthermore,

⁶ At the time of the original submission (Dec 19, 2002), only half of the patients included these studies were submitted for a 6months data analysis.

considering the pivotal trial data as a historical control arm for A2306 and A2307 would be inappropriate due to the fact that pivotal studies were extensively amended and impacted by numerous other conditions.

On December 19, 2002, Novartis submitted NDAs 21-560 and 21-628 for the use of Certican® (Everolimus) Tablets 0.25 mg, 0.5 mg, 0.75mg, and 1.0 mg. for the prophylaxis of organ rejection in allogeneic kidney and heart transplant patients, respectively. The chemistry, manufacturing and control sections were pre-submitted to the FDA on October 4, 2002 (IND 52,003 for Certican®).

Subsequently, on January 31, 2003, NDA's 21-561 and 21, 631 for Certican® dispersible tablets 0.1 and 0.25 mg were submitted for the renal and heart indications respectively. In these NDA submissions, Novartis also requested a determination for pediatric exclusivity (See Pediatric Exclusivity section).

On April 17, 2003, the agency requested a review of the nomenclature for "CERTICAN," which was previously reviewed by the FDA (Novartis refers to their January 13, 1999 submission to IND 52,003, Serial No. 125) that resulted in a preliminary approval from DMETS which was communicated to the applicant on June 21, 2000.

The applicant is presently submitting (December 19, 2002) the proposed indication of Certican in combination with Neoral® and corticosteroids for prophylaxis of rejection in allogeneic adult kidney and heart transplantation.

During the initial phase of the review the FDA reviewers raised concerns that led to the request for additional information on Clinical Pharmacology, Pharmacology/toxicology, Medical, and Statistical areas (June 24, 2003)

120-day safety updates were submitted to the respective NDAs on May 2, and June 26, 2003. The updates provided new information on:

- Additional data on efficacy and safety data for studies 2306 and 2307. 50% of missing patients at the original submission was included in this "Synoptic" analysis that only included 6 months data.
- Serious adverse events (SAEs), deaths, malignancies, rejections, graft losses and life-threatening infections.
- New analyses of long-term stability of renal function, (renal amendment analysis Study B253)
- Long-term follow-up of endocrine findings.
- Modifications to the originally proposed labeling:
 - Supporting Renal Transplant studies with Low Dose Cyclosporine. This new section includes data on studies A2306 and A2307.
 - Result on the Cyclosporine Dosing Amendment – Heart Study B253 was included.
 - Therapeutic Drug Monitoring section was modified, and the upper level of 12 ng/mL for the everolimus trough concentration is recommended.
 - Cyclosporine dose recommendations for renal and heart transplant patients taking Certican sections were added: C2 monitoring is recommended for renal patients (no

therapeutic range was recommended), and trough concentration concentrations of 100ng/mL for the heart patients with evidence of nephrotoxicity during the maintenance phase is recommended.

Reviewer's comments:

- ***In the 120-day safety updates, new information on the combination of Certican® with low dose CsA is included in the label from partial information from on-going studies A2306 and A2307.***
- ***The TDM section was updated recommending an upper everolimus trough level of 12 ng/mL. However, no information was included on the relationship of the recommended upper limit of everolimus to efficacy and safety.***
- ***Cyclosporine dose recommendations for renal and heart transplant patients taking Certican were added in this new proposed label. The C2 monitoring was recommended for the kidney transplant patients on Certican®, although, there was no therapeutic range recommended; furthermore, the time after transplantation to start CsA reduction was not described and this recommendation was derived summary and short term information on studies A2306 and A2307.***
- ***For heart transplant patients on Certican®, trough concentrations of 100ng/mL were recommended for patients with evidence of nephrotoxicity during the maintenance phase.***

The June 26, 2003 safety update provided the results on longer term (24 month) data in renal pediatric study B351. FDA received the "Responses to the request for information" on June 10, 2003, July 9, 2003 and August 6, 2003.

On September 4, a teleconference with Novartis to discuss the status of our review was held and on September 12, Novartis' concerns regarding pediatric exclusivity were addressed. During this teleconferences a new request for information was addressed for the heart study was issued. The response to our last request for information was received on September 19, 2003.

On September 19, 2003, additional information was received on studies A2306 and A2307 containing the "First interpretable results of the 12 month data." Novartis also communicated the intention to submit a restricted labeling proposal.

On September 26, 2003, the electronic submission was received making reference to the teleconference on September 12th and the renal transplant program and also included documents previously submitted on September 19, 2003.

All responses and additional submitted data were reviewed and integrated in the final review.

9. CLINICAL TRIALS

9.1. Key Heart Study

In December 19, 2002 Novartis Pharmaceuticals Corporation submitted NDA 21-628 containing studies supporting the proposed indication of Certican[®] for the prophylaxis of organ rejection in heart transplantation. Table 11.1 summarizes the key and supportive studies for the proposed indication.

Table 1: Key Study B253.

Study no.	Design	Duration	No. of patients
B253	R, DB, DD, AC,	3 years	Total – 634
Key heart study	MC, MD, E, S,PK, <i>de novo</i>	(1-year DB /1 year OL by amendment) + 1-year OL extension	RAD 1.5 mg – 209 RAD 3 mg – 211 AZA 1-3 mg/kg/day – 214

AC = active controlled, bid = twice daily, BSA = body surface area, DB = double blind, DD = double dummy, E = efficacy, MC = multicenter, MD = multiple dose, OL = open label, PK = pharmacokinetics, R = randomized, S = safety, and T = tolerability. From Table 1-1 Clinical Data Summary, page 17.

Reviewer's Comments:

The key heart study was modified by three amendments.

9.2. Review Procedures

9.2.1. Efficacy and Safety evaluation

The applicant presented efficacy and safety results. All data were analyzed by treatment group using the intent-to-treat population (all randomized patients).

Safety data was submitted and reviewed with special emphasis on safety laboratory evaluations (hematology, urinalysis, biochemistry, and endocrinology), and adverse events including incidence of infections.

- For 12-month analyses, the cut-off date was Day 450 for all safety evaluations and Day 381 for efficacy evaluations. Patients were considered lost to follow-up if there was no patient contact after Day 329.
- For 6-month efficacy analyses, the cut-off date was Day 194.
- In the efficacy analyses, a subject was considered lost to follow-up if no efficacy assessment is available after Days 154 and 329 for the 6- and 12-month analyses, respectively.

Efficacy analyses were performed on the intent-to-treat (ITT) population, which included all patients who were randomized. Safety and tolerability analyses were performed on the Safety population, defined as all randomized patients who received at least one dose of study medication and then had at least one safety assessment.

Table 2. Number of patients in each analysis population - Key Heart Study B253

	RAD 1.5 (n = 209)	RAD 3 (n = 211)	AZA (n = 214)
ITT	209	211	214

Safety	209	211	214
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Data obtained from Post-text Table 7.3-1 (Page 1 of 1) Analysis Populations by Treatment Group (ITT Population - 12-Month Analysis)

10. KEY HEART STUDY CRAD001 B253 (12 and 24-month analyses)

A two-year randomized, multicenter study (one year DB and one year OL per protocol amendment # 3) of the efficacy and safety of RAD versus azathioprine as part of a triple immunosuppressive therapy regimen in *de novo* heart transplant recipients.

10.1. Background

This study was designed to assess the safety and efficacy of two fixed doses of RAD compared to azathioprine in *de novo* heart transplant recipients. The original protocol was submitted to IND 52,003/N-028 on August 19, 1998, and the last patient completed the study on June 26, 2002.

The Novartis Heart Transplant Program was not discussed with the Agency prior to its initiation. During the last Pre-NDA meeting on October 20, 2000, the applicant discussed regimen changes for the Key Renal Studies only. The applicant has not been able to locate the amendments submission dates for the heart study and we have no record of these submissions. The agency was unaware of the details of the heart transplant proposed indication until the day of the formal NDA submission.

Study B253 was a 1-year, double-blind, double-dummy, randomized, multicenter, parallel-group study phase followed by a 1-year open-label extension phase (per amendment #3). Table 13.1, summarizes the study B253 design characteristics.

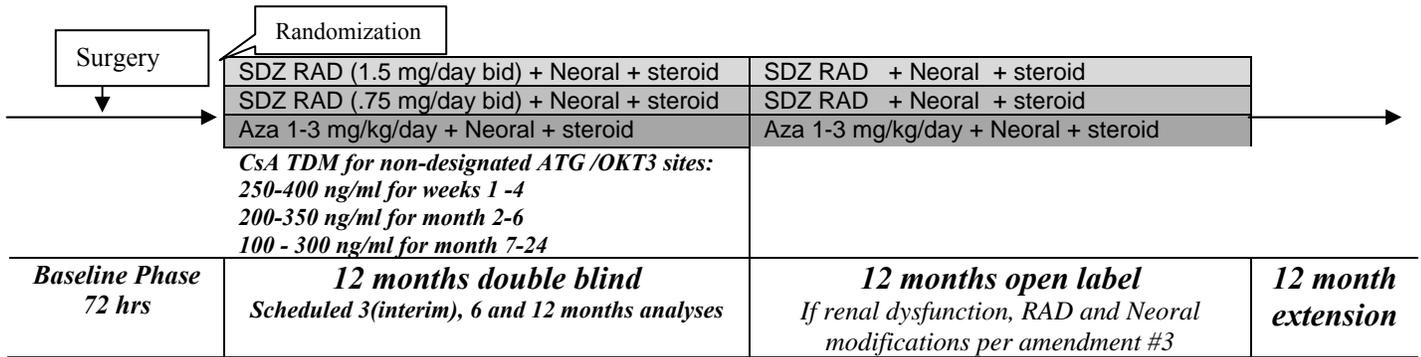
Table 3. Study Design of Trial B253

Study #	Design	Duration	Treatment groups* and No. of patients
B253	MC, R, DB/OL, DD, PG, E, S, PK, <i>de novo</i>	2 years (1-year DB and 1-year OL by amendment)	Total – 634 RAD 1.5 mg – 209 RAD 3 mg – 211 AZA 1-3 mg/kg/day – 214

*All treatment groups received Neoral and steroids during the first 6 months thereafter patients received or not steroids per local practice.

DB = double blind, DD = double dummy, PG = Parallel group E = efficacy, MC = multicenter, OL = open label, PK = pharmacokinetics, R = randomized, S = safety, and T = tolerability. From Table 1-1 Clinical Data Summary, page 17.

Table 4: Protocol design



Fifty two centers were included in this multicenter trial [US (24), Italy (5), Canada (4), Belgium, France, Spain (3 each), Germany and UK (2 each), and Argentina, Austria, Denmark, Norway, Poland, and Switzerland (1 each)]

All treatment groups received Neoral and steroids. Steroids were received during the first 6 months after which patients continued or not to receive steroids per local practice. The use of Rabbit Anti-human Thymocyte Globulin use was permitted only at selected sites as an induction therapy. Use of RATG for treatment of rejection was allowed at all centers.

The 2-year double blind study phase was modified (See Protocol amendment #3). One interim analysis at 3 months, and 6 and 12 month analyses were carried out.

10.2. Inclusion criteria

Male or female cardiac patients 16-65 years of age in North America and 18-65 years of age in Europe undergoing primary heart transplantation with a donor heart cold ischemia time of less than 8 hours. The graft must be functional at the time of randomization.

Informed consent was required. A negative pregnancy test and use of a medically approved birth control method was required for all female subjects of child bearing potential.

10.3. Exclusion criteria

Older donors >60 years and donors with known CAD were excluded. Other usual and reasonable exclusion criteria were also applied, i.e., HIV, Hepatitis C, HbsAg positivity, hypercholesterolemia, hypertriglyceridemia, PRA \geq 20%, WBC \leq 5000 mm³, platelets \leq 70,000 mm³, etc.

10.4. Main Study objectives

The primary endpoint was to compare the efficacy of the 0.75 and 1.5 mg/bid oral doses of RAD versus azathioprine (AZA) in *de novo* heart transplant recipients at 6 month post-transplantation. All three groups also received Neoral® and steroids as part of their immunosuppressive regimen.

Efficacy was measured by the incidence of the composite endpoint (death, graft loss/retransplant, biopsy-proven acute rejection episode (BPAR) \geq Grade 3A, or any clinically suspected acute rejection episode associated with hemodynamic compromise (HDC) in the first 6 months post-transplant). (See HDC under definitions for a more detailed explanation of this term.) The primary endpoint was assessed at 12 and 24 months. Efficacy was also measured by the incidence of all treated acute allograft rejections (whether biopsy proven or not) at 6, 12 and 24 months.

The incidence of chronic rejection was a secondary endpoint evaluated by intravascular ultrasound (IVUS) to determine the degree of intimal thickening in the LAD coronary artery (per amendment #1). Other coronary arteries were interrogated when the LAD was not suitable for study (RCX and/or RCA) at 12 and 24 months. Heart function on echocardiography at 6, 12, and 24 months after transplantation was also evaluated.

10.5. Patient Evaluation

Patients had a baseline evaluation within 72 hrs post-transplant. Randomization occurred, and the first dose of study medication was given during the first postoperative day.

10.6. Efficacy

Acute rejections were assessed by endomyocardial biopsies on Days 7, 14, 21, and 28 and on months 2, 3, 4, 5, 6, 9, 12, 18, and 24. Any suspected rejection episode was to be biopsied at the investigators' discretion. In addition, echocardiograms were performed to assess whether the acute rejection was associated with HDC.

Allograft vasculopathy (chronic rejection): Intimal proliferation of the coronary arteries was assessed by IVUS during the first 6 weeks post-transplantation (baseline) and at 12 and 24 months.

10.7. Safety

Safety parameters were monitored by electrocardiograms (ECGs), vital signs, physical examinations, safety laboratory evaluations (hematology, urinalysis, biochemistry, and endocrinology), adverse events (AEs), and infections.

10.8. Concomitant medications

- *ATG or OKT3*: Only sites using ATG or OKT3 were predesignated and allowed to use these antibodies as induction therapy; other sites were not allowed to use them except for the treatment of AR.
- *Neoral*: used per local practice at designated ATG/OKT3 sites. TDM ranges (250-400 ng/ml for weeks 1-4, 200-350 ng/ml for months 2-6 and 100-300 ng/ml for months 7-24) were used for non-ATG/ OKT3 designated sites.
- *Steroids*: 125 mg IV methylprednisolone 8-12 h x 3 doses, then oral prednisone at 0.5-1.0 mg/kg/day. Subsequently, it was tapered to 0.3-0.5 mg/kg per day by Day 21 and no less than 0.1 mg/kg per day by Month 6. After this period, steroids were given by local practice.
- *Lipid lowering agents*: Hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (excluding lovastatin) were to be administered to all patients even if the patient did not have an elevated total or low-density lipoprotein (LDL) cholesterol value at Baseline. The target LDL level of 130 mg/dL
- *CMV prophylaxis*: “prophylactic therapy” or “antigenemia based therapy” was instituted as preferred per site. The prophylactic regimen consisted of IV ganciclovir for 14-28 days followed by oral ganciclovir or acyclovir for 10-12 weeks. (For Donor CMV +, or Recipient CMV + or both). Antigenemia based therapy allowed for weekly antigenemia testing during the first 3 months. For the presence of antigenemia, IV ganciclovir was to be administered until antigenemia cleared. CMV prophylaxis was recommended following any antibody treatment of acute rejection episodes, with doses according to local practice.

