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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-628/000 (tablet: 0.25, 0.50, 0.75, 1.0 mg)
	Resubmission to original NDA (submitted 12/19/2002)
Drug Name:	Certican® (everolimus, RAD) 1.5 and 3.0 mg
Indication(s):	Prophylaxis of organ rejection in allogeneic heart transplantation
Applicant:	Novartis Pharmaceuticals Corporation
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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This resubmission contains retrospective analyses of study B253 (previously submitted in original NDA) in *de novo* cardiac transplantation based on measured plasma everolimus (RAD) and cyclosporine (CsA) drug concentrations. Study B253 was a prospective active controlled randomized trial using fixed doses of RAD (1.5 mg/day and 3.0 mg/day) in combination with full dose CsA and corticosteroids. Due to unacceptable renal toxicity associated with full dose CsA and fixed dose RAD, the Sponsor is now proposing a treatment regimen based on therapeutic drug monitoring (TDM) with reduced dose CsA however this regimen has not been prospectively studied in heart transplantation. This resubmission contains additional analyses attempting to evaluate an appropriate TDM regimen by regrouping patients according to measured plasma RAD and CsA concentrations. These concentration groups are then compared for efficacy and safety. Due to the loss of original study randomization with patient regrouping and the bias associated with exposure-response (E-R) retrospective analyses these analyses do not conclusively support a safe and effective TDM RAD regimen. These analyses are useful for generating hypotheses about an appropriate RAD dosing regimen in combination with reduced dose CsA in *de novo* heart transplantation; however prospective testing of this regimen is necessary to confirm efficacy and safety.

Additionally, the Sponsor submitted new uncontrolled data in kidney transplantation using TDM RAD monitoring. The Sponsor states that there will be an ease in translating results from therapeutic drug monitoring in these studies in kidney to heart transplantation however there is insufficient justification for this conclusion. Furthermore, extrapolation of results from one organ to another is scientifically unacceptable.

Recommend that the Sponsor conduct a new active controlled study in *de novo* cardiac transplantation to prospectively evaluate the safety and efficacy of TDM RAD in combination with reduced dose CsA.

1.2 Brief Overview of Clinical Studies

This resubmission consists of retrospective analyses (exposure-response) of previous data submitted in heart transplantation (study B253). No new data in *de novo* cardiac transplantation were submitted.

1.3 Statistical Issues and Findings

This resubmission for the heart indication consists of additional analyses of study B253. The Sponsor's conclusions are based on <u>retrospective</u> blood-concentration response relationships from the variable concentrations attained from the fixed doses (1.5 mg/day and 3.0 mg/day) of RAD administered to heart recipients. These analyses fail to demonstrate a safe and effective TDM regimen of RAD in combination with reduced dose CsA for the following reasons:

a. **Loss of original treatment randomization:** analyses resulted in a regrouping of patients according to observed blood-concentrations of CsA and RAD which differs from the original randomized grouping of patients by fixed dose treatment. There is also significant variation resulting in patient concentrations falling into several ranges during

the study thus requiring that the analyses consider an overall time-weighted mean concentration per patient.

b. **Confounding factors potentially biasing results:** These analyses contain many confounding factors, such as unobservable relationships between pharmacokinetics and outcome leading to biased and misleading results. For example, patients with better absorption due to metabolic characteristics, and thus higher concentrations, may have a different response to treatment compared to those that had worse absorption. Similarly, renal failure could simultaneously lead to increased plasma concentrations and susceptibility to adverse effects, leading to an erroneous relation of concentration to adverse effects.

c. **Inability to explain observed renal toxicity:** These analyses are unable to demonstrate the effects of CsA concentration during the first month following transplantation due to significant interaction between amount of CsA received and renal function. Given the importance of measuring renal function during this critical time, prospective data during this time period is essential to fully understand the safety of TDM RAD.

d. **Failure to address high number of treatment discontinuations:** Analyses do not address the significantly high number of early treatment discontinuations among patients in the RAD treatment groups. Failure to consider this outcome can lead to biased concentration averages and misinterpretation of efficacy and safety results.

