

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-560s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21-560
Priority or Standard	Resubmission
Submit Date(s)	January 22, 2010
Received Date(s)	January 22, 2010
PDUFA Goal Date	July 30, 2010
Division / Office	DSPTP/OAP/OND/CDER
Reviewer Name(s)	Ergun Velidedeoglu
Review Completion Date	April 18, 2010
Established Name	Everolimus
(Proposed) Trade Name	Zortress*
Therapeutic Class	Immunosuppressant (M-TOR inhibitor)
Applicant	Novartis
Formulation(s)	Tablet
Dosing Regimen	Initial dose of 0.75 mg bid; then adjusted to a trough concentration of 3 to 8 ng/mL
Indication(s)	Prevention of allograft rejection
Intended Population(s)	Kidney transplant recipients

(b) (4)
The Applicant submitted the name Zortress on October 19, 2009,
which DMEPA found to be acceptable.

I- Regulatory Background:

The current submission from the Applicant was received on January 22, 2010 in response to a Complete Response (CR) letter issued to the applicant on December 23, 2009. [For a discussion of regulatory terminology see Section VII.]

The Clinical Review of the previous resubmission (submission date June 30, 2009) was completed on December 23, 2009; the Clinical Reviewer recommended non-approval; the Division was in favor of approval, but several outstanding issues related to the Risk Evaluation and Mitigation Strategy (REMS) and labeling prevented approval in that review cycle. The Division decided that a REMS was necessary to ensure that the benefits of the drug outweigh the five major risks (among others) of: wound healing complications, hyperlipidemia, proteinuria, and graft thromboses, as well as nephrotoxicity when co-administered with standard doses of cyclosporine. [For additional details, see the December 23, 2009 CR letter in Section III of this review.]

The current submission contains a revised REMS and an updated package insert (PI), as noted in the 2009 CR letter.

This updated clinical review discusses the revised REMS and PI and also contains minor revisions to the previous clinical review dated December 18, 2009 (DARRTS date December 23, 2009).

II- Recommendations of the Clinical Reviewer:

Upon review of the current submission, I continue to recommend non-approval of everolimus for the prevention of allograft rejection for the following reasons:

As explained in detail in the December 18, 2009 clinical review (attached to the end of this review) the risks associated with everolimus regimen are both higher in number and more significant in terms of mortality and morbidity associated with them when compared to the risks associated with the control regimen or probably to any other commonly employed immunosuppressive regimen in transplant patients. Most of these risks were communicated to the investigators in the Investigator Brochure before the initiation of Study A2309, but proved not to be enough to prevent the safety imbalance between the two regimens under strictly controlled trial conditions. I do not see any possible means to mitigate these risks associated with the everolimus regimen other than those already attempted in Study A2309.

In addition, everolimus and cyclosporine interact with each other such that an adjustment to the dose of one may require an adjustment to the other and the effect of the dose adjustment of everolimus on trough concentrations cannot be assessed before a minimum of five days due to the long plasma half-life. In clinical practice it may be difficult to manage two drugs requiring TDM (Therapeutic Drug Monitoring)

simultaneously which may increase the likelihood of concentration-associated adverse reactions even further.

In my opinion, the Applicant did not demonstrate an efficacy benefit, or any other type of benefit, of the proposed everolimus regimen over the control regimen or over other approved therapies, which might have counterbalanced the safety problems associated with the use of everolimus.

However upon review of the current submission, the Division of Special Pathogen and Transplant Products (DSPTP) is recommending approval. Despite my recommendation of non-approval, I have continued to work with the team to finalize the REMS and package insert, as discussed below.

The following discussions and recommendations about REMS and labeling reflect the Division's point of view and do not necessarily reflect the Clinical Reviewer's opinion or recommendations.

III- Complete Response Letter from the FDA issued on December 23, 2009

Applicant received a CR letter from FDA on December 23, 2009 which included the following deficiencies:

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Zortress (everolimus) to ensure that the benefits of the drug outweigh the risks of wound healing complications, hyperlipidemia, proteinuria, and graft thromboses, as well as nephrotoxicity when co-administered with standard doses of cyclosporine. The REMS, once approved, will create enforceable obligations.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Zortress (everolimus) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Zortress (everolimus). FDA has determined that Zortress (everolimus) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which

patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Zortress (everolimus).

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed everolimus.

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe Zortress (everolimus) will support implementation of the elements of your REMS and should be implemented at the time of product launch. The communication plan must provide for the dissemination of information about wound healing complications, hyperlipidemia, proteinuria, and nephrotoxicity when co-administered with standard doses of cyclosporine, and graft thromboses. The communication plan must include, at minimum, the following:

- Dear Healthcare Professional Letter
- Dear Pharmacist Letter
- Dear Professional Association Letter

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Include additional information in the template that is specific to your proposed REMS for Zortress (everolimus). Additionally, all relevant proposed REMS materials including communication materials should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include:

- a. An evaluation of patients' understanding of the serious risks of Zortress (everolimus)

- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 021560
PROPOSED REMS**

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 021560
PROPOSED REMS-AMENDMENT**

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

LABELING

Please submit draft labeling in the physician labeling rule (PLR) format that includes the revisions proposed in the Zortress (everolimus) draft package insert attached as Appendix C to this letter.

Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

In addition, please update the information in the proposed Medication Guide to reflect the information summarized in the package insert.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

IV - Recommendations for REMS

As noted in the CR letter above, the Division required the submission of a REMS, including a Medication Guide and Communication Plan, in order to ensure that the benefits of the drug outweigh the risks. The Division believed that the following risks could be mitigated by the REMS: graft thrombosis, wound healing complications, hyperlipidemia, proteinuria, and nephrotoxicity when co-administered with standard doses of cyclosporine. It was decided by the Division that Elements To Assure Safe Use (ETASU) was not required as a part of the REMS.

The following is the final REMS document, which includes the goals, elements, and time table of assessments.

GOALS

The goals of the ZORTRESS REMS are:

- 1) To inform healthcare providers about the following serious risks associated with ZORTRESS: wound-healing complications, hyperlipidemia, proteinuria, graft thrombosis, as well as nephrotoxicity when ZORTRESS is co-administered with standard doses of cyclosporine.
- 2) To inform patients about the serious risks associated with ZORTRESS.

REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed as part of the Package Insert with each prescription for ZORTRESS. The product is supplied as 0.25 mg, 0.5 mg, and 0.75 mg tablets. Each strength is available in boxes of 60 (6 blister strips of 10 tablets each), approximately a one-month supply of ZORTRESS per box. One copy of the ZORTRESS Medication Guide will be enclosed in each box of ZORTRESS. The Medication Guide will be available for distribution to patients with each prescription that is dispensed. A reminder to pharmacists to provide the Medication Guide each time ZORTRESS is dispensed will be printed on each box.

In compliance with 21 Code of Federal Regulation (CFR) 208.24, the Sponsor will institute the following measures:

- * The Medication Guide will be enclosed in all ZORTRESS packaging.

1 Page(s) has been withheld in full immediately following this page as duplicative – see the final REMS document

E. Timetable for Assessments

Novartis will submit REMS Assessments to the FDA by 18 months, by 3 years, and in the 7th year from the date of approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Novartis will submit each assessment so that it will be received by the FDA on or before the due date.

V - Recommendations for Postmarket Requirements and Commitments

The Division included submission of the 24 month results of Study A2309 as a postmarketing requirement.

Clinical Reviewer's Comment: *In the Clinical Reviewer's opinion, the safety information available at 24 months in this study will be limited. At 24 months it is expected that there will be more study drug discontinuations and drop outs in both of the everolimus arms compared to the control arm since this was the observation with 12 month study results. As stated in the original clinical review, this relatively higher rate of study drug discontinuations and drop outs in the everolimus arms will probably continue to favor the everolimus arms since adverse events are reported for only up to 7 days and serious adverse events are only reported up to 30 days after discontinuing the study drug per protocol.*

VI – Package Insert

The following is based upon a comparison between the applicant's original proposed PI submitted on June 30, 2009 and the final text.

(b) (4)

[Redacted]

[Redacted]

4 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

(b) (4)

VII - Medication Guide

The DSPTP review team worked with the Patient Labeling reviewers of DRISK to finalize the Medication Guide. The final Medication Guide focused on the five risks of everolimus, which were the subject of the REMS.

The following is the first section of the agreed upon Medication Guide, which discusses the risks in the Boxed Warning, including that reduced doses of CsA are needed in order to reduce the risk of nephrotoxicity, as noted in the REMS.

What is the most important information I should know about ZORTRESS?

ZORTRESS can cause serious side effects, including:

- **Increased risk of getting certain cancers.** People who take ZORTRESS have a higher chance of getting lymphoma and other cancers, especially skin cancer. Talk to your doctor about your risk for cancer.
- **Increased risk of serious infections.** ZORTRESS weakens the body's immune system and affects your ability to fight infections. Serious infections can happen with ZORTRESS that may lead to death. People taking ZORTRESS have a higher chance of getting infections caused by viruses, bacteria, and fungi (yeast).
 - Call your doctor if you have symptoms of infection including fever or chills.
- **Serious problems with your transplanted kidney (nephrotoxicity).** You will need to start with a lower dose of cyclosporine.
- **Blood clot in the blood vessels of your transplanted kidney.** If this happens, it usually occurs within the first 30 days after your kidney transplant. Tell your doctor right away if you:

1 Page(s) has been withheld in full immediately following this page as duplicative – see the final Medication Guide

VII - Revised Clinical Review

Attached is the 12/18/09 Clinical Review (DARRTS date of 12/23/09) which has been revised to include minor clarifications and corrections.

Also, below is some additional clarification regarding regulatory terminology used in the Clinical Review.

Clinical Reviewer's Note:

The following information is necessary for the general audience to understand the Regulatory Background.

Approval letter means a written communication to an applicant from FDA approving a New Drug Application (NDA), Biologic License Application (BLA) or an abbreviated application (ANDA). (ref. 314.3)

Approvable Letter means a written communication to an applicant from FDA stating that the agency will approve the application or abbreviated application if specific additional information or material is submitted or specific conditions are met. An *Approvable Letter* does not constitute approval of any part of an application or abbreviated application and does not permit marketing of the drug that is the subject of the application or abbreviated application. (ref. 314.3)

Beginning August 11, 2008, FDA discontinued issuing *Approvable* and *Not Approvable* letters, regardless of when the application was submitted. The terms *Approvable* and *Not Approvable* letters were both consolidated under one term, ***Complete Response*** letters. This new policy was implemented with the rationale that a *Complete Response* letter provided a more consistent and neutral mechanism to convey that FDA's initial review of an application is complete and FDA cannot approve the application in its present form. Complete response letters are only issued for applications that are not approved.

The adoption of Complete Response letters is one of the Agency's commitments under the Prescription Drug User Fee Act (PDUFA).

- **At present there are two types of FDA Actions:**
 - Approval (AP)
 - Complete Response (CR) = Not Approved (NA). CR is the new term which has replaced the old terminology of both *Approvable* and *Not Approvable* and covers them both.

Caution: An Applicant's response to an FDA issued CR letter is also referred to as Complete Response (CR) if it is submitted to fully address the FDA cited deficiencies.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21-560
Priority or Standard	Resubmission
Submit Date(s)	June 30, 2009
Received Date(s)	July 2, 2009
PDUFA Goal Date	December 30, 2009
Division / Office	DSPTP/OAP/OND/CDER
Reviewer Name(s)	Ergun Velidedeoglu
Review Completion Date	December 18, 2009
Revision date [minor editorial changes]	April 18, 2010
Established Name	Everolimus
(Proposed) Trade Name	Zortress*
Therapeutic Class	Immunosuppressant (M-TOR inhibitor)
Applicant	Novartis
Formulation(s)	Tablet
Dosing Regimen	Initial dose of 0.75 mg bid; then adjusted to a trough concentration of 3 to 8 ng/mL
Indication(s)	Prevention of allograft rejection
Intended Population(s)	Kidney transplant recipients

(b) (4)
The Applicant submitted the name Zortress on October 19, 2009,
which DMEPA found to be acceptable.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Everolimus is being developed for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant. Everolimus is to be administered in combination with basiliximab and concurrently with reduced doses of cyclosporine and corticosteroids.

To exert its activity everolimus (and other M-TOR inhibitors) needs to form a complex with a cytoplasmic binding protein, FKBP-12; this everolimus/FKBP-12 complex in turn is thought to bind to and disable Mammalian Target of Rapamycin (M-TOR). M-TOR is a protein kinase that controls cell growth, proliferation, and survival. On a cellular level everolimus inhibits growth factor-stimulated cell proliferation irrespective of the cell lineage or growth factor involved. The immunosuppressive activity of everolimus is explained by its ability to prevent IL-2/IL-15-stimulated T cell proliferation.

Sirolimus (Rapamune®) is another M-TOR inhibitor that was approved in 1999, also for the indication of prevention of kidney transplant rejection. Several M-TOR inhibitors, using a different dose and regimen than in kidney transplant, are also approved for use in renal cell carcinoma, including everolimus (Afinitor®).

The initial New Drug Application (NDA 21-560) for everolimus for the prophylaxis of organ rejection was submitted to the FDA on December 19, 2002 by the applicant, Novartis. The submission contained the results from two Phase 3 trials (Studies B201 and B251) in *de novo* renal transplant recipients and one study in *de novo* heart transplant recipients (Study B253). The regimen that was studied was fixed-dose everolimus (1.5 mg and 3.0 mg per day given in two divided doses) with standard dose CsA, which was compared to mycophenolate mofetil (MMF; CellCept®) also with standard dose CsA.

Efficacy of everolimus was demonstrated in Studies B201 and B251; however, interpretation of the results was complicated by the premature treatment discontinuations due to reduced graft function and higher serum creatinine concentrations seen in the everolimus groups compared to the MMF control groups. The 12 month analysis of GFR showed increased rate of renal impairment in both of the everolimus groups compared to the MMF control group in both studies.

Due to these observed renal toxicities, the applicant was given an Approvable letter on October 20, 2003. The applicant was asked to establish a safe and effective dosing regimen for everolimus and CsA that minimized renal function impairment while

maintaining efficacy, such as concentration-controlled regimens of everolimus and cyclosporine using therapeutic dose monitoring (TDM).

Data from two additional open-label, non-comparative kidney transplant trials (A2306 and A2307), along with some exposure-response analyses, were submitted to the NDA as a Complete Response by the applicant on February 27, 2004. Studies A2306 (without basiliximab) and A2307 (with basiliximab) were conducted, using concentration-controlled everolimus dosing (initial doses of 1.5 mg and 3.0 mg per day adjusted to trough concentrations above 3 ng/mL) and reduced-dose CsA. As these studies were designed to compare the 1.5 mg and 3.0 mg doses of everolimus and did not include an active control group, the analyses in the submission were based primarily on cross-study comparisons between A2306 and A2307 and studies in the original submission. FDA noted these and other limitations in the studies' design, therefore the applicant was issued a second Approvable letter on August 27, 2004 and asked to provide additional information to establish a safe and effective dosing regimen for everolimus and CsA.

Subsequently Novartis designed a new study of concentration-controlled everolimus with low dose CsA both adjusted using TDM in *de novo* kidney transplant recipients, and the protocol was discussed with FDA. Study A2309, which is the basis for this NDA resubmission, is a 24-month, multicenter, multinational, randomized, open-label, three-group trial that enrolled 833 *de novo* adult renal transplant recipients. The current submission contains data from the first 12-months of the study.

Patients were randomized to one of three groups: everolimus starting at either 1.5 or 3.0 mg per day combined with reduced dose CsA or mycophenolic acid (MPA; Myfortic®) 1.44 gm per day with standard dose CsA. The starting dose of everolimus in this study was the same as used in the initial studies B201 and B251. However, in this study everolimus doses were adjusted to achieve blood trough concentrations of 3 to 8 ng/mL (low dose group, starting at 1.5 mg/day) and 6 to 12 ng/mL (high dose group, starting at 3.0 mg/day) combined with reduced exposure to CsA, which was tapered over time. Both drug concentrations were guided by TDM. Dosing regimens and target trough concentrations for everolimus and CsA in Studies B201, B251, and the current A2309 are compared in the table below

Table 1. Dose and Target Concentrations for Everolimus and CsA across Studies

Study Treatment Group	Drug	Study B201	Study B251	Study A2309
Everolimus 1.5 mg/day group	Everolimus	0.75 mg bid	0.75 mg bid	Target trough 3-8 ng/mL
	CsA	Full Dose: 150 to 400 ng/mL (Weeks 1-4), 100 to 300 ng/mL (Months 2-12), 50 to 75 ng/mL (after Month 12)	Full Dose: 200 to 350 ng/mL (Weeks 1-4), 100 to 300 ng/mL (Months 2-12), 50 to 75 ng/mL (after Month 12)	Reduced Dose:* 100 to 200 ng/mL (until Month 2), 75 to 150 ng/mL (Months 2-4), 50 to 100 ng/mL (Months 4-6) and 25 to 50 ng/mL (after Month 6)
Everolimus 3.0 mg/day group	Everolimus	1.5 mg bid	1.5 mg bid	Target trough 6-12 ng/mL
	CsA	Full Dose – same as above	Full Dose – same as above	Reduced Dose:* same as above
Control group	MMF or MPA	MMF 1gm bid	MMF 1 mg	MPA 720 mg bid per day
	CsA	Full Dose – same as above	Full Dose – same as above	Standard:* 200 to 300 ng/mL (Month 1), 100 to 250 ng/mL (Month 2-12)

* Pages 113 and 5772 of 14,328 from Study Report RAD001A2309, submitted June 30, 2009.

The control regimen in studies B201 and B251 contained MMF (Mycophenolate Mofetil), while in this study it was MPA (Mycophenolic Acid) in conjunction with CsA. The dose of MPA was selected to provide the same molar dose as 1 gm of MMF (720 mg Myfortic is the molar equivalent of 1 gm MMF) and is the approved dose for use in combination with cyclosporine. All patients were given basiliximab as induction therapy and maintained on concomitant corticosteroids, which were dosed based on local practice.

In this NDA resubmission, the applicant is seeking approval only of the everolimus 1.5 mg per day regimen which is adjusted to target trough concentrations of 3 to 8 ng/mL. The everolimus 3.0 mg regimen was used primarily in the safety analysis to determine a dose-response for adverse events.

The efficacy results from Study A2309 showed that both everolimus treatment regimens were non-inferior to the Myfortic control regimen at 12 months with regard to the primary efficacy composite endpoint consisting of the first occurrence of treated BPAR (Biopsy Proven Acute Rejection), graft loss, death or loss to follow-up. In terms of GFR (Glomerular Filtration Rate), there were no statistically significant differences between any of the treatment groups at month 12.

The efficacy results from Study A2309 adequately address the deficiencies noted in the October 20, 2003 and August 27, 2004 everolimus Approvable letters but some safety issues still persist. The results of the safety analysis in Study A2309 showed that compared to the Myfortic control group, the everolimus 1.5 mg group had:

- Numerically more deaths with a causality association with everolimus treatment, as assessed by the Reviewer,
- Numerically more graft losses
- Three times as many graft thromboses which all resulted in graft losses
- Higher rates of study drug discontinuations with more being due to adverse events
- More patients with abnormally high lipid levels with a diminished response to statins
- Higher levels of proteinuria mainly driven by male patients
- Higher incidence of NODAT (New Onset Diabetes After Transplantation)
- More patients with wound problems with a higher proportion of these requiring surgical and non-surgical intervention for treatment
- More patients with peripheral edema and localized fluid collections
- More patients with mouth ulcerations
- More male patients with testosterone associated adverse events

The Myfortic control group had:

- More patients with Cytomegalovirus (CMV) and BK virus infections
- More patients with benign and malignant neoplasms (however, the only tumor-related death in Study A2309 was in the everolimus 1.5 mg group)
- More study drug dose adjustments and interruptions
- More tremor, hirsutism and gingival hyperplasia.

These safety differences are explained in more detail in Section 1.2 and other relevant sections of this review.

It is evident from the 12 month data from Study A2309 that there are imbalances between the safety profiles of the two regimens in favor of the Myfortic control arm. The Clinical Reviewer believes that these everolimus-related adverse effects will become more pronounced over time, as supported by the published literature on the use of other M-TOR inhibitors in transplant patients.

It is not unreasonable to expect that these adverse effects, especially those related to cardiovascular risk (hyperlipidemia, NODAT, proteinuria and thrombogenicity) will result in higher rates of mortality and other complications over the course of years. Cardiovascular events are the number one cause of long term mortality in kidney transplant patients and everolimus therapy is further de-optimizing the cardiovascular risk factors in this patient group.

Other adverse events like peripheral edema, mouth ulcerations and gonadal effects will further lower the quality of life in these patients who are already struggling with various issues related to chronic immunosuppression.

M-TOR inhibitors are known to be associated with proteinuria and hyperlipidemia, which are also seen with other immunosuppressants, but their severity and frequency increase with M-TOR inhibitors. In addition, M-TOR inhibitors cause other adverse effects related to their mechanism of action, like thromboembolic complications, wound healing problems, non-infectious pneumonitis, localized fluid collections, mouth ulcerations and gonadal dysfunction.

In the Clinical Reviewer's opinion, although Study A2309 succeeded in demonstrating non-inferior efficacy of the everolimus 1.5 mg regimen to the active comparator (Myfortic regimen), as measured by the composite end point, and also showed similar renal function at the end of 12 months, the magnitude and importance of the safety problems above pose serious risks for kidney transplant patients.

In addition, the Clinical Reviewer believes that the applicant has not demonstrated the role of everolimus in the treatment of kidney transplant patients. CNIs (Calcineurin inhibitors), mainly CsA and tacrolimus remain the backbone of immunosuppressive regimens despite attempts to reduce or eliminate them from the regimen, in an effort to prevent CNI-related toxicities, primarily nephrotoxicity. The current everolimus treatment regimen utilizes reduced doses of CsA; however, M-TOR class toxicities outweigh any advantages that may be gained from reducing exposure to CsA. Finally, everolimus may be considered an alternative to CNIs in the population of patients who fail or are intolerant of CNIs. However, the Reviewer believes this population is very small and there are other alternative therapies available.

Therefore, the Clinical Reviewer's recommendation is non-approval of the everolimus 1.5 mg regimen (adjusted to a target trough concentration of 3 to 8 ng/mL) in combination with reduced dose CsA for the indication of prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant.

1.2 Risk Benefit Assessment

In this risk/benefit analysis only the everolimus 1.5 mg group (targeted trough concentrations: 3-8 ng/mL) will be compared to the control (Myfortic) group since this is

the everolimus regimen which the indication is sought for by the Applicant. The everolimus 3.0 mg group (targeted trough concentrations of 6 to 12 ng/mL) will be mentioned where it is thought to be relevant such as pointing to an exposure-response association. It is important to remember that the targeted trough levels in both of the everolimus groups overlap so for safety purposes it may not be always possible and appropriate to completely differentiate them.