10.9. Drug levels and pharmacokinetic assessments

- Analysis of CsA whole blood trough levels at specific time points throughout the study. Analysis of RAD whole blood trough levels was carried out at Novartis using an ELISA method or a liquid chromatography/mass spectrometry (LC/MS) method. At selected centers, 8-hour abbreviated PK profiles of RAD during steady-state were performed at Months 2, 3 and 6 for an exploratory population PK analysis.
- Safety laboratory tests, CsA and RAD trough levels were assessed at 2, 7, 14, 21 and 28 days and at 2, 3, 6, 9, 12, 18 and 24 months. A baseline was obtained for all safety lab tests. (See: Drug concentration and pharmacokinetic evaluations after CsA and RAD dose modifications [Unblinded phase]).

10.10. Protocol amendments for Study CRAD001 B253

The protocol for study B-253 was finalized on May 8, 1998, with the study modified by three subsequent amendments. The most relevant changes provided by these amendments are listed below. Boldface and underline to emphasize the most critical changes.

Reviewer's comment:

We do not have any record of the submission of amendment #3 to the FDA and the Sponsor could not find any record either.

10.10.1. Amendment #1 (Released: 10-Sep -98)

- Patient safety guidelines for hyperlipidemia and neutropenia
 - A HMG Co-A reductase was to administered to all patients even if the patient does not have an elevated total or LDL cholesterol at Baseline
 - The study medication (RAD or AZA) dose can be reduced or temporarily interrupted according to the investigator's judgment.
- IVUS procedure changes and chronic rejection definition (**See IVUS section**):
 - The interrogation of only one coronary and comparing the average mean intimal thickness at 12 and 24 months.
 - The degree of increase in intimal thickening that defined chronic rejection was changed.

10.10.2. Amendment # 2 (Released: 02-Nov-98)

- Addressed induction therapy, changes of surrogate markers, parameters and timing of blood collection for genotyping, as well as primary and secondary endpoints for IVUS
- As established in amendment #1, only one vessel (LAD) will be examined. If LAD cannot be interrogated due to technical reasons, then LCX (second choice), or RCA (third choice) will be interrogated. By this amendment, the incidence of chronic rejection will not be considered the primary IVUS efficacy variable anymore (See IVUS section).

10.10.3. Amendment #3 (Released: 29-Nov-01:

The applicant's rationale for this amendment was based on the 12-month analyses of renal studies CRA001 B201 and B251 and heart study CRAD001 B253. These preliminary analyses raised Novartis' concerns regarding renal toxicity and gonadal endocrine dysfunction in males.

The applicant made special reference to supportive study CRAD001 B156, A Phase IIIb open-label renal study that compared the use of low vs. standard doses of Neoral in patients treated with RAD (3 mg/day), Simulect and steroids.

The results from study B156 indicated that both efficacy and safety were better in the low dose Neoral treatment arm. Based on this analysis, Novartis decided to unblind CRAD001 B253 and modify the immunosuppressive regimen with the objective of minimizing the risk of nephrotoxicity while maintaining efficacy.

The applicant also made reference to CNI sparing studies using sirolimus and to the observation that RAD trough levels <3 ng/ml appear to be associated with an increased incidence of rejection. (Key renal studies 12-month analyses.)

Additionally, per this amendment an endocrinologic assessment at 18 months was incorporated into the protocol to detect low testosterone levels (<10 nmol/l for males less than 50 years old; <7 nmol/l for males 50 years of age or older).

Reviewer's comment:

RAD fixed dose regimens were demonstrated to be unsafe due to marked nephrotoxicity. In an attempt to decrease nephrotoxicity while maintaining efficacy, the applicant implemented amendment #3.

Amendment #3 provided for very important modifications in study design and RAD arms therapeutic regimen. In study B253, the 2-years double-blind, double dummy and randomized study design was considered adequate originally. After extensive and crucial modifications, the strength of randomization was lost and the potential for bias increased due to the following reasons:

- ***Study B253 was unblinded at 12-month.***
- ***The therapeutic regimen was changed from RAD fixed doses to RAD target blood concentration and reduced dose Neoral.***
- ***A sub-population of patient with renal dysfunction was specifically targeted in the RAD arms to modify the immunosuppressive regimen. The RAD blood levels were optimized to >3 ng/ml, and the cyclosporine A target trough concentration was decreased.***

The TDM approach proposed in amendment #3 still raised concerns since the upper limit for RAD TDM had not been well defined. Similarly, the lower limit for CsA trough levels in this regimen is still undefined.

During the pre-NDA meeting, the Agency pointed out that the sponsor did not have as much experience with reduced-dose cyclosporine in heart transplant recipients. The sponsor agreed that they did not have data or experience available to give recommendations with regard to CsA reductions below 100 ng/mL.

In conclusion, the safety and efficacy of this regimen and the appropriate time and degree for CsA reduction and RAD optimization has not been prospectively evaluated⁷.

⁷ The DSMB communication on July 23, 2002, recognized that Certican has a "clinically meaningful interaction with CsA" and recommended that cyclosporine blood concentrations should be maintained at the lower therapeutic range (This communication was issued 8 month after amendment 3 was implemented.) In this document, the DSMB also communicated to the investigators of a not statistically significant trend towards increased deaths in the RAD 3 mg dose arm.

10.11. Study Unblinding and Clinical Approach at 12 months

(See Figure 1, algorithm for Open-Label treatment for RAD Patients with signs of renal dysfunction.)

- RAD patients with satisfactory renal function and allograft status could remain on their current doses of immunosuppressants; no intervention is necessary.
- If RAD trough level is below 3 ng/mL, an increase of the RAD dose can be taken into consideration (potentially with carefully decreasing the CsA exposure), but the dosing strategy should be discussed with the sponsor on a case by case basis.
- For RAD patients with renal dysfunction RAD trough levels should be checked and dosing adjusted to ensure an adequate exposure (Through levels > 3 ng/mL) before any significant CsA reduction is performed.

10.12. Drug concentration and pharmacokinetic evaluations after CsA and RAD dose modifications (unblinded phase)

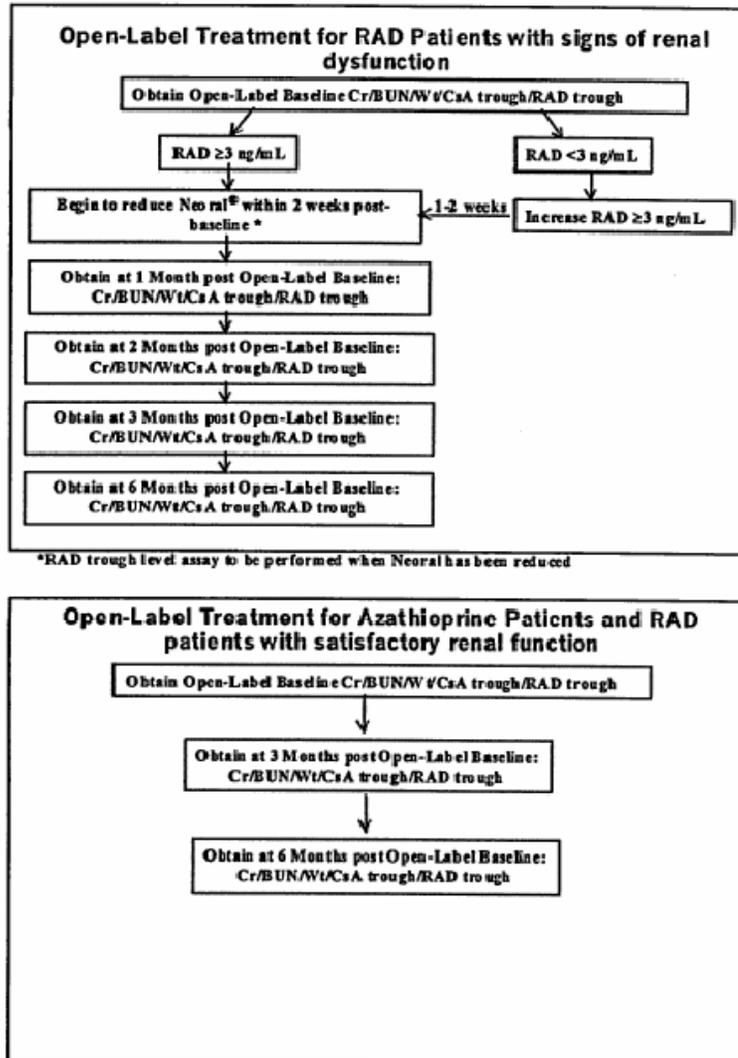
- RAD and CsA trough levels prior to any Neoral and/or RAD dose adjustment, and at 1, 2, 3 and 6 months following the open-label baseline visit. (This TDM approach was not carried out in patient with satisfactory renal function.)
- For the AZA patients, CsA levels were obtained at 3 and 6 months following the open-label baseline visit.

Reviewer's comments:

We agree with the applicant that when RAD is used in combination with cyclosporine (CsA), nephrotoxicity is related to CsA itself. However, we emphasize that the combination will enhance the nephrotoxic effect of cyclosporine, this effect being more important when using both drugs in combination than when using CsA alone.

After amendment #3, the data collected on drug concentrations and PK was insufficient to support the regimen and indications as proposed. In addition, the new target concentration levels for RAD with decreased CsA target levels, has not been prospectively tested during the early phase post-transplantation.

Figure 1. Algorithm for Open-Label treatment for RAD Patients with signs of renal dysfunction
(From Protocol amendment # 3, Study B253-24 month analysis, page 16.)



Reviewer's comments:

This study was designed to evaluate fixed dose of RAD and to assess the PK of RAD at steady state. Modifications in the drug doses for RAD and cyclosporine impede identification of a safe and effective regimen.

11. KEY HEART STUDY: Demographic Characteristics

11.1. Recipient Characteristics

The majority of patients were male (79% to 85%) and Caucasian (87% to 91%) in all groups. The mean ages were 51 to 52 years (range: 16 to 69 years), with the most common primary causes of end stage heart disease being idiopathic cardiomyopathy (46% to 54%) and coronary artery disease (32% to 40%).

Tables 14-1, 14-2, and 14-3 summarize baseline demographic characteristics, age groups and leading caused to ESHD. (Obtained from the original application Table 7-3, Clinical Study Report).

Table 5: Patient Demographics

Characteristics	RAD 1.5 mg (N=209)	RAD 3 mg (N=211)	AZA (N=214)
Male	166 (79.4%)	171 (81.0%)	182 (85.0%)
Female	43 (20.6%)	40 (19.0%)	32 (15.0%)
Age	51(± 11)	52 (± 11)	50.5 (±11.5)
Caucasian	181 (86.6%)	192 (91.0%)	193 (90.2%)
Black	21 (10.0%)	11 (5.2%)	13 (6.1%)
Oriental	2 (1.0%)	3 (1.4%)	3 (1.4%)

Modified from post-text table 7.4-1, Study B253 12 month analyses, page 218

Table 6: Patient Age Categories

Age Categories	RAD 1.5 mg (N=209)	RAD 3 mg (N=211)	AZA (N=214)
0-19	3 (1.4%)	2 (0.9%)	3 (1.4%)
20-29	10 (4.8%)	8 (3.8%)	13 (6.1%)
30-39	16 (7.7%)	16 (7.6%)	21 (9.8%)
40-49	52 (24.9%)	47 (22.3%)	41 (19.2%)
50-59	74 (35.4%)	78 (37.0%)	88 (41.1%)
60+	54 (25.8%)	60 (28.4%)	48 (22.4%)

Modified from post-text table 7.4-1, Study B253 12 month analyses, page 219

Table 7: End Stage Heart Disease Leading to Transplantation

ESHD Leading to Transplantation	RAD 1.5 mg (N=209)	RAD 3 mg (N=211)	AZA (N=214)
Idiopathic cardiomyopathy	100 (47.8%)	98 (46.4%)	115 (53.7%)
Coronary artery disease	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%)
Other	19 (9.1%)	18 (8.5%)	15 (7.0%)

Modified from post-text table 7.4-3, Study B253 12 month analyses, page 222

Reviewer's comments:

Demographic characteristics (Age, sex, race, weight and height) were comparable between treatment groups with no statistically significant differences seen. In all groups, the majority of patients were male and Caucasian. African American and other minorities were underrepresented in this study.

11.2. Organ Donor and Recipient Baseline Characteristics

Transplant-related background characteristics⁸ were reviewed to assess balance between treatment groups. These characteristics on the donors and recipients are summarized in table 13.3-1 (Obtained from the original application Table 7-4, Clinical Study Report.) Table 13.3-1

⁸ Demographics of the donor, Primary disease leading to transplantation, viral serology: HBsAg, hepatitis C, HIV, Panel reactive antibodies (PRAs), Cold ischemia time, Past/coexisting medical conditions and Prior medications and therapies.

Table 8: Selected Transplant-Related Baseline Characteristics

Table 7-4. Selected transplant-related baseline characteristics (ITT population)		RAD 1.5 mg (N=209)	RAD 3 mg (N=211)	AZA (N=214)
Characteristics	Category summary statistics			
Donor age (years)	Mean (\pm SD)	32.5 (\pm 12.5)	34.1 (\pm 12.9)	33.6 (\pm 13.2)
Male donors	n (%)	138 (66.0%)	138 (65.4%)	147 (68.7%)
Female donors	n (%)	69 (33.0%)	73 (34.6%)	66 (30.8%)
Caucasian donors	n (%)	171 (81.8%)	174 (82.5%)	174 (81.3%)
Black donors	n (%)	12 (5.7%)	13 (6.2%)	12 (5.6%)
Oriental donors	n (%)	0	2 (0.9%)	1 (0.5)
Others	n (%)	25 (12.0%)	22 (10.4%)	26 (12.1%)
Primary disease for HTx, n(*)	Idiopathic cardiomyopathy	100 (47.8%)	98 (46.4%)	115 (53.7%)
	Coronary artery disease	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%)
PRA, n(%)	0%	172 (82.3%)	175 (82.9%)	182 (85.0%)
	1% - 20%	32 (15.3%)	33 (15.6%)	28 (13.1%)
	21% -50%	1 (0.5%)	1 (0.5%)	1 (0.5%)
	51% -100%	1 (0.5%)	0	0
Positive viral serology n (%)	CMV: donor+/recipient -	36 (17.2)	48 (22.7%)	37 (17.3%)
	CMV: donor +/recipient +	75 (35.9%)	80 (37.9%)	83 (38.8%)
Cold ischemia time (hrs)	Mean (\pm SD)	2.9 (\pm 1.1)	3.2 (\pm 1.1) ^a	3.0 (\pm 1.1)
Diabetes, n (%)	At Baseline	35 (16.7%)	49 (23.2%)	36 (16.8%)

Source: Post-text tables 7.4-2, 7.4-3, 7.4-5b, 7.4-6, 7.4-7 and 7.4-12 [diabetes]

Note: Numbers in a specific category do not necessarily add up to the total number of patients in this group

^a Statistically significant difference between the RAD 3 mg and 1.5 mg group (p=0.009)

Reviewer's comments:

Donor characteristics of gender, age, and race were similar across arms. Idiopathic cardiomyopathy and coronary artery disease were the primary causes of end stage heart disease leading to transplantation. There were no statistically significant differences among groups. The incidence and degree of PRA donor status was similar between groups.

HBsAg, hepatitis C, or HIV tests were positive or not performed in 2.2%, 1.3% and 0.5% of subjects in the RAD 1.5, RAD 3, and AZA arms, respectively. While these represent minor potential protocol violations, it is not expected that these would influence the overall study results.