2 INTRODUCTION

2.1 Overview

On December 19, 2002, the Sponsor submitted NDAs 21,560 and 21,628 for Certican® (everolimus, RAD) tablet for prophylaxis of organ rejection in adult renal and heart transplantation respectively. This review will focus on the information provided in the resubmission in support of NDA 21,628 and is submitted as an addendum to the original review (submitted to DFS on 10/16/2003).

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

Although shown to be superior to AZA in reducing the incidence of acute rejection, both RAD doses were found to be unsafe due to unacceptable renal toxicity. Statistically and clinically significant elevations in creatinine and decreases in creatinine clearance were observed as early as three months following therapy initiation and persisted up through twenty-four months. Treatment unblinding and therapeutic drug monitoring of RAD in combination with CsA (initiated at month 12 among those patients still on randomized treatment) did not result in statistically relevant improvements in renal function. Additionally, there were higher numbers of bacterial infections, particularly pneumonias, and a lower incidence of viral infections, primarily cytomegalovirus infections, in both everolimus groups compared to AZA.

The Division took an approvable action on the original NDA citing insufficient evidence for safety and efficacy of everolimus (as prospectively studied) when used in combination with full dose cyclosporine. The approvable action letter indicated that in order for everolimus to be approved for heart transplantation, additional information supporting a safe and effective dosing regimen that minimizes renal function while maintaining adequate protection against graft loss, death and rejection in de novo cardiac transplantation is required. This resubmission is in response to the approvable letter and contains additional analyses from the previously submitted heart study (B253) along with new data in kidney (A2306 and A2307). This review will only focus on information pertaining to study B253.

2.2 Data Sources

No new clinical data for heart transplantation were provided in this resubmission. Summary of retrospective analyses can be located in the integrated safety summary located at \\Cdesub1\N21560\N_000\2004-02-27\update\iss.
EDR Link to resubmission: \\Cdesub1\N21560\N_000\2004-02-27
EDR Link to Original Submission: \\Cdesub1\N21560\N_000\2002-12-19

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Statistical Methods

The following are the Sponsor's statistical methods. Given that these analyses are retrospective and based on measured plasma RAD and CsA drug concentrations there is a loss of original treatment randomization (due to regrouping of patients based on measured concentration ranges) and an overall loss of study integrity. Therefore, these analyses are considered by the reviewer as hypothesis generating only.

3.1.1.1 Mean CsA Levels

To measure the impact of CsA plasma concentrations on efficacy, patients were grouped into quartiles according to average CsA levels measured between day 1-day 28 and between day 1-month 12. The percentiles (25th, 50th, and 75th) used to define the quartiles were determined using the CsA levels from all patients. The values were also given for each treatment group. Efficacy failure was then provided for each exposure quartile.

To measure the impact of CsA plasma concentrations on safety, patients were grouped into quartiles according to average CsA levels from day 1-month 12. Renal function (serum creatinine and creatinine clearance) was assessed for each CsA quartile. However, given interactions between renal function and mean CsA plasma concentration the Sponsor acknowledges that there is significant difficulty in interpreting results from these analyses.

3.1.1.2 Exposure-response analyses

RAD and CsA plasma concentrations measured during the first six months in study B253 were quantified using a time-normalized averaging approach (as requested by FDA clinical pharmacology reviewers). This approach was recommended due to the tremendous inter-subject variability in time of plasma

sampling and frequency of sampling. The time-normalized mean concentrations were log transformed and treated as predictors of efficacy (primary composite endpoint and BPAR) and safety events (renal function measured as creatinine clearance) in logistic and Cox regression models. The Cox regression model assumed that the risk of experiencing the endpoint was proportional throughout the study duration. The statistical fit of the regression models was evaluated using goodness-of-fit testing.