The efficacy results from Study A2309 showed that both everolimus treatment regimens were non-inferior to the Myfortic control regimen at 12 months with regard to the primary efficacy composite endpoint consisting of the first occurrence of treated BPAR, graft loss, death or loss to follow-up. The incidence rate of efficacy failure was 25.3% (70/277) in the everolimus 1.5 mg group and 24.2% (67/277) in the Myfortic group [95% CI of the difference (-6.1%, 8.3%)]. Based on the protocol defined and justified non-inferiority margin of 10%, and using the Hochberg's procedure to adjust for multiple comparisons, non-inferiority of everolimus 1.5 mg to Myfortic was demonstrated by the fact that the upper limits of the 95% confidence interval of the difference was less than the 10% non-inferiority margin

Both everolimus regimens were also demonstrated to be similar to the Myfortic regimen in the incidence of graft loss, death or loss to follow-up at 12 months (main secondary efficacy endpoint). Similar results were shown for the other secondary efficacy endpoints, including treated biopsy proven acute rejection (BPAR) at 12 months.

The calculated 12-month GFR, using the modification of diet in renal disease (MDRD) formula, was similar between both everolimus groups and the Myfortic group: 54.6 mL/min in the everolimus 1.5 mg group and 52.3 mL/min in the Myfortic group, using the using a Last Observation Carried Forward (LOCF) approach for missing data. Various sensitivity analyses, modeling and imputation methods for missing values resulted in similar results in 12-month GFR across treatment groups.

The difference in GFR of approximately 2 mL at 12 months, in favor of the everolimus 1.5 mg group which was not statistically significant, can be compared to a difference of 6 mL/min and 8 mL/min in Studies B201 and B251, respectively, with fixed dose everolimus 1.5 mg and standard dose CsA at 12 months, in favor of the MMF (control) groups.

There was a disproportionate rate of premature treatment discontinuation within the initial 12 months of Study A2309, driven by higher rates of adverse events in both everolimus groups compared to Myfortic which may bias the interpretation of the study safety and efficacy results. Premature treatment discontinuations occurred in 30% of patients in the everolimus 1.5 mg group compared to 21.7% in the Myfortic group.

The following is a discussion of the safety profile of everolimus from Study A2309.

1.2.1 Deaths:

A total of 23 patients died during the first 12 months of the study, 7 (2.5%) in the everolimus 1.5 mg group, 10 (3.6%) in the 3.0 mg everolimus group, and 6 (2.2%) in the Myfortic control group. The most common causes of death across the study groups were related to cardiac conditions and infections. The Reviewer evaluated the narratives and Case Report Forms (CRFs) for the patients who died in this study and, after excluding five deaths because of lack of any discernable association between the cause of death and the study medication, concluded a probable association between the other 18 deaths and the study medication as follows:

- 7 deaths in the 1.5 mg everolimus group
- 8 deaths in the 3.0 mg everolimus group
- 3 deaths in the Myfortic (control) group

According to this final assessment of study drug attributability of patient deaths there are more than twice as many deaths in both of the everolimus groups compared to the Myfortic group that shows a probable association with the study medication.

Although a direct comparison is not possible because of the differences in the study designs and treatment regimens, it may be relevant to mention that in both of the previous studies of fixed dose everolimus with standard dose CsA (Studies B201 and B251) there were numerically more deaths in both of the everolimus groups compared to the MMF control group.

1.2.2 Serious Adverse Events (SAEs):

SAEs in the following MedDRA System Organ Classes (SOCs) were reported at a higher rate in the everolimus 1.5 mg group compared to the Myfortic group:

- Blood and lymphatic system disorders, (4% vs. 2.9%)
- Gastrointestinal disorders (7.7% vs. 6.6%)
- General disorders and administration site conditions (5.5% vs. 4.4%)
- Injury, poisoning and procedural complications (14.2% vs. 11.7%)
- Investigations (8.4% vs. 8.1%)
- Metabolism and nutrition disorders (7.3% vs. 4.8%)
- Musculoskeletal and connective tissue disorders (1.8% vs. 0.4%)
- Nervous system disorders, psychiatric disorders (2.2% vs. 1.8%)
- Psychiatric disorders (1.1% vs. 0%)
- Reproductive system and breast disorders (1.1% vs. 0%)
- Respiratory, thoracic and mediastinal disorders (3.3% vs. 2.9%)
- Vascular disorders (9.5% vs. 7.3%)

SAEs in the following SOC were higher in the Myfortic group compared to the everolimus 1.5 mg group:

- Infections and infestations (25.3% vs.19.7%)
- Neoplasms (1.8% vs. 1.5%)
- Renal and urinary disorders (13.2% vs. 10.2%)

The higher incidence of renal and urinary disorders in the Myfortic group is mainly due to the higher number of cases with hydronephrosis and ureteric obstruction which are usually due to poor surgical technique. Also 5 patients who were reported to have toxic nephropathy or blood creatinine increase in the Myfortic group were concomitantly receiving sirolimus (another M-TOR inhibitor) in addition to the Myfortic study regimen.

Graft Losses and Graft Thromboses

Another M-TOR inhibitor, sirolimus, has a Boxed Warning regarding the increased incidence of hepatic artery thromboses in liver transplant patients, so this is a recognized class effect. The number of graft losses was 12 (4.3%) in the everolimus 1.5 mg group, 14 (5.0%) in the everolimus 3.0 mg group and 8 (2.9%) in the Myfortic group over the 12 month study period. One of the patients with renal vein thrombosis in the everolimus 1.5 mg group died later as a result of the events started by this complication (patient 0114-0001).

The Reviewer and the Applicant agreed on the assessment of the number of patients who developed graft thrombosis (artery and vein) and consequently lost their grafts:

- 6 graft thromboses (4 renal artery and 2 renal vein) in the everolimus 1.5 mg group
- 4 graft thromboses (4 renal artery) with another probable 5th patient again with renal artery thrombosis according to the narrative in the everolimus 3.0 mg group
- 2 graft thromboses (2 renal artery) in the Myfortic group.

In the everolimus 1.5 mg group the incidence of early graft thromboses (within 30 days of transplant) is 1.8% and we see the same trend in the everolimus 3.0 mg group with an incidence of 1.4% which are both above the national average¹ of 0.9% and in line with the well known thrombogenic effect of M-TOR inhibitors.

1.2.3 Discontinuations due to Adverse Events

Significantly more patients prematurely discontinued study medication due to adverse events in the everolimus group (18.1%) compared to the Myfortic group (9.4%) (P-value=0.004). This difference was primarily driven by significant differences between the female patients in the treatment groups.

1 Ojo AO, Hanson JA, Wolfe RA, et al. Dialysis modality and the risk of allograft thrombosis in adult renal transplant recipients. *Kidney Int.* 1999;55:1952-1960

1.2.4 Significant Adverse Events

Infections

Infections reported as AEs had a lower incidence in the everolimus 1.5 mg group compared to the Myfortic group (62% vs. 68%) which is mainly due to the more frequent CMV, BK virus and other herpes virus infections in the Myfortic group. When we look at the infections reported as SAEs the only notable differences between the two groups are 9 CMV infections and 4 herpes zoster infections in the Myfortic group vs. no CMV infection and 1 herpes zoster infection in the everolimus 1.5 mg group. All the CMV and herpes zoster infections reported as SAEs were successfully treated without any patient or graft losses.

There are no deaths due to infections in the Myfortic group whereas 2 deaths in the everolimus 1.5 mg group and 5 deaths in the everolimus 3.0 mg group are due to infections. Although numerically there were more infections in the Myfortic group the infections in the everolimus groups were more serious and contributed to some of the deaths.

Proteinuria

The median UP/UC ratios over the 12 months of the study in the safety on-treatment population, which was defined as the population of safety patients whose assessments were obtained on and after day 1 but no later than two days after the discontinuation of randomized study medication. The median ratios in the everolimus 1.5 mg group were consistently higher than those of Myfortic throughout the study including the Month 12 TEP², as shown as Month 13. The differences between the groups became significant starting at Month 6 onwards.

There is a difference of 210 mg/g between the everolimus 1.5 mg group and the Myfortic group in favor of the Myfortic group using the Month 12 TEP values and this difference is even higher for the male patients since higher levels of proteinuria in the everolimus 1.5 mg group is driven by the male patients. The biological mechanism for higher levels of proteinuria in males is not known. Therefore, the Reviewer believes there is an augmented risk for the male patients over female patients. The fact that the differences between the two treatment groups became significant starting Month 6 raises concerns that the gap may continue to widen in favor of the Myfortic group with longer follow-up and may be more severe for the male patients. Proteinuria is a known risk factor for cardiovascular disease, diabetes and may contribute to hyperlipidemia at high levels. It has also been shown to decrease patient and graft survival in kidney transplantation^{8,9}.

² TEP=treatment endpoint (imputation by LOCF)

Hypertriglyceridemia, diabetes and proteinuria (at the microalbuminuria level) are all components of the metabolic syndrome, which is linked to adverse patient and graft outcomes^{3,4} and they occur with higher incidence and severity in both of the everolimus treatment groups compared to the Myfortic group. It is not unreasonable to assume that this coexistence of hyperlipidemia, NODAT and proteinuria with higher severity or higher incidence compared to the control group will result in higher cardiovascular morbidity and mortality in this high cardiac risk population in the long term if not during shorter periods of follow-up like one year.

Hyperlipidemia

Hyperlipidemia was reported as an AE in 57 (20.8%) patients in the everolimus 1.5 mg group, 60 (21.6%) patients in the everolimus 3.0 mg group, and 43 (15.8%) patients in the Myfortic group.

All through the 12 month study period mean total cholesterol and triglyceride values were significantly higher in both of the everolimus groups compared to the Myfortic group. Generally, after the 9 month time point, the mean values of both total cholesterol and triglycerides came down to the normal range in the Myfortic group, whereas the mean values in both of the everolimus groups stayed above the upper limit of normal ranges. LDL values in the everolimus groups were also significantly higher in the everolimus groups compared to the Myfortic group. In the everolimus 1.5 mg group almost three times as many patients (16% vs. 6%) had total cholesterol levels above 350 mg/dL and almost twice as many patients (4.4% vs. 2.6%) had triglyceride values above 500 mg/dL compared to the Myfortic group.

Lipid lowering agents were taken by a higher percentage of patients in the everolimus treatment groups (64.6%, 72.3% and 57.5% of patients in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm treatment groups, respectively).

Among patients with high baseline cholesterol values before the statin treatment was initiated, 27.4% (17/62) in the everolimus 1.5 mg group compared to 13.9% (5/36) in the Myfortic group did not move down to the normal range despite the statin treatment. A similar trend was also observed for triglycerides in a similar analysis. Among patients with high baseline triglyceride values before the statin treatment was initiated, 49% (22/45) in the everolimus 1.5 mg group compared to 26% (5/19) in the Myfortic group did not move down to the normal range despite the statin treatment.

3 De Vries et al. Metabolic Syndrome Is Associated with Impaired Long-term Renal Allograft Function; Not All Component criteria Contribute Equally. American Journal of Transplantation 2004; 4: 1675–1683

4 Sharif. Metabolic Syndrome and Solid-Organ Transplantation. American Journal of Transplantation 2009; 9: 1–6

Usage of statins in the everolimus groups also resulted in significantly higher levels of CK (Creatine kinase) levels which may indicate excessive muscle tissue breakdown despite the mean levels stayed within the normal range.

A 39 year old male patient (0124-00076), whose death was attributed to acute myocardial infarction, developed severe dyslipidemia (hypercholesterolemia) after the transplant which gradually worsened until his death on Day 85. His total cholesterol increased from 147 mg/dL to 432 mg/dL and his LDL cholesterol increased from 81 mg/dL to 212 mg/dL (normal levels: up to 129 mg/dL) during the course of the study. Although this patient had a history of hypertensive heart disease the rapid rise of all lipid levels from normal range to very high values in a short period of time might have contributed to his death.

Hyperlipidemia is common in chronic kidney disease patients and the incidence increases after kidney transplantation. Various immunosuppressants, including CsA, corticosteroids, and M-TOR inhibitors, have been recognized as major contributors to dyslipidemia seen after transplantation. According to published research¹⁵ even mild elevations in cholesterol levels may double the risk of developing ischemic heart disease in kidney transplant recipients unlike the milder increase of risk in the general population and the associated increase in mortality affects the younger recipients more than the older recipients.

Wound Healing and Wound Fluid Collections

Incisional wound complications were more frequent in the two everolimus groups compared to the Myfortic group with the highest number occurring in the 3.0 mg group. In each of the Dehiscence, Hernia and Infection categories, more patients required surgical intervention (i.e., intraoperative repair or debridement/ drainage) in the everolimus groups compared to the Myfortic group. The total number of surgical interventions was 19 in the everolimus 1.5 mg group, 22 in the everolimus 3.0 mg group, and 9 in the Myfortic group.

Similar to the incidence of wound-related events, fluid collections (lymphoceles and seromas) were also more commonly reported in the everolimus groups compared to the Myfortic group

Fluid Accumulation, Including Peripheral Edema, Ascites, and Pleural Effusions

At Month 12 the incidence of edema related events were significantly higher in both everolimus groups than in the Myfortic group (55.5% and 54.7% versus 45.1%). Peripheral edema possibly contributed to the death of 1 patient in study 2309 who was in the everolimus 1.5 mg group. This patient (0516-00002) was treated with furosemide because of edema on day 102 and died on day 156 due to congestive heart failure.

MACE (Major Cardiac Adverse Events)

Although the overall incidence of MACE events are much higher in the everolimus 3.0 mg group compared to the other two groups in the study, everolimus 1.5 mg group and the Myfortic group look similar to each other except for the numerical increase in myocardial infarctions in the Myfortic group (2 vs 4). When those cases with myocardial infarctions are analyzed in the reviewer's assessment only one case, 39 year old male patient (0124-00076) in the everolimus 1.5 mg treatment group can be associated with the study medication (everolimus).

Hematologic Adverse Events including Thrombocytopenia

The overall incidence of hematologic AEs was 33.9% in the 1.5 mg group, 40.3% in the 3.0 mg group, and 40.7% in the Myfortic group. The higher incidence in the Myfortic group was mainly driven by the higher incidence of leucopenia. Leucopenia associated with mycophenolic-acid (MPA) is very common in clinical practice and is usually responsive to dose reductions or interruptions. Hematologic events reported as SAEs were reported in eleven patients in the everolimus 1.5 mg group, ten in the everolimus 3.0 mg group, and eight patients in the Myfortic group.

Thrombocytopenia contributed to one patient's death in the everolimus 3.0 mg group (patient 0549-0001).

TMA/TTP/HUS

Thrombotic microangiopathies [TMA (Thrombotic Microangiopathy), TTP (Thrombotic Thrombocytopenic Purpura) and HUS (Hemolytic Uremic Syndrome)] are rare events traditionally associated with calcineurin inhibitors (CNIs), like CsA, until the recent discovery that they are also associated with M-TOR immunosuppression and the combined usage of M-TOR inhibitors and CNIs may increase the incidence. In Study A2309 a total of 4 TMA cases (1 TMA, 1 TTP and 2 cases of HUS) were reported all in the everolimus 1.5 mg group. TTP reported in the everolimus 1.5 mg group also contributed to one graft loss (patient 0192-00002).

Non Infectious Pneumonitis, Including Alveolar Proteinosis

Non infectious pneumonitis, including alveolar proteinosis, is a class effect of M-TOR inhibitors. It is relatively rare but may have a fatal outcome, especially if it is not recognized or treated appropriately. The diagnosis must be considered in every patient who develops dyspnea especially if they are on an M-TOR inhibitor. Infectious pneumonia is also commonly superimposed. Treatment includes discontinuation of the M-TOR inhibitor and steroids.

A total of six patients were reported to have interstitial lung disease identified by the applicant. Two cases were in the everolimus 1.5 mg group, three in the everolimus 3.0 mg group, and one is in the Myfortic group. The patient reported to have interstitial lung disease in the Myfortic group had no record of lung related pathology in the narrative provided by the Applicant.

One patient developed alveolar proteinosis (0304-00016) in the everolimus 1.5 mg group following the initial 12 months of the study and died due to pneumonia and septic shock 60 days after the diagnosis of alveolar proteinosis.

Neoplasms

Neoplasms, benign and malignant combined, were reported at a lower incidence in the everolimus 1.5 mg group compared to the Myfortic group (9 patients compared to 16 patients, respectively) but the only malignancy related death in the study (malignant melanoma) was also reported in the everolimus 1.5 mg group and the only lymphoma in the study (PTLD) was observed in the everolimus 3.0 mg group.

New Onset Diabetes after Transplantation (NODAT)

Fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), which is part of the standard definition for NODAT¹⁵ by the ADA (American Diabetes Association) was not included as part of the screening criteria for NODAT in this study. Therefore, the Reviewer believes the resulting estimation of NODAT in all three study groups is lower than anticipated in a kidney transplant patient population. The incidence of NODAT was 9.1% in the everolimus 1.5 mg group, 12.2% in the everolimus 3.0 mg group, and 6.6% in the Myfortic group.

The reported incidence of NODAT among kidney transplant recipients with standard immunosuppression in the literature is around 30%¹⁶ though it may be higher depending on the type of CNi inhibitor utilized and in some publications it is reported to be as high as 50%. The numbers reported in Study A2309 are not compatible with the published literature. If the screening criteria had been more stringent (ADA recommended criteria) the incidences would be higher in all treatment groups with a possible increase of the difference between the everolimus group and the Myfortic group in favor of the Myfortic group.

Gastrointestinal Adverse Events

Gastrointestinal adverse events like nausea vomiting and diarrhea are commonly observed with MPA treatment. However, in the study gastrointestinal adverse events overall had a similar incidence in the everolimus 1.5 mg and the Myfortic groups (72% compared to 76%, respectively).

Gastrointestinal events reported as SAEs were more frequent and tended to be more severe, as described below, in the everolimus 1.5 mg group. The everolimus 3.0 mg group had the highest incidence of SAEs in the SOC of Gastrointestinal Disorders (28 patients) followed by the 1.5 mg group (21 patients) and the Myfortic group (18 patients), respectively.

Two cases of hemorrhagic esophagitis in the everolimus 1.5 mg group and one case of mesenteric vessel thrombosis in the everolimus 3.0 mg group were reported as SAEs, which may be associated with the ulcerative and thrombogenic class effects of M-TOR inhibitors.

Male Endocrine Effects

According to the study protocol sex hormones were measured at 9 months and there was no scheduled measurement for 12 Month time point. At 9 months patients in the everolimus 1.5 mg group displayed a lower mean testosterone level and higher mean LH and FSH levels when compared to the Myfortic group. The mean values for all three hormones were still within the normal ranges with FSH level in the everolimus 1.5 mg group being at the upper level of normal,. The difference between the testosterone levels across the two treatment groups at 9 months appeared to be caused by a decrease of testosterone levels in the everolimus 1.5 mg group throughout the 9 month period during which the testosterone levels in the Myfortic group stayed the same. Month 9 mean testosterone levels are still within the normal range in both groups despite the significant decrease in the everolimus 1.5 mg group.

The mean FSH levels in the everolimus 1.5 mg group increased and rose up to the upper limit of the normal range (11.1 ± 9 U/L) at 9 months which may be indicative of decreased testosterone production. Sperm counts were not performed as part of the protocol in Study A2309. However, oligospermia or azospermia, which is usually reversible, is reported in the literature for other M-TOR inhibitors and documented in the non-clinical studies for everolimus. The effect is partly due to the anti-proliferative effects of M-TOR inhibitors.

1.2.5 Other Concerns: Drug-Drug Interactions (DDI)

Both everolimus and CsA are metabolized through the CYP3A4 enzyme system in the liver. On the other hand, MPA is mainly metabolized through glucuronidation.

Therefore concomitant administration of CYP3A4 inducers or inhibitors like some beta blockers and antifungals may affect the blood concentrations of both the CsA and everolimus in a regimen that utilizes both of them whereas CYP3A4 inducers or inhibitors may affect the blood concentrations of only CsA in a CsA-MMF containing regimen.

DDI due to CYP3A4 interaction between CsA and everolimus is another concern. Co-administration of CsA with everolimus significantly increases the concentrations of everolimus. Therefore, if the dose of CsA is increased, everolimus toxicity is possible if everolimus concentrations are not carefully monitored and the dose of everolimus adjusted. On the other hand, there is no CYP3A4 interaction between MPA and CsA. In fact, there is a small effect of CsA on the enterohepatic circulation of MPA such that an increase in CsA exposure decreases MPA exposure and reduces the possibility of increased toxicity due to this interaction.

Another difficulty with the TDM (Therapeutic Drug Monitoring) of everolimus is the relatively long plasma half life which is around 30 hours in kidney transplant recipients.

At least 5 days need to elapse before a meaningful trough concentration can be obtained every time either the everolimus or the CsA dose is changed. For comparison the plasma half lives of CsA and mycophenolic acid (Myfortic) on average, are 8 hours and 16 hours respectively and mycophenolic acid does not require TDM.

1.2.6 Conclusion

The efficacy results from Study A2309 showed that both everolimus treatment regimens were non-inferior to the Myfortic control regimen at 12 months with regard to the primary efficacy composite endpoint consisting of the first occurrence of treated BPAR, graft loss, death or loss to follow-up. Although the incidence rate of death, graft loss and loss to follow-up was similar between both everolimus groups and Myfortic group, numerically these events were more frequent in the everolimus groups and displayed a clear association with everolimus treatment.

In terms of GFR, there were no statistically significant differences between any of the treatment groups at month 12.

However, there were significant safety findings in the everolimus 1.5 mg group compared to the Myfortic control group, specifically:

- Numerically increased mortality with more causality associations,
- Numerically increased graft losses with an increased incidence of graft thromboses one of which resulted in death.
- More hyperlipidemia
- More NODAT
- More proteinuria
- More wound healing problems with more patients requiring surgical or non-surgical interventions for treatment
- Interstitial lung disease which contributed to the death of one patient
- TMA/TTP/HUS one of which contributed to the graft loss in one patient
- Severe thrombocytopenia which contributed to the death of one patient in the everolimus 3.0 mg group. It is not known if this adverse effect is exposure dependent. Thrombocytopenia has been frequently associated with M-TOR inhibition in the literature. Although it may also be encountered with MPA treatment it is usually milder in nature.
- Adverse effects on the male gonadal function.
- More study drug discontinuations due to adverse events which may partly be due to the difficulty of managing the regimen.

Therefore, it is the Reviewer's opinion that the safety concerns with the everolimus 1.5 mg regimen outweigh the benefits of the regimen and probably will result in increased mortality, morbidity and lower quality of life both in the short and long term when compared to the comparator Myfortic regimen or other similar immunosuppressive

regimens currently being used. The higher morbidity and mortality associated with everolimus may become more noticeable in the long term since some of the associated risks like hyperlipidemia, NODAT and proteinuria continue to exert their effects over the course of the years and immunosuppression is a life long treatment unlike many other treatments.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Division required the submission of a Risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide and Communication Plan, in order to ensure that the benefits of the drug outweigh the risks. The Division believed that the following risks can be mitigated by the REMS: graft thrombosis, wound healing complications, hyperlipidemia, proteinuria, and nephrotoxicity when co-administered with standard doses of cyclosporine. It was decided that Elements To Assure Safe Use (ETASU) was not required as a part of the REMS.

1.4 Recommendations for Postmarket Requirements and Commitments

If approved, in the Clinical Reviewer's opinion, possible effects on short and long term cardiovascular morbidity and mortality, effects on the lens and effects on gonads should be studied; and the 24 month results of Study A2309 should be submitted for review.

