

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
(REVIEW FOR AMENDMENT OF FEBRUARY 27, 2004)**

NDA(s)	21-560, 21-628
Submission Date(s)	2/27/04, 4/14/04, 7/7/04, 7/22/04 (letter dates)
Brand Name	Certican
Generic Name	Everolimus (code name; RAD001, SDZ RAD)
Reviewer	Jang-Ik Lee, Pharm.D., Ph.D.
Team Leader	Philip Colangelo, Pharm.D., Ph.D.
OCPB Division	DPE III (HFD-880)
OND Division	ODE IV DSPIDP (HFD-590)
Sponsor	Novartis Pharmaceuticals Corp.
Relevant IND(s)	52,003
Submission Type; Code	NDA Amendment; AZ
Formulation; Strength(s)	Tablets; 0.25, 0.5, 0.75, 1.0 mg
Indication	Prophylaxis of organ rejection in allogeneic kidney (N21-560) and heart (N21-628) transplants
Dosage and Administration	Oral doses of 0.75 mg b.i.d. or larger to maintain whole blood concentrations \geq 3.0 ng/mL in combination with Neoral and corticosteroids

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I. EXECUTIVE SUMMARY

Everolimus is a macrolide immunosuppressant which is derived by chemical modification of the natural product rapamycin. Novartis Pharmaceuticals has developed everolimus as an adjunctive therapy to cyclosporine and steroids in the prophylaxis of acute rejection in patients receiving allogeneic kidney and heart transplants.

The sponsor submitted the original NDAs on December 19, 2004 and the applications were approvable (see the approvable letter of October 20, 2003 in DFS). The sponsor amended the NDAs on February 27, 2004. This amendment contains two new clinical studies (A2306 and A2307) conducted in *de novo* renal transplant patients, a partial reevaluation of basic everolimus pharmacokinetic data, and the analyses of everolimus-cyclosporine exposure-response (E-R) relationships using data collected from a heart transplant study (B253).

This Clinical Pharmacology/Biopharmaceutics (CPB) review is focused on whether this NDA amendment fulfills the deficiencies listed in the approvable letter (i.e., insufficient dosing and safety information) and in the previous CPB review for the original submission (i.e., insufficient information on dosing, basic pharmacokinetic parameters, and drug-drug interactions; see the CPB review of October 17, 2003 in DFS). Labeling recommendations are deferred because these NDAs will still be approvable. Based on the Clinical Division's judgment, the amendment does not fulfill the deficiencies listed in the approvable letter of October 2003.

A. Recommendation

The Clinical Pharmacology/Biopharmaceutics (CPB) information in this amendment is not sufficient to support the approval of Certican tablets. Deficiencies and recommendations are listed below.

- (1) The regression analyses of the exposure-response (E-R) data performed by the sponsor from the *de novo* heart transplant study B253 suggest that the probability of the occurrence of renal toxicity (i.e., reduction in creatinine clearance; CrCL) following administration of everolimus-full dose cyclosporine combination regimen was greater than the probability determined in the control group following administration of azathioprine-full dose cyclosporine combination regimen. In addition, based on the outcome of therapeutic drug monitoring (TDM) in renal transplant studies A2306 and A2307, the TDM strategy for the everolimus-reduced dose cyclosporine combination regimen does not appear to be clinically feasible.

To demonstrate the safety and efficacy of the proposed everolimus-cyclosporine combination regimens, the sponsor needs to adequately determine a starting dose and a target trough concentration (C_{min}) range (upper as well as lower limits) for both everolimus and cyclosporine for each indication.

The OCPB Pharmacometrics review team is currently reviewing the adequacy of the sponsor's regression analyses and is also developing additional models that may be able to better characterize the everolimus-cyclosporine exposure-response (E-R) relationships than the regression models. Once completed, the findings of the Pharmacometrics review of the

sponsor's work as well as the Pharmacometrics review team's own additional analyses may be used to update this review and provide further insight into the everolimus-cyclosporine E-R relationships for future discussions with the sponsor.

- (2) From the review of the everolimus pharmacokinetic data collected by the sponsor thus far, this reviewer concludes that the sponsor has not adequately determined the terminal $t_{1/2}$ of everolimus in target patients of interest following the administration of proposed everolimus regimen at steady state. This reviewer recommends that the sponsor should adequately determine the everolimus $t_{1/2}$ at the range of proposed clinical doses or concentrations of everolimus and cyclosporine following multiple (steady state) administrations of proposed everolimus-cyclosporine combination regimen to transplant patients.
- (3) This reviewer concluded in the previous CPB review that the information on *in vivo* everolimus-drug interactions was not sufficient and notified such deficiency to the sponsor in a subsequent teleconference (see teleconference minutes of November 25, 2003 in DFS). Although the sponsor did not address this deficiency in this amendment, the Division has been in contact with the sponsor regarding this issue and has reviewed the drug interaction study protocols for those drugs in which the CPB reviewer and Medical Officer deemed to be important to evaluate (i.e., ketoconazole, verapamil, and erythromycin). The reviewer recommends following up on the status of these everolimus-drug interaction studies.

B. Phase IV Commitments

Not applicable

C. Summary of CPB Findings

Everolimus Exposure in Kidney Transplant Studies: In Studies A2306 and A2307, everolimus was initiated with a starting dose of 0.75 mg b.i.d. or 1.5 mg b.i.d in combination with reduced-dose cyclosporine administration in which cyclosporine C_{min} was reduced to 50% or lower compared to full-dose administration. Everolimus doses were adjusted to achieve everolimus $C_{min} \geq 3$ ng/mL. Everolimus doses were reduced when patients had serious adverse events or laboratory abnormalities associated possibly with everolimus administration. Everolimus C_{min} values were in an increasing trend in the lower dose group, particularly in Study A2307, whereas the C_{min} values were relatively stable in the higher dose group. The respective mean \pm SD C_{min} values at one year post transplant in lower and higher dose groups were 5.6 ± 2.1 ng/mL and 7.6 ± 3.3 ng/mL in Study A2306, and 7.0 ± 3.0 ng/mL and 7.4 ± 3.2 ng/mL in Study A2307. The inter-individual variability of everolimus C_{min} in these studies (coefficients of variations, CVs; approx. 50%) appears to be similar to the variability observed previously in Studies B201 and B251.

Everolimus Exposure in Heart Transplant Study: In Study B253, everolimus doses were fixed to 0.75 mg b.i.d. or 1.5 mg b.i.d in combination with full-dose cyclosporine administration in which cyclosporine C_{min} was targeted to the C_{min} range that is frequently used in current clinical practice. Everolimus doses were adjusted only when study patients had adverse events or laboratory abnormalities associated possibly with everolimus administration for the first year post transplant. Everolimus mean C_{min} values were stable over the first year: the respective

mean C_{min} values in the lower and higher everolimus dose groups were 5.4 ± 4.4 ng/mL and 9.6 ± 6.8 ng/mL. The inter-individual variability of everolimus C_{min} in Study B253 (CV, approx. 75%) was larger than the variability observed in kidney transplant studies.