3.1.2 Demographics and Patient Disposition

The original patient dataset (discussed in detail in original review dated 10/16/2003) was used for the E-R analysis.

3.1.3 Sponsor's Analyses

3.1.3.1 Mean CsA Levels

Plasma CsA concentration levels were obtained for two time periods (day 1-day 28 and day 1-month 12) and then grouped into quartiles based on percentile. The percentiles were determined using the CsA levels obtained from all patients over specified time periods. Mean CsA concentrations by percentile and treatment group are shown in Table 3.1.

Table 3.1 Measured CsA concentrations (mg/mL) by percentile

	25th percentile	**50th percentile**	**75th percentile**
CsA Levels from Day 1- 28			
Overall	172	219	271
RAD 1.5 mg	165	211	276
RAD 3.0 mg	171	218	268
AZA	183	224	274
CsA Levels from Day 1- Month 12			
Overall	175	214	252
RAD 1.5 mg	173	211	256
RAD 3.0 mg	171	210	246
AZA	186	220	255

The primary efficacy endpoint (graft loss, biopsy-proven acute rejection of grade ≥ 3A, acute rejection associated with hemodynamic compromise, death, or loss to follow-up) up until month 12 post-transplantation by measured mean CsA quartile, using the available CsA levels obtained between day 1 and day 28 are presented below. The purpose of this analysis was to evaluate the potential for increase in the primary endpoint by month 12 as a function of reduced CsA exposure during the first month. The results suggest that lower CsA exposure during the first month of treatment did not increase the risk of experiencing the primary endpoint up to month 12 among the RAD arms.

Table 3.2 Primary Efficacy Failure (%) at 12 months by measured CsA quartile (between days 1-28)

Original Treatment	0-25% CsA	25-50%	50-75%	75-100%
RAD 1.5 mg	40	44	47	33
RAD 3.0 mg	40	23	23	44
AZA	62	53	57	37

Efficacy failures up to month 12 grouped according to CsA quartiles using CsA levels obtained between day 1 and month 12 are presented below.

Table 3.3 Primary Efficacy Failure (%) at 12 months by measured CsA quartile (between days 1-month 12)

Original Treatment	0-25% CsA	25-50%	50-75%	75-100%
RAD 1.5 mg	42	44	38	39
RAD 3.0 mg	36	23	28	41
AZA	64	43	53	51

The Sponsor performed additional analyses evaluating renal function according to mean CsA levels. These analyses are seriously confounded due to interactions between CsA levels and renal function, which invalidate the results.

Sponsor's conclusion of analyses of mean CsA levels:

- The efficacy failure rates in the RAD arms were not significantly different at 1 year across the range of average CsA levels. However, there does appear to be a greater incidence of efficacy failure associated with lower CsA levels in the AZA treatment group.
- As previously demonstrated (in other sections safety update) in studies A2306 and A2307, renal function was improve with prospective CsA reduction. However, this can not be demonstrated prospectively in study B253 due to the confounding factors that renal function influenced CsA levels and CsA levels influenced renal function.
- Due to complex interplay in which impaired renal function may lead to ad hoc CsA dose reduction, no relationship between renal function and average CsA exposure by quartile could be tested in early follow-up (first month post-transplant).

These analyses may suggest that reduced CsA exposure, especially during the first month post-transplant did not lead to an increase in efficacy failure in the RAD groups, however they do not address the interactions between CsA and RAD, which are crucial in understanding the observed efficacy and toxicity in study B253. The early onset of renal toxicity observed with the prospectively studied fixed dose RAD and full dose CsA regimen has not been addressed in these analyses due to the complex interactions noted. Also, these analyses group patients according to measured plasma drug concentrations, and not to originally randomized treatment groups. This regrouping is statistically invalid resulting in a loss of study randomization and the inability to explain differences in drug response due to unobservable covariates. Furthermore, these analyses do not address the significantly high number of treatment discontinuations, which occurred by month 6 and persisted through month 12. Since treatment discontinuation was frequent, especially in the high RAD dose group, these values could be biased towards those patients who switched to alternative therapy while staying in the study (i.e. prior to reaching the primary efficacy endpoint). Lastly, since these analyses are using overall population mean CsA levels, they fail to address the inter- and intra-subject variability in frequency and timing of plasma

sampling.