2.0 Introduction and Regulatory Background

An NDA supporting the use of everolimus in combination with cyclosporine (Neoral®; cyclosporine, USP MODIFIED) for the prophylaxis of organ rejection in allogeneic kidney and heart transplant patients was submitted on December 19, 2002 (NDA 21-560). In the original submission the Applicant presented two Phase III *de novo* renal allograft trials (B201 and B251) for the kidney indication and one key *de novo* heart study (B253) for the heart indication. Although efficacy was demonstrated, an unacceptable safety profile was observed with the original everolimus fixed dose regimen and use of full dose CsA. An approvable letter dated October 20, 2003 was issued with the following deficiencies from letter:

1. Provide information supporting a safe and effective dosing regimen for everolimus and cyclosporine that would minimize renal function impairment while maintaining adequate protection against graft rejection, graft loss or death in *de novo* renal transplantation.
 - One approach would be to provide data from an adequate and well-controlled study or studies

concentration-controlled cyclosporine in *de novo* renal transplant recipients, which would support therapeutic drug monitoring (TDM) schemes for everolimus and cyclosporine.

2. Provide information supporting a safe and effective dosing regimen for everolimus and cyclosporine that would minimize renal toxicity while maintaining adequate protection against graft rejection, graft loss and death in *de novo* cardiac transplantation. In order to do this, we believe that it will be necessary for you to provide data from an adequate and well-controlled study or studies prospectively evaluating concentration-controlled regimens of everolimus in combination with concentration-controlled cyclosporine in *de novo* cardiac transplantation, which would support therapeutic drug monitoring (TDM) schemes for everolimus and cyclosporine.

On November 16, 2005 the Cardiovascular and Renal Drugs Advisory Committee met to discuss the use of everolimus for prophylaxis of rejection in heart transplantation.⁵ While the committee agreed that a fixed-dose regimen of everolimus with standard-dose CsA should not be used in heart transplant due to short-term and long-term loss of renal function, they also commented that additional data were needed to characterize the safety and efficacy of everolimus using TDM regimens to maintain everolimus concentrations while rapidly tapering CsA to minimize renal toxicity.

Study A2309 was designed as a 24-month study, but FDA agreed to accept 12-month results from the study and the NDA was resubmitted with this data on June 30, 2009.

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED] (b) (4)

[REDACTED]

⁵ <http://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4183M1.pdf>

[Redacted] (b) (4)

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2.1 Product Information

Everolimus combined with CsA, first received marketing authorization in *de novo* renal and *de novo* heart transplantation, in Mexico, on July 8, 2003. Everolimus, marketed as Certican®, is currently approved in 70 countries for the prophylaxis of organ rejection in adults receiving a renal or cardiac transplant and has not been withdrawn from marketing for safety or efficacy reasons in any country. (b) (4)

[Redacted]

On March 30, 2009, everolimus (Afinitor®), as monotherapy, received US marketing authorization for patients with advanced renal cell carcinoma after treatment failure with sunitinib or sorafenib.

As of March 31, 2009, the Applicant's estimated cumulative exposure to everolimus was:

- for *commercialized* everolimus (transplant indications): approximately 44,000 treatment-years
- for exposure in *clinical trials* (trials with at least 1 month planned exposure)
 - kidney transplantation: 4,807 patients
 - heart transplantation: 1,358 patients
 - liver transplantation: 455 patients
 - other transplant: 507 patients
 - autoimmune diseases, other indications: 378 patients
- for *clinical development* in oncology: approx. 4,915 advanced cancer patients.

2.2 Currently Available Treatments for Proposed Indications

The following products for use in kidney transplant recipients as induction, prevention, or treatment of acute rejection have been approved. The wording from the **Indications and Usage** sections of the package insert is provided below.

Induction

Basiliximab (Simulect®)

Simulect® is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplantation when used as part of an immunosuppressive regimen that includes cyclosporine, USP (MODIFIED) and corticosteroids.

The efficacy of Simulect® for the prophylaxis of acute rejection in recipients of other solid organ allografts has not been demonstrated.

Daclizumab (Zenapax®)

ZENAPAX is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplants. It is used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids.

The efficacy of ZENAPAX for the prophylaxis of acute rejection in recipients of other solid organ allografts has not been demonstrated.

Thymoglobulin® (rabbit-derived antithymocyte globulin), Campath® (alemtuzumab), Atgam® (anti-thymocyte globulin, Orthoclone OKT3® (muromomab-CD3)

Off-label use only for prophylaxis of rejection; all are indicated for the treatment of rejection (see below), except Campath® which is approved only for treatment of B-cell chronic lymphocytic leukemia (B-CLL).

Prevention of Rejection

Tacrolimus (Prograf® and generics)

Prograf is indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants. It is recommended that Prograf be used concomitantly with adrenal corticosteroids. Because of the risk of anaphylaxis, Prograf injection should be reserved for patients unable to take Prograf capsules orally. In heart and kidney transplant recipients, it is recommended that Prograf be used in conjunction with azathioprine or mycophenolate mofetil (MMF). The safety and efficacy of the use of Prograf with sirolimus has not been established

Cyclosporine A (Neoral® and generics)

Kidney, Liver, and Heart Transplantation

Neoral® is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Neoral® has been used in combination with azathioprine and corticosteroids.

Mycophenolic acid (Myfortic®)

Myfortic® (mycophenolic acid) delayed-release tablets are indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids.

Mycophenolate mofetil (CellCept® and generics)

Renal, Cardiac, and Hepatic Transplant

CellCept is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. CellCept should be used concomitantly with cyclosporine and corticosteroids. CellCept Intravenous is an alternative dosage form to CellCept capsules, tablets and oral suspension. CellCept Intravenous should be administered within 24 hours following transplantation. CellCept Intravenous can be administered for up to 14 days; patients should be switched to oral CellCept as soon as they can tolerate oral medication.

Sirolimus (Rapamune®)

Prophylaxis of Organ Rejection in Renal Transplantation

Rapamune (sirolimus) is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants. Therapeutic drug monitoring is recommended for all patients receiving Rapamune.

In patients at low- to moderate-immunologic risk, it is recommended that Rapamune be used initially in a regimen with cyclosporine and corticosteroids; cyclosporine should be withdrawn 2 to 4 months after transplantation.

In patients at high-immunologic risk (defined as Black recipients and/or repeat renal transplant recipients who lost a previous allograft for immunologic reason and/or patients with high panel-reactive antibodies [PRA; peak PRA level > 80%]), it is recommended that Rapamune be used in combination with cyclosporine and corticosteroids for the first year following transplantation.

Azathioprine (Imuran® and generics)

IMURAN is indicated as an adjunct for the prevention of rejection in renal homotransplantation. It is also indicated for the management of active rheumatoid arthritis to reduce signs and symptoms. **Renal**

Homotransplantation: IMURAN is indicated as an adjunct for the prevention of rejection in renal homotransplantation. Experience with over 16,000 transplants shows a 5-year patient survival of 35% to 55%, but this is dependent on donor, match for HLA antigens, anti-donor or anti-B-cell alloantigen antibody, and other variables. The effect of IMURAN on these variables has not been tested in controlled trials.

Corticosteroids

No specific labeling regarding use in transplantation

Treatment of Rejection

Lymphocyte immune globulin, anti-thymocyte globulin [equine] sterile solution (Atgam®)

Renal Transplantation

ATGAM Sterile Solution is indicated for the management of allograft rejection in renal transplant patients. When administered with conventional therapy at the time of rejection, it increases the frequency of resolution of the acute rejection episode. The drug has also been administered as an adjunct to other immunosuppressive therapy to delay the onset of the first rejection episode. Data accumulated to date have not consistently demonstrated improvement in functional graft survival associated with therapy to delay the onset of the first rejection episode.

Muromonab-CD3 (Orthoclone OKT®3) Sterile Solution – murine monoclonal antibody

ORTHOCLONE OKT3 is indicated for the treatment of acute allograft rejection in renal transplant patients.

ORTHOCLONE OKT3 is indicated for the treatment of steroid-resistant acute allograft rejection in cardiac and hepatic transplant patients.

The dosage of other immunosuppressive agents used in conjunction with ORTHOCLONE OKT3 should be reduced to the lowest level compatible with an effective therapeutic response.

Anti-Thymocyte Globulin (Rabbit) (Thymoglobulin®)

Thymoglobulin is indicated for the treatment of renal transplant acute rejection in conjunction with concomitant immunosuppression.

2.3 Availability of Proposed Active Ingredient in the United States

Afinitor® (everolimus) NDA 22-334 (stamp date: June 30, 2008) was recently approved by the FDA on March 30, 2009 for the treatment of patients with advanced renal cell carcinoma.

2.4 Important Safety Issues with Consideration to Related Drugs

The first drug to be approved in the M-TOR inhibitor class of immunosuppressants for the indication of prevention of rejection in renal transplant patients was sirolimus (Rapamune®, NDA 21-083), oral solution, in September, 1999. Later, a 1 mg tablet (in August 2001) and a 2 mg tablet (August 2002) were approved under NDA 21-110.

The initial safety profile of sirolimus in the original NDA was characterized by reductions in platelet, white blood cell, and hemoglobin counts; and in elevation of fasting triglycerides, cholesterol and lactate dehydrogenase (LDH) concentrations. Therapeutic drug concentration monitoring (TDM) was not used in the clinical trials leading to approval and no specific recommendations was made about the TDM at the time. New-onset hypercholesterolemia required treatment in a significant proportion of patients treated with sirolimus. No excess in cardiovascular adverse events were reported in the initial 12 months follow-up of patients treated in the phase 3 studies, but it was thought there was insufficient follow-up to evaluate the long term consequences of toxicity. In pivotal trials seventeen patients (all in the sirolimus treatment groups) had non-fatal life threatening adverse events during the first 12 months post-transplant: severe pneumonia (due to opportunistic infections such as *Pneumocystis jiroveci*, tuberculosis, and coccidioidomycosis), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS).

Hyperlipidemia

In the Phase 3 trials of renal transplant patients, increased serum cholesterol and triglycerides were significantly more frequent in patients on Rapamune (sirolimus) than azathioprine (AZA) or placebo control, and significantly more patients on Rapamune required lipid-lowering agents (42-52%) than patients on AZA (22%) or placebo (16%). Information about these findings was summarized in the WARNINGS and PRECAUTIONS sections of the Rapamune labeling to incorporate the following:

Increased serum cholesterol and triglycerides that may require treatment occurred more frequently in patients treated with Rapamune compared to azathioprine or placebo controls (see PRECAUTIONS).

Renal Effects

In the Phase 3 trials of renal transplant patients in the original NDA submission, elevated serum creatinine and decreased glomerular filtration rate (GRF) was more frequent in the Rapamune group than the AZA or placebo groups, and the information was included in the WARNINGS and CLINICAL Studies sections of the package insert.

These studies compared two dose levels of Rapamune oral solution (2 mg and 5 mg, once daily) with AZA (Study 1) or placebo (Study 2) when administered in combination with CsA and corticosteroids (Table 2).

Table 2. Overall Calculated GFR (Mean±SEM, cc/min) Post-Transplant

Parameter	Rapamune® 2 mg/day (n=233)	Rapamune® 5 mg/day (n=226)	Azathioprine 2-3 mg/kg/day (n=127)	Placebo
Study 1				
Mean (SE)	57.4 (1.28)	55.1 (1.28)	65.9 (1.69)	

Study 2	(n=190)	(n=175)	(n=101)
Mean (SE)	54.9 (1.26)	52.9 (1.46)	61.7 (1.81)

*Adapted from the Rapamune package insert, September 1999, GRF calculated using Nankivell Equation

Hepatic Artery Thrombosis in Liver Transplantation

In two multicenter, randomized controlled studies in *de novo* liver transplant recipients, the use of sirolimus in combination with cyclosporine or tacrolimus was associated with an increase in hepatic artery thrombosis. Enrollment was suspended in a Phase 2 clinical study comparing sirolimus in combination with tacrolimus/corticosteroids to tacrolimus/corticosteroids alone in *de novo* liver transplant patients. This action was prompted by an imbalance in the observed rates of hepatic artery thrombosis with a rate of 5.5% (6/110) in the sirolimus-tacrolimus treatment group, all of which occurred within 16 days post-liver transplantation, compared to 0.9% (1/112) in the tacrolimus-treated control group.

(b) (4)

(b) (4)

Interstitial Lung Disease

(b) (4)

Some of the cases were fatal. Also in some of the cases, interstitial lung disease resolved upon discontinuation or dose reduction of sirolimus. The risk is thought to be increased with higher sirolimus trough concentrations.

Abnormal Healing

In addition, the reports of abnormal healing following transplant surgery have been added, including fascial dehiscence and anastomotic disruption (e.g. wound, vascular, airway, ureteral, biliary).

Dehiscence in Lung Transplantation

(b) (4)



(b) (4)



(b) (4)



(b) (4)



6 Airway Anastomotic Dehiscence Associated with Use of Sirolimus Immediately after Lung Transplantation. King-Biggs M, Dunitz JM, Park SJ, et al. Transplantation. 2003 (75): 1437-1443.

- [Redacted] (b) (4)

[Redacted] (b) (4)

The new information was obtained from a conversion study in which stable patients were randomized to conversion from a calcineurin inhibitor (CNI)-based regimen to a sirolimus-based regimen or continuation of the CNI. The data showed an increased urinary protein excretion observed from 6 months through 24 months in the group converted to sirolimus. Patients with the greatest amount of urinary protein excretion prior to sirolimus conversion were also those whose protein excretion increased the most after conversion. New onset nephrotic syndrome was also reported as a treatment emergent adverse event in 2.2% of the sirolimus conversion group in comparison to 0.4% in the CNI continuation group of patients. Nephrotic range proteinuria, defined as urinary protein to creatinine ratio > 3.5 was reported in 9.2% in the sirolimus conversion group of patients in comparison to 3.7% in the CNI continuation group of patients. In some patients, reduction in the degree of urinary protein excretion was observed following the discontinuation of sirolimus. In this study, enrollment in patients with baseline calculated GFR less than 40 mL/min was discontinued due to higher rate of serious adverse events, including pneumonia, acute rejection, graft loss and death.

Angioedema

[Redacted] (b) (4)

[Redacted] new subsection was created to provide information on the association of sirolimus with the development of angioedema and that the concomitant use of sirolimus with other drugs known to cause angioedema, such as ACE-inhibitors, may increase this risk.

Fluid Accumulation and Wound Healing

[Redacted] (b) (4)

[Redacted]

[Redacted]

[Redacted]

(b) (4)

Male Hypogonadism and Azospermia:

In the foreign labels of everolimus (Certican) male hypogonadism is mentioned as an adverse reaction associated with everolimus. There are also published articles about the adverse effects of M-TOR inhibitors on male gonads.

According to the 2007 data reported by OPTN (Organ Procurement and Transplant Network), 4.8% of the kidney transplant recipients are on a immunosuppressant regimen containing at the time of discharge from the hospital after the transplantation.⁷

This number might have further decreased since 2007 (this data is not published yet) since the percentage of kidney transplant patients who have been discharged from the hospital on a sirolimus containing regimen have constantly declined since 2001, which was the peak level of usage (17.2%) achieved after FDA approval in 1999.

In summary, information on the adverse reactions associated with the use of sirolimus, the first approved drug in the M-TOR class has been evolving since its approval, based on the data obtained from additional studies in renal, hepatic, lung transplantation and from post-marketing reports.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The protocol for Study A2309 was discussed with the applicant and comments were sent regarding the study design (IND 52-003; FDA comments on A2309 concept sheet, December 3, 2004 and FDA comments on A2309 protocol design, April 14, 2005).

In designing the protocol for Study A2309, the Applicant also followed the EMEA guidance on the use of combination therapy in transplantation [CHMP, EMEA Guideline on Clinical Investigation of Immunosuppressants for Solid Organ Transplantation 24-July-2008].

In addition to the 12 month results from Study A2309, the Applicant agreed to submit the following additional data in the NDA resubmission:

- a safety update that provides a side-by-side presentation of the new data and the data submitted in the original NDA (i.e., Studies B201 and B251)
- a PK/PD analysis of exposure–response relationships from Study A2309
- an update of foreign marketing history and labeling

⁷ http://optn.transplant.hrsa.gov/ar2008/data_tables.htm

The Applicant also agreed to cross-reference documents already reviewed in the everolimus renal and heart transplantation NDAs (21-560 and 21-628).

2.6 Other Relevant Background Information

None.

3.0 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

DSI Inspections were not performed, since this is not an NME (approved recently as Affinitor).

3.2 Compliance with Good Clinical Practices

The study and any amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each center. The study was conducted according to the ethical principles of the Declaration of Helsinki and US Code of Federal Regulations 21 CFR part 50 and 51. Informed consent was obtained from each subject in writing before randomization.

3.3 Financial Disclosures

OMB Form 0910-0396 was submitted and reviewed. The applicant obtained certification from each investigator and sub-investigator who enrolled subjects in Study A2309. No investigator had any disclosable information to reveal.

4.0 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to CMC Review by Mark R. Seggel, PhD (final December 22, 2009)

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. However, labeling issues are still pending as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the labeling issues are resolved.

4.2 Clinical Microbiology/Immunology

Please refer to Microbiology/Immunology Review by Simone M. Shurland, PhD (11/24/2009)

Everolimus is a chemical derivative of the macrolide, rapamycin (a macrolide produced by *Streptomyces hygroscopicus*). The main structural difference between everolimus and rapamycin is that the hydrogen of the 40-hydroxyl group in rapamycin was replaced with a 2-hydroxyethyl group, thus forming an ether bond [40-O-(2-hydroxyethyl)-rapamycin]. The ether bond is metabolically stable, that is everolimus is not converted to rapamycin.

Mechanism of Action

On a cellular level everolimus inhibits growth factor-stimulated cell proliferation irrespective of the cell lineage or growth factor involved. This inhibition is reversible, that is, everolimus is not a cytotoxic compound. On a molecular level, growth factor-stimulated phosphorylation of p70 S6 ribosomal protein kinase (p70S6K) is inhibited in the presence of everolimus. To exert its activity everolimus needs to form a complex with a cytoplasmic binding protein, FKBP-12; this everolimus/FKBP-12 complex in turn is thought to bind to and disable mTOR. p70S6K is a key translational regulator which controls protein synthesis, in particular that of pivotal proteins involved in cell growth and cell cycle regulation. p70S6K is a downstream effector of mTOR, it gets activated by mTOR-catalyzed phosphorylation. Inhibiting the activation of p70S6K by interfering with mTOR eventually results in cell cycle arrest and inhibition of cell proliferation.

The immunosuppressive activity of everolimus is explained by its ability to prevent IL-2/IL-15-stimulated T cell proliferation. Antigen-induced activation of an antigen-specific T cell, reflected by the production of cytokines/interleukins (i.e. IL-2), and subsequent proliferation of the activated T cell (i.e. clonal-expansion) are the hallmark features of a T cell immune-response. Immunosuppressive treatment strategies are therefore aimed at prevention of T cell activation and/or proliferation. While cyclosporine or tacrolimus prevent the first step, the activation of T cells, everolimus inhibits the interleukin-driven clonal expansion of activated T cells by inhibiting mTOR function. The different modes of action for everolimus and cyclosporine provide an adequate rationale for the pharmacodynamic synergy which has been demonstrated in vitro and in animal models of allotransplantation.

Some of the Comments from the Review:

The applicant stated that everolimus prolongs lung allograft survival in rats and nonhuman primates, as well as heterotopic heart transplants in rats. Studies in rats and primates showed that everolimus did not appear to have a significant effect at prolonging lung transplants; severe rejection by day 14 and 21 post-lung allograft was reported which was similar to that of vehicle control animals.

Only one experiment was conducted to measure the activity of everolimus in the heterotopic heart transplant model; the range of survival in everolimus treated animals was higher (12 to 33 days) than vehicle treated animals (6 to 8 days). However, testing is limited to one experiment and efficacy in clinical trials was not demonstrated. (b) (4)

The applicant claims that everolimus is able to reverse ongoing allograft rejection as was shown in the rat unilateral lung allotransplantation. The study referenced showed that everolimus followed by the administration of CsA 6 hours later were effective in improving lung graft survival. Treatment with everolimus and Neoral was initiated at the time of surgery. However, there were no studies in rats that showed that everolimus was able to reverse ongoing allograft rejection after unilateral lung allotransplantation. (b) (4)

4.3 Preclinical Pharmacology/Toxicology

See Pharmacology Toxicology Review by Steve Kunder, PhD (10/20/03; original NDA submission):

Animal reproductive toxicology studies showed effects in rats and rabbits. In a 13-week fertility study in male rats, testicular morphology was altered at a dose of 0.5 mg/kg/day (providing a systemic exposure approximately 0.2x that of the maximum clinical dose). Marked effects on male fertility occurred at 5.0 mg/kg (providing a systemic exposure approximately 1.0x that of the maximum clinical dose) including inability to impregnate females as well as testicular atrophy, oligospermia, aspermia and vacuolation of duct epithelium of the epididymides. Sperm motility, testicular sperm head count and plasma testosterone levels were reduced.

Pregnancy Category C

In the reproductive toxicity studies in female rats, everolimus crossed the placenta. At all doses, toxicity to fetus was observed. Increased pre- and post implantation losses and an increased incidence in skeletal retardations occurred at all doses. *An increase in the incidence of spontaneously occurring malformations was seen at doses of 0.3 and 0.9 mg/kg (providing an exposure approximately 0.9 x that of the maximum clinical dose based exposure comparisons).*

Toxicities affected by immunosuppression included myocardial degeneration/myocarditis in monkeys and rats at 1.5 mg/kg (approximately 1.7-4.5x human exposure); this is likely related to viral infection emerging under immunosuppression. Other toxicities included reproductive organ toxicity in all species tested including testicular atrophy in monkeys at 0.3 mg/kg (0.9x human exposure)

Lung toxicity in mice at 1.5 mg/kg (15x human exposure) and rats at 0.5 mg/kg (0.1x human exposure); and toxicity to the eye as swelling and disruption of cortical fibers of the lens at a dose of 0.9 mg/kg in rats (0.4 x human exposure).

Some of the nonclinical safety issues relevant to clinical use from the review:
-Eye toxicity seen in rats (disruption of fibers in lens) may cause vision problems.
-Decreased male fertility may prevent males from impregnating partners after transplantation.

The preclinical safety profile of everolimus was assessed in mice, minipigs, monkeys and rabbits. The major target organs were male and female reproductive systems (testicular tubular degeneration, reduced sperm content in epididymides, and uterine atrophy) in several species: lungs (increased alveolar macrophages) in rats and mice; and eyes (lenticular anterior suture line opacities) in rats only. Minor kidney changes were seen in the rat (exacerbation of age-related lipofuscin in tubular epithelium, increases in hydronephrosis) and mouse (exacerbation of background lesions).

There was no indication of kidney toxicity in monkey or minipigs. Spontaneously occurring background disease (chronic myocarditis in rats, Coxsackie virus infection of plasma and heart in monkeys, coccidian infestation of the gastrointestinal tract in minipigs, skin lesions in mice and monkeys) appeared to be exacerbated by the treatment with everolimus. These findings were generally observed at systemic exposure levels within the range of therapeutic exposure or above, with the exception of the findings in rats, which occurred below the therapeutic exposure-due to a high tissue distribution.