Cyclosporine Exposure in Kidney Transplant Studies: In Studies A2306 and A2307, cyclosporine administration was initiated with a starting dose of 8 mg/kg/day and 4 mg/kg/day, respectively, in combination with everolimus administration stated above. In Study A2306, cyclosporine doses were adjusted to the targeted cyclosporine concentrations at 2 hr post dose (C₂) of 1200 ng/mL for Weeks 0 - 4, 800 ng/mL for Weeks 5 - 8, 600 ng/mL for Weeks 9 - 12, and 400 ng/mL for Months 4 - 12. Approximately 30% (range, 15% - 39%) of patients were within these limits. In Study A2307, cyclosporine doses were adjusted to achieve the cyclosporine C₂ of 600 ng/mL for Weeks 0 - 8 and 400 ng/mL for Months 3 - 12. Approximately 50% (range, 39% - 72%) of patients were within these limits. Thus, the TDM goals could not be achieved as planned for both studies in the majority of patients. Cyclosporine exposure in Study A2306 was substantially higher for the first 6 months post transplant than that in Study A2307.

Based on the current lack of definitive studies evaluating the use cyclosporine C₂ monitoring to adjust the cyclosporine dosage regimen, there appears to be no scientific justification to use C₂ monitoring over C_{min} monitoring.

In Studies A2306 and A2307, cyclosporine C_{min} was also determined. For the first month post transplant, the mean cyclosporine C_{min} values in Study A2306, when used with everolimus, were similar to the cyclosporine C_{min} values in Studies B201 and B251 when combined with mycophenolate mofetil (control group). However, in Months 6 - 12 post transplant, cyclosporine C_{min} values in Study A2306 were lower by approximately 100 ng/mL than the values in the mycophenolate mofetil group. The mean C_{min} values in Study A2307 were lower by approximately 150 ng/mL and 100 ng/mL in the first month and Months 6 - 12 post transplant, respectively, than the values in the mycophenolate mofetil group. Thus, the cyclosporine exposure in Studies A2306 and A2307 was considerably lower (< 50%) than the exposure in Studies B201 and B251.

Cyclosporine Exposure in Heart Transplant Studies: In Study B253, full dose cyclosporine administration was initiated with a starting dose of 12 mg/kg/day in combination with a fixed everolimus dose described above. Cyclosporine doses were adjusted to the cyclosporine C_{min} range of 250 - 400 ng/mL for Weeks 1 - 4, 200 - 350 ng/mL for Months 1 - 6, and 100 - 300 ng/mL for Months 7 - 24. For the first 6 month post transplant, approximately 50% of patients had cyclosporine C_{min} below the lower targeted C_{min}, which may have contributed to the poorer efficacy outcome of the study compared to current statistics in the United States in heart transplantation. Cyclosporine mean C_{min} values were not appreciably different between treatments.

Exposure-Efficacy Relationship Determined in Heart Transplant Study: The sponsor performed logistic regression analyses using efficacy data from 201 evaluable patients in the azathioprine-cyclosporine control group in Study B253. These analyses suggested that the time-normalized C_{min} (C_{min,TN}) of cyclosporine significantly affected (p = 0.015) the probability of the primary composite efficacy event (i.e., occurrence of acute rejection, graft loss, patient death,

and lost to follow-up, whichever came first). The overall probability in the control treatment was approximately 45%. The sponsor also performed logistic regression analyses using efficacy data from 387 evaluable patients in the everolimus-cyclosporine treatment group. These analyses suggested that the time-normalized everolimus $C_{min,TN}$ ($p = 0.03$), but not cyclosporine $C_{min,TN}$ ($p = 0.29$), significantly affected the probability of the efficacy event. Additionally, it appeared that the effect of cyclosporine $C_{min,TN}$ on the efficacy event diminished in the presence of increases in the everolimus C_{min} . The overall probability of the occurrence of the composite efficacy event in the everolimus treatment group was approximately 29% and therefore was better by approximately 16% than that in azathioprine control group.

Additional exposure-response analyses are currently being performed by the OCPB Pharmacometrics review team. The primary goals of these analyses is to better understand the relationships between everolimus and cyclosporine exposure with the primary composite efficacy endpoint, and to help determine the optimal dosage regimens and/or therapeutic drug concentration ranges for both everolimus and cyclosporine when used in combination for heart transplantation. It is anticipated that the results of such work would be conveyed as an amendment to this review as well as conveyed to the sponsor in future discussions regarding study design issues. Thus, at this present time, no definitive CPB recommendations/conclusions can be made regarding the optimal dosage regimen for everolimus.

Exposure-Safety Relationship Determined in Heart Transplant Study: The sponsor performed logistic regression analyses using safety data from 208 evaluable patients in the azathioprine-cyclosporine control group in Study B253. These analyses suggested that cyclosporine $C_{min,TN}$ (time-normalized C_{min}) significantly affected ($p = 0.047$) the probability of the renal safety event defined as the decrease in creatinine clearance (CrCL) by $\geq 30\%$ from that at Day 11 post transplant. The overall probability of the occurrence of this safety event in the control treatment was 32%. The sponsor also performed logistic regression analyses using safety data from 404 evaluable patients in the everolimus-cyclosporine treatment group. These analyses suggested that the cyclosporine $C_{min,TN}$ ($p < 0.0001$), but not everolimus $C_{min,TN}$ ($p = 0.94$), significantly affected the probability of the occurrence of the safety event. The overall probability in everolimus-cyclosporine treatment group was approximately 55%, and therefore was poorer by approximately 23% than that in the azathioprine-cyclosporine control treatment.

Additional exposure-response analyses are currently being performed by the OCPB Pharmacometrics review team. The primary goals of these analyses is to better understand the relationships between everolimus and cyclosporine exposure with renal toxicity (i.e., reduction in CrCL), and to help determine the optimal dosage regimens and/or therapeutic drug concentration ranges for both everolimus and cyclosporine when used in combination for heart transplantation. It is anticipated that the results of such work would be conveyed as an amendment to this review as well as conveyed to the sponsor in future discussions regarding study design issues. Thus, at this present time, no definitive CPB recommendations/conclusions can be made regarding the optimal dosage regimen for everolimus.

Basic Everolimus Pharmacokinetic Parameters: The mean $t_{1/2}$ value of 28 hrs estimated following a single oral dose of everolimus in the range between 0.25 mg and 25 mg to renal transplant patients receiving cyclosporine co-administration in Study W101 is not acceptable for the following reasons: everolimus pharmacokinetics were not linear at the studied dose range

when using dose-normalized AUC, apparent clearance (CL_b/F), and apparent volume of distribution (V_{z,b}/F); the difference of the mean values at doses of 0.75 mg and 2.5 mg was unusually large (by approx. 10 hours); and the estimated mean ± SD value (28 ± 7 hr) is unreasonably shorter than the value (40 - 50 hr) determined in healthy subjects who received no concomitant cyclosporine administration. The mean t_{1/2} value estimated and alternatively proposed by the sponsor in Study B154 of 18 to 19 hrs is also not acceptable. The CPB reviewer is in agreement with the sponsor's statements in the submission of April 14, 2004, which indicate that the study underestimated the true t_{1/2} due to inadequate blood sampling on outpatient basis. Thus, this reviewer concludes from the review of the data provided thus far that the sponsor has not adequately determined everolimus t_{1/2} in patients of interest at steady state. The sponsor needs to determine everolimus t_{1/2} at steady state following the administration of the proposed everolimus-cyclosporine combination regimen to transplant patients.