High risk for CMV subjects (CMV-positive donors / CMV-negative recipient) were numerically higher in the RAD 3 group (22%) compared with 17% in the RAD 1.5 and AZA arms. The differences between groups were not statistically significant.

Mean cold ischemia time was similar across arms although the difference between the RAD 3 and 1.5 mg group was statistically significant. This difference is not clinically relevant. Pre-study diabetes occurred more frequently in the RAD 3 mg group than in the other groups, but the difference was not statistically significant

Transplant-related characteristics in donors (sex, age and race) and recipients (ESHD, CIT, Pre-existing DM, and serologic status for CMV, HBsA, hepatitis C or HIV) were similar across arms. Minor differences were not considered clinically significant.

Past/Coexisting Medical Conditions related to Certican® adverse events i.e. anemia nos, leukopenia nos, thrombocytopenia, alanine aminotransferase, aspartate aminotransferase and hyperlipidemia were similar across treatment arms.

12. EFFICACY REVIEW - HEART STUDY B253

12.1. Overall Results

Table 9: Patient disposition - Premature Discontinuation from study medication (ITT population - 12 and 24 Month Analyses)

Discontinued from study medication # (%)	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214
12 month analysis. Time window: 312 -415 days	62 (30%)	84 (40%)	61 (28.5%)
24 month analysis. Time window: up to 810 days	82 (39%)	104 (49%)	83 (39%)
Adverse event(s)	43 (21%)	58 (27.5%)	40 (19%)
Abnormal laboratory value(s)	9 (4%)	18 (8.5%)	10 (5%)
Unsatisfactory therapeutic effect	15 (7%)	3 (1%)	18 (8.4%)
Protocol violation	2 (1%)	4 (2%)	2 (0.9%)
Withdrawn consent	6 (3%)	11 (5%)	3 (1%)
Death/Lost to follow-up and Administrative problems	7 (3%)	10(5%)	10(5%)

Modified from table 1, Study B253, page 11.

After discontinuation of study medication, the most commonly used immunosuppressive agent other than Neoral and corticosteroids was mycophenolate mofetil for all 3 groups (39% to 49% across groups).

Patient discontinuations from the study at 24 months were 23 (11.0%), 33 (15.6%), and 31 (14.5%) in the RAD 1.5, RAD 3 and AZA arms, respectively. Death was the most common cause of patient study discontinuation accounting for most of the cases of study discontinuation (21 (10.0%), 29 (13.7%), and 24 (11.2%) in the RAD 1.5, RAD 3 and AZA arms, respectively).

Reviewer's comments:

- *Rate of discontinuation from study drug was high across arms at 24 months (39%, 49% and 39% in the RAD 1.5, RAD 3, and AZA groups, respectively).*

- **Regardless of RAD dose adjustment and CsA minimization during the open label period, discontinuation rate continued to increase an extra 10% more from 12 to 24 months across arms.**
- **Adverse events were the most common cause for treatment discontinuation across treatment groups.**
- **The RAD 3 arm presented the highest rate of discontinuations among the three treatment arms at 12 and 24 months. Adverse events, abnormal laboratory values and consent withdrawal were the main contributing factors for the highest discontinuation rates in this arm.**
- **Premature discontinuations of study medication due to lack of efficacy was lower in the RAD 3 arm, but similar between the RAD 1.5 and AZA at 12 months.**

Table 10: Antimetabolite Immunosuppressive Agents Administered After the Discontinuation of Randomized Study Medication (Safety Population - 24 Month Analysis)

	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214
No. of patients who discontinued study medication	82 (39%)	104 (49%)	83 (39%)
Azathioprine	17 (21%)	29 (28%)	5 (6%)
Mycophenolate Mofetil	37 (45%)	41 (39%)	41 (49%)

Data obtained from Post-text Table 8.2-3.

This table includes only patients prematurely discontinued from study medication.

The medications summarized in this table are medications that were administered one or more days after the discontinuation of randomized study medication. (Calcineurin inhibitors, corticosteroids and antibody therapy are not included in this table).

Reviewer's comment:

After discontinuation of study medication, mycophenolate mofetil was the most commonly used antimetabolite immunosuppressive agent in both RAD and AZA arms (39% to 49%). Discontinued patients from the RAD arms received either Azathioprine (comparator) or MMF in the 66% of the cases. There is concern about the potential contribution of switching to these agents after patient discontinuation to the final outcome across treatment groups in the ITT analyses.

Table 11: Number (%) of patients with efficacy-related events
(Months 6, 12 and 24 - ITT population)

	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214	
Antibody-treated acute rejection episode of ISHLT \geq grade 3A:	12 (5.7%)	6 (2.8%)	14 (6.5%)	ns
of any grade:	15 (7.2%)	7 (3.3%)	15 (7.0%)	
Efficacy failure⁹ (Month 6)	76 (36.4%)	57 (27.0%)	100 (46.7%)	0.031 ^a <0.001 ^b 0.037 ^c
Acute rejection of ISHLT \geq grade 3A	58 (27.8%)	40 (19.0%)	89 (41.6%)	0.003 ^a <0.001 ^b 0.032 ^c
Efficacy failure (Month 12)	87 (41.6%)	68 (32.2%)	113 (52.8%)	0.020 ^a <0.001 ^b 0.045 ^c
Acute rejection of ISHLT \geq grade 3A	64 (30.6%)	45 (21.3%)	98 (45.8%)	0.001 ^a <0.001 ^b 0.029 ^c
Efficacy failure (Month 24)	96 (45.9%)	76 (36.0%)	123 (57.5%)	0.016 ^a <0.001 ^b 0.038 ^c
Acute rejection of ISHLT \geq grade 3A	73 (34.9%)	48 (22.7%)	103 (48.1%)	0.005 ^a <0.001 ^b 0.005 ^c
Acute rejection associated with HDC	19 (9.1%)	17 (8.1%)	28 (13.1%)	n.s.
Graft loss	10 (4.8%)	14 (6.6%)	13 (6.1%)	n.s.
Death	21 (10.0%)	29 (13.7%)	24 (11.2%)	n.s.
Lost to follow up	0	0	2 (0.9%)	n.s.

Data obtained from: Post-text Table 9.1-5a Post-text Table 9.1-5b Post-text Table 9.1-5c Post-text Table 9.4-5 Post-text Table 9.1-1a Post-text Table 9.1-1b

a: RAD 1.5 mg vs. AZA; b: RAD 3 mg vs. AZA; c: RAD 1.5 mg vs. RAD 3 mg (pairwise Z-test, $p \leq 0.05$)

Patients are counted in all rows that apply. Individual components of efficacy failure are not mutually exclusive. Cut-off for events other than lost to follow up were Days 194 and 381 (6- and 12-month analyses, respectively).

The 120-day safety update reported 13 acute rejection episodes: 6, 5 and 2 in the RAD 1.5, RAD 3, and AZA groups, respectively.

⁹ Defined as the incidence of the composite efficacy endpoint (biopsy-proven acute rejection episode International Society of Heart and Lung Transplantation (ISHLT) \geq grade 3A or any clinically suspected acute rejection episode associated with hemodynamic compromise [HDC], graft loss/re-transplant, death, and loss -to-follow-up.

Reviewer's comments:

- *The incidence rates of efficacy failure at Months 6, 12 and 24 were statistically significantly lower in both RAD groups compared with the AZA group.*
- *The incidence rates of acute rejection ISHLT \geq grade 3A were significantly lower in the RAD arms at month 24 (35%, 23% and 48% in the RAD 1.5, RAD 3 and AZA arms , respectively.)*
- *Not significant differences were observed for graft loss, death, LOF, and acute rejection with HDC.*

12.2. Primary Efficacy Endpoint by Induction Antibody Therapy

In the original protocol only RATG (Mérieux rabbit Anti-human Thymocyte Globulin) was permitted at selected sites. A standardized regimen of RATG 2.5 mg/kg for a maximum of 3 days was used.

Per amendment #2, other antibodies for induction therapy were allowed. A standardized regimen of RATG < 2.5 mg/kg/day (Mérieux) or RATG < 5 mg/kg/day (Fresenius) or OKT3 < 5 mg/day for a maximum of 3 days was used. Antibody therapy was permitted in non-designated sites only for treatment of acute rejection episodes.

Table 12: Number (%) of patients with efficacy failure related events (ITT population, with and without induction antibody therapy 12-month analysis)

	RAD 1.5 n = 209		RAD 3 n = 211		AZA n = 214	
<i>Induction Therapy</i>	YES n=104	NO n=105	YES n=102	NO n=109	YES n=109	NO n=105
<i>Primary Efficacy Endpoint</i> ¹⁰	41 (39%)	46 (44%)	31 (30%)	37 (34%)	55 (50.5%)	58 (55%)
Acute rejection of grade \geq 3A	28 (27%)	36 (34. %)	17 (17%)	28 (26%)	45 (41%)	53 (51.5%)
Acute rejection associated with HDC	9 (9%)	8 (8%)	7 (7%)	7 (6%)	10 (9%)	13 (12%)
Graft loss	4 (4%)	3 (3%)	6 (6 %)	5 (5 %)	8 (7%)	2 (2%)
Death	12 (11.5%)	6 (6%)	16 (16%)	8 (7%)	11 (10%)	6 (6 %)
Lost to follow up	0	0	0	0	2 (2%)	0

Data obtained from Post-text Table 9.1-5c (Page 1 of 1) Number (%) of Patients with Efficacy Failure within 12 Months of the Initial Dose of Study Medication (ITT Population - 12 Month Analysis)

Components of efficacy failure are not mutually exclusive, except for the category 'lost to follow-up'.

Reviewer's comments:

- *The number of patients who received or who did not receive induction therapy was comparable in all treatment groups. Therefore, this intervention did not affect the overall conclusions.*
- *In patients receiving antibody induction therapy, the incidence of efficacy failure was consistently lower than in those patients who did not receive it. The incidence of acute rejections of grade \geq 3A was considerably lower in patients who received induction therapy and it mainly accounted for the differences in efficacy failure. However, this difference was blunted due to a notable increase in the number of deaths among patients that received induction therapy.*
- *For acute rejections associated with HDC, no substantial differences between patients with and without induction therapy were observed.*

¹⁰ Primary efficacy endpoint: Acute rejection of grade \geq 3A, acute rejection associated with HDC, graft loss, death or lost to follow-up. Graft losses were defined as re-transplants and all deaths due to cardiac events (e.g., heart failure and myocardial infarction).

- **Induction therapy decreases the acute rejection $\geq 3A$ rates, however, this benefit is counterbalanced by increasing death rates and predisposing to infection (See CMV infection section)**

12.3. Protocol Violations

In general, if the study medication was interrupted for more than 21 consecutive days, or more than 2 episodes of any length for safety reasons in the first 6 months, the patient could have been prematurely discontinued after consultation with the sponsor. The study medication could have been interrupted during antibody treatment for rejection episodes and resumed following antibody therapy.

Table 13: Protocol Violations

	RAD 1.5 209	RAD 3 211	AZA 214
Any violation (12 months)	66%	71%	73%
Any violation (24 months)	65%	71%	71%
Study med. Related violations (12 months)	21%,	31%	24%,
Non-compliance to study med. (12 months)	7.7%,	13.3%	9.8%
Study med related violations (24 months)	21%	29%	21%
Non-compliance to study med.(24 months)	5.3%	8.5%	4.7%

Reviewer's comments:

- **The overall rate of protocol violations at 12 and 24 months analyses were similar in the RAD 3 and AZA arms and lower in the RAD 1.5.**
- **The specific reasons were generally comparable in all groups. However, protocol violations related to the study medication had higher rates in the RAD 3 arm at 12 and 24 months. The main contributor to this difference was non-compliance with the study medication.**
- **Protocol violations due to abnormal WBC count were more frequent in the RAD 3 arm (2.4%, 5.2% and 3.7 % in the RAD 1.5, RAD 3 and AZA group, respectively).**

12.4. Biopsy Compliance

Biopsy compliance is an important concern in this review due to the fact that acute rejection of ISHLT \geq grade 3A was the main contributor for the differences in the primary efficacy endpoint at 6, 12 and 24 months.

Table 14 below shows the percentages of missed biopsies due to missed visits or after discontinuation from study medication. (Deaths, lost of follow up and withdrew consent cases are excluded from this analysis.)

Table 14: Percentage of Patients without Biopsy Due To Missed Visits or D/C from Study Medication - Study B253

Pts without biopsy (# of subjects without biopsy* / # of evaluable subjects **)	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214
6-month analysis	12% (21/197)	18% (35/200)	11% (22/201)
12-month analysis	22% (42/192)	25% (48/190)	19% (37/198)
24-month analysis	38% (71/188)	45% (82/181)	39% (72/186)

Data obtained from: Response to FDA’s question #1 Table 1: RADB253 Biopsy Compliance

* The numerator contains the no. of subjects without biopsy at this time point due to missed visits or d/c study med. (Deaths, lost of follow up and withdrew consent cases are excluded)

** Evaluable subjects are all subjects with functioning graft (i.e. those who had not died or had graft loss, discontinued the study, or become lost-to-follow-up up to this time point)

It was established in the protocol that all prematurely discontinued patients from the study medication, will be contacted at 3, 6, 12, and 24 months after the first dose of study medication to obtain follow-up information on rejection episodes (with or without hemodynamic compromise), graft loss/retransplant, malignancies, opportunistic infections, patient survival and immunosuppressive therapy.

Reviewer's comment:

The percentages of patients without biopsy due to missed visits or discontinuation of study medication at 6, 12 and 24 months were higher in the RAD3 arm compared with the RAD 1.5 and AZA groups which demonstrated similar rates between them.

At 24 months post-transplantation, the percentages of patients without biopsy were 38%, 45% and 39% in the RAD1.5, RAD3 and AZA groups, respectively. These rates are excessively high and have a direct effect on the ITT analysis of the composite endpoint in this study.

The main causes for discontinuation from study medication were unsatisfactory therapeutic effect and adverse events (AE). AE alone accounted for 52%, 56% and 48% of the discontinuations from study medication in the RAD 1.5, RAD 3 and AZA arms, respectively. Missed biopsies due to discontinuation from study medication reflect the importance of this adverse event in determining which patients would have a biopsy.

Adverse events leading to discontinuation (DAE) from study medication were higher in the RAD 3 arm (35%) compared to RAD 1.5 and AZA groups (26 and 26%), which explains the higher rates of missing biopsies in this group. But most important is the fact that DAEs were different between the RAD and AZA arms.

The main DAEs in the RAD arms were related to renal dysfunction renal impairment nos (blood creatinine increased) and pneumonia. In the AZA arm leukopenia nos. and heart transplant rejection were the most common DAEs.

In summary, missed biopsies were indirectly driven by specific drug related toxicities i.e. renal dysfunction, leukopenia nos, pneumonia, which had the potential to influence which patients are biopsied and therefore, have the opportunity or not to detect a rejection episode. One wonders if the higher rate of missed biopsies in the RAD 3 arm had an influence in the lower rejection rates observed in this arm.

CMV infection as DAE was reported in only two cases. One Cytomegalovirus infection in the RAD 3 group and one case of Cytomegaloviral pneumonia in the AZA group.