Cyclosporine in combination with everolimus caused higher systemic exposure to everolimus and increased toxicity. There were no new target organs in the rat. Monkeys showed hemorrhage and arteritis in several organs.

Nonclinical safety issues relevant to clinical use

(As stated by Steve Kunder PhD.):

- **-Renal toxicity** is of prime importance, especially for renal transplantation. It is well characterized for calcineurin inhibitors.
- **-Pancreatic toxicity**, also well characterized for calcineurin inhibitors, potentially leading to post-transplantation diabetes mellitus.
- **-Reproductive toxicity/male fertility**, counter indicates Certican (review written in 2003) for pregnant women; however, organ transplantation is typically not conducted in pregnant women. Decreased male fertility may prevent males from impregnating partners after transplantation.

- **-Eye toxicity** seen in rats (disruption of fibers in lens) may cause vision problems.
- **-Hypercholesterolemia and hypertriglyceridemia**, seen in rats and monkeys, and typical of other immunosuppressant drugs used for organ transplantation, may be treated with current antihyperlipodemic therapies following transplantation.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Everolimus (40-O-(2-hydroxyethyl)-rapamycin) is a macrolide immunosuppressant and has a stable 2-hydroxyethyl chain substitution at position 40 on the sirolimus (rapamycin) as apparent from the chemical formula. It was developed to increase the oral bioavailability of sirolimus.

The mechanism of action of everolimus is similar to sirolimus. Everolimus, like sirolimus, binds to FKBP12 (FK506-binding protein), forming a complex that binds to mammalian target of rapamycin (M-TOR), a key regulatory kinase. The M-TOR protein is a serine-threonine kinase that is pivotal for a number of important processes such as cell growth and proliferation, cellular metabolism, autophagy, and angiogenesis. The FKBP12-everolimus-M-TOR complex dephosphorylates and inhibits p70S6 kinase which, when activated, stimulates the ribosomes for protein synthesis and cell-cycle progression. This blockade by everolimus inhibits:

- T cell activation and proliferation that occurs in response to antigenic and cytokine (IL-2 and IL-15) stimulation;
- IL-6 stimulated B cell activation, proliferation, and antibody production;
- Proliferation of non-immune cells like smooth muscle cells.

4.4.2 Pharmacodynamics

Not applicable

4.4.3 Pharmacokinetics

Please refer to Clinical Pharmacology Review conducted with the original NDA submission by Ike Lee, PhD. The following version is from the final label:

1 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

4.4.4 Pharmacokinetics/Pharmacodynamics

Please refer to Pharmacometrics Review by Kevin M. Krudys PhD (12/17/2009).

Potential relationships between blood trough levels of everolimus and various efficacy events were explored by the Applicant using the pooled data from both everolimus dose groups and are summarized in Table 3.

4.4.4.1 Exposure-Response for Efficacy

A whole blood trough concentration of 3 ng/mL was previously identified as the minimum target concentration to preserve efficacy in renal and heart transplantation from the exposure-response (ER) analyses from the renal transplantation studies B201 and B251, and heart transplantation study B253.

Both everolimus groups were pooled together (everolimus 1.5 mg group had target of 3-8 ng/mL and the everolimus 3.0 mg group had a target level of 6-12 ng/mL). The

efficacy results from Study A2309 were used to evaluate the robustness of this trough concentration of 3 ng/mL, as shown in Table 3. Consistent with the defined everolimus target ranges, a low number of patients had exposure lower than 3 ng/mL or higher than 12 ng/mL. The frequency of treated BPAR becomes progressively lower as everolimus trough concentrations increase. The risk of graft loss was higher at everolimus trough concentrations less than 3 ng/mL (11.4%) than between 3 and 8 ng/mL (3.7%). Above a minimum everolimus level of 3 ng/mL rates of treated BPAR are all numerically reduced compared to that with Myfortic. However, the risk of death was the highest (5.0%) at everolimus trough concentrations above 8 ng/mL, the upper limit of the sponsor proposed target therapeutic range. These results therefore support the 3 to 8 ng/mL target range for everolimus trough concentrations with regard to efficacy. Within these ranges BPAR, graft loss and death rates are comparable to those occurring with Myfortic.

Table 3. Association between Everolimus Target Trough levels and Efficacy

(Source: Pharmacometrics Review by Kevin Krudys Ph.D)

Everolimus trough levels	Treated BPAR	Graft Loss	Death
< 3 ng/mL	6/33 (18.2%)	4/35 (11.4%)	1/37 (2.7%)
3 – 8 ng/mL	64/415 (15.4%)	15/410 (3.7%)	9/411 (2.2%)
> 8 ng/mL	9/99 (9.1%)	3/101 (3.0%)	5/101 (5.0%)
Myfortic	47/277 (17%)	9/277 (3.2%)	6/277 (2.2%)

4.4.4.2 Exposure-Response for Safety

The relationship between whole blood everolimus trough concentrations and selected safety events up to 12 months post transplant in Study A3209 was established for the following:

- Proteinuria, defined as the urinary protein / urinary creatinine (UP/UC) ratio ≥ 0.3 g/g after Month 1

Reviewer's Comment: According to NKF (National Kidney Foundation) the cut-off value is (UP/UC) ratio ≥ 0.2 which is a lower cut-off value than as stated by the Applicant. Having a higher cut-off value may decrease the incidence of proteinuria in all of the treatment groups simultaneously but also the differences in-between the groups also become smaller losing their significance.

- Wound healing complications/events based on the applicant's analysis of all the relevant preferred terms
- Peripheral edema adverse events
- Hypercholesterolemia, defined as total cholesterol ≥ 6.2 mmol/L, or ≥ 240 mg/dL
- Hypertriglyceridemia, defined as triglycerides ≥ 5.6 mmol/L, or 500 mg/dL

Reviewer's Comment: These events were selected because they are associated with the M-TOR inhibitor class of drugs (i.e., sirolimus), were identified as clinically relevant, and were observed at higher rates in the everolimus treatment groups compared to the Myfortic control treatment group in Study A2309.

Figure 1. Everolimus Trough Concentrations and Proteinuria
(Source: Pharmacometrics Review by Kevin Krudys Ph.D)

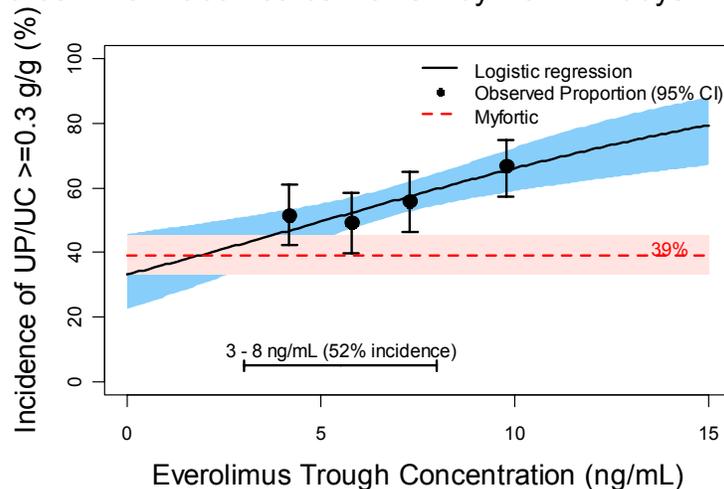
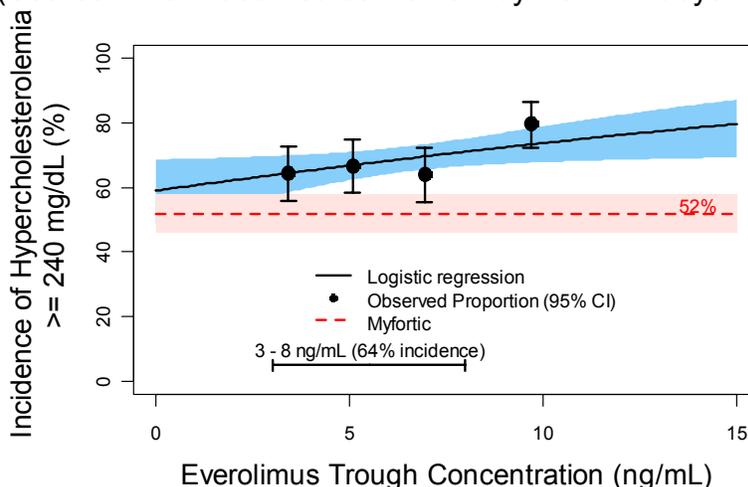


Figure 2. Everolimus Trough Concentrations and Hypercholesterolemia.
 (Source: Pharmacometrics Review by Kevin Krudys Ph.D)



There was not a strong relationship between higher everolimus concentrations and the incidence of the following events:

- Peripheral edema adverse events
- Wound healing complications
- Hypertriglyceridemia (triglycerides >490 mg/dL)
- New onset diabetes mellitus

However, the incidence of these events was higher in everolimus treatment groups

The increased incidence rate of these safety events observed in the everolimus treatment groups suggests these events more closely correspond to everolimus exposure than CsA exposure because CsA whole blood trough concentrations were lower in the everolimus + CsA treatment groups than in the Myfortic + CsA. Time normalized everolimus concentrations calculated up to Month 12 post transplant or the occurrence of the event were used in the analysis.

Table 4. Everolimus Trough Concentrations are not Associated with Renal Function Impairment

(Source: Pharmacometrics Review by Kevin Krudys Ph.D)

Relationship between everolimus and cyclosporine trough concentrations and GFR < 30 mL/min/1.73m ²			
Everolimus trough levels	Cyclosporine trough 0-100 ng/mL	Cyclosporine trough 100-200 ng/mL	Cyclosporine trough >200 ng/mL
3 – 8 ng/mL	10/171 (5.8%)	35/183 (19.0%)	10/19 (52.6%)
> 8 ng/mL	1/34 (2.9%)	6/43 (14%)	7/15 (48.7%)

5.0 Sources of Clinical Data

ECTD submission: <\\Cdsesub1\evsprod\NDA021560\0010>

Current submission contained Study A2309 which will be the subject of this review. The sponsor submitted electronic datasets located at <\\Cdsesub1\evsprod\NDA021560\0010>.

Previously the sponsor conducted other studies B201 and B251 which will be utilized in the safety analysis. The sponsor also resubmitted the listing and analysis datasets for these studies as well.

5.1 Tables of Studies/Clinical Trials

Study A2309 and the previous studies B251 and B201, which used fixed dose everolimus and full dose CsA, are summarized in Table 5.

Table 5. Summary of main Phase III studies
 (Source: Clinical Overview section of CSR)

Study	Objective, Population	No.	Time	Treatments	Efficacy Endpoint
Key, new study A2309 (blood level control of everolimus, <i>reduced dose</i> CsA, steroids)					
[A2309]	efficacy / safety (renal, overall) of titrated everolimus with titrated reduced dose CsA versus Myfortic with titrated standard dose CsA (both with steroids and basiliximab induction) in <i>de novo</i> kidney recipients	833	12 mo + 12 mo	1.5 mg/d everolimus 3.0 mg/d everolimus (with reduced CsA) versus 1.44 g/d Myfortic (with standard CsA)	BPAR, GL, death, LTFU (6mo) BPAR, GL, death, LTFU (12 mo)
Studies in the NDA amendment (blood level control of everolimus, <i>reduced dose</i> CsA, steroids)					
A2306	efficacy / safety / tolerability of titrated everolimus with titrated reduced dose CsA (with steroids but no induction) in <i>de novo</i> kidney recipients	237	12 mo	1.5 mg/d everolimus 3.0 mg/d everolimus (with reduced CsA)	Renal function (6mo) BPAR, GL, death, LTFU (6mo) BPAR, GL, death, LTFU (12 mo)
A2307	efficacy / safety / tolerability of titrated everolimus with titrated reduced dose CsA (with steroids and basiliximab induction) in <i>de novo</i> kidney recipients	256	12 mo	1.5 mg/d everolimus 3.0 mg/d everolimus (with reduced CsA)	Renal function (6mo) BPAR, GL, death, LTFU (6mo) BPAR, GL, death, LTFU (12 mo)

Pivotal studies in the original NDA (fixed dose everolimus, <i>standard dose</i> CsA, steroids)					
B201	efficacy / safety of fixed dose everolimus with titrated standard dose CsA versus MMF with titrated standard dose CsA (both with steroids but no induction) in <i>de novo</i> kidney recipients	588	12 mo (double blind) + 24 mo	1.5 mg/d everolimus 3.0 mg/d everolimus (with standard CsA) versus 2 g/d MMF (with standard CsA)	BPAR, GL, death, LtFU (6mo) GL, death, LtFU (12 mo)
B251	efficacy / safety of fixed dose everolimus with titrated standard dose CsA versus MMF with titrated standard dose CsA (both with steroids but no induction) in <i>de novo</i> kidney recipients	583	12 mo (double blind) + 24 mo	1.5 mg/d everolimus 3.0 mg/d everolimus (with standard CsA) versus 2 g/d MMF (with standard CsA)	BPAR, GL, death, LtFU (6mo) GL, death, LtFU (12 mo)

MMF = mycophenolate mofetil, Myfortic® = enteric-coated mycophenolate sodium, CsA = cyclosporine A; basiliximab = interleukin-2 receptor antagonist, BPAR = biopsy-proven acute rejection, LtFU = loss to follow up, GL=graft loss

5.2 Review Strategy

The focus of this review is Study A2309 but safety information will be compared across the three studies (i.e., A2309, B201, and B251).

5.3 Discussion of Individual Studies/Clinical Trials

The original NDA submission contained the results from Studies B201 and B251 in *de novo* renal transplant recipients.

Both studies compared two fixed-dose regimens of everolimus, 1.5 mg per day and 3 mg per day given in two divided doses twice daily, to the approved dose of MMF 1g twice daily and standard CsA plus corticosteroid regimens. Induction therapy was not given in these trials. A total of 193 and 194 subjects were randomly assigned to the 1.5 mg total dose of everolimus, while an additional 194 and 198 subjects were assigned to the 3.0 mg total dose of everolimus, in studies B201 and B251, respectively. For a detailed discussion of these studies and the results, see the Statistical Review by Ruthanna Davi, MS filed with the original NDA.

Both studies were double-blind for the first 12 months following transplantation and were extended as open-label studies for an additional two years. The 12 month analysis of GFR showed increased rate of renal impairment in the everolimus groups compared to the MMF control group in both studies.

Efficacy of everolimus was demonstrated in Studies B201 and B251; however, interpretation of the results was complicated by the premature treatment discontinuations due to reduced graft function and higher serum creatinine concentrations seen in the everolimus groups compared to the MMF control groups.

Due to these observed renal toxicities, the NDA was not approved and the applicant was asked to establish a safe and effective dosing regimen for everolimus and CsA that minimizes renal function impairment while maintaining efficacy, such as concentration-controlled regimens of everolimus and cyclosporine using therapeutic dose monitoring (TDM).

GFR is considered to be an endpoint for safety because of its association with chronic allograft injury but GFR may also reversibly change due to acute factors like CsA induced afferent arteriole vasoconstriction.

The reason there was interest in this endpoint is because in the previous renal transplant studies, B201 and B251, which evaluated fixed doses of everolimus and full-dose CsA, renal function was worse in the everolimus groups compared to the MMF control group, as estimated by the Nankivell method. Therefore, the question was whether a regimen consisting of concentration-controlled everolimus and reduced-dose CsA would yield renal function similar to a regimen of Myfortic and CsA. The results of the statistical analysis to test if there was a difference in mean GFR between treatment groups in Study A2309 are shown in Table 20. The difference in GFR was approximately 2 mL at 12 months, in favor of everolimus, compared to a difference of 6 mL (B201) and 8 mL (B251) at 12 months, in favor of MMF. In the comparison of the 3.0 mg everolimus group compared to the MMF control group, the differences were 7 mL (B201) and 11 mL (B251) at 12 months, also in favor of MMF.

Data from two additional open-label, non-comparative kidney transplant trials (A2306 and A2307), along with some exposure-response analyses, were submitted to the NDA as a Complete Response by the applicant on February 27, 2004. Studies A2306 (without basiliximab) and A2307 (with basiliximab) were conducted, using concentration-controlled everolimus dosing (initial doses of 1.5 mg and 3.0 mg per day adjusted to trough concentrations above 3 ng/mL) and reduced-dose CsA. As these studies were designed to compare the 1.5 mg and 3.0 mg doses of everolimus and did not include an active control group, the analyses in the submission were based primarily on cross-study comparisons between A2306 and A2307 and studies in the original submission. FDA noted these and other limitations in the studies' design, therefore the applicant was asked to provide additional information to establish a safe and effective dosing regimen for everolimus and CsA.

Subsequently Novartis designed a new study of concentration-controlled everolimus with low dose CsA both adjusted using TDM in *de novo* kidney transplant recipients, and the protocol was discussed with FDA. Study A2309, which is the basis for this NDA resubmission, is a 24-month, multicenter, randomized, open-label, three-arm trial that enrolled 833 *de novo* adult renal transplant recipients in Africa, Asia, Australia, Europe, North and South America. Patients were randomized to one of three groups: everolimus starting at either 1.5 or 3.0 mg per day combined with reduced dose CsA or mycophenolic acid (MPA; Myfortic®) 1.44 gm per day with standard dose CsA.

The starting dose of everolimus in this study was the same as used in the initial studies B201 and B251. However, in this study everolimus doses were adjusted to achieve blood trough concentrations of 3 to 8 ng/mL (low dose group, starting at 1.5 mg/day) and 6 to 12 ng/mL (high dose group starting at 3.0 mg/day) combined with reduced exposure to CsA, which was tapered over time. Both drug concentrations were guided by TDM. The upper limit of the CsA target range for everolimus groups at Day 3 was 200 ng/mL compared to 300 ng/mL in the control group. At Month 2, CsA target concentrations were a maximum of 150 ng/mL in the everolimus groups, while in the control group, the target CsA maximum was 250 ng/mL. The target trough concentrations for CsA were lower in the everolimus groups compared to the everolimus groups in studies B201 and B251, while exposure to CsA in the control groups was similar in all 3 studies and higher than in the everolimus groups in this study.

The control regimen in studies B201 and B251 was MMF, while in this study it was MPA. The dose of MPA was selected to provide the same molar dose as 1 gm of MMF (720 mg Myfortic is the molar equivalent of 1 gm MMF) and is the approved dose for use in combination with cyclosporine. All patients were given basiliximab as induction therapy and maintained on concomitant corticosteroids, which were dosed based on local practice. The current submission contains data from the first 12-months of the study.

Table 6. Dose and Target Concentrations for Everolimus and CsA across Studies

Study Treatment Group	Drug	Study B201	Study B251	Study A2309
Everolimus 1.5 mg/day group	Everolimus	0.75 mg bid	0.75 mg bid	Target trough 3-8 ng/mL
	CsA	Full Dose: 150 to 400 ng/mL (Weeks 1-4), 100 to 300 ng/mL (Months 2-12), 50 to 75 ng/mL (after Month 12)	Full Dose: 200 to 350 ng/mL (Weeks 1-4), 100 to 300 ng/mL (Months 2-12), 50 to 75 ng/mL (after Month 12)	Reduced Dose:* 100 to 200 ng/mL (until Month 2), 75 to 150 ng/mL (Months 2-4), 50 to 100 ng/mL (Months 4-6) and 25 to 50 ng/mL (after Month 6)
Everolimus 3.0 mg/day group	Everolimus	1.5 mg bid	1.5 mg bid	Target trough 6-12 ng/mL
	CsA	Full Dose – same as above	Full Dose – same as above	Reduced Dose:* same as above
Control group	MMF or MPA	MMF 1gm bid	MMF 1 mg	MPA 720 mg bid per day
	CsA	Full Dose – same as above	Full Dose – same as above	Standard:* 200 to 300 ng/mL (Month 1), 100 to 250 ng/mL (Month 2-12)

* Pages 113 and 5772 of 14,328 from Study Report RAD001A2309, submitted June 30, 2009.

6.0 Review of Efficacy

Note: Tables in this section were obtained from the Applicant's Clinical Study Report (CSR) of Study A2309, as noted. Tables created by the Clinical Reviewer, or obtained elsewhere are also noted.

6.1 Indication

Zortress (everolimus) is indicated for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant [see *Clinical Studies (14.1)*]. Zortress is to be administered in combination with basiliximab and concurrently with reduced doses of cyclosporine and corticosteroids.

In the current study low-moderate immunologic risk patient is defined as ABO blood type compatible first time organ or tissue transplant recipient with anti-HLA Class I panel reactive antibodies < 20% by a Complement Dependent Cytotoxicity (CDC)-based assay or < 50% by a flow cytometry or Enzyme Linked Immunosorbent Assay (ELISA)-based assay and with a negative T-cell crossmatch.

6.1.1 Methods

6.1.1.1 Objectives

The primary objective of the study was to demonstrate that at least one of the everolimus treatment regimens was not inferior to the Myfortic treatment regimen within 12 months of the initial dose of study medication with respect to primary efficacy failure, namely, the composite efficacy endpoint of treated BPAR episodes, graft loss, death, or loss to follow-up.

The main secondary efficacy objective was to compare the composite incidence of graft loss, death, or loss to follow-up between everolimus and Myfortic treatment groups at 12 months post-transplantation.

The main safety objective was to demonstrate that non-inferior renal function was achieved in the everolimus treatment groups compared to the Myfortic treatment group at 12 months post-transplantation. Renal function was measured with calculated glomerular filtration rate (GFR) using the MDRD formula (Coresh et al 2003).

6.1.1.2 Study Design

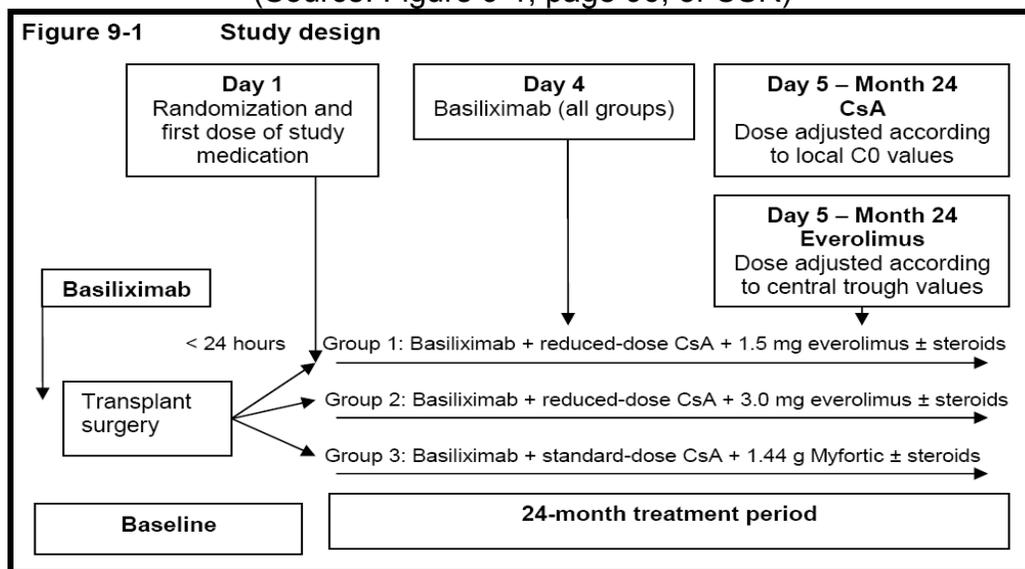
Study A2309 is a 24-month, multi-national, open-label, randomized (1:1:1) trial comparing two concentration-controlled everolimus regimens of 1.5 mg per day starting dose (targeting 3 to 8 ng/mL) and 3.0 mg per day starting dose (targeting 6 to 12 ng/mL) with reduced doses of cyclosporine (CsA) and corticosteroids, to 1.44 gm per day of mycophenolic acid (Myfortic) with standard doses of CsA and corticosteroids. All patients received basiliximab induction therapy.