3.1.3.2 Exposure-response analyses

The Sponsor used a time-normalized average trough approach (as recommended by FDA clinical pharmacology reviewers) to calculate patient cyclosporine exposure levels (patients treated with full dose CsA in heart study B253) and RAD exposure levels (patients randomized to fixed doses of everolimus). This approach used measured plasma concentrations from Day 7 post-transplant up to primary event (death, graft loss, acute rejection, or loss to follow-up) or month 6 to calculate a time weighted normalized mean (or weighted average) for each patient. Concentration values prior to Day 7 were used only in the case where no subsequent values were obtained.

Cox and logistic regression analyses were used to model and predict, using the log time-weighted RAD and CsA exposures as predictors, the time-to-event for key safety and efficacy events. Regression model goodness-of-fit (GOF) and interaction between RAD and CsA time-normalized mean concentrations were also tested.

3.1.3.2.1 Efficacy

Regression analyses (Cox and logistic) on the primary efficacy endpoint (graft loss, biopsy-proven acute rejection of grade ≥ 3A, acute rejection associated with hemodynamic compromise, death, or loss to follow-up) with predictors log RAD and log CsA concentrations (time-normalized using levels obtained up to time of event or month 6) are presented below for primary events occurring between days 1-225 and between days 15-225. Results suggest that both CsA and RAD concentrations (log transformed time-weighted average) may have an effect on the primary endpoint. Both variables suggest that an increase in log concentration decreases the hazard of having of reaching the primary endpoint in the Cox model for events between days 1 and 225. Omitting the first two weeks of efficacy failure events, log RAD showed a borderline influence on reducing the probability of the primary event.

Table 3.4 Cox Regression for primary event

Variable	Chi-Square	Hazard Ratio	P>Chi-Square
Day 1-225			
Log RAD	5.416	0.735	0.0196
Log CsA	8.3195	0.644	0.0039
Day 15-225			
Log RAD	3.7697	0.741	0.0522
Log CsA	0.0128	1.029	0.9100

Table 3.5 Logistic Regression for primary event

Variable	Estimate	Wald Chi-Square	P>Chi-Square
Day 1-225			
Log RAD	-0.3632	4.9214	0.0265
Log CsA	-0.4064	3.2795	0.0702
Day 15-225			
Log RAD	-0.3384	3.4799	0.0621
Log CsA	0.1011	0.1156	0.7339

Cox and logistic regression analysis on the efficacy endpoint of biopsy proven acute rejection with predictors log RAD and log CsA concentrations (time-normalized using levels obtained up to time of event or month 6) are presented below for events occurring between day 1-225 and between day 15-225. Results suggest that log RAD concentration may have an effect on the decreasing the risk of BPAR from day 15 and 225.

Table 3.6 Cox Regression for event (BPAR)

Variable	Chi-Square	Hazard Ratio	P>Chi-Square
Day 1-225			
Log RAD	8.8769	0.633	0.0029
Log CsA	7.6768	0.610	0.0056
Day 15-225			
Log RAD	7.4840	0.0062	0.610
Log CsA	0.0782	0.7798	0.926

Table 3.7 Logistic Regression for event (BPAR)

Variable	Estimate	Wald Chi-Square	P>Chi-Square
Day 1-225			
Log RAD	-0.5173	8.1747	0.0042
Log CsA	-0.4794	3.7733	0.0521
Day 15-225			
Log RAD	-0.5476	7.1868	0.0073
Log CsA	-0.0494	0.0235	0.8783