Table 15: Dose reductions and dose interruptions from study medication (ITT Population- 24 month analysis)

	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214
Any Dose Interruption Total	72(34%)	85(40%)	97(45%)
Adverse Event	36(17.2%)	39(18.5%)	39(18.2%)
WBC Abnormality	28(13.4%)	41(19.4%)	52(24.3%)
Platelet Abnormality	10(4.8%)	11(5.2%)	8(3.7%)
Any Dose Reduction Total	121(58%)	134(64%)	112(52%)
Adverse Event	56(26.8%)	68(32.2%)	20(9.3%)
WBC Abnormality	51(24.4%)	58(27.5%)	71(33.2%)
Platelet Abnormality	22(10.5%)	25(11.8%)	3(1.4%)

Data obtained from Post-text Table 8.1-5 (Page 1 of 5) Protocol CRAD001 B253 24 months analysis pages 148-152

1. Patients may reduce dose for more than one reason
2. These reason categories are generally not mutually exclusive
3. Temporary dose interruptions/permanent treatment discontinuations are considered dose interruptions
4. Dose interruptions are not considered dose reductions

Reviewer's comments:

- ***Renal impairment NOS was the most common adverse event that led to discontinuation (DEA) from study medication (See SAFETY RESULTS STUDY B253)***
- **Dose reductions:**
 - ***The incidence of dose reductions was higher in the RAD 1.5 and 3 mg groups (58% and 64%, respectively) compared with the AZA group (52%)***
 - ***The most common reason for dose reductions was AE's in the RAD 1.5 and 3 mg groups and white blood cell (WBC) count abnormalities in the AZA group.***
 - ***Platelet abnormalities were also an important contributor for dose reduction in the RAD arms.***
- **Dose interruptions:**
 - ***The incidence of dose interruptions was lower in the RAD 1.5 and 3 mg groups (34% and 40%, respectively) compared with the AZA group (45%).***

- *The most common reason for dose interruptions was AEs in the RAD 1.5 mg group (17%) and WBC abnormalities in the RAD 3 mg and AZA groups (19% and 24%, respectively).*

12.5. Intravascular Ultrasound (IVUS) Examination

To assess allograft vasculopathy (chronic rejection) intravascular ultrasound (IVUS) imaging was to be performed at Baseline (during the first 6 weeks post-transplantation) and at Months 12 and 24 to measure the intimal proliferation in the coronary arteries.

Amendment #2 redefined the primary and secondary efficacy endpoints (See Amendments section). After this amendments the efficacy variables were defined as follows:

Primary IVUS efficacy variable: Change in average maximum intimal thickness from baseline, at Month 12.

Secondary efficacy IVUS variables: Incidence of chronic rejection, change in average intimal area and change in average intimal index.

12.5.1. Changes in IVUS Protocol after Amendments

12.5.1.1. Amendment #1 (Released: 10-Sep -98)

- Amendment #1 restricted the IVUS vessel interrogation to only one coronary artery (LAD being the first choice). It changed from determining the degree of intimal thickening of ALL coronary arteries to ONLY ONE CORONARY ARTERY, preferably in the left anterior descending (LAD) coronary artery, and comparing average mean intimal thickness at 12 and 24 months. (RCX and/or RCA were the alternatives if LAD was not interrogated for any reason)
- The original definition to diagnose Chronic Rejection (≥ 0.3 mm increase in intimal thickening from Baseline) was changed to ≥ 0.5 mm increase in average mean intimal thickening from Baseline. A second amendment included further modifications and chronic rejection was finally defined as ≥ 0.5 mm increase from Baseline in maximum intimal thickness in at least one matched slice of an automated pullback sequence.

12.5.1.2. Amendment # 2 (Released: 02-Nov-98)

- IVUS endpoints: The incidence of chronic rejection was originally considered the primary efficacy variable. Amendment #2 redefined the primary IVUS efficacy endpoint as the change in average maximum intimal thickness from Baseline at month 12. The incidence of chronic rejection was considered as a Secondary IVUS efficacy variables (See efficacy variables above)

- The diagnosis of chronic rejection was made by using results from IVUS as established in the original protocol. However, the definition of CR was again modified, from ≥ 0.5 mm increase in average mean intimal thickening from Baseline to "Chronic rejection will be defined as ≥ 0.5 mm increase from Baseline in maximum intimal thickness in at least one matched slice of an automated pullback sequence."

Reviewer's Comments:

The original protocol was submitted under the IND 52,003/N-028 on 8/19/98. However, Novartis' Heart Transplant Program was not discussed during the Pre-NDA meeting with the Agency. Therefore, we did not have the opportunity to discuss these amendments with the applicant.

Technical difficulties due to decreased vessel lumen, i.e., advanced vessel intimal proliferation, may determine which vessels are actually interrogated leading to selection bias. In addition, we cannot extrapolate IVUS findings from one vessel to the rest of the coronary arteries. We want to emphasize that IVUS efficacy endpoints were modified and accommodated according to the difficulties observed during the study.

12.6. Clinical investigator inspections

On February 14, 2003 the Agency requested international inspections of specific centers due to the fact that:

- There were insufficient domestic data to support the application without the inclusion of foreign data.
- Domestic and foreign data showed some conflicting results pertinent to decision making.

A single superiority study was submitted to support the indication of prevention of rejection in heart transplantation (Study B253). Almost half of the subjects in this study (310/634) were enrolled in non-U.S. sites. Therefore, inspection of the largest U.S. and Non-U.S sites would provide information regarding the quality of the study.

The following sites were identified and inspected:

Indication	Protocol #	Site (Name and Address)
Data Audit	B253 Site #131	Iradj Gandjbakhch, Paris FRANCE
Data Audit	B253 Site #142	Mario Vigano, ITALY
Data Audit	B253 Site #2	Howard Eisen, USA
Data Audit	B253 Site #11	Randall Starling, USA

Reviewer's comments:

Protocol violations and lack of adherence to the approved protocol were observed during the investigation. The main reason for not performing the IVUS study, according to the

investigator, were technical difficulties, equipment failures and disease related factors (smaller vessel diameter) that can be directly related to the parameter that is being investigated.

At the Cleveland Clinic Foundation, safety issues were the main reasons IVUS was not performed according to the principal investigator.

At the European sites, severe vascular lesions with lumen compromise and technical failures were the main cause for missing IVUS studies (according to the investigators). Dr. Gerard Drobinski, the physician who performed the studies at Hospital La Pitie, stated that, "the large majority of the exams at his site were skipped because subjects developed severe lesions that compromised the lumen. The remainders of the exams were skipped due to poor anatomy or mechanical failure. Per Dr Robert Shibuya's report (FDA site investigator), "I had the strong sense that the investigators at the European sites did not consider IVUS a very important tool since they do not maintain the equipment in good conditions, so mechanical failures were common."

Vascular lesions compromising the lumen could well be the manifestation of the process everolimus was supposed to suppress (post transplant coronary artery intimal hyperplasia). Thus, those patients with the most severe form of post transplant coronary artery disease (the lesion of interest) would not undergo IVUS. This definitely undermines any ability to draw reliable conclusions from analysis of IVUS results on a heavily selected subset.

FDA Request for Additional Information:

On May 30, 2003 a request was sent to the applicant for additional information on the specific reasons that prevented IVUS evaluation at baseline, 12 and 24 months. A response was received on August 7, 2003. After reviewing data submitted in the original application and the additional requested data, we observed that:

Table 16: Reasons for not performing IVUS - 24 month analysis (ITT population)

	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214
IVUS not performed (Baseline)	72	69	74
IVUS not performed (12 months)	139	142	142
IVUS not performed (24 months)	164	167	154
Not done due to patient discontinuation, death or AE.	33	45	38
Not done due to renal issues	16	24	12
No Baseline	68	65	62
Technical issues/administrative problems/not analyzable	36	21	39

Data obtained from: Response to FDA's question #2
Patient Disposition for IVUS Analysis
Reasons for not performing IVUS at Baseline, Month 12 and Month 24
(ITT Population)

Reviewer's Comments:

- *Evaluation at 12 months was only done in one third of the patients across arms.*
- *Evaluation at 24 months further decreased to 18 to 20% of the patients across arms.*
- *The major causes for not performing IVUS were due to*
 - *Patient discontinuation, death or adverse events*
 - *Renal issues*
 - *Not having a baseline*
 - *Not analyzable data*

In the "Not having a baseline" category were patients that were excluded because they did not have a baseline for the purpose of comparison, therefore, those patient were no longer eligible for IVUS.

"Patient discontinuation" and "renal issues" were patients eligible for IVUS re-assessment and together were the main culprits for not performing IVUS, which are factors directly related to the study drug.

Technical issues and administrative problems were minor contributors that did not correlate with the site investigators' comments that noted technical problem as a major factor for not performing IVUS.

12.7. Summary of Potentially Introduced Bias and Conclusions

- *The criteria used to select a subset of patients for IVUS analysis was not prospectively defined in the original protocol for S-B253 and unbalances in enrollment at different sites were observed.*
- *The amount of missing data is an important concern since only about 1/2 of the 419 patients who had baseline IVUS were evaluated by IVUS at 12 months. The number of evaluable patients further dropped significantly. After 24 months only about 1/5 of the patients were eligible for IVUS evaluation and analysis, and not equally distributed among the treatment arms.*
- *The imbalance in the proportion of subjects included at the 24 month time point raises concern about the introduction of bias after the study was unblinded at 12 months.*
- *The subjects selected for IVUS must have successfully completed at least 12 months of treatment (only those patients who could tolerate drug, and were healthier, were selected).*
- *Disease related factors that can be related to the parameter that is being investigated (smaller vessel diameter) were reasons for not performing the study which will exclude the most severe cases of allograft vasculopathy.*

- *It cannot be excluded that events which occurred after randomization, related or unrelated to treatment assignment, including post-transplant coronary arteriopathy, may have interfered with performing the test and influenced which subjects were included in the analysis.*
- *Renal issues were evoked as an important reason for not performing the test. Thus, renal impairment due to study regimes could also have influenced which subjects were included in the IVUS analyses.*
- *Amendment #3 allowed the immunosuppressive regimen to be modified in those patients assigned to everolimus who had evidence of renal toxicity. It may be difficult to attribute IVUS findings to the originally randomized treatment or subsequent modification of that treatment.*
- *Most IVUS studies have selectively interrogated the LAD making the assumption that allograft vascular disease occurring in the LAD can be extrapolated to the rest of the coronary arteries which is a questionable issue.*

12.8. Conclusions

IVUS is an investigational method for evaluating intimal thickening in the coronary arteries of the heart allograft.

The patient selection for IVUS was potentially biased and therefore does not accurately reflect the effect of everolimus on arterial intimal thickening and chronic rejection. Overall, the large amount of missing data, and the way this part of the study was conducted does not allow one to draw reliable conclusions and diminishes the need to do any further analyses of this data.

Based on this subset of patients, it would be difficult to link a comparative claim based on IVUS to patient survival and graft loss without an additional adequate and well-controlled study.

13. SAFETY REVIEW - HEART STUDY B253

The safety population is defined as all randomized patients who receive at least one dose of study drug and have at least one safety assessment. All randomized patients in this study received at least one dose of study drug and one safety assessment; therefore, the safety population is the same as the ITT population.

The safety analyses include on-treatment assessments or on-treatment events. AEs with an onset up to 7 days after the premature discontinuation of study drug are included. Any event occurring ≥ 8 days after drug discontinuation are omitted from the analysis.

SAEs that occurred during treatment of study medication (or within 90 days following treatment discontinuation) were followed until they are resolved.

Reviewer's comment:

All randomized patients in this study received at least one dose of study drug and one safety assessment, therefore safety population is the same as the ITT population. However, patients that developed AE after 7 days from discontinuation were not included in the safety analysis. The denominator in all safety analyses never changes regardless of the number of discontinued patients overtime; therefore, affecting the crude rates, which should be interpreted with caution.

13.1. Patient Discontinuations

Patient discontinuation rates from study medication at 24 months were (82/209) 39.2%, (104/211) 49.3%, and (83/214) 38.8% in the RAD 1.5, RAD 3 and AZA arms, respectively. Adverse events were the most common cause of patient discontinuation across arms in the (43/82) 52%, (58/104) 56% and 48% (40/83) of the cases in the RAD 1.5, RAD 3 and AZA arms, respectively.

The RAD 3 arm presented the highest rate of patient discontinuation and the main contributors were adverse events and abnormal laboratory values accounting for 73% (76/104) of the discontinued patients in this arm.

**Table 17: Patients Who Discontinue Study Medication
(24 Month ITT Population Study B253)**

Reason for Discontinuation from Study Medication	RAD 1.5 mg (n = 209)	RAD 3 mg (n = 211)	AZA (n = 214)
Adverse events	43 (21%)	58 (28%)	40 (19%)
Abnormal laboratory value(s)	9 (4%)	18 (9%)	10 (5%)
Unsatisfactory therapeutic effect	15 (7%)	3 (1%)	18 (8%)
Withdrawn consent	6 (3%)	11 (5%)	3 (1%)
Death	7 (3%)	9 (4%)	7 (3%)
TOTAL	82 (39%)	104 (49%)	83 (39%)

Modified from table 1, Study B253, page 11.

Patient discontinuations from the study at 24 months were 23 (11.0%), 33 (15.6%) and 31 (14.5%) in the RAD 1.5, RAD 3 and AZA arms, respectively. Death was the most common cause of patient study discontinuation accounting for most of the cases, 21 (10.0%), 29 (13.7%), and 24 (11.2%) in the RAD 1.5, RAD 3 and AZA arms, respectively.

Reviewer's comments:

The RAD 3 arm presented the highest rates of discontinuation from study medication in the study (49%). Seventy three percent (73%) of these cases were due to AE or abnormal laboratory values.

Adverse events were the most common cause of patient discontinuations from study medication. AEs accounted for approximately 50% of the discontinuations from study medications in each arm.

Discontinuation rates from study medication were similar between the RAD 1.5 (39.2%) and AZA (38.8%) arms.

13.2. Adverse Events Leading To Discontinuation of Study Medication (DAE)

Table 18 summarizes the most frequent and relevant adverse events that led to discontinuation from study medication.

There was inconsistency in the coding and usage of the preferred terms, and two or more of these terms may describe the same entity. These terms were mutually exclusive, and each patient was included under one term only. We are taking this into consideration and we will specify when two or more preferred terms are merged into one category.

Table 18: Incidence Rates of DAE by System Organ Classification and Preferred Term (Safety Population - 24 Month Analysis)

DAE System Organ Classification Preferred Term	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214
Any DAE	56 (27%)	74 (35%)	56 (26%)
Renal and urinary disorders	13 (6%)	20 (9.5%)	6 (3%)
Renal impairment nos	7 (3%)	11 (5%)	3 (1%)
Blood creatinine increased	5 (2%)	3 (1%)	2 (1%)
Microangiopathic hemolytic anemia (including HUS and TTP)¹¹	4 (2%)	3 (1.5%)	0
Infections / infestations	4 (2%)	11 (5%)	5 (2%)
Pneumonia ^a	1 (0.5%)	6(3%)c.	2(1%)
Leukopenia nos	4 (2%)	5 (2%)	7 (3%)
Anaemia nos	0	5 (2%)	1 (0.5%)
Thrombocytopenia	1 (0.5%)	4 (2%)	1 (0.5%)
Gastrointestinal hemorrhage nos	0	3 (1%)	0
Heart transplant rejection	3 (1%)	0	4 (2%)

^a Including *Pneumocystis carinii pneumonia*, *Pneumonia aspergillus*, *Pneumonia chlamydial*, *Pneumonia cytomegaloviral*, *Pneumonia legionella*, *Pneumonia nos*, *Pulmonary tuberculosis*.

Data obtained from study B253, 24 month analysis Post-text Table 10.2-1c (Page 1 of 9)

One case of neutropenia in the AZA group was reported as a DEA. This case was not included in the leucopenia cases.