It was anticipated that 100 centers would be needed to enroll approximately 825 patients in Africa, Asia, Australia, Europe, North and South America. Enrollment was to be stopped after randomization of 825 patients.

The trial is open-label. However, the Applicant's staff supporting the conduct of the study were blinded with regard to treatment assignments, doses and blood levels of study medication and CsA for the entire 12 month treatment period. The investigator, pharmacist, and patient were aware of which treatment was administered to the patient. The investigator should have, however, withheld the treatment assignment from the local pathologist interpreting the biopsies. The local pathologist provided the investigator their interpretation for clinical management of the patient.

The planned duration of treatment is 24 months. The data in this review represent the 12 month analysis. Within 24 hours after transplantation, after having met all eligibility criteria, patients were randomized to one of the three treatment groups in a 1:1:1 ratio. Patients were not randomized until they were able to take oral medication.

Figure 3. Study A2309 Design
(Source: Figure 9-1, page 96, of CSR)



6.1.1.3 Discussion of Endpoints

Primary Endpoint

The primary efficacy endpoint was efficacy failure at 12 months post transplantation, where efficacy failure was defined as the composite endpoint of treated biopsy-proven acute rejection (BPAR), graft loss, death, or loss to follow-up. Each of these components is further defined below.

Treated Biopsy-Proven Acute Rejection (BPAR)

Biopsies were read by the local pathologist according to the 1997 updated Banff criteria. Determination of the need for treatment was made according to the local pathologist's findings and the overall clinical presentation of rejection. The local pathologist was blinded to patient treatment. A BPAR episode was defined as a biopsy graded IA, IB, IIA, IIB, or III that was treated with anti-rejection therapy.

Death

Death was recorded at either study completion, follow-up, or as the outcome of an adverse event, if it occurred.

Graft loss

Graft loss was defined as any of the following:

- Loss of the graft. The allograft was presumed to be lost on the day the patient started dialysis and was not able to be subsequently removed from dialysis.
- Re-transplant

Loss to Follow-up

A patient who did not experience treated BPAR, graft loss or death and whose last day of contact was prior to study Day 316, which is the protocol defined lower limit of Month 12 visit window, was considered lost to follow-up.

Note: Loss to follow-up in the analysis of death, graft loss and loss to follow-up was defined as any patient who did not experience a graft loss or death and whose last day of contact was prior to Day 316.

Secondary Endpoints

The main secondary endpoint was the incidence rate of the composite endpoint of graft loss, death or loss to follow up at 12 months. Other secondary endpoints included efficacy failure (as defined for the primary endpoint) at 6 months, treated BPAR at 6 and 12 months, graft loss at 6 and 12 months, death at 6 and 12 months, biopsy proven chronic allograft nephropathy (CAN) at 12 months, graft loss or death at 6 and 12 months, graft loss, death or loss to follow up at 6 months, and antibody treated BPAR at 12 months.

Primary Safety Endpoint

The main safety endpoint of Study A2309 was serum creatinine at month 12 by calculated glomerular filtration rate (GFR) using the MDRD (Modification of Diet in Renal Disease) formula. The main safety objective was to show that the mean GFR of either everolimus 1.5 mg or 3.0 mg group was no worse than (non-inferior to) the Myfortic group by 8 mL/min/1.73m² at month 12 using t-test based, two-sided 95% and 97.5% confidence intervals.

Reviewer's Comment: *There is no justified non-inferiority margin for GFR in de novo kidney transplantation. Results of this endpoint will be assessed for clinical importance.*

6.1.1.4 Inclusion/Exclusion Criteria

Male and female renal transplant patients aged 18 to 70 years receiving a primary cadaveric, living unrelated or non-human leukocyte antigen (HLA) identical living related, donor kidney were eligible for study participation if they met all of the inclusion/exclusion criteria defined below.

Inclusion Criteria

Eligible patients were required to meet all of the following inclusion criteria:

- Male or female renal recipients 18-70 years of age undergoing primary kidney transplantation
- Provided written informed consent to participate in the study
- Females must have had a negative pregnancy test prior to randomization

Exclusion criteria

Patients were excluded from the study if they met any of the following exclusion criteria:

- No evidence of graft function within 24 hours of transplantation
- Receipt of kidneys from HLA-identical living related donors
- Donor organ with a cold ischemia time > 40 hours
- Received kidney from a non-heart beating donor
- Donor age > 65 years
- Platelet count < 100,000/mm³ at the evaluation before randomization
- Absolute neutrophil count (ANC) < 1,500/mm³ at baseline before surgery or white blood cell (WBC) count < 4,500/mm³
- Receipt of dual kidney transplants
- Recipients of multiple solid organ or tissue transplants or recipients of a previous organ or tissue transplant
- Severe hypercholesterolemia (> 350 mg/dL; > 9 mmol/L) or hypertriglyceridemia (> 500 mg/dL; > 8.5 mmol/L); controlled hyperlipidemia was acceptable
- Abnormal liver profile such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, or total bilirubin > 3 times the upper limit of normal (ULN)

- Known hypersensitivity to either of the study drugs or their class, or to any of the excipients
- Treatment with drugs that are strong inducers or inhibitors of cytochrome P450
- Treatment with terfenadine, astemizole, or cisapride
- Inability to take oral medication at the time of randomization
- Receipt of an investigational drug or treatment with a non-protocol immunosuppressive drug or treatment within 30 days or five half-lives prior to randomization
- History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there was evidence of local recurrence or metastases, with the exception of localized excised non-melanomatous skin lesions
- Most recent anti-HLA Class I panel reactive antibodies > 20% by a Complement Dependent Cytotoxicity (CDC)-based assay or > 50% by a flow cytometry or Enzyme Linked Immunosorbent Assay (ELISA)-based assay
- Receipt of ABO incompatible transplants or T-cell crossmatch positive transplant
- Patients who have tested positive for HIV, hepatitis C, or hepatitis B surface antigen.
- Laboratory results obtained within 6 months prior to randomization were acceptable, otherwise these tests were performed within 1 week of randomization
- Receipt of organs from donors who tested positive for hepatitis B surface antigen, hepatitis C, or HIV
- Clinically significant systemic infection at the time of transplant or within 2 weeks of transplant
- Severe diarrhea, active peptic ulcer disease, or uncontrolled diabetes mellitus
- Cardiac failure at the time of screening (resting dyspnea with grade ≥ 3 according to old New York Heart Association classification or any severe cardiac disease as determined by the investigator)
- Any surgical or medical condition, which, in the opinion of the investigator, might have significantly altered the absorption, distribution, metabolism, and excretion of study medication
- • Abnormal physical or laboratory findings of clinical significance within 2 weeks of randomization which could have interfered with the objectives of the study
- Any history of coagulopathy or medical condition requiring long-term anticoagulation that would preclude renal biopsy after transplantation (low dose aspirin treatment or interruption of chronic anticoagulant was allowed)
- Women of childbearing potential who were pregnant and/or lactating, planning to become pregnant, or who were unwilling to use effective means of contraception

6.1.1.5 *Treatments administered*

Everolimus

Therapeutic drug monitoring of everolimus trough concentrations was mandatory throughout the study. From Day 5 onwards, the following dose adjustments applied:

Everolimus 1.5 mg group: the 0.75 mg bid dose was increased if the everolimus trough level was < 3 ng/mL and reduced if the trough level was > 8 ng/mL to maintain the everolimus trough levels within the 3-8 ng/mL target range.

Everolimus 3.0 mg group: the 1.5 mg bid dose was increased if the trough level was <6 ng/mL, and reduced if the trough level was > 12 ng/mL to maintain the everolimus trough levels within the 6-12 ng/mL target range.

Follow-up everolimus trough levels were measured 5 days after any dose adjustment to everolimus to ensure that the recommended troughs were achieved. An everolimus trough was also measured 5 days after the 6-month CsA dose adjustment.

Cyclosporine

Neoral capsules were administered orally bid unless Neoral oral solution or intravenous administration of CsA could not be avoided. The lowest permitted dosing of Neoral in this study was 25 mg bid. If CsA was discontinued for more than 21 days, study drug was to be discontinued.

If CsA was administered via NG tube, it was to be administered immediately after everolimus or MMF. The drugs were not to be mixed. Two different syringes were to be used for the two drugs. After each administration, the NG tube was to be clamped for a minimum of 30 minutes.

CsA dosing was managed by monitoring local CsA trough levels as described below. In the event of CsA intolerance (e.g. nephrotoxicity, neurotoxicity), dose reduction of CsA may have been necessary.

CsA dose adjustments were based on CsA trough levels (C0). Although a central laboratory was utilized to collect trough levels for data analysis, patient clinical management was determined by the local laboratory results for the trough levels. C0 levels were determined from whole blood samples taken 12 ± 1 hour after the last evening dose at the time points indicated in the assessment schedule table (Table 8). The patients were instructed to adjust the medication schedule on the day prior to the blood draw to achieve proper timing and to bring the morning study medication dose to the visit so the next dose of study medication could be administered after the blood sampling was completed.

C0 values in both everolimus groups and in the Myfortic group were used to adjust the CsA dose to achieve CsA trough concentrations within the specified target ranges as

shown in Table 7. Follow-up CsA trough levels were measured 5 days after any dose adjustment to CsA to ensure that the recommended troughs were achieved.

Table 7. Targeted CsA Trough Levels in Study 2309

(Source Page 113 of CSR)

Table 9-3 C0 value ranges for CsA		
Day/month	Everolimus treatment groups	Myfortic treatment group
Starting Day 5	100-200 ng/mL	200-300 ng/mL
Starting Month 2 visit	75-150 ng/mL	100-250 ng/mL
Starting Month 4 visit	50-100 ng/mL	100-250 ng/mL
Starting Month 6 visit	25-50 ng/mL	100-250 ng/mL

The upper limit of the CsA target range for everolimus groups at Day 3 was 200 ng/mL compared to 300 ng/mL in the Myfortic group. At Month 2, CsA target levels were a maximum of 150 ng/mL in the everolimus treatment groups, while in the Myfortic group, the target maximum was 250 ng/mL.

Myfortic

1.44 g Myfortic qd (two 360-mg tablets bid) was administered to patients in the control group. If Myfortic MMF suspension was administered NG tube, it was to be administered according to the package insert. After each administration, the NG tube was to be clamped for a minimum of 30 minutes.

Basiliximab Induction:

All patients received two 20 mg doses of basiliximab administered intravenously. The first dose was to be given within 2 hours prior to transplant surgery and the second dose was to be administered on Day 4, or each dose could have been administered according to local practice.

Corticosteroids:

Oral corticosteroids were administered according to local practice during the trial. At the same center, all patients were to follow the same steroid administration protocol.

The results showed that the mean and median doses of prednisone equivalent corticosteroids were highest on Day 1 (means of 3.73, 3.69 and 3.64 mg/kg/day for everolimus 1.5 mg, everolimus 3.0 mg and Myfortic 1.44 gm, respectively),. Doses of glucocorticoids decreased in all treatment groups over the course of the study with mean values at Month 12 of 0.10, 0.10 and 0.09 mg/kg/day for everolimus 1.5 mg, everolimus 3.0 mg and Myfortic 1.44 gm, respectively.

6.1.1.6 *Study Drug Supply*

Everolimus and the specific proprietary products of mycophenolic acid (MPA; Myfortic), cyclosporine (Neoral), and basiliximab (Simulect) used in the study are manufactured by Novartis.

Everolimus and Myfortic were also supplied by Novartis. Neoral and basiliximab were obtained by the sites using a commercial supply, or per local practice based on local health authority regulations.

6.1.1.7 *Dose Adjustments Based on Adverse Events or Laboratory Findings*

For patients unable to tolerate the protocol-specified dosing schedule, dose adjustments were permitted in order to keep the patient on study drug. Reasons for study drug dose reductions included a decrease in WBC count or platelet count, an increase in cholesterol or triglyceride level, or other AEs. Severe and unremitting changes may have resulted in study drug discontinuation. If study medication was interrupted for safety reasons for longer than 21 consecutive days or more than two episodes of 7 days or longer, discontinuation of study medication was discussed between the investigator and the Applicant. Study drug was permitted to be interrupted during antibody treatment of rejection episodes. A twice daily schedule was to be followed at all times.

The following guidelines for dose reductions due to safety reasons were provided to investigators:

- Everolimus 1.5 mg group: reduce everolimus dose from 0.75 mg bid to 0.5 mg bid. For further flexibility, 0.25 mg tablets were provided.
- Everolimus 3.0 mg group: reduce everolimus dose from 1.5 mg bid to 1.0 mg bid. For further flexibility 0.25 and 0.5 mg tablets were provided.
- Myfortic 1.44 gm group: reduce Myfortic dose from 720 mg bid to 360 mg bid.

Complete guidelines for everolimus and Myfortic dose reduction based on laboratory findings were provided in the CSR (Appendix 16.1.1-Protocol-Appendix 6).

6.1.1.8 *Treatment Interruptions*

If a patient developed a short-term intolerance of oral medication after the initial dose of study medication, study drug may have been temporarily interrupted. Alternatively, everolimus or MMF suspension may have been administered via a nasogastric (NG) tube. Such administration of study drug was considered study drug interruption. If this period was more than 21 consecutive days or more than two episodes of 7 days or longer, study drug discontinuation was discussed between the investigator and the

Applicant. Patients were to return to oral medication as soon as possible after an interruption of oral administration of study medication.

6.1.1.9 *Treatment Discontinuations*

In addition to the standard criteria for patient discontinuation (i.e., adverse event, withdrawal of consent, protocol violation) Patients were discontinued from study treatment in the case of pregnancy or administration of prohibited immunosuppressive medication (excluding immunosuppressive medications used to treat acute rejection).

All patients discontinuing study treatment prior to the 12 month treatment period were contacted at scheduled Months 3, 6, 9, and 12 visits to obtain follow-up information and were not considered withdrawn from the study. Information was collected on vital signs, hospitalizations, rejection episodes, central laboratory samples (proteinuria and serum creatinine), graft loss/re-transplant, SAEs, malignancies, opportunistic infections, patient survival, cytomegalovirus (CMV) infections, and immunosuppressive therapy. In addition, major adverse cardiac events (MACE) were reported during the follow-up period.

If patients refused to return for these visits or were unable to do so, every effort was to be made to contact them or a knowledgeable informant by telephone to determine the information on survival status, graft loss/re-transplant, rejection episodes, malignancies, opportunistic infections, and immunosuppressive therapies. Because patients were followed even after discontinuation of study medication, the Study Completion electronic Case Report Form (eCRF) page was only to be completed at Month 12 or earlier if the patient could no longer be followed (e.g. death, lost to follow-up, withdrawal of consent). No study drug was provided for patients who discontinued study treatment prior to Month 12.

6.1.1.10 *Concomitant Therapy*

Nephrotoxic Drugs

Co-administration of nephrotoxic drugs and drugs known to interfere with CsA metabolism were to be avoided if possible. If these drugs were required, the investigator was to carefully monitor renal function and adjust the CsA dose if needed. A for a list of drugs with the potential to interact with CsA can be found in the CSR (Appendix 16.1.1-Protocol-Appendix 5).

Cytomegalovirus (CMV) Prophylaxis

CMV prophylaxis for a minimum of 30 days was mandatory for all cases in which the donor tested positive and the recipient tested negative for CMV. Treatment with ganciclovir, cytomegalovirus hyperimmune globulin, acyclovir, or valacyclovir was permitted and was administered according to local practice. All cases other than CMV-positive donors to CMV-negative recipients were treated according to local practice.

***Pneumocystis jiroveci* Pneumonia Prophylaxis**

All patients were started on trimethoprim-sulfamethoxazole when oral medication could be tolerated and continuing for the first year of study medication per local practice. The same regimen was to be administered to all patients at a given study center. Aerosolized pentamidine or dapsone could have been administered to patients unable to tolerate trimethoprim-sulfamethoxazole.

Treatment of Oral Candida

For oral thrush (Candida), nystatin may have been used in a swish and swallow regimen. Alternatively, clotrimazole lozenges/troches could have been used. Routine use of systemic antifungal agents (i.e. itraconazole, voriconazole, and fluconazole) was not allowed unless patients were systemically infected. Because administration of azoles can increase blood concentrations of both CsA and everolimus, their use was to be minimized and particular attention to side effects was required.

Lipid Lowering Medications

HMG CoA reductase inhibitors (e.g. fluvastatin (Lescol®)) were to be administered according to local practice for the management of hyperlipidemia. Patients requiring treatment with this class of medication (especially lovastatin)* were to be monitored closely for signs of rhabdomyolysis. Lipid-lowering therapy was to be optimized before dose reduction of study medication was considered.

Reviewer's Comment: *Although lovastatin and simvastatin were strongly discouraged according to the study protocol the Applicant still placed guidelines for watching signs of rhabdomyolysis in case they are used.*

6.1.1.11 Study Assessments

Baseline assessments occurred in the time period starting 24 hours pre-transplantation and ended at the time of randomization. No deviation in the evaluation schedule was allowed during Days 1 through 3. After Day 3, a visit window of 2 days up to Day 28, 1 week from Day 28 to Month 6, and 2 weeks after Month 6 was acceptable.

Table 8. Assessment Schedule
(Source: Table 9-2 Assessment schedule, page 108, CSR)

Examination	Pre-op ¹	Base-line ²	Day							Month								
	-2	-1 ³	1	3	4 ¹⁶	5 ¹⁶	7	14	28	2	3	4	6	7	9	12	18	24 ¹⁷
Randomization			X															
Background information	X																	
Inclusion/exclusion	X	X																
Medical history	X	X																
Transplant information		X																
Viral serology ⁴	X																	
Pregnancy test ⁵	X																	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam.		X														X		
Laboratory test ⁶		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Endocrine tests ⁷		X										X		X		X	X	
Pharmacogenetic sample ⁸	X																	
Study medication ⁹			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Basiliximab dosage ¹⁰	X				X													
CsA dosage																		Per protocol
RAD trough level ¹¹				X		X	X	X	X	X	X	X	X	X	X	X	X	X
CsA trough level (C0) ¹¹				X		X	X	X	X	X	X	X	X	X	X	X	X	X
CsA C ₂ level (optional)				X		X	X	X	X	X	X	X	X	X	X	X	X	X
Immunosuppressive therapy																		As needed
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events ¹²																		As needed
Hospitalizations ¹³							X	X	X	X	X	X	X	X	X	X	X	X
MACE events																		As needed
CMV infections																		As needed
Renal biopsy ¹⁴		X															X	As needed
Allograft rejection																		As needed
Graft loss record																		As needed
Dialysis log																		As needed
Infection log																		As needed
End of treatment																		As needed
Comments																		As needed
Follow-up record ¹⁵	Completed at 3, 6, 9, 12, 18, and 24 months after the first dose of study medication for patients who prematurely discontinued study medication prior to Month 24. Renal biopsies performed at 12 months ¹⁴ (patients with proteinuria or where 1 year post-transplantation biopsies were performed as part of standard institutional protocol).																	

¹Informed consent was obtained at the pre-op visit (Visit 1), prior to any study-related procedures. The pre-op visit was normally Day -2 but may have extended up to 4 weeks prior to transplant (e.g. for scheduled living donor transplants).

²Baseline covered the period from 24 hours prior to surgery until randomization. The post-surgery baseline assessments (e.g. functioning graft, ability to take oral medication) occurred within 24 hours prior to randomization.

³Study days -2 and -1 may have been the same date depending on the time of transplant.

⁴Viral serology included hepatitis C, HIV, and hepatitis B surface antigen. Measurements made within the last 6 months were accepted, otherwise these tests were to be performed within 1 week of randomization. Patients testing positive for any such viral serology test were discontinued from study medication and entered the follow-up period.

⁵Only for females, a pregnancy test may have been carried out according to local practice. Local results must have been available and negative within 48 hours prior to randomization. A pregnancy test was also obtained at end of study.

⁶Safety laboratory included: biochemistry (sodium, potassium, chloride, calcium, magnesium, inorganic phosphate, urea, creatinine, glucose, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, creatine phosphokinase (CPK), lipase, amylase (LDL and HDL only at baseline, Week 4, Month 6, 12, 18, and 24); urinalysis (protein, glucose); hematology, platelets, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) and differential count), spot urine for a quantitative protein/creatinine ratio (central labs) at every visit.

⁷Testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH) (males only).

⁸Pharmacogenetic sample may have been obtained at a later timepoint if the patient was unable to provide a baseline sample.

⁹First dose of study medication was given (together with CsA) immediately following randomization, which occurred within 24 hours of transplantation.

¹⁰The first dose of basiliximab was given within 2 hours prior to transplant or according to local practice. The second dose was given on Day 4 or according to local practice.

¹¹Blood draw for everolimus and CsA trough concentrations 5 days \pm 2 days following each clinic visit in which everolimus or CsA doses were changed. Patient clinical management for CsA was based on local C₀ levels.

¹²Serious adverse events, infections, and pregnancies were reported for up to 30 days after the last dose of study medication.

¹³Hospitalization data: data to be collected at each visit for economic analyses.

¹⁴Baseline renal biopsies were performed on all patients. Renal biopsies were performed in cases of suspected acute rejections and at Month 12 in all patients with significant proteinuria (defined as > 0.5 g/day (on or off ACE inhibitors or ARBs) or suboptimal renal function (estimated GFR by MDRD < 50 mL/min/1.72m²)). In a subset of centers, renal biopsies were performed on all patients at Month 12.

¹⁵Follow-up evaluations included vital signs, hospitalizations, rejection episodes, central lab samples (proteinuria and serum creatinine), graft loss/re-transplant, SAEs, malignancies, opportunistic infections, patient survival, CMV infections, immunosuppressive therapy, and MACEs.

¹⁶Day 4 and Day 5 procedures and assessments could have been performed earlier if the patient was discharged from the hospital in accordance with local practice.

¹⁷All Month 24 evaluations were performed at end of study or at the time of premature discontinuation of study medication. Study completion form was only to be completed after patients completed 24 months in study (whether on or off study medication).

Timing of Kidney Biopsies

Baseline biopsies were obtained on all patients. At selected centers, 12-month biopsies were obtained for all patients at the site. In addition, biopsies were also collected for any patient with significant proteinuria (defined as > 0.5 g/day, on or off ACE inhibitors or

ARB) or suboptimal renal function (defined as estimated GFR by MDRD < 50 mL/min/1.72m²) at Month 12 in all centers.

Renal biopsies were also collected for all cases of suspected acute rejection. For all suspected rejection episodes, regardless of initiation of anti-rejection treatment, a graft core biopsy must have been performed within 48 hours.

