CARDIO-RENAL ADVISORY COMMITTEE
N21-628 CERTICAN® (EVEROLIMUS)
CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS SUMMARY
NOVEMBER 16, 2005

Recommendation

Alternative dosing regimens of cyclosporine and everolimus should be studied to achieve a better benefit-risk profile than that obtained in the heart transplant Study B253. Specifically, the results from our additional analyses suggest that a treatment regimen that employs faster tapering of cyclosporine and maintenance of a threshold everolimus exposure should be evaluated in prospective, randomized clinical trials.

Executive Summary

The FDA review and analysis of the exposure-effectiveness and exposure-renal toxicity relationships of the everolimus and cyclosporine combination regimen used in the heart transplant Study B253 and other clinical pharmacology studies led to the following key conclusions:

1. Higher cyclosporine and everolimus concentrations were associated with fewer of the events that defined treatment failure for the primary effectiveness endpoint, e.g., acute rejection.
2. Patients with higher cyclosporine and everolimus concentrations had more renal toxicity as defined by a greater reduction in creatinine clearance.
3. The observation that both effectiveness and renal toxicity are drug exposure dependent strongly supports the feasibility of optimizing cyclosporine and everolimus dosing to achieve a better benefit-risk profile.
4. Computer assisted projections of alternate dosing strategies indicate that initiating treatment with cyclosporine trough concentrations similar to those used in B253, followed by a faster tapering of cyclosporine trough concentrations while maintaining everolimus in a target concentration range, may lead to achieving effectiveness with a lower likelihood of renal toxicity.

Summary

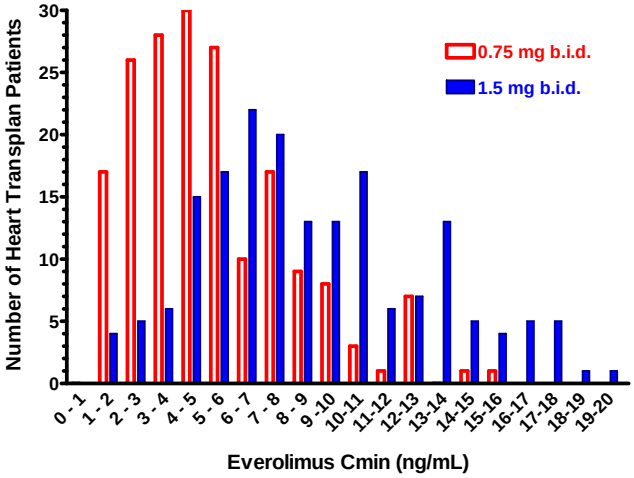
The clinical pharmacology of everolimus and cyclosporine relevant to the Advisory Committee discussion is provided in this summary.

Everolimus Pharmacokinetics

The apparent blood clearance (CL/F) and terminal half-life ($t_{1/2}$) of everolimus, in healthy subjects, are in the range of 16.5 - 19.7 L/hr and 31.5 - 55.8 hr, respectively. The everolimus uptake into human erythrocytes is approximately 85% (14% in plasma) at the blood concentration range of 5 - 100 ng/mL. The binding of everolimus to plasma proteins is approximately 75% and considered to be concentration independent. The within- and between-patient variability were about 40% each following fixed everolimus doses of 0.75 mg b.i.d. and

1.5 mg b.i.d. in heart transplant patients also receiving cyclosporine. There was a significant overlap between the low and high everolimus dose groups in the frequency distribution of Cmin despite the 2-fold difference in dose (Figure 1). CYP3A4 and/or P-gp inhibitors, such as ketoconazole and cyclosporine increase the everolimus exposure of everolimus considerably (2-15 fold). Everolimus exposures were reduced by 50% upon co-administration of rifampin, an inducer of CYP450 and P-gp.