Tests for interactions between log RAD and log CsA concentrations, in the Cox model, were insignificant (p=0.65, primary efficacy endpoint, p=0.9981, BPAR) resulting in omission of the interaction term from the regression models. Tests for lack of fit in the logistic regression models (including RAD and CsA trough levels as covariates) using the Hosmer and Lemeshow GOF test were insignificant for all efficacy models

3.1.3.2.2 Safety

Regression analyses (Cox and logistic) on renal function were conducted by treating a renal event as a decrease in creatinine clearance (CRT CL) of 30% or more from baseline and from month 1 (used since

pre-transplant heart patients are azotemic due to poor cardiac output and therefore CRT CL values at baseline are abnormal). Log RAD concentration and log CsA concentration (time-weighted average trough until time of event or to time of censoring at day 225/month 6) were used as predictors in the analyses. No statistically significant effects on the renal event were noted for either log RAD (p=0.71) or log CsA (p=0.15) based on pre-transplant baseline creatinine clearance values. However, Cox regression analysis [Table 3.8] suggested that a one log CsA concentration increase may double the risk of decreased CRT CL (<30) from month 1 values. Similar conclusions can be drawn from the logistic regression models [Table 3.9].

The test for interaction between RAD and CsA was significant in Cox models with outcome of creatinine clearance decrease of 30% from baseline (p=0.0238) and from month 1 (p=0.0198).

A significant test for GOF was observed in the model including the outcome of CRT CL decrease of 30% from baseline (p=0.0320). Given the significant interaction between renal function and CsA concentration during the first month post-transplant this model should be interpreted with caution. The test of GOF for the model including CRT CL decrease of 30% from month 1 was insignificant (p=0.2695).

Table 3.8 Cox Regression for CRT CL decrease of 30% from month 1

Variable	Chi-Square	Hazard Ratio	P>Chi-Square
Log RAD	0.0670	1.035	0.7957
Log CsA	7.8422	2.105	0.0051

Table 3.9 Logistic Regression of CRT CL decrease of 30% from month 1

Variable	Estimate	Wald Chi-Square	P>Chi-Square
Log RAD	0.0111	0.0044	0.9470
Log CsA	0.8677	7.0736	0.0079

3.1.3.2.3 Conclusions from exposure-response analyses

Efficacy conclusions:

- The Cox regression showed a statistically significant effect of everolimus on the primary efficacy endpoint (p=0.0196) and on BPAR (p=0.0029) over the first 6 months (day 1-day 225).
- CsA had a statistically significant effect on both efficacy measures, p=0.0039 for the primary efficacy endpoint, and p=0.0056 for BPAR over the first 6 months (day 1-day 225).
- RAD showed a borderline statistically significant effect on the primary efficacy endpoint (p=0.052) and a statistically significant effect on BPAR (p=0.0062) over the first 6 months omitting the first 2 weeks (day 15-day 225).
- CsA did not show a statistically significant effect on the primary efficacy endpoint (p=0.91) and BPAR (p=0.78) when omitting events that occurred during the first two weeks (day 15-day 225).

Safety conclusions:

- The Cox regression analysis did not show any statistically significant effect of RAD or CsA concentrations in decreasing CRT CL 30% or more from baseline. However the analysis

showed a statistically significant effect of CsA (p=0.0051) on decreasing CRT CL from month one.

- The Cox regression analysis with renal event of a 30% or higher decrease in creatinine clearance from Month 1 showed a statistically significant interaction between RAD and CsA time-weight log concentrations.

These regression analyses suggest favorable trends for efficacy and safety and may help to develop an appropriate treatment regimen of RAD in combination with CSA. However the regimen proposed must be prospectively studied to fully evaluate safety and efficacy. Since these analyses regroup subjects according to measured plasma drug concentration, there is a complete loss of study randomization and thus of study integrity. Additionally, these regression analyses are unable to evaluate an effective and safe RAD and CsA regimen since the RAD and CsA variables are continuous in the model.