Determination of Acute Rejection

In all suspected rejection episodes, regardless of initiation of anti-rejection treatment, a graft core biopsy was to be performed within 48 hours. Biopsies were read by the local pathologist according to the 1997 updated Banff criteria (full criteria provided in CSR; Appendix 16.1.1-Protocol-Appendix 7). Determination of the need for treatment was made according to the local pathologist's findings and the overall clinical presentation of rejection. The local pathologist remained blinded to the patient treatment.

The results of the biopsy read by the local pathologist were listed on the Kidney Allograft Biopsy eCRF and were used for patient management of acute rejection. A treated BPAR was defined as a biopsy graded IA, IB, IIA, IIB, or III and which was treated with anti-rejection therapy. Biopsy specimen slides from all biopsies were submitted to a independent central pathologist(s) for blinded review.

If the investigator chose to permanently stop CsA or to switch to another primary immunosuppressive agent, study medication was discontinued. However, the patient was to be followed until completion of the trial.

Acute rejections were considered protocol-exempted Serious Adverse Events (SAEs). They were not to be reported simply because they resulted in hospitalization and thus met the criteria for SAEs. However, acute rejections were to be reported as SAEs if they were unusual in appearance or clinical course or were graft threatening.

Definition and Timing of Graft Loss

An allograft was presumed to be lost on the day a patient started dialysis and was not able to subsequently be removed from dialysis. If the patient underwent a graft nephrectomy, then the day of nephrectomy was the day of graft loss.

Graft loss was considered a SAE.

6.1.1.12 Analysis Populations

The Intent-To-Treat (ITT) population consisted of all patients randomized after transplantation. Following the intent-to-treat principle, patients were analyzed according to the treatment they were assigned to at randomization.

The Safety population consisted of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. Patients were analyzed according to treatment received.

The Per-protocol (PP) population consisted of all randomized patients who took study treatment according to the protocol without any major deviations from the protocol procedures.

The following deviations were considered as major deviations and led to exclusion of the corresponding patients from the PP population:

- The patient had received multiple transplants or had previous transplants;
- Renal cold ischemia time was > 40 hours;
- The transplant donor's age was > 65 years.

Non-protocol deviation criteria which must have been satisfied for inclusion in the PP population were:

- At least 6 months treatment with study medication;
- At least one post-baseline safety evaluation;
- Had received 2 doses of Simulect (around Day -1 and Day 4) administered intravenously.

All Per-Protocol analyses were on-treatment analyses, using data observed while on treatment. An on-treatment observation was assessment obtained on and after Day 1 but no later than two days after the discontinuation of randomized study medication.

Safety data was analyzed on the Safety population as defined above except for the analysis of renal function which was performed on the ITT and PP populations. Efficacy analyses were performed on the ITT and PP population.

Table 9 Analysis Populations
 (Source: Table 11-1, page 142, CSR)

Table 11-1	Analysis populations – n (%) of patients by treatment group (12 month analysis)		
	Everolimus 1.5 mg (N=277) n (%)	Everolimus 3.0 mg (N=279) n (%)	Myfortic 1.44 g (N=277) n (%)
Population category			
Intent-to treat (ITT) population	277 (100.0)	279 (100.0)	277 (100.0)
Safety population	274 (98.9)	278 (99.6)	273 (98.6)
Per protocol (PP) population	215 (77.6)	205 (73.5)	230 (83.0)

Source: [Table 14.1-2.1](#)

6.1.1.12 *Statistical Analysis*

Analysis was performed on the ITT and PP populations. Patients who discontinued study drug were included in the 12 month analyses and evaluated according to their study drug assignment. Patients who discontinued study before the 12 month endpoint but otherwise had no efficacy failures were treated as efficacy failures and included in the efficacy analyses as lost to follow-up. Sensitivity analyses were performed to confirm the appropriateness of this approach.

The primary objective of the study was tested for each of the 2 treatment comparisons of everolimus to Myfortic, with regard to the following null hypothesis:

H0: the proportion of patients experiencing efficacy failure at 12 months on the everolimus group is higher than that of the Myfortic group by 10% or more, where 10% represents the non-inferiority margin chosen.

The non-inferiority tests were based on confidence intervals (CI) constructed using the Z-test statistic, performed on the ITT population. The trial was to be claimed as successful if the incidence rate of the primary composite efficacy failure from either of the two everolimus groups was non-inferior to the Myfortic group. Hence, to control for multiple comparisons (i.e., everolimus 1.5 mg vs. Myfortic and everolimus 3.0 mg vs. Myfortic) the Hochberg procedure was used to maintain the overall Type I error rate at 0.05.

Following the Hochberg procedure, two-sided 95% and 97.5% CIs for the difference in primary efficacy failure rates at 12 months between the everolimus and Myfortic groups were computed. An everolimus group was claimed to have non-inferior efficacy failure rate at 12 months to Myfortic if the upper limit of the appropriate CI was less than 10%. As a supportive analysis and robustness check, the primary analysis was repeated using the PP population.

The main safety objective of the trial was to demonstrate that non-inferior renal function (calculated GFR using the MDRD formula) was achieved between an everolimus treatment group and the Myfortic treatment group at 12 months post-transplantation. The main safety endpoint was calculated GFR using the MDRD formula. Central laboratory serum creatinine values were used for all renal function data analysis. If the serum creatinine value from central laboratory was missing within a visit window, the serum creatinine value from local laboratory was used for that visit window. Again the multiple comparison method outlined for the primary endpoint was applied. T-test based, two-sided 95% and 97.5% confidence intervals (CI) for the difference in mean GFR at 12 months between the everolimus and Myfortic groups were computed. An everolimus group was claimed to have non-inferior renal function at 12 months to the Myfortic group if the lower limit of the appropriate CI was greater than -8 mL/min.

Reviewer's Comment: *There is no NI margin agreed upon for calculated GFR. The results of GFR analysis are evaluated according to the clinical significance of the findings.*

6.1.1.13 Justification of the Non-Inferiority (NI) Margin

Please refer to Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D. for a detailed discussion of the justification of the NI margin

For confirmatory non-inferiority trials, the Applicant is required to provide a detailed justification of the proposed NI margin using information from historical trials. For Study A2309, the Applicant submitted a justification for the primary efficacy endpoint (i.e. efficacy failure: a composite of treated BPAR, death, graft loss or loss to follow-up at 12 months), which is acceptable. Additionally, a margin for the endpoint of death, graft loss or loss to follow-up was not able to be justified due to a lack of sufficient information on these endpoints from historical information. It should be noted that while the primary endpoint includes components of death, graft loss, and loss to follow-up; proof of efficacy is mainly driven by the treated BPAR component of the composite endpoint in trials of *de novo* kidney transplantation.

Study A2309 was designed as a non-inferiority trial comparing everolimus to the current standard of care (Myfortic) for assessing efficacy failure using this composite endpoint (treated BPAR, graft loss, death or loss to follow-up) with a 10% non-inferiority margin.

To justify the selected non-inferiority margin a meta-analysis of historical trials was performed by the Applicant to estimate the efficacy failure rates of the Myfortic group (control group) and basiliximab + standard-dose CsA ± corticosteroids (putative placebo). A detailed description of literature search, statistical methodology to estimate control effect, and the results for the justification was submitted separately to the everolimus IND (52,003).

The control effect was estimated to be 24.6% [95% CI: 18.9%, 30.2%]. Based on the conservative 95_{NI}-95_H confidence interval approach, a non-inferiority margin of 18.9% would have been statistically justified to demonstrate indirectly the efficacy of everolimus+ basiliximab + reduced-dose CsA ± corticosteroids over putative placebo. The 10% noninferiority margin selected for the new study represents approximately 50% preservation of the estimated control effect.

The applicant's methods and the three additional methods, performed by the FDA, provide estimates that are supportive of the proposed 10% margin. Given the lack of historical RCTs, the approach used to derive these estimates is acceptable.

6.1.2 Demographics

Transplant recipients had a mean age of 46.1 years and were predominantly Caucasian males (Table 10). All patients were aged between 18 and 70 as per the protocol, and there was little difference between treatment groups with regard to any recipient demographics.

Recipient Demographics:

Table 10. Baseline Demographics by Treatment Group (ITT population)
(Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 g (N=277)
Recipient Age (years) Mean (\pm SD) Range	45.7 (12.7) 18 – 70	45.3 (13.4) 18 – 70	47.2 (12.7) 18 – 70
Donor Age (years) Mean (\pm SD) Range	41.4 (13.9) 5 – 67	41.1 (13.0) 5 – 69	41.8 (13.6) 5 – 67
Recipient age group < 50 years \geq 50 years Unknown	156 (56.3%) 120 (43.3%) 1 (0.4%)	153 (54.8%) 126 (45.2%) 0 (0%)	143 (51.6%) 134 (48.4%) 0 (0%)
Donor age group < 50 years \geq 50 years Unknown	181 (65.3%) 95 (34.3%) 1 (0.4%)	203 (72.8%) 76 (27.2%) 0 (0%)	182 (65.7%) 94 (33.9%) 1 (0.4%)
Recipient gender Male Female Unknown	176 (63.5%) 100 (36.1%) 1 (0.4%)	191 (68.5%) 88 (31.5%) 0 (0%)	189 (68.2%) 88 (31.8%) 0 (0%)
Donor gender Male Female Unknown	154 (55.6%) 122 (44.0%) 1 (0.4%)	139 (49.8%) 140 (50.2%) 0 (0%)	136 (49.1%) 140 (50.5%) 1 (0.4%)
Recipient race Caucasian Black Asian Other Unknown	193 (69.7%) 34 (12.3%) 32 (11.6%) 17 (6.1%) 1 (0.4%)	180 (64.5%) 40 (14.3%) 38 (13.6%) 21 (7.5%) 0 (0%)	190 (68.6%) 38 (14.1%) 36 (13.0%) 12 (4.3%) 0 (0%)

	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 g (N=277)
Donor race			
Caucasian	193 (69.7%)	191 (68.5%)	197 (71.1%)
Black	20 (7.2%)	22 (7.9%)	25 (9.0%)
Asian	32 (11.6%)	35 (12.5%)	31 (11.2%)
Other	27 (9.8%)	26 (9.3%)	19 (6.9%)
Unknown	5 (1.8%)	5 (1.8%)	5 (1.8%)

Table 11. Height, Weight and BMI of the Recipients
(Source: Table 14.1-3.1a, Page 334 of CSR)

Table 14.1-3.1a (Page 2 of 2) Patient Demographics - Recipient (ITT Population - 12 Month Analysis)				
Demographic Variable	RAD 1.5mg N=277	RAD 3.0mg N=279	Myfortic 1.44g N=277	Total N=833
Height (cm)				
n	270	272	270	812
Mean	170.0	170.0	170.7	170.2
SD	10.78	11.20	10.45	10.81
Minimum	143	145	142	142
Median	170.0	169.0	172.0	170.0
Maximum	197	221	198	221
Weight (kg)				
n	271	268	269	808
Mean	75.06	75.35	75.67	75.36
SD	18.278	19.040	16.554	17.966
Minimum	36.7	35.5	43.0	35.5
Median	72.90	72.65	74.50	73.45
Maximum	140.0	138.5	127.0	140.0
Body Mass Index (kg/m**2)				
n	265	264	264	793
Mean	25.79	25.84	25.86	25.83
SD	5.140	5.010	4.709	4.950
Minimum	15.7	15.2	17.2	15.2
Median	24.97	25.18	25.31	25.15
Maximum	43.6	39.5	42.3	43.6

The primary disease leading to end stage renal disease in recipients was similar across the treatment groups (Table 12); the most frequent diseases being hypertension/nephrosclerosis, glomerulonephritis/glomerular disease and diabetes mellitus. The majority of patients were receiving hemodialysis at the time of transplantation, and approximately one-half had not had a previous blood transfusion. Over one-half of patients had at least one HLA mismatch at the A, B and DR loci, and over 70% of patients had more than 3 mismatches. A higher proportion of patients in the everolimus 1.5 mg group had 3 or more HLA mismatches than the everolimus 3.0 mg group. The mean percentage of panel reactive antibodies (most recent evaluation) was 2.0%, 1.4% and 0.9% for the everolimus 1.5 mg, everolimus 3.0 mg and Myfortic 1.44

gm groups, respectively, with all groups having a median of 0%. There were no major differences between treatment groups with regards to recipient disease characteristics.

Table 12. Recipient background characteristics summary by treatment group
(ITT population - 12 month analysis, Source: page 144 CSR)

	Everolimus 1.5mg N=277 n (%)	Everolimus 3.0mg N=279 n (%)	Myfortic 1.44g N=277 n (%)
Primary disease leading to transplantation			
Glomerulonephritis/glomerular disease	43 (15.5)	55 (19.7)	40 (14.4)
Pyelonephritis	8 (2.9)	3 (1.1)	7 (2.5)
Polycystic disease	36 (13.0)	29 (10.4)	33 (11.9)
Hypertension/nephrosclerosis	50 (18.1)	56 (20.1)	45 (16.2)
Drug induced toxicity	1 (0.4)	4 (1.4)	0 (0.0)
Diabetes mellitus	39 (14.1)	29 (10.4)	45 (16.2)
Interstitial nephritis	3 (1.1)	4 (1.4)	5 (1.8)
Vasculitis	2 (0.7)	3 (1.1)	0 (0.0)
Obstructive disorder/reflux	15 (5.4)	7 (2.5)	10 (3.6)
Renal hyperplasia/dysplasia	0 (0.0)	1 (0.4)	0 (0.0)
IgA nephropathy	18 (6.5)	17 (6.1)	29 (10.5)
Unknown	34 (12.3)	37 (13.3)	39 (14.1)
Other	27 (9.7)	34 (12.2)	23 (8.3)
Missing	1 (0.4)	0 (0.0)	1 (0.4)
Current dialysis			
None	46 (16.6)	37 (13.3)	46 (16.6)
Hemodialysis	182 (65.7)	197 (70.6)	188 (67.9)
Peritoneal dialysis	48 (17.3)	45 (16.1)	42 (15.2)
Missing	1 (0.4)	0 (0.0)	1 (0.4)
Number of previous blood Transfusions			
None	143 (51.6)	157 (56.3)	132 (47.7)
< 5	71 (25.6)	61 (21.9)	80 (28.9)
5 - 10	12 (4.3)	7 (2.5)	9 (3.2)
> 10	1 (0.4)	3 (1.1)	3 (1.1)
Unknown	48 (17.3)	51 (18.3)	52 (18.8)
Missing	2 (0.7)	0 (0.0)	1 (0.4)
HLA mismatches			
0	10 (3.6)	15 (5.4)	15 (5.4)
1	19 (6.9)	18 (6.5)	19 (6.9)
2	37 (13.4)	51 (18.3)	40 (14.4)
3	85 (30.7)	78 (28.0)	85 (30.7)
4	46 (16.6)	49 (17.6)	45 (16.2)
5	50 (18.1)	37 (13.3)	45 (16.2)
6	29 (10.5)	30 (10.8)	27 (9.7)
< 3	66 (23.8)	84 (30.1)	74 (26.7)
≥ 3	210 (75.8)	194 (69.5)	202 (72.9)
Missing	1 (0.4)	1 (0.4)	1 (0.4)
Panel reactive antibodies			
Most recent evaluation ≥ 20%	7 (2.6)	5 (1.8)	4 (1.5)
Peak evaluation ≥ 20%	17 (6.3)	13 (4.8)	11 (4.1)

Donor Demographics

Organ donors were more equally distributed amongst the sexes than recipients (Table 13). Donor mean ages were similar to recipients but with a slightly lower age range. Donors were predominantly Caucasian. The majority of organs came predominantly from living donors, and groups were balanced with respect to the number of patients who received a graft from living donors (53.0%, 54.1%, 53.5%). There were no differences between treatment groups with regard to donor characteristics.

Table 13. Donor Characteristics
 (Source: Table 11-4, Page 145, CSR)

Table 11-4 Donor characteristics summary by treatment group (ITT population - 12 month analysis)		Everolimus 1.5 mg N=277	Everolimus 3.0 mg N=279	Myfortic 1.44g N=277
Age (years)	Mean ± SD	41.4 ± 13.87	41.1 ± 12.97	41.8 ± 13.59
	Median (range)	43.0 (5.0-67.0)	43.0 (5.0-69.0)	45.0 (5.0-67.0)
Gender - n (%)	Male	154 (55.6)	139 (49.8)	136 (49.1)
	Female	122 (44.0)	140 (50.2)	140 (50.5)
	Missing	1 (0.4)	0 (0.0)	1 (0.4)
Race - n (%)	Caucasian	193 (69.7)	191 (68.5)	197 (71.1)
	Black	20 (7.2)	22 (7.9)	25 (9.0)
	Asian	32 (11.6)	35 (12.5)	31 (11.2)
	Native American	0 (0.0)	1 (0.4)	1 (0.4)
	Other	27 (9.7)	25 (9.0)	18 (6.5)
	Missing	5 (1.8)	5 (1.8)	5 (1.8)
Characteristics - n (%)	Cadaveric heart beating	128 (46.2)	126 (45.2)	127 (45.8)
	Cadaveric non-heart beating	1 (0.4)	2 (0.7)	1 (0.4)
	Living related	99 (35.7)	111 (39.8)	101 (36.5)
	Living unrelated	48 (17.3)	40 (14.3)	47 (17.0)
	Missing	1 (0.4)	0 (0.0)	1 (0.4)
Hypotension prior to procurement - n (%)	Yes	21 (7.6)	28 (10.0)	28 (10.1)
	No	196 (70.8)	195 (69.9)	196 (70.8)
	Unknown	59 (21.3)	56 (20.1)	52 (18.8)
	Missing	1 (0.4)	0 (0.0)	1 (0.4)

Source: [Table 14.1-3.1b](#) and [14.1-3.4](#)

Relevant medical histories and current medical conditions showed no major differences

between treatment groups (Table 12). Preferred terms where more than 10% of the ITT population were affected were; hypertension (89.3%), anemia (37.3%), hyperlipidemia (20.4%), arteriovenous fistula operation (18.4%), chronic renal failure (15.8%), drug hypersensitivity (14.8%), gout (12.1%), incision site pain (12.0%), hyperparathyroidism (11.3%), gastroesophageal reflux disease (10.6%), hyperphosphatemia (10.4%) and depression (10.4%). Medical history preferred terms which had a difference in incidence of 5% or more of patients between treatment groups were diabetes mellitus (5.1%, 6.8% and 10.8% for the everolimus 1.5 mg, everolimus 3.0 mg and Myfortic 1.44 gm groups, respectively) and hypercholesterolemia (6.1%, 6.5%, 11.6%, for the everolimus 1.5 mg, everolimus 3.0 mg and myfortic 1.44 gm groups, respectively).

Over 60% of both recipients and donors were positive for CMV, and 99% were negative for hepatitis C. Six recipient patients were positive for HBsAg (two in each treatment group), and one recipient patient in the myfortic treatment group was positive for HIV.

6.1.3 Subject Disposition

Baseline demographics and characteristics for recipients and donors were similar among the three treatment groups. All randomized patients were between the ages of 18 and 70 years; more than 43% were 50 years of age or older. More than 63% of all recipients were male and more than 64% were Caucasian. Among donors, more than 49% were male and more than 68% were Caucasian. The primary disease leading to end stage renal disease in recipients was similar across the treatment groups. The most frequent diseases leading to transplantation were hypertension/nephrosclerosis, glomerulonephritis/glomerular disease and diabetes mellitus. There were no major differences among treatment groups with regards to recipient disease characteristics.

Among the 833 randomized patients in the ITT population, approximately 29% prematurely discontinued study medication by Day 450, which was the protocol defined cutoff date for 12 month analyses. As presented in Table 14, the incidence of premature treatment discontinuation was imbalanced across the three treatment groups. At Month 12, the incidence of premature treatment discontinuation in the everolimus 1.5 mg group, 3.0 mg and Myfortic groups were 30.0% (83/277), 34.1% (95/279), and 21.7% (60/277). Compared to the Myfortic group, the incidence was statistically significantly higher in the everolimus 1.5 mg group (p-value=0.03, Fisher's exact test) and in the everolimus 3.0 mg group (p-value=0.001, Fisher's exact test).

The most common reason for premature discontinuation of study treatment was adverse events, which accounted for 18%, 20%, and 9% in the everolimus 1.5 mg, 3.0 mg and Myfortic groups respectively. In the everolimus 1.5 mg group, 18.1% of the patients prematurely discontinued treatment due to adverse events, which was statistically significantly higher than the incidence in the Myfortic group (9.4%) with p-value=0.004 (Fisher's exact test). The incidence of treatment discontinuation due to adverse events was also statistically significantly higher in the everolimus 3.0 mg group than in the Myfortic group (20.4% versus 9.4%, with p-value<0.0001, Fisher's exact test).

Approximately 12% of the randomized patients prematurely discontinued study. Study discontinuations were more frequent in both of the everolimus groups than in the Myfortic group (13.7% and 11.8% versus 10.1%), but the differences were not statistically significant (p-value= 0.24 and 0.59 respectively, Fisher's exact test).

Table 14. Premature Study Medication or Study Phase Discontinuation by Treatment Group (ITT Population- 12 Month Analysis)
 (Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 g (N=277)
Discontinued study medication	83 (30.0%)	95 (34.1%)	60 (21.7%)
Adverse event(s)	50 (18.1%)	57 (20.4%)	26 (9.4%)
Unsatisfactory therapeutic effect	11 (4.0%)	14 (5.0%)	13 (4.7%)
Subject withdrew consent	11 (4.0%)	4 (1.4%)	5 (1.8%)
Graft loss	3 (1.1%)	6 (2.2%)	6 (2.2%)
Death	3 (1.1%)	3 (1.1%)	4 (1.4%)
Protocol deviation	2 (0.7%)	5 (1.8%)	2 (0.7%)
Abnormal lab value	1 (0.4%)	4 (1.4%)	1 (0.4%)
Administrative problems	2 (0.7%)	1 (0.4%)	2 (0.7%)
Abnormal test procedure	0 (0%)	1 (0.4%)	0 (0%)
Unknown	0 (0%)	0 (0%)	1 (0.4%)
Discontinued study phase	38 (13.7%)	33 (11.8%)	28 (10.1%)
Subject withdrew consent	20 (7.2%)	8 (2.9%)	12 (4.3%)
Graft loss	9 (3.3%)	10 (3.6%)	7 (2.5%)
Death	7 (2.5%)	9 (3.2%)	6 (2.2%)
Unknown	2 (0.7%)	6 (2.2%)	3 (1.1%)

6.1.4 Analysis of Primary Endpoint(s)

The efficacy portion of the review was conducted by Xiao Ding, Ph.D. and LaRee Tracy, Ph.D, Biostatistics. See complete review filed with the NDA resubmission.

The primary endpoint of the study was primary efficacy failure, defined as the composite endpoint (treated BPAR episodes, graft loss, death, or loss to follow-up at 12 months). Each of these components are defined below.

Treated BPAR

A treated BPAR episode was defined as a biopsy graded IA, IB, IIA, IIB, or III that was

treated with anti-rejection therapy. The identification of treated BPAR was based on local laboratory biopsy results.

Death

Death was recorded at either study completion, follow-up, or as the outcome of an AE or infection, if it occurred.