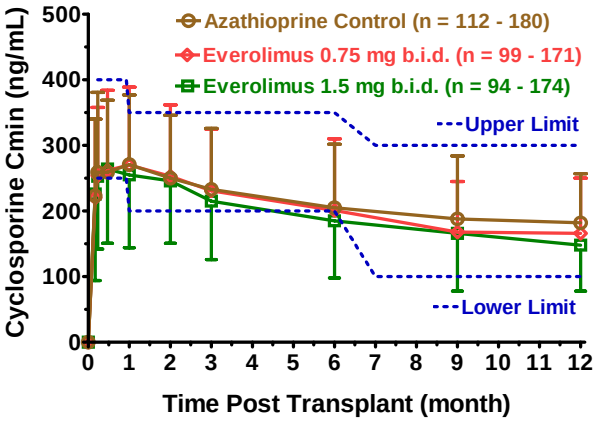
Figure 1: Everolimus Cmin after 0.75 mg and 1.5 mg bid are markedly overlapping in *de novo* heart transplant patients (n = 371, Study B253).



Cyclosporine Pharmacokinetics

In Study B253, cyclosporine administration was initiated with a starting dose of 12 mg/kg/day in combination with everolimus. Cyclosporine doses were adjusted to the cyclosporine Cmin 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 months post transplant, approximately 50% of patients had cyclosporine Cmin below the lower targeted range (Figure 2). Cyclosporine mean Cmin values were not appreciably different between treatments.

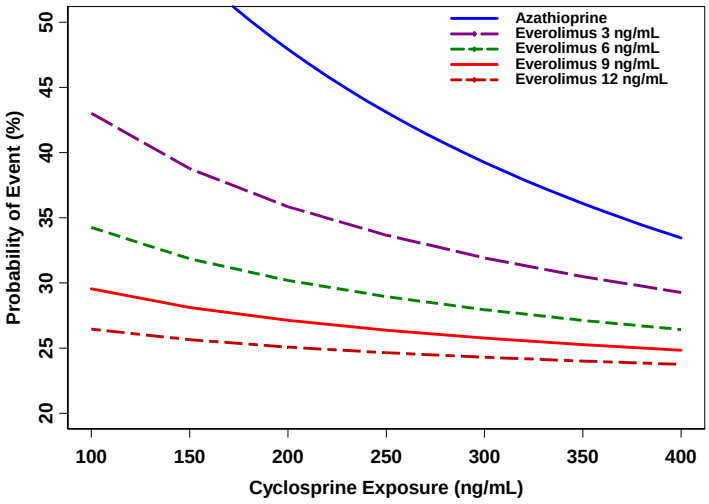
Figure 2: Mean ± SD cyclosporine Cmin determined in *de novo* heart transplant patients (Study B253). The upper and lower target cyclosporine Cmin are also shown.



Everolimus/Cyclosporine Exposure-Effectivenvess Response Relationship

Logistic regression analyses were performed using effectivenvess data from evaluable patients in the azathioprine control group (n = 201) and everolimus treatment groups (0.75 mg & 1.5 mg bid; n = 387) in heart transplant Study B253 (Figure 3). The analyses suggested that, for the azathioprine control group, patients with higher cyclosporine Cmin had a lower probability of reaching the primary composite effectiveness event, i.e., occurrence of acute rejection, graft loss, patient death. and loss to follow-up, whichever came first). A similar analysis suggested that, overall, cyclosporine and everolimus Cmin affected the probability of the effectivenvess event.