Date: _____

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II. QUESTION-BASED REVIEW

A. General Attributes

1. *What is the proposed dosage and route of administration?*

General Recommendation

The sponsor proposes 0.75 mg b.i.d. everolimus in combination with cyclosporine and corticosteroids as a starting dosage regimen for kidney and heart transplant patients. In addition, in the Indications and Usage section of the February 17, 2004 version of the label, the sponsor is also proposing/recommending that everolimus be administered concurrently with reduced doses of cyclosporine. Additional exposure-response analyses are currently being performed by the OCPB Pharmacometrics review team. The primary goals of these analyses is to better understand the relationships between everolimus and cyclosporine exposure with renal toxicity (i.e., reduction in CrCL), and to help determine the optimal dosage regimens and/or therapeutic drug concentration ranges for both everolimus and cyclosporine when used in combination for heart transplantation. It is anticipated that the results of such work would be conveyed as an amendment to this review as well as conveyed to the sponsor in future discussions regarding study design issues. Thus, at this present time, no definitive CPB recommendations/conclusions can be made regarding the optimal dosage regimen for everolimus.

Dosage Adjustments and TDM

The sponsor proposes to increase the everolimus dose at 1 - 2 week intervals when everolimus C_{min} remains < 3 ng/mL, but has not provided any specific recommendations regarding how the dose should be increased. As was stated previously, additional Pharmacometrics analyses are currently being conducted by OCPB to help determine the appropriate targeted drug concentrations for both everolimus and cyclosporine (i.e., with respect to maintaining efficacy and minimizing renal toxicity). It should also be noted that everolimus and cyclosporine dose adjustments should be based not only on C_{min} but also on tolerability, individual response, and the clinical situation. At the present time, however, no definitive CPB recommendations/conclusions can be made regarding the appropriate targeted drug concentrations for everolimus and cyclosporine when used concurrently.

B. General Clinical Pharmacology

1. *What is the basis for selecting the exposure and response parameters?*

The E-R relationship analyses in the previous CPB review had limitations in that the analyses ignored the relative contribution of each concentration value to overall exposure estimate by using simple mean C_{min} value and the effect of cyclosporine exposure on the efficacy and safety response by using everolimus exposure only. Because everolimus and cyclosporine concentrations were measured more frequently at earlier time points but less frequently at later time points post transplant (i.e., Week 1, Week 2, Week 3, Week 4, Month 2, Month 3, and Month 6 post transplantation), the relative contribution of concentration values measured at an earlier time point (e.g., at Week 2) to the overall exposure value estimate was greater than that at

a later time point (e.g., at Month 6) in the previous analysis. Because cyclosporine is a mainstay of immunosuppression and considerably nephrotoxic, the effect of cyclosporine exposure on the efficacy and safety response should be as important as that of everolimus exposure.

In the new E-R relationship analyses in this NDA amendment, the sponsor was asked to perform regression analyses on the time-normalized mean or weighted average C_{min} (C_{min,TN}) instead of simple mean C_{min} as the exposure parameter. The new analyses also accounted for both everolimus C_{min,TN} and cyclosporine C_{min,TN} as the exposure parameters. C_{min,TN} values were computed as follows:

$$C_{min,TN} = \sum A_i / (D_k - D_0)$$

where A_i is the trapezoid area $[(C_{i-1} + C_i) \times (D_i - D_{i-1})] / 2$ under the concentration levels C_{i-1} and C_i, and D_i is the blood sampling day for C_i, i = 1, 2, ..., k.

The same efficacy and safety parameters used in the previous review were used by the sponsor: incidence of primary composite efficacy event (i.e., occurrence of acute rejection, graft loss, patient death, and lost to follow-up, whichever came first) and incidence of the renal event (i.e., a decrease in CrCL by 30% or greater), respectively. Any efficacy event that occurred for the first week post transplant was removed from the analysis because the event does not appear to be associated directly with everolimus or cyclosporine exposure (non-steady state concentrations). Any safety event that occurred for the first 11 days post transplant was removed because the value at Day 11 was chosen as baseline CrCL value.

Heart transplant patients enrolled in Study B253 achieved the highest CrCL value between 1 and 218 days post transplant when estimated using Cockcroft-Gault formula. The median time for the highest value was 11 days post transplant (mean ± SD, 28.4 ± 44.8 days). Whereas the sponsor initially provided E-R relationship information analyzed using the mean CrCL value determined from Day 1 to Day 11 as baseline CrCL (submission on April 14, 2004), the sponsor subsequently updated the information using the CrCL value at Day 11 or at a latest day prior to Day 11 if no value was recorded at Day 11 (submission on July 7, 2004). Overall conclusions were not appreciably different using either baseline value. The median CrCL value calculated using the latter approach was 62.2 mL/min (mean ± SD, 67.8 ± 29.5 mL/min; range, 11.9 - 229.4 mL/min). The median value is close to the midpoint value of mild renal impairment (50 - 80 mL/min based on the Agency's renal study guidance) and a 30% decrease from this value resulted in 43.5 mL/min, which is close to the midpoint value of moderate impairment (30 - 50 mL/min).

The sponsor evaluated other efficacy parameters including primary efficacy event after the first two weeks post transplant (Days 15 - 225), biopsy proven acute rejection (BPAR), and BPAR at Days 15 - 225. This review excluded the results for these parameters because the composite event is closer to intent-to treat analysis than BPAR and because the sponsor did not provide a convincing rationale in the use of the events that occurred at Days 15 - 225.

The sponsor also evaluated other safety parameters including hypercholesterolemia (> 250 mg/dL), hypertriglyceridemia (> 250 mg/dL), thrombocytopenia (< 100 x 10⁹/L), hypohemoglobinemia (< 7 g/dL), leukocytopenia (< 4 x 10⁹/L), renal impairment (serum creatinine > 200 μmol/L), and CrCL decrease by ≥ 30% from value at pre transplant or Month 1

post transplant. This review excluded the results for the parameters because the parameters contained inseparable confounding factors (anti-lipidemic drug use for hypercholesterolemia and hypertriglyceridemia), were less serious or reversible in clinical nature (thrombocytopenia), had no relationship with everolimus exposure (hypohemoglobinemia and leukocytopenia), or were less reliable (serum creatinine and CrCL decrease by $\geq 30\%$ from time point other than Day 11).