Graft loss

Graft loss was defined as any of the following:

- Graft loss (the allograft was presumed to be lost on the day the patient started dialysis and was not able to subsequently be removed from dialysis)
- Re-transplant

Loss to follow-up

A loss to follow-up patient was a patient who did not experience treated BPAR, graft loss, or death and whose last day of contact is prior to study Day 316, which is the lower limit of Month 12 visit window. For 6 Month analysis, study Day 151, the lower limit of Month 6 visit window, was used.

The percentage of patients experiencing the composite endpoint and each individual variable is shown in Table 15. Treated BPAR was the most frequently reported of all the endpoints, affecting 65.5% of all patients who met the definition of the composite efficacy endpoint.

**Table 15. Primary Efficacy Endpoint Analysis by Treatment Group
 (ITT Population - 12 Month Analysis)
 (Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)**

	everolimus 1.5 mg (N=277)	everolimus 3.0 mg (N=279)	Myfortic 1.44 g (N=277)
Efficacy Failure	70 (25.3%)	61 (21.9%)	67 (24.2%)
Treated BPAR	45 (16.3%)	37 (13.3%)	47 (17.0%)
Graft Loss	12 (4.3%)	13 (4.7%)	9 (3.3%)
Death*	7 (2.5%)	10 (3.6%)	6 (2.2%)
Loss to follow-up**	12 (4.3%)	8 (2.9%)	9 (3.3%)
95% CI (everolimus-Myfortic)	(-6.1%, 8.3%)	(-9.3%, 4.7%)	N/A
97.5% CI (everolimus-Myfortic)	(-7.1%, 9.3%)	(-10.3%, 5.7%)	N/A

* One patient who died 10 days after withdrew consent was included

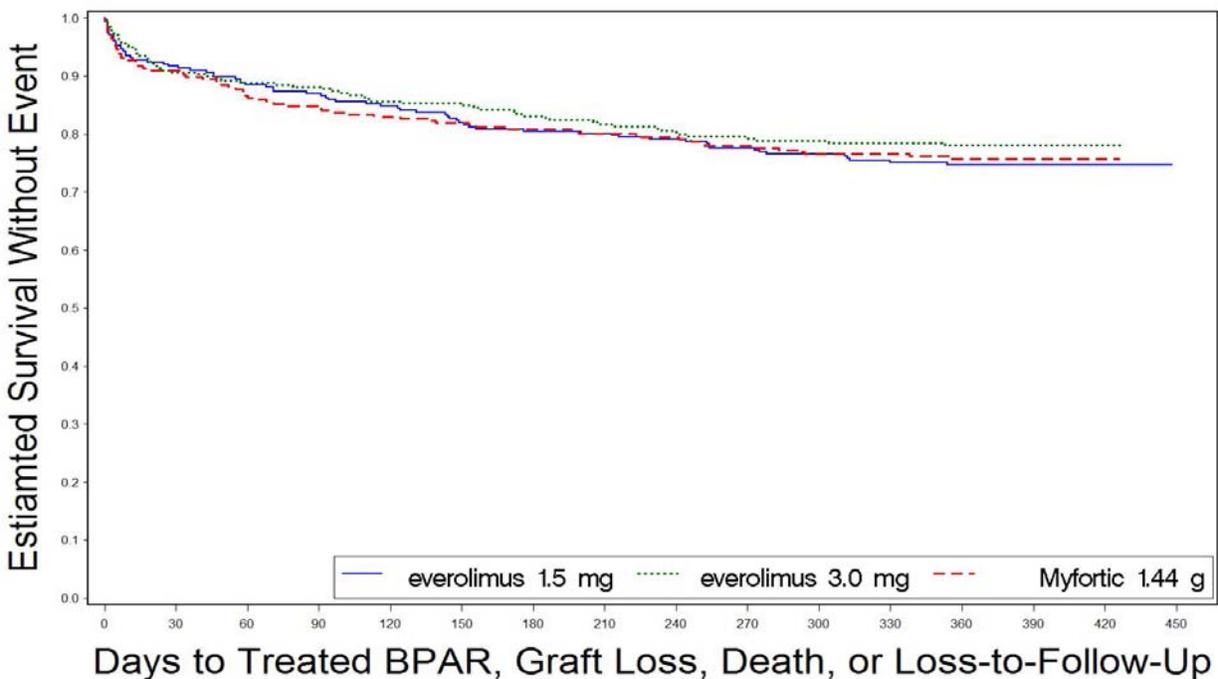
** One patient who had graft loss before the randomization was considered as loss to follow-up

Based on the protocol defined and justified non-inferiority margin of 10% and using the Hochberg's procedure to adjust for multiple comparisons, non-inferiority of both everolimus groups to Myfortic with respect to the primary efficacy endpoint was

achieved. This was demonstrated by the fact that the upper limits of both 95% confidence interval were less than the 10% non-inferiority margin.

The Kaplan Meier plot for the primary efficacy endpoint within 12 months was provided in Figure 4. Based on the log-rank test, median time to event was not statistically significantly different between everolimus 1.5 mg (p-value=0.83) and everolimus 3.0 mg (p-value=0.49) and Myfortic. No statistically significantly difference of time to event was shown between the two everolimus groups (p-value=0.37). If loss to follow-up patients were treated as censored rather than efficacy failure, similar results were reported by using time-to-event analyses. The p-value of log-rank test was 0.97 for everolimus 1.5 mg group versus Myfortic 1.44 g group, and was 0.53 for everolimus 3.0 mg group versus 1.44 g group, demonstrating that no significant differences between each of the everolimus groups and the Myfortic group.

Figure 4. Kaplan-Meier Estimates for the Primary Efficacy Endpoint by Treatment Group (ITT population- 12 Month Analysis)
(Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)



As a sensitivity analysis, the primary efficacy analysis was repeated using the central pathologist's assessment. The rate of composite efficacy failure was 17.3%, 15.4% and 15.9% for the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm treatment groups. These results are lower for all treatment groups than those obtained when using the local pathologist's evaluation, due to a number of missing central biopsy readings for patients who had an acute rejection confirmed by local readings.

To assess the impact of the disproportionate rates of premature treatment discontinuation on the primary efficacy endpoint, treatment discontinuation was treated as failure along with the primary efficacy composite endpoint. *In this sensitivity analysis, both everolimus groups failed to demonstrate non-inferiority to Myfortic, given that the upper limits of both 95% confidence interval exceed 10% (Table 16).* The Kaplan Meier plot for this sensitivity analysis was provided in Figure 4. The survival curve of the Myfortic group was always above either of the everolimus group, while median time to event was not statistically significantly different based on log-rank test (p=0.12 for everolimus 1.5 mg versus Myfortic, and p=0.08 for everolimus 3.0 mg versus Myfortic).

Table 16. Primary Efficacy Endpoint with Premature Treatment Discontinuation as Failure by Treatment Group (ITT Population- 12 Month Analysis)
 (Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

	everolimus 1.5 mg (N=277)	everolimus 3.0 mg (N=279)	Myfortic 1.44 g (N=277)
Efficacy Failure or Premature Treatment Discontinuation	103 (37.2%)	106 (38.0%)	84 (30.3%)
95% CI (everolimus - Myfortic)	(-1.0%, 14.7%)	(-0.2%, 15.5%)	N/A
97.5% CI (everolimus - Myfortic)	(-2.1%, 15.8%)	(-1.3%, 16.7%)	N/A

6.1.5 Analysis of Secondary Endpoints(s)

The main secondary efficacy objective was to compare the incidence rate of the composite endpoint of death, graft loss, or loss to follow-up between the everolimus and Myfortic treatment groups at 12 months post-transplantation.

As presented in Table 17 the incidence of death, graft loss or loss to follow up was similar between the two everolimus groups (11.6% and 11.1% respectively), and was 9.4% in the Myfortic group. Note that a non-inferiority margin for the endpoint of death, graft loss or loss to follow-up was not able to be justified due to a lack of sufficient data from historical information (see Appendix 2). However, the applicant stated that a 10% margin would be used. As shown in bold in Table 17, both 95% confidence intervals for the everolimus groups compared to Myfortic excluded this margin based on the upper bound.

**Table 17. Main Secondary Efficacy Endpoint Analysis by Treatment Group
(ITT Population -12 Month Analysis)**

(Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 gm (N=277)
Graft loss, death or loss to follow up	32 (11.6%)	31 (11.1%)	26 (9.4%)
Graft Loss	12 (4.3%)	13 (4.7%)	9 (3.3%)
Death	7 (2.5%)	9 (3.2%)	6 (2.2%)
Loss to follow-up *	14 (5.1%)	10 (3.6%)	11 (4.0%)
95% CI (Everolimus-Myfortic)	(-2.9%, 7.3%)	(-3.3%, 6.8%)	N/A
97.5% CI (Everolimus-Myfortic)	(-3.7%, 8.0%)	(-4.0%, 7.5%)	N/A

A loss to follow-up patient is a patient who did not experience graft loss or death and whose last day of contact is prior to study Day 316

Treated BPAR at 12 months was also a secondary endpoint of the study. As presented in Table 18, the grade and the number of treated BPAR episodes were similar between the two everolimus groups and the Myfortic group. In all three treatment groups, more than 85% of patients who experienced treated BPAR had only one treated BPAR event during the first 12 months of the study (Table 19).

**Table 18. Grade of Treated BPAR by Treatment Group
(ITT Population -12 Month Analysis)**

(Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

N (%) of patient with any grade of treated BPAR	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 gm (N=277)
Total episodes	45 (16.3%)	37 (13.3%)	47 (17.0%)
Banff Type IA	21 (7.6%)	16 (5.7%)	22 (7.9%)
Banff Type IB	7 (2.5%)	9 (3.2%)	6 (2.2%)
Banff Type IIA	7 (2.5%)	9 (3.2%)	15 (5.4%)
Banff Type IIB	1 (0.4%)	3 (1.1%)	2 (0.7%)
Banff Type III	1 (0.4%)	0 (0%)	1 (0.4%)
Missing grade	6 (2.2%)	4 (1.4%)	3 (1.1%)

**Table 19. Number of Treated BPAR Episodes by Treatment Group
 (ITT Population -12 Month Analysis)**

(Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

N (%) of patient with treated BPAR by number of BPAR	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 gm (N=277)
0 treated BPAR	232 (83.8%)	242 (86.7%)	230 (83.0%)
1 treated BPAR	39 (14.1%)	32 (11.5%)	41 (14.8%)
2 treated BPAR	5 (1.8%)	5 (1.8%)	5 (1.8%)
3 treated BPAR	0 (0%)	0 (0%)	0 (0%)
4 treated BPAR	1 (0.4%)	0 (0%)	0 (0%)

6.1.6 Other Endpoints

Primary Safety Endpoint – Renal Function

See Statistical Review of Safety by John Stephen Yap Ph.D.

The main safety endpoint of Study A2309 was serum creatinine at month 12 by calculated glomerular filtration rate (GFR) using the MDRD (Modification of Diet in Renal Disease) formula. The main safety objective was to show that the mean GFR of either everolimus 1.5 mg or 3.0 mg group was no worse than (non-inferior to) the Myfortic group by 8 mL/min/1.73m² at month 12 using t-test based, two-sided 95% and 97.5% confidence intervals.

Reviewer’s Comment: *There is no justified non-inferiority margin for GFR in de novo kidney transplantation. Results of this endpoint will be assessed for clinical importance.*

As shown in Table 20, Study A2309 demonstrated that calculated 12-month GFR, using the modification of diet in renal disease (MDRD) formula, was similar between both everolimus groups and the Myfortic group. Various sensitivity analyses, modeling and imputation methods for missing values resulted in similar results in 12-month GFR across treatment groups. Analyses of GFR trends found that the median GFR levels in the everolimus 1.5 mg group were numerically higher than those of Myfortic across most study visit windows but the treatment groups were not statistically significantly different at all time points.

Table 20. Renal Function (MDRD calculated GFR) at 12 Months
 (Source: Statistical Review of Safety by John Stephen Yap Ph.D.)

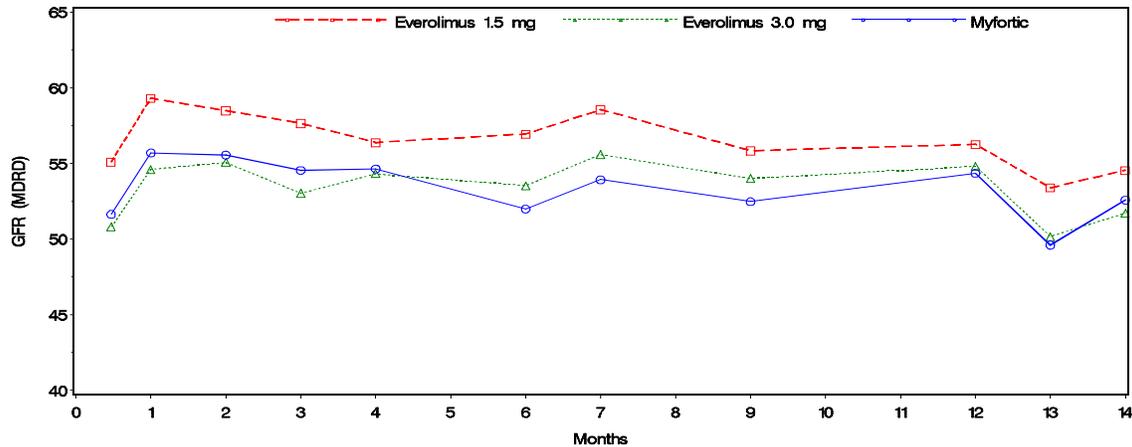
Method	Everolimus 1.5 mg	Everolimus 3.0 mg	Myfortic 1.44 gm
Method 1: LOCF*	n=275	n=278	n=277
Mean (SD)	54.6 (21.7)	51.3 (22.7)	52.2 (26.7)
Median (Range)	55.0 (0-140.9)	51.6 (0-124.0)	49.7 (0-366.40)
Difference in Mean*	2.4	-0.9	
t-test based 95% CI	(-1.7,6.4)	(-5.0,3.2)	
t-test based 97.5% CI	(-2.3,7.0)	(-5.6,3.8)	
p-value, t-test (no difference)	0.3**	0.7**	
Method 2: No imputation at 12 months	n=245	n=244	n=248
Mean (SD)	56.2 (20.1)	54.8 (19.6)	54.4 (26.4)
Median (Range)	55.3 (4.6-140.9)	53.8 (8.7-124.0)	50.8 (6.8-366.4)
Difference in Mean*	1.9	0.5	
t-test based 95% CI	(-2.3,6.0)	(-3.7,4.6)	
t-test based 97.5% CI	(-2.9,6.6)	(-4.3,5.2)	
p-value, t-test (no difference)	0.4**	0.8**	
* Everolimus-Myfortic; **Satterthwaite approximation for unequal variances			

LOCF=last observation carried forward approach for missing

* The actual numbers of patients with non-missing GFR values were 275, 278 and 277 in the everolimus 1.5 mg, 3.0 mg and Myfortic groups respectively.

Using the protocol defined last observation carried forward (LOCF) imputation approach (primary imputation approach) and with no imputation, mean GFR values were similar across treatment groups. In the LOCF analysis, patients with a graft loss were considered as having a GFR of 0, while those who died had their last value used. Additional methods for imputation were also used and similar results were obtained. Figure 5 shows the mean GFR over time of the complete data (no imputation).

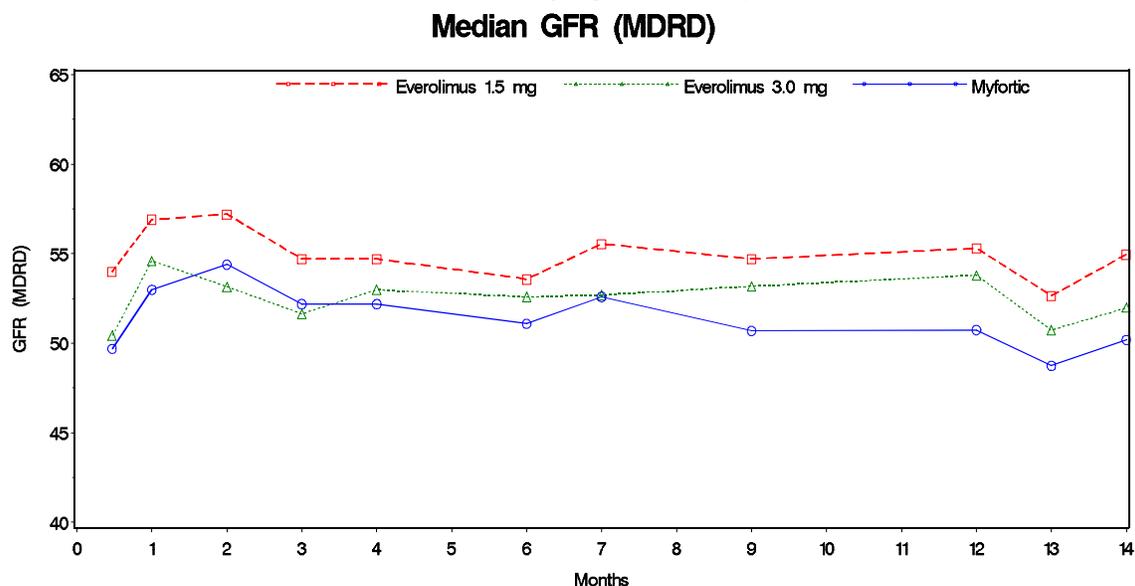
Figure 5. Mean GFR (MDRD) Over Time
(Statistical Review of Safety by John Stephen Yap Ph.D.)
Mean GFR (MDRD)



Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit. Month 14 represents the month 12 study endpoint consisting of the last post-baseline observation up to and including the month 12 visit.

Figure 6 shows the median GFR plots for the 12-months of study. The medians at each visit window for the everolimus 1.5 mg group were consistently higher than those of the Myfortic group and of the everolimus 3.0 mg group. The treatment groups were statistically significantly different (based on the Wilcoxon rank-sum test) at months 1 (p-value 0.0371), 6 (p-value 0.0135), 7 (p-value 0.0153), 9 (p-value 0.0228), 12 TEP (p-value 0.0412) and 12 SEP (p-value 0.0324). Note: The month 12 TEP (defined as the last post-baseline on-treatment observation up to and including month 12 visit) and month 12 SEP (defined as the last post-baseline observation up to and including month 12 visit) are shown in Figure 6 as months 13 and 14, respectively. There were no statistically significant differences between the everolimus 3.0 group and the Myfortic group at any visit windows. *Note: These multiple comparisons are unadjusted.*

Figure 6. Median GFR (MDRD) Over Time
(Statistical Review of Safety by John Stephen Yap Ph.D.)



Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit. Month 14 represents the month 12 study endpoint consisting of the last post-baseline observation up to and including the month 12 visit.

Reviewer's Comment: At the end of 12 month study period the difference between the mean calculated GFR values of the everolimus 1.5 mg and the Myfortic groups is 1.9 mL without LOCF (Last Observation Carried Forward) method and 2.4 mL with the LOCF method which are both statistically non-significant. Since there is higher CsA exposure in the Myfortic group compared to the everolimus groups a relative decrease in GFR is expected due to the CsA induced afferent glomerular arteriole vasoconstriction even if the both groups have the same degree of chronic allograft injury.

6.1.7 Subpopulations

Gender

Subgroup analysis of the primary efficacy endpoint by gender is presented in Table 21. Among male patients, the efficacy failure rate at 12 months post-transplantation was 28.4%, 21.5%, and 29.6%, in the everolimus 1.5 mg, 3.0 mg and Myfortic groups respectively. Compared to the Myfortic group, the everolimus 1.5 mg group had a slightly lower incidence of efficacy failure with risk difference of -1.2% (95% CI: -10.5, 8.1). The incidence was marginally significantly lower in the everolimus 3.0 mg group compared to the Myfortic group (RD= -8.1% (-16.9, 0.6), p-value=0.08).

In contrast, the primary efficacy failure among female patients was more frequent in both everolimus groups than in the Myfortic groups. The incidence rate in the everolimus 1.5 mg, 3.0 mg and Myfortic groups was 19.0%, 22.7%, and 12.5% respectively. The difference between everolimus 1.5 mg and Myfortic was 6.5% (95% CI: -3.8, 16.8, p=0.24), and difference between everolimus 3.0 and Myfortic was 10.2% (95% CI: -0.9, 21.4, p=0.11). Additionally, a statistically significant interaction between treatment and gender (Breslow-Day test p-value=0.01) was indentified in the comparison of everolimus 3.0 mg to Myfortic. No statistically significant interaction between treatment and gender was found in the comparison between everolimus 1.5 mg to Myfortic (Breslow-Day test p-value=0.24). When interpreting these subgroup analysis results, one must take into account that multiple comparisons according to various subgroups were not adjusted.

Table 21: Primary Efficacy Endpoint Analysis by Gender and Treatment Group (ITT Population - 12 Month Analysis) *

(Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

	Males Total =556			Females Total =276		
	Everolimus 1.5 mg (N=176)	Everolimus 3.0 mg (N=191)	Myfortic 1.44 g (N=189)	Everolimus 1.5 mg (N=100)	Everolimus 3.0 mg (N=88)	Myfortic 1.44 g (N=88)
Efficacy Failure*	50 (28.4%)	41 (21.5%)	56	19 (19.0%)	20 (22.7%)	11
Treated BPAR	33 (18.8%)	25 (13.1%)	(29.6%)	12 (12.0%)	12 (13.6%)	(12.5%)
Graft Loss	7 (4.0%)	7 (3.7%)	39	5 (5.0%)	6 (6.8%)	8 (9.1%)
Death **	3 (1.7%)	7 (3.7%)	(20.6%)	4 (4.0%)	3 (3.4%)	2 (2.3%)
Loss to follow-up	10 (5.7%)	7 (3.7%)	7 (3.7%)	1 (1.0%)	1 (1.1%)	0 (0%)
			6 (3.2%)			1 (1.1%)
			8 (4.2%)			
95% CI (everolimus – Myfortic)	(-10.5%, 8.1%)	(-16.9%, 0.6%)	N/A	(-3.8%, 16.8%)	(-0.9 %, 21.4%)	N/A
P-value***	p=0.82	p=0.08		p=0.24	p=0.11	

* One subject's gender was unknown and is excluded from this analysis

** One patient who died 10 days after withdrew consent was included

** P-value for the Fisher's exact test

Subgroup analysis of the main secondary endpoint (graft loss, death, or loss to follow-up) by gender is presented in Table 22. The observed incidence of graft loss, death, or loss to follow-up was similar across all three treatment groups (12.5% and 10.5% in the everolimus groups versus 12.7% in the Myfortic group) in male patients. Among female patients, the rate of graft loss, death, or loss to follow-up was 11.0%, 12.5%, 5.7% in the everolimus 1.5 mg, 3.0 mg and Myfortic groups respectively (p=0.09, everolimus1.5 mg v. Myfortic; p=0.05 everolimus 3.0 mg v. Myfortic, Fisher's exact test). Additionally, a statistically significant interaction between treatment and gender (Breslow-Day test p-value=0.03) was indentified in the comparison of everolimus 3.0 mg to Myfortic. No

statistically significant interaction between treatment and gender was found in the comparison between everolimus 1.5 mg to Myfortic (Breslow-Day test p-value=0.11).