Two cases of CMV were reported as DAEs. (One Cytomegalovirus infection in the RAD 3 group and one case of CMV pneumonia in the AZA group.)

Reviewer's comments:

- ***Renal and urinary disorders (System Organ Classification) were the most common adverse events that led to discontinuation from study medication (DAE), and were consistently higher in the in the RAD arms (6%, 10% and 3% in the RAD1.5, RAD 3 and AZA, respectively)***

¹¹ HUS (Hemolytic uremic syndrome) and TTP(Thrombotic thrombocytopenic purpura) are consumptive coagulopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia both preferred terms are merged as shown in table 2.

- ***Renal impairment (nos) was the most common adverse event (Preferred Term) that led to discontinuation (DAE) from study medication in the RAD 1.5 and RAD 3 arms. A dose related effect was observed in the discontinuation rates in the RAD arms.***
- ***Leukopenia (nos) was the most frequent DAE in the AZA group.***
- ***The RAD 3 arm presented the highest incidence rates of AE that led to discontinuation from study medication (DAE). DAE rates in the RAD 1.5 and AZA groups were similar.***
- ***Anemia, thrombocytopenia, pneumonia and gastrointestinal hemorrhage DAEs were higher in the RAD 3 arm compared to the AZA and RAD 1.5 arms.***
- ***Heart rejection led to DAE in 3 cases in the RAD 1.5 and 4 cases in the AZA group.***

13.3. Incidence Rate of Most Frequent and Relevant Adverse Events/Infections by System Organ Classification and Preferred Term (Safety Population - 24 Month Analysis)

There was inconsistency in the coding and usage of the preferred terms, and two or more of these terms may describe a same entity.

These terms were mutually exclusive, and each patient was included under one term only. We are taking this into consideration and we will specify when two or more preferred terms are merged into one category. (See Tables 5, 6, and 10).

The dictionary used was the MedDRA and the adverse events/infections with onset date eight or more days after the discontinuation of randomized study medication were not included in this analysis.

Table 19: Frequent Adverse Events/Infections (Rates > 20%) by Preferred Term (Safety Population - 24 Month Analysis)

Preferred Term	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214
<i>Any AE / Infection</i>	208 (99.5%)	211 (100%)	213 (99.5%)
<i>Constipation</i>	45 (21.5%)	42 (20%)	46 (21.5%)
<i>Nausea</i>	58 (28%)	60 (28%)	67 (31%)
<i>Edema peripheral</i>	83 (40%)	80 (38%)	76 (35.5%)
<i>Back pain</i>	24 (11.5%)	46 (22%)	31 (14.5%)
<i>Insomnia</i>	51 (24%)	43 (20%)	47 (22%)
<i>Hypertension nos.</i>	139 (66.5%)	125 (59%)	129 (60%)
<i>Headache nos</i>	74 (35%)	55 (26%)	63 (29%)

1. The dictionary used is MedDRA

2. Adverse events/infections with onset date eight or more days after the discontinuation of randomized study medication are not included in this analysis

Data obtained from: Post-text Table 10.1-1 (Page 5 of 76) and Post-text Table 10.1-2b (Page 1 of 4)

Incidence Rate of Adverse Events/Infections by System Organ Classification and Preferred Term (Safety Population - 24 Month Analysis)

Reviewer's comments:

Adverse events / Infections in table 3, presented incidence rates > 20%. The differences across arms were ≤ 7% and NO dose-related effect between RAD arms was observed except for back pain. We do not believe that these differences are clinically relevant.

Table 20: Incidence of Adverse Events/Infections with Relevant Differences among Treatment Groups by Preferred Term (Safety Population - 24 Month Analysis)

Preferred Term	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214
<i>Anemia NOS</i>	70 (33.5%)	93 (44%)	58 (27%)
<i>Leukopenia NOS</i>	43 (21%)	44 (21%)	63 (29%)
Neutropenia	1(0.5%)	5(2%)	10(5%)
<i>Thrombocytopenia</i>	21 (10%)	37 (17.5%)	16(7.5%)
<i>TMA¹² (Microangiopathic hemolytic anemia, HUS & TTP)</i>	5 (2%)	6 (3%)	0%
<i>Diarrhea NOS</i>	43 (21%)	49 (23%)	31 (14.5%)
<i>hypokalemia</i>	23 (11%)	35 (17%)	27 (13%)

¹² TMA (Thrombotic Microangiopathy) including HUS (Hemolytic uremic syndrome) and TTP (Thrombotic thrombocytopenic purpura) are consumptive coagulopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia.

<i>Pericardial effusion</i>	48 (23%)	49 (23%)	36 (17%)
<i>Cardiac tamponade</i>	6 (3%)	10 (5%)	3 (1%)
<i>Cytomegalovirus infection</i>	15 (7%)	15 (7%)	45 (21%)
<i>Herpes simplex</i>	17 (8%)	12 (6%)	23 (11%)
<i>Pneumonia nos</i>	29 (14%)	20 (9.5%)	6 (3%)
<i>Dyspnea NOS</i>	36 (17%)	46 (22%)	29 (14%)
<i>Nasopharyngitis</i>	20 (10%)	21 (10%)	11 (5%)
<i>Post procedural site wound infection</i>	15 (7%)	11 (5%)	6 (3%)
<i>Incisional hernia nos</i>	9 (4%)	8 (4%)	3 (1%)
<i>Renal impairment NOS</i>	61 (29%)	65 (31%)	40 (19%)
<i>Blood creatinine increased</i>	24 (11.5%)	18 (8.5%)	10 (5%)
hyperlipidemia nos	38 (18%)	29 (14%)	13 (6%)
hypercholesterolemia ¹³	27 (13%)	25 (12%)	20 (9%)
hypertriglyceridemia ¹⁴	13 (6%)	21 (10%)	11 (5%)
<i>Total Lipid Abnormalities¹⁵</i>	78 (37%)	75 (35.5%)	44 (20.5%)
<i>Edema peripheral</i>	83 (40%)	80 (38%)	76 (35.5%)
<i>Lymphocele</i>	10 (5%)	9 (4%)	2 (1%)
<i>Pyrexia</i>	46 (22%)	57 (27%)	43 (20%)
<i>Hypogonadism male</i>	0	0	1 (0.5%)

Data obtained from: Post-text Table 10.1-1 (Page 5 of 76) and Post-text Table 10.1-2b (Page 1 of 4)
Incidence Rate of Adverse Events/Infections by System Organ Classification and Preferred Term (Safety Population - 24 Month Analysis)

Reviewer's comments:

- ***Anemia NOS, thrombocytopenia, TMA¹⁶, diarrhea nos, cardiac tamponade, renal impairment nos, edema, gastrointestinal haemorrhage, pyrexia, and bacterial infections were present at higher rates in the RAD arms with a dose related effect observed.***
- ***Pneumonia, nasopharyngitis, pericardial effusion, lymphocele, incisional hernia nos, post procedural site wound infection and total lipid abnormalities¹⁷, were present higher rates in both RAD arms compared to AZA. However, a dose related effect was not clearly defined.***

¹³ Includes blood cholesterol increased and Hypercholesterolemia aggravated

¹⁴ Includes blood triglycerides increased and V Blood triglycerides abnormal

¹⁵ Includes hypertriglyceridemia, hypercholesterolemia and hyperlipidemia nos

¹⁶ TMA (Thrombotic Microangiopathy) including HUS (Hemolytic uremic syndrome) and TTP (Thrombotic thrombocytopenic purpura) are consumptive coagulopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia.

¹⁷ Includes hypertriglyceridemia, hypercholesterolemia and hyperlipidemia nos

- *Leukopenia NOS and viral infections (cytomegalovirus infection and herpes simplex) presented higher rates in the AZA group compared to the RAD arms.*
- *CMV infection presented significantly higher rates in the AZA group compared with the RAD arms. (See CMV infection section)*
- *An inconsistency was observed in the incidence rates for "Incisional hernia nos" reported at the 12 months analysis [18 (9%), 8 (4%), 4 (2%)] and 24 month analysis [9 (4%), 8 (4%), 3(1%)] for the RAD1.5, RAD3 and AZA groups, respectively.*

13.3.1. Edema

Table 21: Incidence Rate of Edema by Preferred Term
(Safety Population - 24 Month Analysis)

Preferred Term	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214
<i>Edema peripheral</i>	83 (40%)	80 (38%)	76 (35.5%)
<i>Edema NOS</i>	27 (13%)	36 (17%)	27 (13%)
<i>Other including: Pitting edema, Edema lower limb, Neck edema, Edema abdomen nos and Edema aggravated.</i>	4 (2%)	5 (2%)	4 (2%)
Total	114(54.5%)	121(57%)	107(50%)

Reviewer's comments:

In general, edema was more frequently observed in the RAD arms compared to the AZA arm.

13.3.2. Gastrointestinal Hemorrhage:

Table 22: Incidence Rate of GI hemorrhage by Preferred Term
(Safety Population - 24 Month Analysis)

Preferred Term	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214
<i>Gastrointestinal hemorrhage NOS</i>	2 (1.0%)	9 (4.3%)	3 (1.4%)
<i>Gastric hemorrhage including Gastric ulcer hemorrhage and Gastritis hemorrhagic</i>	3 (1.4%)	4 (1.8%)	0
<i>Other including: Haematemesis, Hematochezia, Rectal Hemorrhoidal hemorrhage, and Mouth hemorrhage</i>	2 (1.0%)	3 (1.4%)	1 (0.5%)
TOTAL	7 (3.3%)	16 (7.5%)	4 (1.6%)

The dictionary used is the MedDRA.

Adverse events/infections with onset date **eight or more** days after the discontinuation of randomized study medication are not included in this analysis.

Data obtained from: Post-text Table 10.1-1 (Page 5 of 76) Incidence Rate of Adverse Events/Infections by System Organ Classification and Preferred Term (Safety Population - 24-Month Analysis)

Reviewer's comments:

Gastrointestinal hemorrhage was three times more common in the RAD 3 arm compared to the AZA arm. A dose related effect was observed in the incidence of GI haemorrhage between the RAD arms. Similarly, the incidence of AEs associated with bleeding in general was significantly higher in the RAD 3 group (30%) compared to AZA group (21%). Bleeding events were similar in the RAD 1.5 and 3 mg groups (26% and 30%, respectively).¹⁸

In the RAD 3 arm, three patients were discontinued from study medication due to gastrointestinal hemorrhage and one patient died from gastric hemorrhage.

13.3.3. Infections

Table 23: Incidence Rates of Infections by Type of Organism or preferred term (Safety Population - 24 Month Analysis)

	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214
<i>Any Infection</i>	160 (77%)	169 (80%)	154 (72%)
<i>Bacterial</i>	78 (37%)	85 (40%)	55 (26%)
<i>Fungal</i>	18 (9%)	27 (13%)	19 (9%)
<i>Viral</i>	34 (16. %)	39 (18.5%)	69 (32%)

Data obtained from Post-text Table 10.1-5a (Page 1 of 14)

Reviewer's comments:

- Higher rates of infections were observed in the RAD1.5 and significantly higher in RAD 3 group when compared to AZA (RAD 3 rate minus AZA rate = 8%; 95% Confidence Interval : 0.1 to 16.2%).***
- Bacterial infections were statistically significantly higher in the RAD arms compared to the AZA arm. In contrast viral infections were statistically significantly higher in the AZA group versus RAD arms.***
- Numerically higher rates of fungal infections were observed in the RAD 3 arm compared to the AZA arm.***
- Bacterial, Viral and fungal infection were numerically higher in the RAD 3 versus RAD 1 suggesting a dose related effect.***

¹⁸ AEs associated with bleeding comprise epistaxis, hematemesis, hematoma, hemoptysis, melena, purpura, hemorrhage.

13.3.4. Cytomegalovirus infections

CMV infection reported as Adverse Events and Serious Adverse Events: The key heart study was not prospectively designed to evaluate comparative differences in rates of CMV infection, CMV syndrome, or tissue invasive CMV.

The definitions for CMV infection and CMV disease was not defined in this protocol, instead it uses the preferred term "cytomegalovirus infection" to include most of the reported events. In this study, "Cytomegalovirus infection" was the preferred term used to include the following reported terms by the investigators:

Cytomegalovirus, CMV, CMV disease, CMV infection, CMV primo infection, CMV reactivation, and Suspected CMV infection.

Because of the differences in severity and clinical relevance between CMV syndrome and tissue invasive disease, it is important to understand the contribution of each these entities to the total rates of CMV infections.

Cytomegalovirus infections reported as SAEs are presented below, including the terms used by the investigator (reported term) to describe the event before it was coded in MedDRA (preferred term). The severity described by the investigator is also included. Patient were counted only once, even though in two cases more than one episode of CMV infection was observed (*).

Table 24: CMV infection reported as Adverse Events and Serious Adverse Events (SAE)
(Safety Population - 24 Month Analysis)

Preferred Term	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214
<i>CMV Infection* reported as AE</i>	16 (7.7%)	16 (7.6%)	46 (21.5%)
<i>Total # of CMV infections reported as SAE's.</i> Preferred term/ Reported term	3	3	7
Cytomegalovirus infection / <i>Cytomegalovirus</i>	1 moderate		1 mild
Cytomegalovirus infection / <i>CMV</i>			1 mild
Cytomegalovirus infection / <i>CMVDisease</i>			1 moderate
Cytomegalovirus infection / <i>CMV Infection</i>			1 moderate 1 severe
Cytomegalovirus infection / <i>Cmv primo_infection</i>			1 severe**
Cytomegalovirus infection / <i>CMV reactivation</i>	1 severe**	1 mild	
Cytomegalovirus infec. / <i>Suspected CMV infectio</i>		1 moderate	
Cytomegalovirus gastritis / <i>Cytomegalovirus Gastrit.</i>		1 moderate***	

Pneumonia Cytomegaloviral / *CMV pneumonia or pneumonitis*

1 moderate***

1 severe***

Data obtained from Post-Text Listing 10.2-2 (Page 1 of 97), Non-Fatal Serious Adverse Events (Including Infections) (Safety Population - 24 Month Analysis) and Post-text Table 10.1-5a (Page 1 of 12) Incidence Rates of Infections by System Organ Classification and Preferred Term (Safety Population - 12 Month Analysis).

*Reported as adverse events Post-text Table 10.1-5a (Page 1 of 12) Incidence Rates of Infections by System Organ Classification and Preferred Term(Safety Population - 12 Month Analysis)

** These two patients presented more than one episode of CMV infection, only the most severe episode was counted.

*** Tissue invasive disease

Reviewer's comments:

Cytomegalovirus infection, used as a preferred term, was the most frequent single infection reported in study B-253. It was three times higher in AZA group compared with RAD 1.5 and RAD 3 (21%, 7%, and 7%, respectively).

The incidence of CMV was not a prospectively defined endpoint or efficacy variable and it did not include any precautions to avoid bias for the collection of CMV related information. CMV infections rates reported as AE or Serious Adverse Events are largely due to mild to moderate cases a condition, which is easily treated with standard therapy. Tissue invasive CMV disease, a more severe entity, was reported in three cases, one case in each arm. There were no patient discontinued from study medication or deaths reported as a consequence of CMV infections.

In conclusion, the observed differences of the RAD over AZA regarding cytomegalovirus infections, is based on mild to moderate cases. These differences may not be clinically relevant, given that this is a retrospective finding.

13.3.5. Cytomegalovirus Infections and Antibody Therapy

Tables 16-9 and 16-10 summarize the relationship between the use of antibody therapy for induction and as a total use (Induction and AR treatment).