2. What are the planned goal and achieved outcome of exposure in pivotal clinical trials?

Everolimus Exposure in Kidney Transplant Studies

In kidney transplant studies B201 and B251, everolimus doses were fixed to 0.75 mg b.i.d. or 1.5 mg b.i.d. and full-dose cyclosporine was administered in combination. However, everolimus doses were adjusted when patients had adverse events or laboratory abnormalities possibly associated with everolimus administration. Figure 1 shows the everolimus C_{min} trend observed up to one year post transplant stratified by everolimus dose and study. The everolimus mean C_{min} values observed in Study B201 were apparently higher than those in Study B251: maximum difference was approximately 2 ng/mL at 1.5-mg dose level. At one year post transplant, the respective values in lower and higher dose groups in Study B201 were 4.7 ± 2.2 ng/mL and 8.1 ± 4.2 ng/mL, whereas the respective values in Study B251 were 3.8 ± 1.8 ng/mL and 6.1 ± 3.3 ng/mL. The inter-individual CVs of everolimus C_{min} values was approximately 55%. The therapeutic everolimus C_{min} range proposed by the sponsor based on Studies B201 and B251 is 3 - 8 ng/mL.

In kidney transplant studies A2306 and A2307, everolimus was initiated at a starting dose of 0.75 mg b.i.d. or 1.5 mg b.i.d. and reduced-dose cyclosporine was administered in combination. Everolimus doses were adjusted subsequently to achieve everolimus C_{min} ≥ 3 ng/mL or to avoid patients from adverse events or laboratory abnormalities possibly associated with everolimus administration. Figure 2 shows the everolimus C_{min} trend observed up to one year post transplant stratified by everolimus dose and study. Everolimus mean C_{min} values in these studies fluctuated less than those in previous studies (B201 and B251). The values for a few weeks post transplant in Study A2307 were lower than that

Figure 1. Mean \pm SD everolimus C_{min} determined in *de novo* renal transplant patients (Studies B201 and B251)

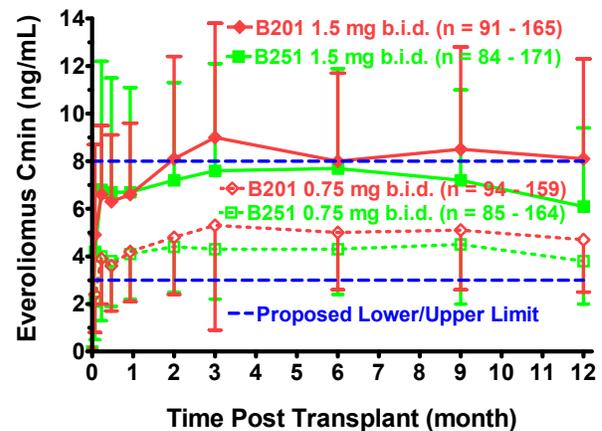
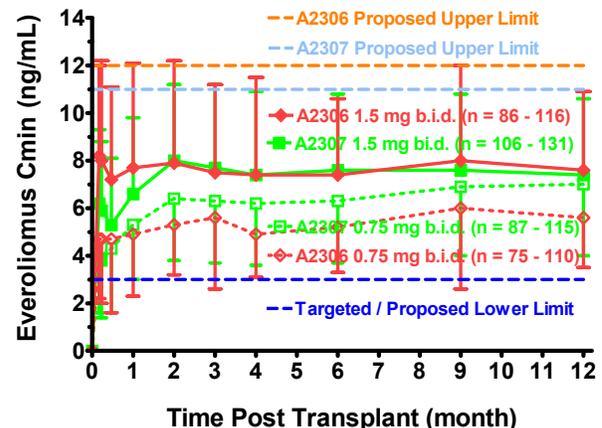


Figure 2. Mean \pm SD everolimus C_{min} determined in *de novo* renal transplant patients (Studies A2306 and A2307)



in A2306 probably due to lower cyclosporine doses (see Cyclosporine Exposure below). In both studies, the values were in an increasing trend in the lower dose groups. Particularly in Study A2307, the mean everolimus C_{min} value determined at one year post transplant in lower dose group (i.e., 7.0 ± 3.0 ng/mL) was almost the same as the value determined in higher dose group (i.e., 7.4 ± 3.2 ng/mL). The values at one year post transplant in lower and higher dose groups in Study A2306 were 5.6 ± 2.1 ng/mL and 7.6 ± 3.3 ng/mL, respectively. The inter-individual CVs (approx. 50%) of everolimus C_{min} values in Studies A2306 and A2307 appears to be similar to the CVs observed in Studies B201 and B151. The therapeutic everolimus C_{min} ranges proposed by the sponsor based on Studies A2306 and A2307 are 3 - 12 ng/mL and 3 - 11 ng/mL, respectively.

Everolimus Exposure in Heart Transplant Study

In heart transplant study B253, everolimus doses were fixed to 0.75 mg b.i.d. or 1.5 mg b.i.d. and full-dose cyclosporine was administered in combination. However, everolimus doses were reduced when the patients had serious adverse events or laboratory abnormalities possibly associated with everolimus administration. Figure 3 shows the everolimus C_{min} trend observed up to one year post transplant stratified by everolimus dose. The mean C_{min} trend was stable over the first year post transplant. The everolimus C_{min} values in lower and higher dose groups were 5.4 ± 4.4 ng/mL and 9.6 ± 6.8 ng/mL, respectively, at one year post transplant. Everolimus C_{min,TN} was 7.3 ± 4.8 ng/mL when determined up to 7.5 months post transplant. The inter-individual CVs of everolimus C_{min} value in Study B253 (approx. 75%) appear to be slightly larger than the CVs observed in kidney transplant studies. The therapeutic everolimus C_{min} range proposed by the sponsor based on Study B253 is 3 - 8 ng/mL.

Figure 3. Mean ± SD everolimus C_{min} determined in *de novo* heart transplant patients (Study B253)

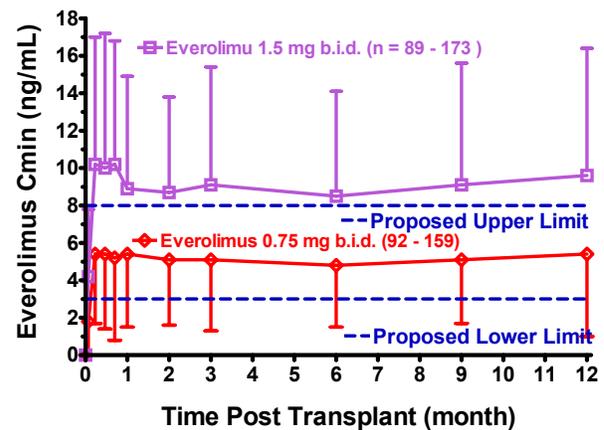
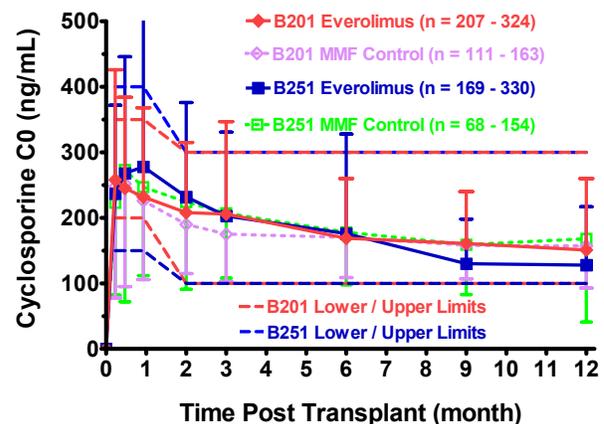