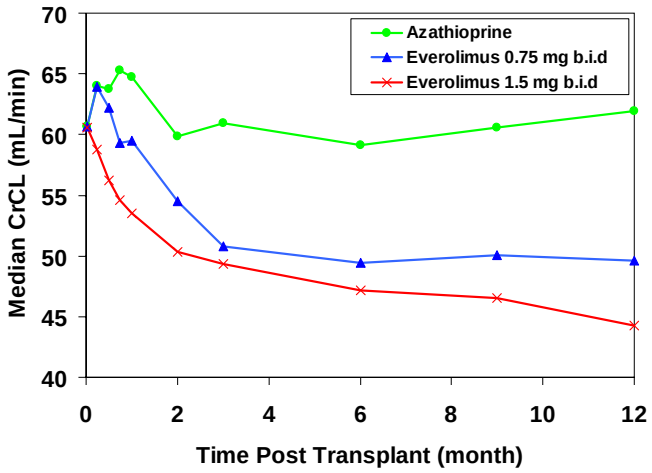
Figure 3: Probability of primary composite effectivenvess event estimated in heart transplant patients (Study B253) as a dependent variable of everolimus and cyclosporine exposure using logistic regression. The different lines are for (top to bottom): azathioprine, everolimus 3 ng/mL, 6 ng/mL, 9 ng/mL and 12 ng/mL.



Everolimus/Cyclosporine Exposure-Safety Response Relationship

Exposure-response analyses were also performed using safety data from evaluable patients in the azathioprine control (n = 208) and everolimus treatment (0.75 mg & 1.5 mg bid; n = 404) groups in Study B253 (Figure 4). Renal toxicity was assessed using two endpoints: 1) decrease in creatinine clearance (CrCL) by ≥ 30% from that at 10 days post transplant and 2) CrCL change over time in each patient. For both endpoints, higher cyclosporine and everolimus levels caused lower renal function. These relationships clearly suggest that carefully selected target concentrations could potentially minimize the renal toxicity of this drug combination in heart transplant recipients. Although not shown here, the incidence of hypertriglyceridemia and thrombocytopenia were correlated with everolimus Cmin.

Figure 4: Time course of creatinine clearance for the azathrioprine and everolimus groups in Study B253.



Everolimus/Cyclosporine Combination Regimen – Predictions Based on Modeling and Simulation

The everolimus-cyclosporine combination regimen employed in heart transplant Study B253 does not appear to be adequately safe for the prevention of acute rejection following *de novo* heart transplantation. Simulations using the quantitative exposure-effectiveness and exposure-renal toxicity relationships were employed to project the likely outcomes of altered dosing schemes. One such alternative is presented here for illustration. The outcome simulations were performed reducing the target cyclosporine Cmin by 45% and 65% of those observed in Study B253, respectively for the low and high everolimus dose groups during 2-6 months post transplantation. All other trial design aspects were assumed to be identical to Study B253, including the everolimus concentrations and first month target trough cyclosporine concentrations. As shown in Table 1, the new dosing regimen projects a mean change in CrCL, relative to baseline, of -5 mL/min for the two everolimus groups at 6 months, compared to -13 mL/min and -19 mL/min for the Study B253 regimen. Effectiveness is essentially unaltered by the new regimen. Faster tapering of cyclosporine trough concentrations and maintaining a threshold of everolimus trough concentrations may further improve the combination benefit/risk profile of this drug combination in heart transplant recipients. The simulations assumed that the first month drug exposures are more critical for the effectiveness relative to subsequent exposures. The model also assumes that the renal toxicity is reversible under the proposed dosage regimens. If considerable portion of the toxicity is irreversible then the impact of faster cyclosporine tapering on improving the renal function may be limited.

Table 1. Observed and simulated benefit (failure rate) and risk (mean change from baseline in CrCL at 6 months) between the Everolimus groups. 47% of the patients in the azathioprine group had at least one of the composite effectiveness events. The mean change in CrCL for the azathioprine group was -4.6 mL/min at 6 months (also see Figure 4).

Treatment	**Benefit**	**Risk**
	Primary effectivenvess events in 6 mo.	**Mean change in CrCL (mL/min) from baseline at 6 mo.**
Observed results with standard CsA trough concentrations from Study B253		
0.75 mg bid Everolimus	36%	-13
1.5 mg bid Everolimus	27%	-19
Simulated results with lower target CsA trough concentrations during 2-6 months post transplantation		
0.75 mg bid Everolimus with trough CsA decreased by 45%	37%	-5
1.5 mg bid Everolimus with trough CsA decreased by 65%	28%	-5