Table 25: Number (%) of patients with efficacy failure related events (ITT population, with and without induction antibody therapy at Month 12)

	RAD 1.5 n = 209		RAD 3 n = 211		AZA n = 214	
Induction Therapy	YES n=104	NO n=105	YES n=102	NO n=109	YES n=109	NO n=105
Viral infections (12 month analysis)	17 (16%)a	14 (13%)	25 (24.5%)b	11 (10%)b	44 (40%)	23 (22%)
CMV infections (12 months analysis)	13 (12.5%)	4 (4%)	13 (13%)	4 (4%)	32 (29%)	15 (14%)

Data obtained from Post-text Tables 9.1-5c (Page 1 of 1) and Post-text Table 9.1-5c (Page 1 of 1) Studies B201 and B251, Number (%) of Patients with Efficacy Failure Within 12 Months of the Initial Dose of Study Medication, (ITT Population - 12 Month Analysis)

Reviewer's comments:

In the 12 months analysis, the incidence of viral infection was consistently higher in the AZA arms regardless induction therapy; however, patients who received antibody induction therapy presented higher viral infection rates compared to those who did not received induction. Similarly, CMV infection rate was higher in patients receiving induction antibody therapy.

Table 26: Concomitant Administration of Immunosuppressive Agents Other than Randomized Study Medication and Neoral by WHO preferred drug name (ITT Population - 24 Month Analysis)

Selective Immunosuppressive Agents	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214
Methylprednisolone Sodium Succinate	101 (48%)	97 (46%)	112 (52%)
Methylprednisolone	59 (28%)	45 (21%)	58 (27%)
<i>Methylprednisolone Total</i>	160 (76.5%)	142 (67%)	170 (79%)
Antilymphocyte Immunoglobulin (Horse)	18 (9%)	21 (10.0%)	13 (6%)
Antithymocyte Immunoglobulin	40 (19%)	39 (18.5%)	47 (22%)
Muromonab-Cd3	28 (13%)	23 (11%)	35 (16%)
<i>Antibody Therapy Total</i>	86 (41%)	83 (39%)	95 (44%)

Data obtained from Post-text Table 8.2-2 (Page 1 of 3), page 197 Study B-253 24 month analysis

Reviewer's comments:

The use of antibody therapy and methylprednisolone was higher in the AZA arm and probably derived from the higher incidence of rejection rates.

It is well known that antibody therapy predisposes to CMV infection and the relative contribution of antibody therapy for the higher cytomegalovirus infections in the AZA group cannot be excluded. This is an additional confounding factor that does not allow us to attribute anti-CMV activity to RAD.

Table 27: Contributing factors for the higher incidence of CMV infections observed in the AZA arm (protocol violations and antibody treated rejections)

Protocol Violations	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214
<i>No Prophylaxis in general:</i>	58 (28 %)	59 (28 %)	70 (33%)
<i>No dose adjustment for WBC</i>	10 (5 %)	14 (7 %)	17 (8 %)
<i>ATG/OKT3 high dose</i>	5 (2 %)	5 (2 %)	11 (5 %)
<i>No CMV prophylaxis</i>	35 (17 %)	42 (20 %)	46 (22%)
<i>Antibody treated rejection episodes of grade \geq 3A or associated to HDC</i>	15 (7 %)	9(4 %)	18 (8 %)

Data obtained from Post-text Table 7.2-1 (Page 2 of 2). Number (%) of Patients with Protocol Violations by Treatment Group (ITT Population - 24 Month Analysis)

Reviewer's comments:

CMV infection was the most frequent single infection reported. It was three times more common in the AZA group compared with RAD 1.5 and RAD 3 (21%, 7%, and 7%, respectively). These differences should be interpreted with caution due to the following confounding factors that could influence these results:

- ***The key heart study was not prospectively designed to evaluate comparative differences in rates of CMV infection, CMV syndrome, or tissue invasive CMV.***
- ***The incidence of CMV was not a prospectively defined endpoint or efficacy variable, and it did not include any precautions to avoid bias for the collection of CMV related information.***
- ***The need for CMV-prophylaxis and treatment was determined according to local practice, which introduces variability regarding dosage, length of therapy and antiviral agent used.***
- ***In general, protocol violations predisposing to CMV infection were higher in the AZA when compared to RAD 1.5 (No CMV prophylaxis), RAD 3 (Antibody treated rejection episodes of grade \geq 3A or associated to HDC), or both (ATG/OKT3 high dose).***
- ***Antibody therapy use was higher in the AZA compared with RAD arms.***
- ***Acute rejection episodes (Higher rates in the AZA arms) may reactivate CMV from latency. In addition, it leads to the use of extra immunosuppression a further predisposition to CMV infection, especially when antibody therapy is used.***

In conclusion, the incidence of CMV was not a prospectively defined endpoint or efficacy variable. This study was not designed to demonstrate rate differences in cytomegalovirus infection. Therefore, caution is advisable when drawing conclusions based on retrospective findings. We were not able to attribute any anti CMV effects to RAD and one cannot exclude that the differences in CMV reported as adverse events or SAE may be due to differences in prophylaxis, and/or to exposure to other risk factors including the use of antilymphocyte antibody therapy. Finally, the observed difference in the RAD arms versus AZA regarding cytomegalovirus infections is based on mild to moderate cases. This

difference may not be clinically relevant given that only a few cases were severe and none of these cases led to discontinuation or deaths.

13.3.6. Pneumonia

Table 28: Incidence Rate of Pneumonia by Preferred Term
(Safety Population - 24 Month Analysis)

PNEUMONIA	RAD 1.5	RAD 3	AZA
	209	211	214
<i>Pneumonia NOS</i>	29 (14%)	20 (9.5%)	6 (3%)
<i>Bacterial pneumonia including:</i> Pneumococcal, staphylococcal, streptococcal, haemophilus, legionella, klebsiella, Escherichia, chlamydial, and other gram- negative bacterial nos)	12 (6%)	9 (4%)	3 (1%)
Cytomegaloviral	0	0	1 (0.5%)
Aspergillus	2 (1%)	2 (1%)	0
Pneumocystis carinii	1 (0.5%)	6 (3%)	1 (0.5%)
Herpes viral	1 (0.5%)	0	0
Pulmonary tuberculosis	1 (0.5%)	1 (0.5%)	0
TOTAL	47(22.5%)	38(18%)	11 (5%)

Data obtained from: Post-text Table 10.1-1 (Page 28 of 76)

Incidence Rate of Adverse Events/Infections by System Organ Classification and Preferred Term (Safety Population - 24 Month Analysis) Pages 377-378

Reviewer's comments:

Pneumonia rates reported as AE or Severe AE (table 12) were higher in the RAD arms. There were three and four fold higher rates in RAD3 and RAD 1.5 group, respectively compared with AZA arm.

Pneumonia led to discontinuation from study medication in 6, 1 and 2 cases in the RAD 3, RAD 1.5 and AZA groups, respectively and was the primary cause of death in 3 cases (2 in RAD3 and 1 in the AZA group).

Pneumonia rate differences are a clinically relevant finding since it is a potential cause for discontinuation and death.

13.3.7. Diabetes Mellitus

DM at base line was reported in 17%, 23% and 17% in the RAD1.5, RAD3 and AZA, respectively. At 24 months the incidence of Diabetes mellitus nos was higher in the RAD groups and dose dependent. 12 (6%), 15 (7%), and 4 (2%), in the RAD 1.5, RAD3 and AZA groups, respectively.

Table 29: New Onset Post-transplant Diabetes Mellitus (PTDM)
(24 month analyses -Safety Population)

<i>New Onset Post-transplant DM</i>	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214
Total	7/174 (4 %)	17/162 (10.5 %)	7/178 (4 %)
Blacks	1/ 16 (6%)	2/ 7 (29%)	1/ 10 (10%)

Data obtained from Post-text Table 10.2-4 (Page 1 of 1) page 552.

Reviewer's comments:

New onset PTDM presented higher rate in the RAD 3 arm compared with RAD1.5 and AZA groups. A dose related effect was clearly observed between RAD 1.5 and RAD 3groups.

The black population appears to have increased tendency to develop PTDM; however this subpopulation was under-represented in the study, which impedes the ability to draw valid conclusions.

13.3.8. Suspected Drug-related Adverse Events/Infections

The incidence of suspected drug-related AEs was higher in the RAD1.5 and RAD 3 groups compared with the AZA group (70% and 73% versus 63% respectively), and significantly higher between RAD 3 and AZA groups (9.9% difference and 95% CI of 1.1 to 18.7%).

Suspected drug-related AEs reported by at least 5% of patients in the RAD 1.5 , RAD 3 and AZA groups, respectively, were: anemia nos (7%, 10%, and 3%), thrombocytopenia (8%, 14%, and 5%), hyperlipidemia NOS (9%, 11%, and 3%), hypercholesterolemia (7%, 8%, and 5%), renal impairment nos (8%, 7%, and 3%), hypertriglyceridemia (3%, 7%, and 3%), and CMV infection (3%, 2%, and 8%), leukopenia nos (20%, 19%, and 26%).

13.4. Severe Adverse Events / Infections:

Table 30: Incidence Rate of Severe Adverse Events/Infections with Relevant Differences among Treatment Groups by Preferred Term
(Safety Population - 24 Month Analysis)

System Organ Classification or Preferred Term	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214
<i>Any Severe Adverse Event</i>	127(61%)	137(65%)	117(55%)
Infections and infestations	30 (14%)	44 (21%)	25 (12%)

Pneumonia 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	13(6%)	21(10%)	4 (2%)
Renal impairment NOS	13 (6%)	12 (6%)	4 (2%)
Pericardial effusion	12 (6%)	11(5%)	6 (3%)
Cardiac tamponade	3 (1.4%)	5 (2.4%)	2 (1%)
Leukopenia NOS	5 (2%)	5 (2%)	11(5%)
CMV infections including: Cytomegalovirus hepatitis Cytomegalovirus infection Encephalitis cytomegalovirus	1 (0.5%)	4 (2%)	5 (2%)
Gastric haemorrhage and Gastrointestinal haemorrhage nos	3 (1%)	5 (2%)	1 (0.5%)
Dyslipidemia including: Hyperlipidaemia nos, Hypercholesterolaemia, Blood cholesterol increased, Hypercholesterolaemia aggravated Hypertriglyceridaemia, Blood triglycerides increased.	5 (2%)	9 (4%)	2 (1%)

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)

The severity of the AE was assessed by the investigator as mild, moderate or severe. The incidence of Severe Adverse Events was higher in both RAD 1.5 and 3 mg groups (61% and 65%, respectively), compared with the AZA group (55%). Similarly, Infections and infestations reported as Severe Adverse Events were higher in the RAD 1.5 and RAD 3 compared with AZA arm, 30 (14%), 44 (21%), and 25 (12%) respectively.

The 120-days safety updated reported two life threatening infections: one in the RAD3 and one in the AZA arm.

Other Severe Adverse Events reported more frequently in the RAD arms were: renal impairment NOS (6%, 6%, and 2%), acute renal failure (3%, 6%, and 5%), and pericardial effusion (6%, 5%, and 3%) in the RAD 1.5, RAD 3 and AZA groups, respectively.

Cardiac tamponade was also more frequently observed in the RAD 1.5 (3%) and RAD 3(5%) compared with AZA group (1%).

Leukopenia nos was most frequently reported in the AZA arm (5.1%) compared to the RAD 1.5 (2.4%) and RAD 3 (2.4%).

Reviewer's comments:

- ***The incidence of suspected drug-related AEs was higher in the RAD 1.5 and RAD 3 groups compared with the AZA group (70% and 73% versus 63%, respectively), and significantly higher between RAD 3 and AZA groups.***

- ***The incidence of Severe Adverse Events and Severe Infections was higher in both RAD 1.5 and 3-mg groups compared with the AZA group.***

Table 31: Primary Cause for Death Reported in ≥ 2 patients in any group (Safety Population)

	RAD 1.5 n = 209	RAD 3 n = 211	AZA N = 214
Any death	21 (10.0%)	29 (13.7%)	24 (11.2%)
Sepsis NOS	3 (1.4%)	1 (0.5%)	4 (1.9%)
Multi-organ failure	2 (1.0%)	3 (1.4%)	1 (0.5%)
Respiratory failure	2 (1.0%)	0	0
Intracranial hemorrhage NOS	1 (0.5%)	2 (0.9%)	0
Pneumonia NOS	0	2 (0.9%)	1 (0.5%)
Transplant rejection*	0	1 (0.5%)	2 (0.9%)
Heart transplant rejection*	2 (1.0%)	0	2 (0.9%)

* There was an inconsistency in coding, and both of these terms that describe rejection are included in the database. These terms were mutually exclusive, and each patient was included under one term only.
Source: [Post-text table 10.2-1a](#) and Table 5 from clinical study report Study B253 24 month analysis.

In the 120 days safety update, sixteen deaths were reported (4 in each RAD dose group and 8 in the AZA group). Two deaths were suspected of being drug related by the investigators (graft failure in a RAD 3 mg subject and an epithelioma in a RAD 1.5 mg subject).

Reviewer's comment:

The incidence of patients who died at months 6 and 12 was numerically higher in the RAD 3 group compared to RAD 1.5 and AZA groups. At 24 months the incidence of deaths was similar across arms (10%, 14%, and 11% in the RAD1.5, RAD3 and AZA arms, respectively).

13.5. Malignancies

The total incidence of malignancies was 8% in each group. Skin malignancies were the most commonly observed malignancy, occurring in 10(59%), 5(31%), and 6(33%) subjects in the RAD 1.5 mg and 3 mg groups and the AZA group, respectively. Three cases (1.4%) of malignant melanoma were reported in the RAD 1.5 arm.

Ten PTLD cases were reported (3 each in the RAD 1.5 mg and AZA groups and 4 patients in the RAD 3-mg group).

In the 120 days safety update 11 patients were reported to have had malignancies (5 each in the RAD 3 mg and AZA groups and 1 in the RAD 1.5 mg group). Of these patients, 5 had malignancies suspected of being drug related by the investigators:

- Epithelioma and lung adenocarcinoma in 1 RAD 1.5 mg patient each
- Squamous cell carcinomas in 1 RAD 3 mg patient
- Gastric neoplasm and squamous cell carcinomas/basal cell carcinoma/Bowen’s disease in 1 AZA patient each.

Table 32: Incidence of Malignancies (Table obtained form the applicant's submission)

Post-text Table 10.2-3 (Page 1 of 1)
 Incidence of Malignancies in First 24 Months
 (Safety Population - 24 Month Analysis)

Malignancy	RAD 1.5mg (N=209)	RAD 3mg (N=211)	AZA (N=214)	p-value
Any malignancy	17 (8.1%)	16 (7.6%)	18 (8.4%)	a = 0.320 b = 0.548 c = 0.439
PTLD	3 (17.6%)	4 (25.0%)	3 (16.7%)	
Skin	10 (58.8%)	5 (31.3%)	6 (33.3%)	
Other	5 (29.4%)	5 (31.3%)	8 (44.4%)	

Reviewer's comments:

Malignancy rates were similar across arms and similar to the rates observed across arms.

Skin cancer was the most frequent cancer observed and the differences across arms were not clinically relevant. PTLDs remained with in acceptable ranges and rates were similar across arms.