Figure 4. Mean ± SD cyclosporine C_{min} determined in *de novo* renal transplant patients (Studies B201 and B251)



Cyclosporine Exposure in Kidney Transplant Studies

In Studies B201 and B251, cyclosporine was initiated with a starting dose of 6 - 12 mg/kg/day in combination with a fixed everolimus dose mentioned above. Cyclosporine doses were subsequently adjusted to achieve cyclosporine C_{min} within the range of 150 - 400 ng/mL for Weeks 1 - 4 and 100 - 300 ng/mL for Months 2 - 36 in Study B201, or

150 - 400 ng/mL for Weeks 1 - 4 and 200 - 350 ng/mL for Months 2 - 36 in Study B251. Figure 4 shows the cyclosporine C_{min} trend observed up to one year post transplant stratified by treatment and study. Cyclosporine C_{min} values were not substantially different between treatments and studies. The inter-individual CVs of cyclosporine C_{min} values were larger during the first month than the later months post transplant.

In Studies A2306 and A2307, cyclosporine was initiated at a starting dose of 8 and 4 mg/kg/day, respectively, in combination with an initial everolimus dose mentioned above. In Study A2306, cyclosporine doses were adjusted to the targeted cyclosporine C₂ of 1200 ng/mL (acceptable range, 1000 - 1400 ng/mL) for Weeks 0 - 4, 800 ng/mL (700 - 900 ng/mL) for Weeks 5 - 8, 600 ng/mL (550 - 650 ng/mL) for Weeks 9 - 12, and 400 ng/mL (350 - 450 ng/mL) for Months 4 - 12. Only approximately 30% (range, 15% - 39%) of study patients were within the acceptable limits (Figure 5). In Study A2307, cyclosporine doses were adjusted to achieve the cyclosporine C₂ of 600 ng/mL (500 - 700 ng/mL) for Weeks 0 - 8 and 400 ng/mL (350 - 450 ng/mL) for Months 3 - 12. Only approximately 50% (range, 39% - 72%) of study patients were within the acceptable limits (Figure 5). Thus, the TDM goals for cyclosporine C₂ monitoring could not be achieved as planned in either study. The author of the study report reasoned that ‘the clinicians aimed for somewhat higher C₂ levels in the post-titration phase in months 4 to 9 than foreseen in the protocol.’ In addition, it appears that the targeted range (lower to upper limit) was too tight to achieve the TDM goals as planned.

In Studies A2306 and A2307, cyclosporine C_{min} was also measured. The mean C_{min} values in everolimus treatment in Study A2306 was similar to for the first month but lower by approximately 100 ng/mL at Months 6 - 12 post transplant than the values in mycophenolate mofetil control in Studies B201 and B251 (Figure 6). In contrast, the mean C_{min} values in Study A2307 was lower by approximately 150 ng/mL for the first month and by 100 ng/mL in Months 6 - 12 post transplant than the values in the control treatment in Studies B201 and B251 (Figure 6). Thus, cyclosporine exposure in Studies A2306 and A2307 was substantially lower (< 50%) than the exposure in Studies B201 and B251.

Figure 5. Mean ± SD cyclosporine C₂ determined in *de novo* renal transplant patients (Studies A2306 and A2307)

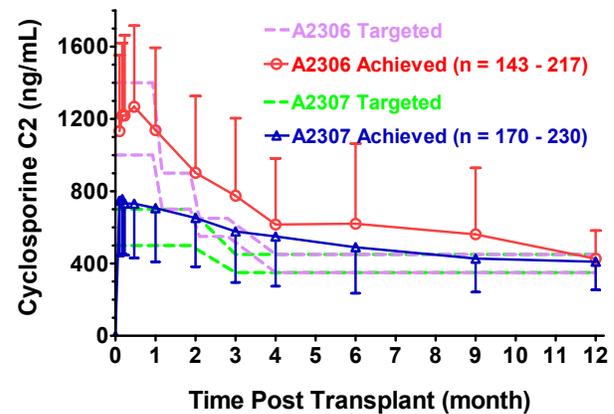
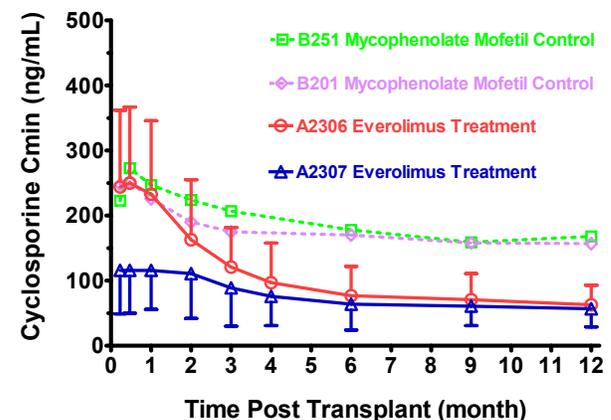


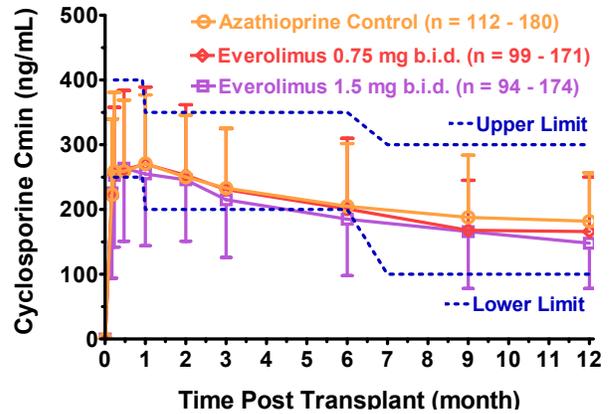
Figure 6. Mean ± SD cyclosporine C_{min} determined in *de novo* renal transplant patients (Studies A2306 and A2307)



Cyclosporine Exposure in Heart Transplant Studies

In Study B253, cyclosporine was initiated with a starting dose of 12 mg/kg/day in combination with everolimus administration mentioned above. Cyclosporine doses were adjusted to the cyclosporine C_{min} range of 250 - 400 ng/mL for Weeks 1 - 4, 200 - 350 ng/mL for Months 1 - 6, and 100 - 300 ng/mL for Months 7 - 24. Figure 7 shows the cyclosporine C_{min} trend observed up to 1 year post transplant stratified by treatment. For the first 6 months post transplant, approximately 50% of patients had the cyclosporine C_{min} below the lower targeted C_{min}: this may have partly contributed to the poorer efficacy outcome of the study compared to current statistics in heart transplantation (see next question). Mean cyclosporine C_{min} values were not appreciably different between treatments. Cyclosporine C_{min},TN was approximately 270 ng/mL when determined for the first 7.5 months post transplant.