A major problem identified in the original review is the significantly high number of early treatment discontinuations, especially in the RAD 3.0 mg/day treatment group. These models do not account for early treatment discontinuation (i.e. treatment discontinuation prior to reaching a protocol defined event). Due to this oversight, these models include all patients regardless of treatment status and thus may be biased towards those patients who switched to alternate treatment prior to reaching a study endpoint and who may have had higher RAD levels prior to treatment discontinuation. A more appropriate model would consider premature treatment discontinuation as both a single endpoint and also an event in the primary composite endpoint.

3.1.4 Reviewer's Analyses

No new analyses were performed since there was no new data submitted. Reviewer disagrees with validity of mean CsA level and exposure-response analyses for the purpose of evaluating efficacy and safety from a fixed dose trial. The efficacy and safety conclusions are based on a non-randomized grouping of patients according to measured exposure to drug treatment. Furthermore, the regression analyses demonstrate trends in concentration exposure however they fail to demonstrate efficacy or safety for a particular treatment concentration or dose. These analyses are useful only for the purpose of generating hypothesis and to aid in the selection an appropriate treatment regimen for prospective confirmatory studies. See detailed comments under Sponsor's efficacy analysis.

3.2 Evaluation of Safety

No new analyses performed. See original review (submitted to DFS on 10-16-03) and comments under Sponsor's safety analysis.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

See original review (submitted to DFS on 10-16-03).

4.2 Other Special/Subgroup Populations

See original review (submitted to DFS on 10-16-03).

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The analyses provided in this resubmission are not statistically valid for purposes of evaluating efficacy and safety of proposed TDM regimen of everolimus in combination with reduced dose CsA from study B253. These analyses results in a loss of randomization due to re-grouping of patients according to measured RAD and CsA concentrations and are heavily confounded due to unobserved factors leading to variations in measured drug concentrations. Furthermore, they do not take into account the large number of premature treatment discontinuations in the RAD groups. Additionally, these analyses are unable to evaluate renal function during the first month post-transplant as a function of CsA concentration due to the significant interaction between CsA dosing and renal function. To fully understand the effects of TDM RAD in combination with reduced dose CsA, this period of time following transplantation must be prospectively evaluated.

5.2 Conclusions and Recommendations

This resubmission contains retrospective analyses of study B253 (previously submitted in original NDA) in *de novo* cardiac transplantation based on measured plasma RAD and CsA drug concentrations. Study B253 was a prospective active controlled randomized trial using fixed doses of RAD (1.5 mg/day and 3.0 mg/day) in combination with full dose CsA and corticosteroids. Due to unacceptable renal toxicity associated with full dose CsA and fixed dose RAD, the Sponsor is now proposing a treatment regimen based on TDM with reduced dose CsA however this regimen has not been prospectively studied in heart transplantation. This resubmission contains additional analyses attempting to evaluate an appropriate TDM regimen by regrouping patients according to measured plasma RAD and CsA concentrations. These concentration groups are then compared for efficacy and safety. Due to the loss of original study randomization with patient regrouping and the bias associated with exposure-response retrospective analyses these analyses do not conclusively support a safe and effective TDM RAD regimen. These analyses are useful for generating hypotheses about an appropriate RAD dosing regimen in combination with reduced dose CsA in *de novo* heart transplantation; however prospective testing of this regimen is necessary to confirm efficacy and safety.

Additionally, the Sponsor submitted new uncontrolled data in kidney transplantation using TDM RAD monitoring. The Sponsor states that there will be an ease in translating results from therapeutic drug monitoring in these studies in kidney to heart transplantation however there is insufficient justification for this conclusion. Furthermore, extrapolation of results from one organ to another is scientifically unacceptable.

Recommend that the Sponsor conduct a new active controlled study in *de novo* cardiac transplantation to prospectively evaluate the safety and efficacy of TDM RAD in combination with reduced dose CsA.

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