13.6. Renal Function

Table 33: Renal Function: (Safety Population – 24 Month Analysis)
Estimated Mean Creatinine Clearance (Cockcroft-Gault) [mL/min] and
Estimated Mean Creatinine Clearance Change from Baseline

	RAD 1.5mg			RAD 3mg			AZA		
	n	Mean ml/m in	Change from BL ml/min	n	Mean ml/min	Change from BL ml/min	n	Mean ml/min	Change from BL ml/min
Day 1		65.5	0.1		66.3	-3.7		67.6	-0.7
Month 3	158	54.3	-10.9	149	55.1	-12.8	159	65.3	-2.3
Month 6	146	52.7	-12.7	149	51.2	-19.3	159	62.4	-4.8
Month 9	129	51.8	-14.2	116	53.2	-18.4	136	61.6	-5.2
Month 12	132	51.7	-14.7	129	51.3	-18.7	145	65.0	-2.8
Month 18	113	52.4	-13.7	99	49.9	-19.0	121	67.5	0.0
Month 24	109	53.5	-13.4	98	50.6	-17.4	118	67.5	1.2
Month 24 TEP	193	50.5	-14.0	206	50.0	-17.5	205	65.5	-1.7

Data obtained from: Post-text Table 10.3-1a (Page 58 of 105) page 610, Study B253 24-month analysis. Summary Statistics of Change from Baseline by Visit 2. Pairwise comparisons of treatment groups use Wilcoxon’s rank sum test were statistically significant at all points for RAD 1.5mg vs. AZA and RAD 3mg vs. AZA. The comparison between RAD 1.5 mg vs. 3mg was not significant. TEP = treatment endpoint (LOCF). BL= CrCl Baseline

Reviewer's comments:

In both RAD arms, estimated mean CrCl significantly decreased over time and did not return to baseline. The differences between RAD 1.5 mg vs. AZA and RAD 3mg vs. AZA were statistically significant at each measurement point. The comparison between RAD 1.5 mg and RAD 3 mg was not significant.

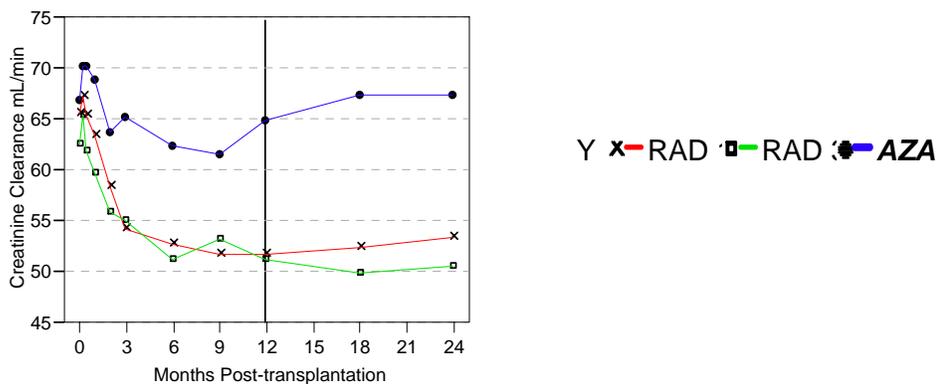
The estimated mean CrCl change from baseline, showed a statistically significant negative change over time in both RAD arm when compared to the AZA arm.

At 24 months post transplantation, the CrCl decreased by -14 ml/min, and -17.5 ml/min in the RAD 1.5 and RAD, respectively. In contrast, the CrCl in the AZA arm returned to baseline at 18 months post-transplantation and remained stable at 24 months analysis.

In both RAD arms, the mean CrCl showed a progressive deterioration over time and regardless dose adjustments implemented at 12 months, (See amendment #3) the CrCl did not improve.

We do not agree with the sponsor's claim that dose adjustments using TDM at 12 months stabilized renal function thereafter since no substantial change in mean GFR were observed at 24 months with respect to mean CrCl at 6 or 12 months post-transplantation. The TEP (LOCF) analysis at 24 months showed the same trend.

Fig. 2: Mean Cockcroft-Gault calculated Creatinine Clearance Study B253 (Safety Population - 24-Month Analysis)



Data obtained from: Post-text Table 10.3-1a (Page 58 of 105)
Page 610, Study B253 24 month analysis.

The mean CrCl after heart transplantation showed a transient improvement, followed by an important drop at 3 months in all treatment arms. The nadir was reached between 9 to 12 months in the RAD 1.5 and AZA arms. The RAD 3 mean CrCl values continued to drop beyond 12 months (After amendment #3 implementation)

Reviewer's comments:

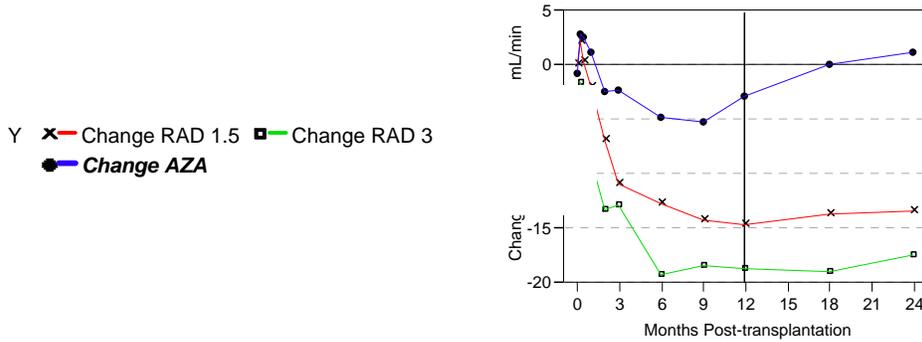
A transient improvement in CrCl after heart transplantation was observed as expected. Afterwards, the CrCl dropped, reaching its nadir between 6 to 9 months post-transplantation in all arms. The drop in CrCl over time was statistically significantly greater in the RAD arms compared to AZA at all comparison points and the differences in CrCl among RAD arms did not reach statistical significance.

After the 12 months immunosuppression dose adjustment intervention (per amendment #3), the mean CrCl, showed no significant improvement in the RAD1.5 and RAD 3 arms. In contrast, the AZA arm showed an important improvement and returned to baseline values by 18 months remaining stable at 24 months follow up.

These observations suggest that the early renal function deterioration observed at 3 months in the RAD arms is not reversible if the recommended therapeutic regimen is sustained up to

12 months. Dose adjustments implemented by amendment #3 at 12 months failed to reverse those changes.

Fig 3: Estimated Mean Creatinine Clearance (mL/min) Change from Baseline (Safety Population - 24 Month Analysis)



Data obtained from: Post-text Table 10.3-1a (Page 58 of 105)

Reviewer's comments:

After the third month post-transplantation, the estimated mean change in CrCl from baseline was statistically significantly negative in both RAD arms compared to the AZA arm. The difference between both RAD arms was not statistically significant.

Table 34: Estimated Mean (n) Creatinine Clearance (Cockcroft-Gault) [mL/min] at 6, 12 and 24 months (ITT Analysis including values observed at follow-up visits)

	RAD 1.5 n = 209	RAD 3 n = 211	AZA n = 214	p-value
Month 6	53 (156)	51.8 (155)	62.7 (168)	p = 0.000 ^a p = 0.000 ^b p = 0.237 ^c
Month 12	52 (144)	53 (137)	64.8 (156)	p = 0.000 ^a p = 0.000 ^b p = 0.286
Month 24	54.5 (160)	53.9 (164)	67.4 (169)	p = 0.000 ^a p = 0.000 ^b p = 0.129 ^c
Month 24 SEP (study endpoint)	51.0 (206)	50.5 (211)	65.7 (214)	p = 0.000 ^a p = 0.000 ^b p = 0.492 ^c

Post-text Table 10.7-28d (Page 1 of 2) Study No. B253 24M

This analysis includes all patients with at least one assessment in any visit-window (particularly, any data obtained after the discontinuation of study medication is included); multiple assessment within a given visit-window are averaged

Pairwise comparisons of treatment groups use Wilcoxon's rank sum test;

^a RAD 1.5mg vs. AZA, ^b RAD 3mg vs. AZA, ^c RAD 1.5 mg vs. 3mg

Reviewer's comments:

ITT mean CrCl analysis showed the same trends as seen in previous analyses. The differences between RAD arms vs. AZA are statistically significant. Based on notable criteria, the incidence rate of high creatinine (> 30% increase from baseline) was significantly higher in RAD 1.5 and RAD 3 arms vs. AZA group (73% and 79% vs. 57%)

13.7. Results of renal function after amendment #3 (120-days safety update)

Patients on the RAD plus full dose Neoral arms with renal dysfunction were eligible to enter the amendment protocol (RAD trough levels >3 ng/mL and CsA reduction when adequate RAD level achieved). Renal function was evaluated at Month 1, 2, 3, and 6 following unblinding.

A total of 170 patients were included (58, 51, and 61 patients in the RAD 1.5, RAD 3 and AZA groups, respectively). However, not all patients included in this amendment had baseline creatinine at amendment entry. Therefore, only data from patients with baseline and corresponding values at Month 6 were included in this analysis. In this sub-analysis, only 66%, 53% and 39% of the patients in the RAD1.5, RAD3 and AZA, respectively, were included (table 16).

Table 35: Mean creatinine values (µmol/L) in patients with amendment baseline and Month 6 creatinine values – Heart study B253 (amendment population)

	RAD 1.5 n = 38/58	RAD 3 n = 27/51	AZA n = 24/61
Baseline at amendment entry	164	183	138
Month 6 post amendment	163	190	135

^a n = # of patient included in this analysis/# of patients included in the amendments
Data obtained from Post-text table 20.3-6.

Reviewer's comments:

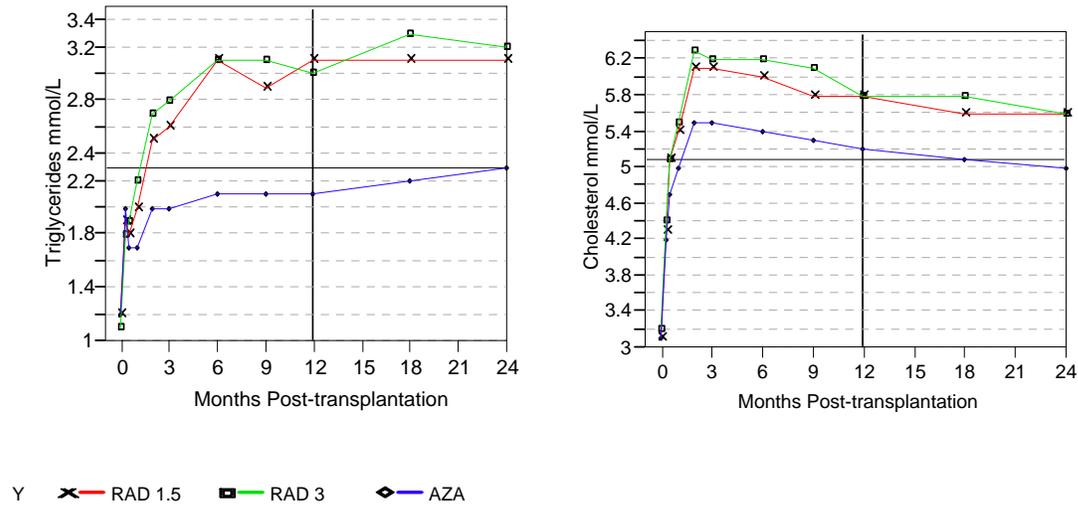
Only 50% of the patients that enter amendment # 3 was included in this analysis and an imbalance in the number of patients included per arm was evident.

After 6 months from amendment entry, the mean CsA through level decreased by -43, -78 and -82 ng/mL in the RAD1.5, RAD3 and AZA arms, respectively. However, the Creatinine levels remain the same in the RAD 1.5 and increased in the RAD3 arm.

13.8. Lipids

Any lipid lowering agent was administered in 91%, 92% and 90% in the RAD1.5, RAD 3 and AZA respectively. HMG CoA reductase medication was used per protocol even in patients with normal lipid at enrollment. 90% of the patients in each treatment group were on HMGCoA reductase. The figures below show the mean cholesterol and triglyceride values over time.

Figure 4: Mean Triglycerides and Cholesterol [mmol/L] by Visit (Safety Population - 24 Month Analysis)



Data obtained from Post-text Table 10.3-1a (Page 103 of 105) and (Page 96 of 105)

The reference line at 2.3 mmol/L represents the limit for the normal triglyceride value according to the NCEP

The reference line at 5.1 mmol/L represents the upper limit for the desirable cholesterol level according to the NCEP.

13.9. Triglycerides

Based on NCEP Guidelines, Month 24 Treatment Endpoint patients with normal baseline triglycerides at randomization remain normal after 24 months in 45%, 35% and 64% in the RAD1.5, RAD 3 and AZA respectively.

At 24 months safety population analysis, triglyceride levels remain at high level¹⁹ (≥ 4.5 mmol/L) in 31%, 37% and 17% of patients in the RAD1.5, RAD 3 and AZA respectively.

Hypertriglyceridemia / Hyperlipidemia were reported as AE in 24%, 22% and 12% in the RAD1.5, RAD 3 and AZA respectively.

13.10. Cholesterol

Based on NCEP Guidelines, Month 24 Treatment Endpoint patients with normal baseline Cholesterol at randomization remain normal after 24 months in 46%, 46 % and 62 % in the RAD1.5, RAD 3 and AZA respectively

At 24 months safety population analysis, cholesterol levels remain at high level²⁰ (≥ 6.2 mmol/L) in 67%, 70% and 47% in the RAD1.5, RAD 3 and AZA respectively.

¹⁹ NCEP high triglycerides : 4.5 -11.2 mmol/L

²⁰ NCEP high total cholesterol : ≥ 6.2 mmol/L

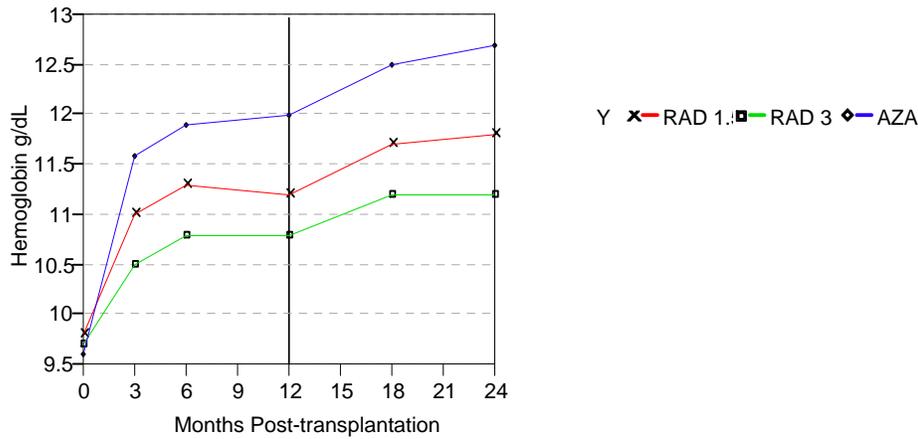
Hypercholesterolemia/Hyperlipidemia were reported as AE in 31%, 25% and 16% in the RAD1.5, RAD 3 and AZA respectively.