Figure 7. Mean \pm SD cyclosporine C_{min} determined in *de novo* heart transplant patients (Studies B253)



3. What are the characteristics of the exposure-response relationships for efficacy and safety?

Everolimus-cyclosporine E-R relationships were determined by the sponsor by logistic regression. Cox regression analyses were also performed by the sponsor and produced essentially the same results and conclusions, and therefore were not included in this review. Furthermore, the relationships were determined for only heart transplant study (B253) because there are no reliable baseline CrCL values in kidney transplant studies. The logistic regression model used was as follows:

$$\begin{aligned} \text{Logit (P)} &= \log (P / (1 - P)) \\ &= \alpha(x - x_m) + \beta(y - y_m) + \gamma(x - x_m)(y - y_m) + \omega \end{aligned}$$

where P = probability of efficacy or safety event
 x = everolimus C_{min},TN (ignored for azathioprine control)
 y = cyclosporine C_{min},TN
 x_m = the mean value of x (ignored for azathioprine control)
 y_m = the mean value of y
 α = parameter for x (ignored for azathioprine control)
 β = parameter for y
 γ = parameter for x-y interaction (ignored for azathioprine control)
 ω = intercept

Everolimus-Cyclosporine Exposure-Efficacy Relationship

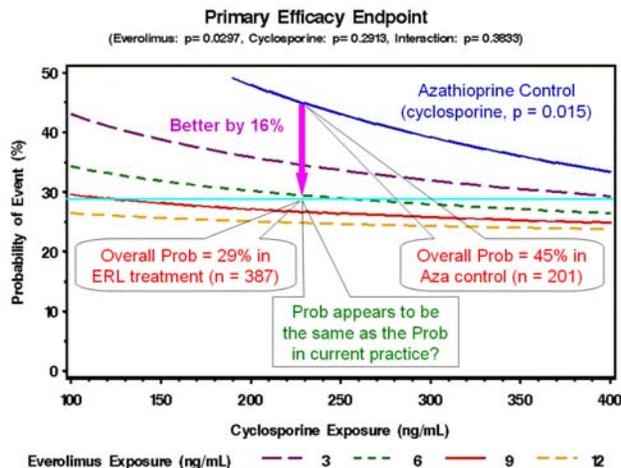
Using 201 evaluable patients' data in azathioprine control group, the regression model was significant (p = 0.0087), β was significant (p = 0.015), and ω was also significant (p = 0.020).

Thus, cyclosporine C_{min,TN} affected significantly the probability of primary composite event, defined in Question B.1. in Question 1 (Figure 8A). The overall probability in control treatment was approximately 45%.

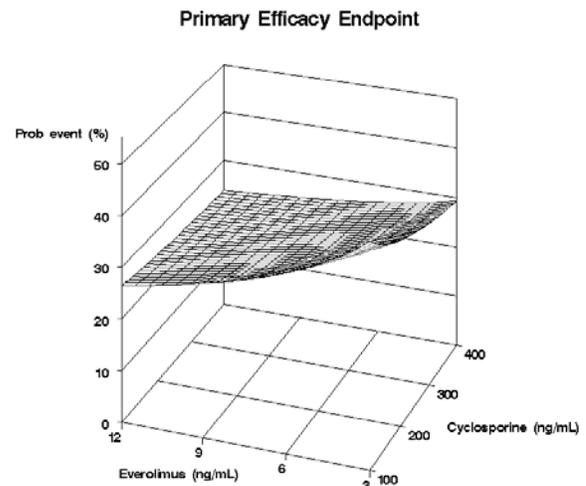
Using 387 evaluable patients' data in everolimus treatment groups, the regression model was significant ($p = 0.0090$), α was significant ($p = 0.03$), β was not significant ($p = 0.29$), γ was not significant ($p = 0.38$), and ω was significant ($p < 0.0001$). The probability as a function of both everolimus C_{min,TN} and cyclosporine C_{min,TN} was shown in a three-dimensional graph (Figure 8B). Thus, everolimus C_{min,TN} but not cyclosporine C_{min,TN} affected significantly the probability of the primary composite event in everolimus treatment groups (Figure 8A). It seems that the effect of cyclosporine C_{min,TN} on the efficacy event disappeared in the presence of considerable everolimus concentration (compare with control). The overall probability in everolimus treatment was approximately 29% and therefore better by approximately 16% than that in control treatment. The statistical interaction between everolimus C_{min,TN} and cyclosporine C_{min,TN} was not significant.

Figure 8. Probability of primary composite efficacy event estimated in a heart transplant study (B253) as a dependent variable of everolimus and cyclosporine exposure (time-normalized trough concentration, C_{min,TN}) using logistic regression ($n = 387$ and 201 for everolimus treatment and azathioprine control, respectively).

A. 2-Dimensional plot stratified by everolimus C_{min,TN} or control



B. 3-Dimensional plot



In Study B253, azathioprine does not appear to have been a reasonable control treatment. In 2002, based on the Scientific Registry of Transplant Recipients (SRTR) report, less than 10% of patients in the United States received azathioprine prior to hospital discharge following heart transplantation, while approximately 80% received mycophenolate mofetil instead. Furthermore, the incidence of acute rejection in azathioprine control in Study B253 was 53% at one year post transplant, while the mean incidence was less than 40% in the United States in 2002 (approx. 15% difference). Therefore, if the sponsor would have used mycophenolate mofetil as a control, the efficacy outcome in the control group could have been closer to the overall probability in everolimus treatment (the probability curve at everolimus C_{min,TN} of 6 ng/mL in Figure 8A).

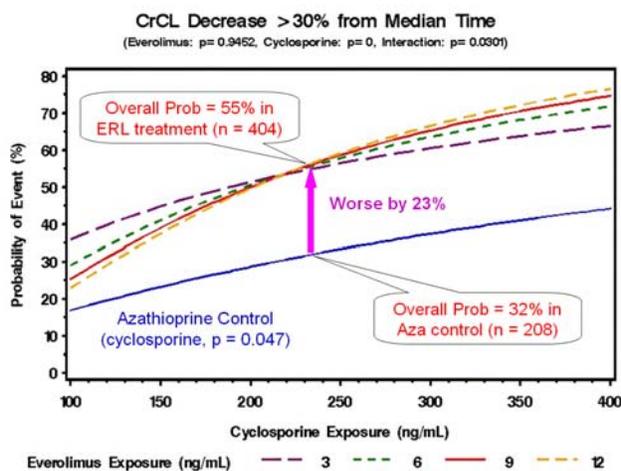
Everolimus-Cyclosporine Exposure-Safety Relationship

Using 208 evaluable patients' data in azathioprine control group, the regression model was significant ($p = 0.033$), β was significant ($p = 0.047$), and ω was also significant ($p = 0.025$). Thus, cyclosporine $C_{min,TN}$ affected significantly the probability of the renal event, defined in Question B.1. (Figure 9A). The overall probability in control treatment was approximately 32%.