Reviewer's comments:

- *Serum cholesterol and serum triglyceride mean values rapidly increased in all groups after drug exposure to immunosuppressive drugs. The RAD groups showed significantly higher changes in mean values from baseline compared to the AZA group.*
- *Patients with normal baseline cholesterol and triglycerides at randomization showed higher rates of dyslipidemias in the RAD groups compared to the AZA group at 24-month analysis.*
- *Hypercholesterolemia/hypertriglyceridemia reported as an AE was seen at higher rates in the RAD arms compared with the AZA group.*
- *A dose related effect was not identified between the high and low RAD doses for lipid abnormalities (hypercholesterolemia/hypertriglyceridemia). Mean values over time, the rate of patients with normal base line values that remain within normal values after 24 months, and the rate of lipid abnormalities related AE was similar between the RAD groups.*

13.11. Anemia

Fig 5: Mean Hemoglobin [g/dL] Summary Statistics by Visit (Safety Population - 24 Month Analysis)



Data obtained from Post-text Table 10.3-1b Page 1 of 22), page 658

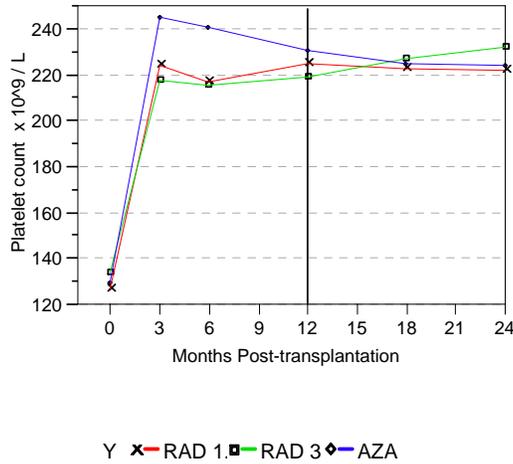
Reviewer's comments:

Hemoglobin mean values improved after transplant in all groups. The improvement in the RAD arms was suboptimal compared to the AZA group and the differences were statistically significant.

There was significant dose related effect toward lower hemoglobin mean values observed between the RAD groups.

13.12. Thrombocytopenia

Fig 6: Mean Platelet count [10^9 /L] Summary Statistics by Visit (Safety Population - 24 Month Analysis)



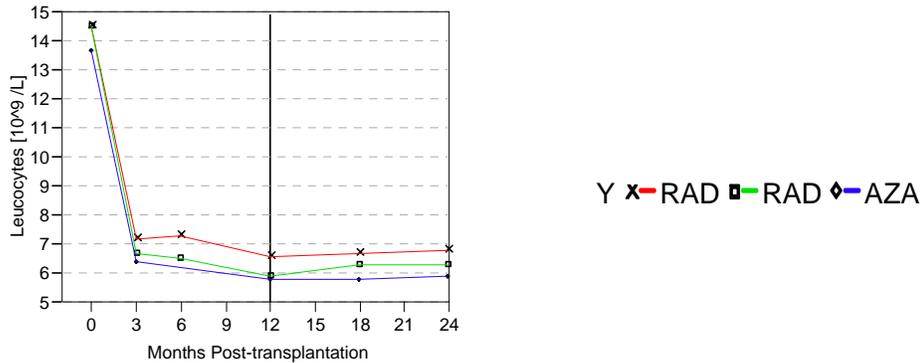
Data obtained from Post-text Table 10.3-1b (Page 7 of 22) page 664

Mean platelet counts increased after transplantation in all treatment arms up to 6 months the mean values were significantly higher in the AZA group compared with both RAD arms. After 24 months mean values were similar across arms. The incidence of thrombocytopenia reported as AE was significantly higher in the RAD 3 mg group (21%) compared with the RAD 1.5 mg and AZA groups (15% and 14%, respectively).

No significant difference was observed in the incidence rate of Thrombocytopenia reported as SAE (1.4%, 3.3%, and 2.3%, RAD 1.5, RAD 3 and AZA, respectively).

13.13. Leucopenia

Figure 7: Mean Leukocyte count [10^9 /L] Summary Statistics by Visit (Safety Population - 24 Month Analysis)



Data obtained from Post-text Table 10.3-1b (Page 3 of 22) page 660

Mean Leukocyte counts decreased significantly after drug exposure in the three arms. Mean values in the AZA were significantly lower compared to the RAD 1.5 arm over time. No significant difference in mean values over time was observed between the AZA and the RAD 3 group.

The incidence of leucopenia reported as AE was significantly higher in the AZA group (41%) compared with the RAD 1.5 and 3 mg groups (23% and 29%, respectively)

Leukopenia reported as SAE was reported in 0.5%, 1.9% and 5.1% in the RAD 1.5, RAD 3 and AZA groups, respectively. These differences were significantly higher in the AZA compared to the RAD 1.5 arm. The difference between RAD 3 and AZA was not statistically significant.

13.14. Liver Function tests

SGOT (AST) mean values were within normal ranges²¹ over time across arms. Mean value change from baseline was similar across arms. High SGOT (AST) incidence rates based on notable criteria ($\geq 3 \times$ ULN after Wk 2) were higher in the RAD3 (8%) vs. RAD 1.5 (3%) and AZA (3%) groups.

SGPT (ALT) mean values were within normal range over time across arms. Mean values were higher in the RAD arms and the mean value changes from base line were significantly higher in both RAD arms compared with AZA group.

²¹ SGOT (AST): 0-41 U/L, SGPT(ALT): 0-45 U/L

Alkaline phosphatase mean values over time were within normal range across arms. However, mean values were higher in the RAD arms and the mean value change from baseline was significantly higher in both RAD arms compared with AZA group.

Total bilirubin mean values over time were within normal range across arms. Mean values were lower in the RAD arms and the mean value change from baseline was significantly lower in both RAD arms compared with AZA group.

Base on notable criteria, high total bilirubin incidence rates (≥ 2 mg/dL [≥ 34.2 umol/L]) were significantly lower in the RAD 1.5 (17%) vs. AZA (29%) and RAD 3 (25%).

13.15. Enzymes -Amylase, CPK, CPK-MB and Lipase

Mean values were within normal range over time across arms and the mean value changes from base line were similar across treatment arms

13.16. Vital Signs

Between Day 1 to Month 24, mean weight and blood pressure increased from baseline and pulse rate decreased from baseline in all groups. There were no clinically meaningful trends among treatment groups. Base on notable criteria²², the incidence high diastolic blood pressure was similar in the RAD 1.5 and 3 mg groups (31% and 27%), and slightly lower in the AZA group (25%).

The incidence of notably high systolic blood pressure was similar in the RAD 3 mg and AZA groups (13% and 11%, respectively), and significantly higher in the RAD 1.5 mg group (19%) compared with the AZA group.

The overall incidence of notably low systolic blood pressure was similar in the RAD 3 mg and AZA groups (2% and 3%, respectively). No low systolic blood pressure was observed in the RAD 1.5 group.

13.17. ECGs

No clinically relevant trends in ECG variables were observed. The incidence of patients with QTc prolongation (males > 450 msec or females > 470 msec) was similar in all groups (57%, 62%, and 59% in the RAD 1.5 and 3 mg groups and the AZA group, respectively)

13.18. Endocrinology:FSH, LH and Testosterone values in men

²² Notably High: Either >200 or (increase of ≥ 30 compare to baseline resulting in ≥ 180)
Notably Low : Either <75 or (decrease of ≥ 30 compare to baseline resulting in ≤ 90)
Notably High: Either >115 or (increase of ≥ 20 compare to baseline resulting in ≥ 105)
Notably Low : Either <40 or (decrease of ≥ 20 compare to baseline resulting in ≤ 50)

Mean FSH and LH values increased from baseline in all groups at 6, 12, and 24 months. At 24 months in the RAD arms, mean FSH and LH values remained slightly above normal range²³ but significantly higher compared to the AZA group.

Testosterone mean values increased from baseline in all groups as expected post-transplantation. Mean values were within normal range in all groups. However, the mean increase was significantly higher in the AZA group compared with both RAD groups. In this study, only one case of hypogonadism was reported as an AE, and it was in the AZA group.

14. SUMMARY AND CONCLUSIONS ON EFFICACY AND SAFETY KEY HEART STUDY

- *Both RAD 1.5 and 3 groups were superior with respect to the incidence of the composite endpoint²⁴ “efficacy failure” at 6, 12, and 24 months compared with the AZA group.*
- *The incidence rates of acute rejection grade $\geq 3A$ ISHLT were significantly higher in the AZA group at 6, 12, and 24 months compared to both RAD 1.5 and RAD 3.*
- *The percentage of patients without biopsy due to missed visits or discontinuation of study medication at 24 months were 38%, 45% and 39% in the RAD1.5, RAD3 and AZA group, respectively. These rates are excessively high and have a direct effect on the ITT analysis of the composite endpoint in this study.*
- *The incidence of patients who died at Months 6 and 12 was numerically higher in the RAD 3 group compared to RAD 1.5 and AZA groups. At 24 months the incidence of deaths was similar across arms (10%, 14, and 11% in the RAD1.5, RAD3 and AZA arms, respectively).*
- *Amendment # 3 introduced critical changes in study design and dose regimen:*
 - *Study unbinding at 12 months introduced the potential for bias in the study. Furthermore, patients with renal dysfunction were targeted to improve their condition by implementing immunosuppression adjustments based on drug trough levels.*
 - *This intervention disqualified the study to reach conclusions based on fixed dose regimens. Amendment #3 had important implications to our review since we had a study that was considered acceptable to carry out its objectives given its original design. The study was changed from double blind to open label, from RAD fixed dose regimen to TDM and from standard CsA trough levels to a lower dose-response for renal function improvement regimen.*
- *Nephrotoxicity is the major concern with the Certican® plus CsA combination. It appears that the combination enhances the nephrotoxic effect of cyclosporine with this effect being more important than when CsA is used alone.*

²³ Values for males :

FSH: 1 -8 U/L, LH: 2 - 12 U/L

Testosterone: 10 -53 nmol/L (16-49 y/o) and 7 - 26 nmol/L (50-120 y/o).

²⁴ ISHLT grade \Rightarrow 3A acute rejection, acute rejection associated with HDC, graft loss, death or lost to follow-up.

- ***RAD 1.5 and 3 mg/day in combination with full dose Neoral was associated with significant increases in creatinine and significant decrease creatinine clearance compared with the AZA and Neoral combination.***
 - *The estimated mean CrCl in both RAD arms significantly decreased over time compared to the AZA arm, and did not return to baseline after 24 months follow up.*
 - *At 24 months post transplantation, the CrCl decreased by -14 ml/min, and -17.5 ml/min in the RAD 1.5 and RAD , respectively. In contrast, the CrCl in the AZA arm returned to baseline at 18 months post-transplantation and remained stable through 24 months.*
 - *In both RAD arms, the mean CrCl showed a progressive deterioration over time. Despite the implemented dose adjustments using TDM (See amendment #3), mean CrCl did not improved.*
 - *We do not agree with the sponsor's claim that dose adjustments using TDM at 12 month stabilized renal function thereafter since no substantial change in mean GFR were observed at 24 month with respect to mean CrCl at 6 or 12 months post-transplantation.*
 - *Early renal function deterioration observed at 3 months in the RAD arms was not reversible when the recommended therapeutic regimen is sustained up to 12 months. Dose adjustments implemented by amendment #3 at 12 months failed to revert those changes. This suggests that an earlier intervention may be required in order to avoid permanent renal damage.*
- ***We observed a dose related effect in the incidence of AE, SAE and AE leading to discontinuation from study medication in the RAD plus Neoral combination.***
- ***RAD3 presented the highest discontinuation rates from study medication (49%) compared with RAD 1.5 (39%) and AZA (39%). Adverse events were the most common cause of patient discontinuation from study medication (50% of the cases in each arm).***
- ***Discontinued patients from the RAD arms received either Azathioprine (comparator) or MMF in the 66% of the cases. There is concern about the relative contribution of these agents after patient discontinuation to the final outcome in the ITT analyses.***

Adverse Events:

- ***Renal impairment (nos) was the most common adverse event that led to discontinuation from study medication (DAE) in the RAD 1.5 and RAD 3 arms, while Leukopenia (nos) was the most frequent DAE in the AZA group. A dose related effect was observed in the discontinuation rates in the RAD arms.***
- ***Anemia NOS, Thrombocytopenia, TMA²⁵, Diarrhea NOS, Cardiac tamponade, Renal impairment NOS, Oedema, Gastrointestinal haemorrhage, Pyrexia, and Bacterial infections presented higher rates in the RAD arms and a dose related effect was observed.***
- ***Pneumonia, nasopharyngitis, pericardial effusion, lymphocele, incisional hernia nos, post procedural site wound infection and lipid abnormalities²⁶, presented higher rates in both***

²⁵ TMA (Thrombotic microangiopathy) including HUS (Haemolytic uraemic syndrome) and TTP (Thrombotic thrombocytopenic purpura) are consumptive coagulopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia.

²⁶ Includes hypertriglyceridemia, hypercholesterolemia and hyperlipidaemia nos

RAD arms compared to AZA. However, a dose related effect was not clearly defined which is difficult to establish after study unblinding and TDM adjustments (amendment #3).

- *Pneumonia rates were three and four fold higher in RAD 3 and RAD 1.5 groups, respectively compared with the AZA arm. Pneumonia led to discontinuation from study medication in 9 patients (1 in RAD1.5, 6 in RAD3 and 2 in the AZA group) and was the primary cause of death in 3 cases (2 in RAD3 and 1 in the AZA group). A pneumonia rate difference is a clinically relevant finding since it is a potential cause for discontinuation and death.*
- *In contrast, Leukopenia NOS, and Viral infections (CMV infection and Herpes simplex) showed higher rates in the AZA group compared to the RAD arms. The incidence of viral infections was significantly higher in the AZA group compared with both RAD groups.*
- *CMV infection was three times higher in AZA group compared with RAD 1.5 and RAD 3 (21%, 7%, and 7%, respectively). The incidence of CMV was not a prospectively defined endpoint or efficacy variable. This study was not designed to demonstrate rates differences in cytomegalovirus infection. Therefore, caution is advisable when drawing conclusions base on a retrospective finding. We were not able to attribute any anti CMV effects to RAD and one cannot exclude that the differences in CMV reported as adverse events may be due to differences in prophylaxis, and or to exposure to other risk factors including the use of antilymphocyte antibody therapy. Finally, the observed differences in the RAD arms versus AZA regarding cytomegalovirus infections, is based on mild to moderate cases. These differences may not be clinically relevant, given that only a few cases were severe and none of these cases led to discontinuation or deaths.*
- *New onset DM, Fungal infections and hypokalaemia presented higher rates in the RAD 3arm but similar rates between RAD1.5 and AZA).*
- *The incidence of SAE's was higher in both RAD 1.5 and 3 mg groups (61% and 65%, respectively), compared with the AZA group (55%). Similarly, SAE-Infections and infestations were higher in the RAD 1.5 and RAD 3 compared with AZA arm, 30 (14%) 44 (21%), and 25 (12%) respectively.*
- *Skin cancer was the most frequent cancer observed and the differences across arms were not clinically relevant. PTLD's remained with in acceptable ranges and rates were similar across arms.*
- *Despite intensive therapeutic intervention, mean values for triglycerides and cholesterol were significantly higher over time in the RAD arms compared with the AZA group. Similarly, patients with normal baseline cholesterol and triglycerides at randomization, presented higher rates of dyslipidemias in the RAD groups compared to the AZA group at 24 month analysis. The long term effect of higher lipid concentration on cardiac events is still a concern.*
- *Lower hemoglobin mean values were observed in the RAD groups with a significant dose related effect.*
- *Clinically significant abnormalities or differences in FSH, LH and testosterone levels were not observed across arms.*
- *Benefit on allograft arteriopathy was not adequately demonstrated in the studied subpopulation. We were unable to draw any valid conclusion from IVUS study due to the amount of missing data and selection bias. (See IVUS section: Summary of potentially introduced bias and conclusions)*