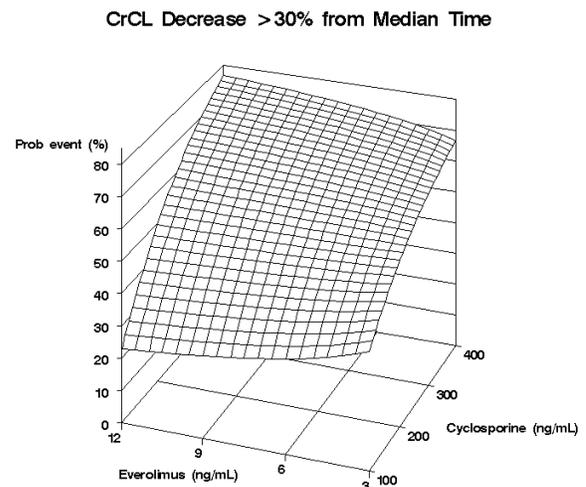
Using 404 evaluable patients' data in everolimus treatment groups, the model was significant ($p < 0.0001$), α was not significant ($p = 0.94$), β was significant ($p < 0.0001$), γ was significant ($p = 0.030$), and ω was not significant ($p = 0.14$). The probability as a function of both everolimus $C_{min,TN}$ and cyclosporine $C_{min,TN}$ was shown in a three-dimensional graph (Figure 9B). Overall, cyclosporine $C_{min,TN}$ but not everolimus $C_{min,TN}$ affected significantly the probability of the renal event in everolimus treatment groups (Figure 9A). However, the overall probability in everolimus treatment was approximately 55% and therefore poorer by approximately 23% than that in control treatment. The statistical interaction between everolimus $C_{min,TN}$ and cyclosporine $C_{min,TN}$ was significant ($p = 0.03$, Figure 9A). The absence of the effect of everolimus $C_{min,TN}$ on the probability may be due to the interaction. The reason for the interaction is not known but may be associated with the relationship between everolimus $C_{min,TN}$ and cyclosporine $C_{min,TN}$ described below.

Figure 9. Probability of renal event estimated in a heart transplant study (B253) as a dependent variable of everolimus and cyclosporine exposure (time-normalized trough concentration, $C_{min,TN}$) using a logistic regression ($n = 404$ and 208 for everolimus treatment and azathioprine control, respectively).

B. 2-Dimensional plot stratified by everolimus $C_{min,TN}$ or control



B. 3-Dimensional plot

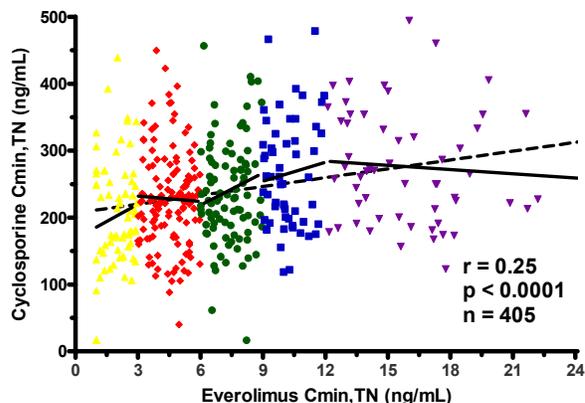


Everolimus $C_{min,TN}$ - Cyclosporine $C_{min,TN}$ Relationship

In addition to the logistic regression analyses, the relationship between everolimus $C_{min,TN}$ and cyclosporine $C_{min,TN}$ was determined. Using data from all 404 evaluable patients, there was a weak (correlation coefficient, $r = 0.25$) but statistically significant ($p = 0.0010$) linear correlation

between the $C_{min,TN}$ of everolimus and cyclosporine (Figure 10). However, when analyzed after stratified by everolimus $C_{min,TN}$ range, the trend line appears to be a convex curve: increasing trend at lower but decreasing trend at higher $C_{min,TN}$. The statistical interaction between the $C_{min,TN}$ of everolimus and cyclosporine appears to be due to the contrasting trend at each other end of the correlation trend line.

Figure 10. Relationship between time-normalized trough concentrations ($C_{min,TN}$) for everolimus and cyclosporine determined in heart transplant patients (Study B253)



4. Were the basic pharmacokinetic parameters for everolimus determined adequately?

In the section **1.1 Recommendation** of the CPB review for the original submission (see review in DFS), this reviewer concluded that basic everolimus pharmacokinetic parameters (i.e., apparent oral clearance: CL_b/F ; apparent volume of distribution: $V_{z,b}/F$; half-life: $t_{1/2}$) were not adequately determined in the targeted patient population. This deficiency was conveyed to the sponsor on November 21, 2003 through fax transmission and a written response from the sponsor was received on December 19, 2003. These deficiencies were also discussed with the sponsor on two subsequent teleconferences on November 25, 2003 and January 6, 2004. During the teleconferences, the CPB reviewer accepted the CL_b/F value of 8.8 L/hr (27% inter-patient variation) estimated in a population pharmacokinetic analysis using data collected from Studies B201 and B251 as well as the $V_{z,b}/F$ value of 342 ± 110 L (range 128 - 589 L, Study W101)

The issue on everolimus $t_{1/2}$ remains to be resolved. In the teleconference held on January 6, 2004, we noted that the value of 28 ± 7 hr estimated and proposed by the sponsor based on Study W101 was not acceptable (please refer to the minutes in DFS) because: (1) everolimus pharmacokinetics are not linear at the studied dose range from 0.75 mg to 25 mg when determined comparing dose-normalized AUC_b , and body weight-normalized CL_b/F and $V_{z,b}/F$ between doses as shown in Table 1, (2) at proposed (0.75 mg) or near-proposed (2.5 mg) doses, the number of subjects was too small to get reliable $t_{1/2}$ estimate ($n = 6$ each). Furthermore, the value of 28 ± 7 hr estimated in transplant patients receiving cyclosporine co-administration is unreasonably shorter than the $t_{1/2}$ range from 40 hours to 50 hours estimated in healthy subjects receiving no cyclosporine co-administration (see previous CPB review in DFS): the patients would be expected to have a longer $t_{1/2}$ than the healthy subjects due to pharmacokinetic everolimus-cyclosporine pharmacokinetic interaction. In addition, the difference of the mean values at the doses of 0.75 mg and 2.5 mg was unexplainably large (by approx. 10 hours, Table 1).

Table 1. Pharmacokinetic parameter values (mean \pm SD) for everolimus estimated following a single dose to renal transplant patients (n = 6 each group) receiving cyclosporine co-administration (Study W101)

Pharmacokinetic Parameters	Everolimus Dose					
	0.25 mg	0.75 mg	2.5 mg	7.5 mg	15 mg	25 mg
Tmax (hr)	2.2 \pm 0.7	1.7 \pm 0.5	1.3 \pm 0.4	1.3 \pm 0.6	1.0 \pm 0.0	1.3 \pm 0.4
Cmax,b (ng/mL)	2.3 \pm 0.8	14 \pm 3	45 \pm 21	85 \pm 16	173 \pm 37	179 \pm 24
Cmax,b/D [(ng/mL)/mg]	9.3 \pm 3.1	18.7 \pm 3.6	18.1 \pm 8.3	11.4 \pm 2.1	11.5 \pm 2.5	7.2 \pm 0.9
Cmax,b/(D/BW) [(ng/mL)/(mg/kg)]	809 \pm 219	1264 \pm 98	1177 \pm 434	881 \pm 169	857 \pm 230	549 \pm 134
Relative Cmax,b/D Ratio (%)	ND	100	97	61	61	39
C12hr,b (ng/mL)	ND	1.9 \pm 0.3	5.2 \pm 2.5	11.9 \pm 2.5	23.7 \pm 2.8	38.1 \pm 7.4
C12hr,b/D [(ng/mL)/mg]	ND	2.5 \pm 0.5	2.1 \pm 1.0	1.6 \pm 0.3	1.6 \pm 0.2	1.5 \pm 0.3
Relative C12hr,b/D Ratio (%)	ND	100	84	64	64	61
AUCb (hr-ng/mL)	ND	171 \pm 50	344 \pm 141	783 \pm 191	1468 \pm 238	2400 \pm 608
AUCb/D [(hr-ng/mL)/mg]	ND	228 \pm 66	138 \pm 56	104 \pm 26	98 \pm 16	96 \pm 24
AUCb/(D/BW) [(hr-ng/mL)/(mg/kg)]	ND	15490 \pm 4093	8964 \pm 2560	8165 \pm 2394	7492 \pm 2622	7538 \pm 2913
Relative AUCb/D Ratio (%)	ND	100	61	46	43	42
Cmax,b/AUCb (1/hr)	ND	0.09 \pm 0.02	0.13 \pm 0.03	0.11 \pm 0.03	0.12 \pm 0.03	0.08 \pm 0.02
AUCb/C12hr [(hr-ng/mL)/(ng/mL)]	ND	91 \pm 14	69 \pm 9	66 \pm 8	62 \pm 8	62 \pm 7
CLb/F (L/hr)	ND	4.7 \pm 1.3	8.3 \pm 3.1	10.1 \pm 2.5	10.5 \pm 1.9	11.2 \pm 3.7
CLb/F/BW [(L/hr)/kg]	ND	0.07 \pm 0.01	0.12 \pm 0.04	0.13 \pm 0.04	0.15 \pm 0.05	0.15 \pm 0.07
Vz,b/F (L)	ND	222 \pm 56	296 \pm 113	366 \pm 52	360 \pm 66	465 \pm 68
Vz,b/F/BW (L/kg)	ND	3.21 \pm 0.73	4.24 \pm 1.21	4.75 \pm 0.74	4.93 \pm 1.19	6.30 \pm 1.72
t _{1/2} (hr)	ND	35 \pm 14	25 \pm 6	26 \pm 4	24 \pm 7	30 \pm 5

D, dose; BW, body weight; ND, not determined

After debating with us about the problems in Study W101 during the teleconference, the sponsor proposed that Study B154 may provide adequate everolimus t_{1/2} estimates. We agreed to review the study upon NDA amendment submission. As a result of the review, the mean t_{1/2} values estimated in Study B154 turned out to be 19.2 \pm 3.4 hr and 18.1 \pm 7.6 hr at the doses of 0.75 mg and 2.5 mg, respectively. Thus, the estimates in Study B154 are even shorter than the estimates in Study W101. The sponsor reasoned that ‘the infrequent blood sampling in the washout phase under outpatient conditions in study B154 may have underestimated the true terminal half-life.’ Thus, the t_{1/2} values estimated in Study B154 are not adequate.

Upon our written request of June 2, 2004 to provide the t_{1/2} values determined adequately from studies following steady-state administration of the proposed everolimus-cyclosporine combination regimen to transplant patients, the sponsor provided on July 7, 2004 the mean value (i.e., 33 \pm 6 hr) estimated from healthy subjects following a single dose of everolimus without cyclosporine co-administration in previously submitted (uninformed study numbers) and non-submitted studies (Studies 2408, 2409, and 2410) instead. The sponsor insisted that the value estimated in Study W101 (i.e., 28 \pm 7 hr) was appropriate in comparison to the value estimated in healthy subjects. We do not know whether the Studies 2408, 2409, and 2410 were adequately conducted and analyzed without the sponsor’s submission and our review. Even under the assumption that those studies were adequate, the sponsor’s claim is not acceptable because the comparison does not give an answer to the question why the everolimus t_{1/2} estimated in transplant patients receiving cyclosporine co-administration was shorter by 7 hours than the t_{1/2} estimated in healthy subjects without cyclosporine co-administration. Furthermore, the sponsor

did not provide the $t_{1/2}$ value determined at steady state of everolimus and cyclosporine co-administration.

Overall, from the review of the data provided thus far by the sponsor, this reviewer concludes that the sponsor has not adequately determined the terminal $t_{1/2}$ for everolimus in the targeted patient population at steady state. Therefore, in future submissions, the sponsor needs to provide an estimate of the $t_{1/2}$ for everolimus determined adequately at the range of proposed clinical doses or concentrations of everolimus and cyclosporine following multiple (steady state) administration of the proposed everolimus-cyclosporine combination regimen to transplant patients.

C. Intrinsic Factors

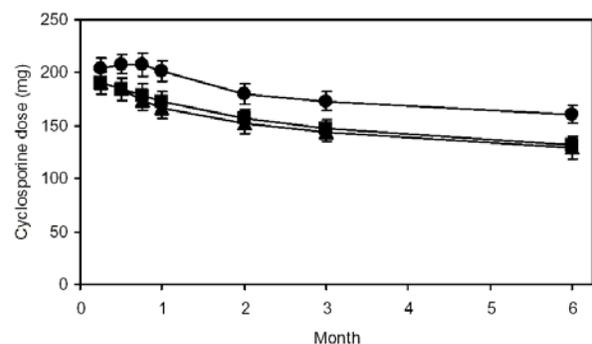
No update.

D. Extrinsic Factors

There is no update regarding extrinsic factors in this amendment. Additional drug-drug interaction studies are assumed to be on-going; the sponsor submitted 3 study protocols and we sent our comments early this year.

Even though mean cyclosporine C_{min} values were not appreciably different between treatment groups in Study B253 (Figure 7), a comparison of the least square mean cyclosporine doses between each everolimus group *versus* the azathioprine control group indicated 14.6% and 19.8% lower cyclosporine doses in the everolimus 0.75 mg b.i.d. and 1.5 mg b.i.d. groups, respectively (Figure 13). Study B201 but not Study B251 showed similar trend (approx. 10% lower cyclosporine dose in everolimus treatment groups). This result implies that everolimus at a dose from 0.75 mg b.i.d. to 1.5 mg b.i.d. may inhibit cyclosporine metabolism and/or transport, and increase cyclosporine C_{min} by 10% - 20%.

Figure 13. Mean \pm 90% CI cyclosporine doses administered in Study B253 (● azathioprine control, ■ everolimus 0.75 mg b.i.d., ▲ everolimus 1.5 mg b.i.d.).



E. General Biopharmaceutics

No update.

F. Analytical

The sponsor provided analytical reports associated with Studies A2306 and A2307. The reports were not reviewed in depth but appear to be acceptable.

III. DETAILED LABELING RECOMMENDATIONS

Labeling recommendations are deferred because the Clinical Division's action for this major amendment will be 'approvable' due to insufficient dosing and safety information.

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/s/

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8/10/04 01:45:54 PM
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