Table 22. Graft Loss, Death, or Loss to Follow-up by Gender and Treatment Group (ITT Population - 12 Month Analysis) *

(Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

	Males Total =556			Females Total =276		
	Everolimus 1.5 mg (N=176)	Everolimus 3.0 mg (N=191)	Myfortic 1.44 g (N=189)	Everolimus 1.5 mg (N=100)	Everolimus 3.0 mg (N=88)	Myfortic 1.44 g (N=88)
Graft Loss, Death or Loss to follow-up	21 (11.9%)	20 (10.5%)	23 (12.2%)	10 (10.0%)	11 (12.5%)	3 (3.4%)
Graft Loss	7 (4.0%)	7 (3.7%)	7 (3.7%)	5 (5.0%)	6 (6.8%)	2 (2.3%)
Death **	3 (1.7%)	7 (3.7%)	7 (3.7%)	4 (4.0%)	3 (3.4%)	0 (0%)
Loss to follow-up	11 (6.3%)	8 (4.2%)	6 (3.2%)	2 (2.0%)	2 (2.3%)	1 (1.1%)
95% CI (everolimus – Myfortic) P-value***	(-6.9%, 6.5%) p=1.0	(-8.1%, 4.7%) p=0.63	N/A	(-0.4%, 13.6%) p=0.09	(1.2 %, 17.0%) p=0.05	N/A

* One subject's gender was unknown and is excluded from this analysis

** One patient who died 10 days after withdrew consent was included

** P-value for the Fisher's exact test

Analysis results for premature discontinuation by gender are presented in Table 23. In female patients, the incidence of premature treatment discontinuation in the everolimus 1.5 mg , 3.0 mg and Myfortic groups was 32.0% (32/100), 38.6% (34/88), and 15.9% (14/88) respectively, resulting in a p-value of 0.01 (everolimus 1.5 mg – Myfortic) and a p-value of 0.001 (everolimus 3.0 mg – Myfortic). Furthermore, in the everolimus 1.5 mg group, approximately 22% of the female patients prematurely discontinued treatment due to adverse events, which was statistically significantly higher (p-value= 0.004) than the Myfortic group (6.8%). Similarly, the incidence of premature treatment discontinuation due to adverse events in female patients in the everolimus 3.0 mg group was statistically significantly higher compared to the Myfortic group (21.6% versus 6.8%, with p-value=0.009). Additionally, female patients prematurely discontinued the study phase more frequently in the everolimus groups than the Myfortic group (14% and 11.8% versus 4.6%, p-value=0.04 and 0.16 respectively).

Difference in rates of premature treatment discontinuation was not observed among male patients in the study. Specially, the incidence of premature treatment discontinuation among male patients in the everolimus 1.5 mg , 3.0 mg and Myfortic groups was 29.0% (51/176), 31.9% (61/191), and 24.3% (46/189) respectively (p-value=0.34 for everolimus 1.5 mg versus Myfortic and p-value=0.11 for everolimus 3.0

mg versus Myfortic). Study discontinuation, among male patients, was similar across all three groups (13.6% and 12.0% versus 12.7%).

Table 23. Premature Study Medication or Study Phase Discontinuation by Gender and Treatment Group (ITT Population - 12 Month Analysis) *

(Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

	Males Total =556			Females Total =276		
	Everolimus 1.5 mg (N=176)	Everolimus 3.0 mg (N=191)	Myfortic 1.44 g (N=189)	Everolimus 1.5 mg (N=100)	Everolimus 3.0 mg (N=88)	Myfortic 1.44 g (N=88)
Discontinued study medication	51 (29.0%)	61 (31.9%)	46 (24.3%)	32 (32.0%)[#]	34 (38.6%)[#]	14 (15.9%)
Adverse event(s)	28 (15.9%)	38 (19.9%)	20 (10.6%)	22 (22.0%) [#]	19 (21.6%) [#]	6 (6.8%)
Unsatisfactory therapeutic effect	8 (4.6%)	9 (4.7%)	9 (4.8%)	3 (3.0%)	5 (5.7%)	4 (4.6%)
Others	15 (8.5%)	14 (7.3%)	17 (9.0%)	7 (7.0%)	10 (11.4%)	4 (4.5%)
Discontinued study phase	24 (13.6%)	23 (12.0%)	24 (12.7%)	14 (14.0%)[#]	10 (11.4%)	4 (4.6%)
Subject withdrew consent	14 (8.0%)	8 (4.2%)	11 (5.8%)	6 (6.0%)	0 (0%)	1 (1.1%)
Death	3 (1.7%)	6 (3.1%)	6 (3.2%)	4 (4.0%)	3 (3.4%)	0 (0%)
Graft loss	6 (1.7%)	5 (2.6%)	6 (3.2%)	3 (3.0%)	5 (5.7%)	0 (0%)
Unknown	1 (0.6%)	4 (2.1%)	6 (3.2%)	1 (1.0%)	2 (2.3%)	1 (1.1%)
			1 (0.5%)			2 (2.3%)

* One subject's gender was unknown and is excluded from this analysis

[#] p<0.05 compared to Myfortic for Fisher's exact test

Age and Race

No significant differences were seen among treatments between older and younger patients (categorized as ≤50 and >50 years of age). Among Black patients, the observed incidence of efficacy failure was lower in both everolimus groups than in the Myfortic group (29.4% and 35.0% versus 38.5%); however, no statistically significant differences were found (p=0.47 and 0.82 respectively). Note that Black patients represent only 13.5% of the total study population, therefore, caution should be used when interpreting findings in this small subgroup

Other Special/Subgroup Populations

Subgroup analysis of the primary efficacy endpoint (composite consisting of treated BPAR, graft loss, death, or loss to follow-up) by diabetic status and delayed graft function were also performed. The incidence of efficacy failure was similar between the everolimus groups and the Myfortic group in all the subgroups, and no statistically significant difference was identified.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The clinical development of everolimus in *de novo* renal transplantation has evolved from using fixed doses of everolimus (0.75 or 1.5 mg bid) with conventional doses of cyclosporine (CsA) to using blood trough level monitoring to adjust initial doses of everolimus (0.75 or 1.5 mg bid) to target trough levels (3-8 or 6-12 ng/mL, respectively) with reduced dose CsA.

The initial pivotal phase 3 studies B251 and B201, which used fixed dose everolimus and full dose CsA showed that an everolimus based regimen was effective in preventing acute rejection. However, the results showed that fixed dose everolimus when used in combination with standard dose CsA could lead to impaired renal function.

Pharmacokinetic/Pharmacodynamic modeling indicated that CsA was the primary factor lowering renal function, and that everolimus levels greater than 3 ng/mL were required to retain efficacy. Based upon these results two prospective studies A2306 (without basiliximab) and A2307 (with basiliximab) were conducted, using everolimus therapeutic drug monitoring (TDM) and reduced-dose CsA. Both studies showed improved renal function compared to the B251 and B201 studies and preserved efficacy, but did not include a non-everolimus control group.

This submission is based on a large new study, A2309, in *de novo* renal transplantation (n=833) that prospectively tested the efficacy and safety of 2 everolimus based regimens against an active comparator (standard treatment regimen combining MPA and standard dose of CsA). The same initial everolimus doses as in the previous pivotal studies B201 and B251 were used. Everolimus doses were then adjusted to reach blood trough level targets of 3-8 ng/mL and 6-12 ng/mL and combined with reduced exposure to Neoral guided by trough monitoring. The target trough levels for CsA in Study A2309 were lower in the everolimus arms compared to the everolimus arms in studies B201 and B251, while exposure to CsA in the MPA control groups was similar in all 3 studies and higher than in the everolimus groups in study A2309.

This new study (A2309) extends the data already submitted in *de novo* renal transplantation of the 2 prior pivotal studies with fixed doses of everolimus (B201 and B251) and the 2 large supportive studies (A2306 and A2307) using trough monitoring of

everolimus (>3 ng/mL) with reduced CsA exposure guided by monitoring blood levels 2 hours after dosing (C2).

The dose of Myfortic, the active comparator, was selected to provide the same molar dose as 1 g of mycophenolate mofetil (MMF) (720 mg Myfortic is equivalent to 1 g MMF) and is an approved dose of Myfortic for use in combination with cyclosporine (Neoral®). The dose selection rationale for everolimus was based on statistical PK/PD modeling of data obtained from earlier studies to determine the exposure of everolimus in combination with CsA that would preserve efficacy while optimizing renal function.

In summary, the 2 previous pivotal de novo renal transplant studies (B201, B251), showed comparable efficacy between everolimus 1.5 or 3.0 mg/day and the MMF comparator, but lower renal function. The PK/PD analyses showed clear relationships between high CsA blood levels and impairment of renal function, and low everolimus blood levels (<3 ng/mL) and higher rates of acute rejection.

Based on these results, 2 open-label studies were performed (A2306, A2307) to re-examine everolimus 1.5 and 3 mg/day, while adapting doses to keep trough levels of everolimus above 3 ng/mL and cyclosporine below those targeted previously. The studies showed improved renal function and efficacy comparable to that of MMF in earlier studies (B201, B251).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Both according to the published literature and according to the results of the Study A2309, a decrease in efficacy over time or development of tolerance has not been a problem with everolimus.

6.1.10 Additional Efficacy Issues/Analyses

It has been shown by Novartis, and confirmed by the Clinical Pharmacology reviewer, that there is an unacceptably high risk of acute rejection below trough levels of 3 ng/mL and the incidence of adverse events increase to unacceptable levels beyond trough levels of 12 ng/mL.

Table 24. Association Between Everolimus Trough Levels and Efficacy
 (Source: Pharmacometrics Review by Kevin Krudys, PhD)

Everolimus trough concentrations > 3 ng/mL demonstrate efficacy			
Everolimus trough levels	Treated BPAR	Graft Loss	Death
< 3 ng/mL	6/33 (18.2%)	4/35 (11.4%)	1/37 (2.7%)
3 – 8 ng/mL	64/415 (15.4%)	15/410 (3.7%)	9/411 (2.2%)
> 8 ng/mL	9/99 (9.1%)	3/101 (3.0%)	5/101 (5.0%)
Myfortic	47/277 (17%)	9/277 (3.2%)	6/277 (2.2%)

6.1.11 Efficacy Summary

Based on protocol specified and justified 10% non-inferiority margin, results from Study A2309 showed that both everolimus treatment regimens were non-inferior to the Myfortic treatment regimen at 12 months with regard to the primary efficacy composite endpoint consisting of the treated BPAR, graft loss, death or loss to follow-up. Additionally, the incidence rate of death, graft loss and loss to follow-up was similar between both everolimus groups and the Myfortic group.

A disproportionate rate of premature treatment discontinuation, driven by higher rates of adverse events, must be taken into consideration in the interpretation of both safety and efficacy outcomes in this study. More patients in both of the everolimus groups prematurely discontinued study treatment and were subsequently switched to alternate therapy than in the Myfortic group, which may bias the interpretation of the study results. A sensitivity analysis including premature treatment discontinuation as failure in the primary efficacy endpoint concluded that neither of the everolimus treatment regimens achieved non-inferiority to the Myfortic treatment regimen.

Analysis by gender revealed that among female patients, rates of premature treatment discontinuation, efficacy failure and the graft loss/death endpoint were considerably higher in both everolimus groups compared to the Myfortic group. Further analyses of these findings are ongoing. No differences were seen in the analysis of age (< 50 years and ≥ 50 years) or in the analysis by race, although about 14% of patients were Black, the others were Caucasian, Asian and other races.

Biostatistics Reviewer's Comment (DARRTS 12/11/2009): *Higher rates of graft loss and death in the everolimus subjects compared to Myfortic are concerning. Study A2309 may not provide adequate information to determine a safe and efficacious everolimus regimen especially for female patients*

The primary safety endpoint of Study A2309 was estimated GFR using the MDRD formula at 12 months following the kidney transplantation. No statistically significant differences in estimated GFR at month 12 were shown between each of the everolimus regimens and the Myfortic regimen.

The majority of patients were maintained within the targeted everolimus and CsA blood levels with the exception of higher than targeted CsA levels between 6 and 9 months in the everolimus groups.

7.0 Review of Safety

Note: Tables in this section were obtained from the Applicant's Clinical Study Report (CSR) of Study A2309, as noted. Tables created by the Reviewer, or obtained elsewhere are also noted.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Individual patient data from Study A2309 was used to evaluate safety. Previous fixed everolimus dose studies B201 and B251 are not included in the evaluation of safety since the drug exposures are different compared to the TDM Study A2309.

7.1.2 Categorization of Adverse Events

According to the study protocol adverse events (AEs) are reported up to 8 days after the discontinuation of the study medication and serious adverse events (SAEs) are reported up to 30 days after the discontinuation of the study medication. There was no cut-off time for reporting the graft losses and deaths.

Reviewer's Comment: *As will be discussed, there was a higher rate of treatment discontinuation in the everolimus groups compared to the Myfortic group. These early cut-off dates for reporting the AEs and SAEs possibly favored the everolimus groups.*

During the study, information on study drug discontinuations due to AEs was collected on two different CRFs. According to the information from the first form (Treatment and Study Completion CRF) the overall incidence of study drug discontinuations due to AEs according to this first data collection form were 18.1% in the everolimus 1.5 mg group, 20.4% in the everolimus 3.0 mg group, and 9.4% in the Myfortic group.

The information collected on the second form (AE/infections CRF) was more specific and contained information about the type of AE leading to study drug discontinuation. According to the second form, the rates of discontinuation were 23.4% in the everolimus 1.5 mg group, 28.4% in the everolimus 3.0 mg group and 15.8% in the Myfortic group. It was assumed that the information obtained from the second form would be more accurate and detailed; therefore this information is utilized for the analysis of AEs leading to drug discontinuation.

Infections Reported as AEs

Infection data was coded with SNOMED for micro-organism and type of infection (viral, bacterial, fungal and others). In addition to being analyzed similarly as AEs and SAEs, as described above, the incidence rate of infection by type and micro-organism was tabulated for each treatment group.

AEs Related to Wound Healing

The applicant identified AEs related to wound healing events through a retrospective search of the AE and infectious events databases. Identified terms were reviewed by their clinical team to determine relevance and then paper CRFs were dispatched to the sites for further information regarding the events prior to database lock.

AEs Related to Interstitial Lung Disease

The study database was searched for adverse event terms entering into the MedDRA special search query (SMQ) for interstitial lung disease (ILD, narrow) which included the adverse event preferred terms: *acute interstitial pneumonitis, allergic granulomatous angiitis, alveolar proteinosis, alveolitis, alveolitis allergic, alveolitis fibrosing, alveolitis, necrotizing bronchiolitis, diffuse alveolar damage, eosinophilia myalgia syndrome, eosinophilic pneumonia, eosinophilic pneumonia acute, eosinophilic pneumonia chronic, interstitial lung disease, lung infiltration, necrosis of bronchioli, obliterative bronchiolitis, pneumonitis, progressive massive fibrosis, pulmonary fibrosis, pulmonary necrosis, pulmonary radiation injury, pulmonary toxicity, pulmonary vasculitis, radiation alveolitis, radiation fibrosis – lung, radiation pneumonitis, transfusion-related acute lung injury.*

The reports identified by this search are included in the analysis.

AEs Related to Major Cardiac Events

A specific case report form was designed in order to capture information on the occurrence of major cardiac events (MACE) in the study. The applicant collected information on the following AEs:

- acute myocardial infarction
- congestive heart failure
- percutaneous coronary intervention
- coronary artery bypass graft
- automatic internal cardiac defibrillator
- cerebrovascular accident
- peripheral vascular disease

Vital signs variables included measurements of systolic and diastolic blood pressures, pulse, and body weight. Vital signs were examined for abnormal values and change from baseline according to pre-specified clinically notable criteria.

Systolic BP

- 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).

Diastolic BP

- 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).

AEs and SAEs were categorized both according to the MedDRA System Organ Class (SOC) and to Preferred Term (PT) in the 12 month analysis of the safety population.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Results from Study A2309 will not be pooled with previous studies, for several reasons: Only Study A2309 uses TDM of everolimus and reduced doses of CsA; Studies B201 and B251 used fixed doses of everolimus and standard doses of CsA.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

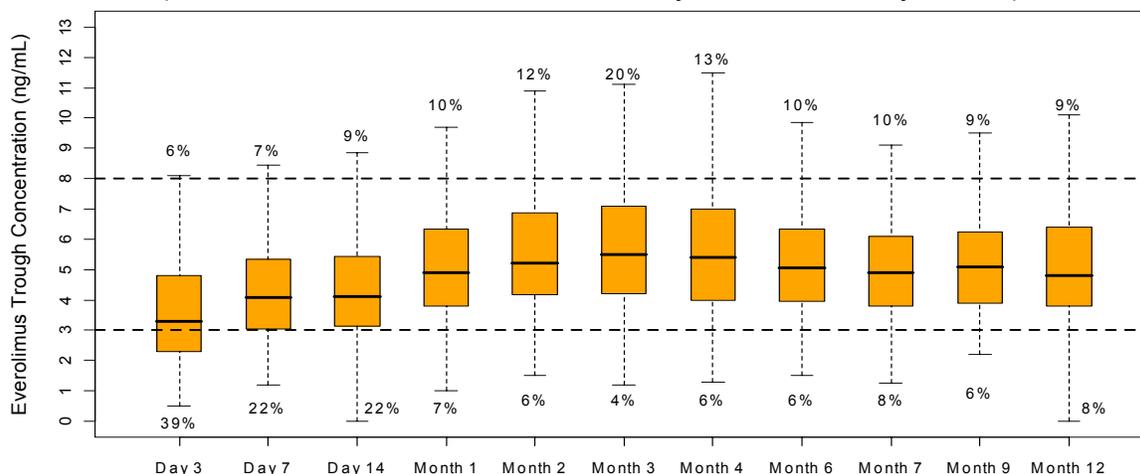
7.2.1.1 Trough Concentrations

Everolimus

The majority of patients in the everolimus 1.5 mg treatment group from Month 1 onwards, had everolimus trough blood levels within the target ranges. As seen in Figure 7 approximately 80% of trough everolimus concentrations were within target (3-8 ng/mL) from Month 1 onwards in the everolimus 1.5 mg group. Up to Month 1, patients were more likely to have had trough levels below the target range rather than above. Over the course of the study the percentage of patients achieving the target range increased. A higher percentage of patients in the everolimus 3.0 mg dose group had trough levels below the target range than in the everolimus 1.5 mg dose group.

Figure 7. Everolimus Cmin throughout the 12 Month Study Period in Everolimus 1.5 mg Group

(Source: Pharmacometrics Review by Kevin M. Krudys Ph.D)



Cyclosporine A

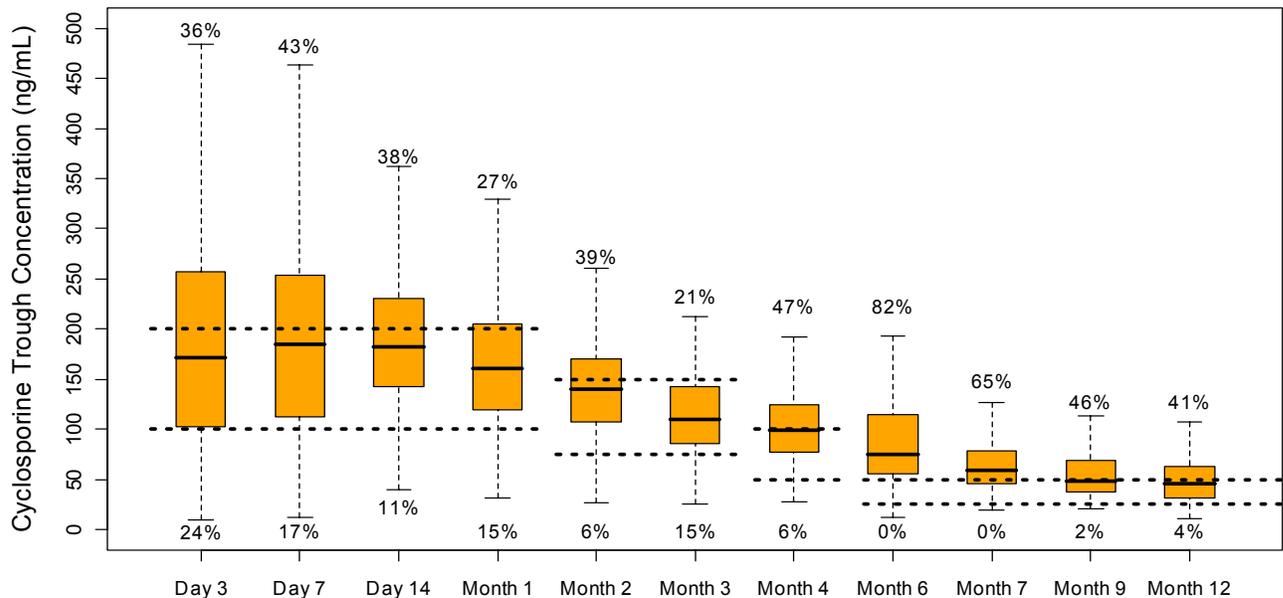
The CsA targets for the investigational groups were different from the control group beginning in the first week post-transplant. The targets were lower and the width of the target CsA windows progressively narrowed for the everolimus groups in contrast to the higher and progression to a wider window for the control group. In addition, the protocol driven CsA reduction was more regimented for the everolimus groups requiring four different windows compared to two different windows for the control group.

Mean CsA trough levels were lower in the everolimus treatment groups than the Myfortic group at all time points, as specified in the study protocol. CsA levels decreased over time for all treatment groups, with levels in the everolimus groups lower than the Myfortic group. At 12 months post-transplant the mean CsA trough levels were approximately three fold lower in the everolimus groups as compared to the Myfortic group. The upper limit of the CsA target range for everolimus groups at Day 3 was 200 ng/mL compared to 300 ng/mL in the Myfortic group. At Month 2, CsA target levels were a maximum of 150 ng/mL in the everolimus treatment groups (with over 50% of patients below this level), whilst in the Myfortic group, the target maximum was 250 ng/mL.

As shown in Figure 8, Cyclosporine concentrations tended to exceed target in everolimus 1.5 mg. group. The percentage of patients with CsA trough levels within the target range was greater than 50% from Day 14 onwards for the everolimus treatment groups, with the exception of Months 6 and 7 for the 1.5 mg group, and Months 4, 6 and 7 for the 3.0 mg group (at these points the target level decreased, and a higher percentage of patients had trough levels above the target range; data not shown).

Figure 8. Cyclosporine Cmin throughout the 12 Month Study Period (Everolimus 1.5 mg Group)

(Source: Pharmacometrics Review by Kevin M. Krudys Ph.D)



Reviewer's Comment: As seen in Figure 8 Cyclosporine Cmin was above the upper limit of targeted trough (50 ng/mL) at Month 6 and 7 and came down to 50 ng/mL starting Month 9 which may be indicative of the difficulty of managing this regimen with 2 simultaneous TDMs and with a significant DDI in-between the drugs monitored.

7.2.1.2 *Dose Adjustment*

Dose variation was permitted in all treatment groups for safety reasons, and from Day 5 onwards doses could be adjusted in order to maintain trough levels within the target window. For everolimus and Myfortic dose changes (including temporary dose interruption), the majority (greater than 97%) were as permitted by the protocol. In the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm dose groups 52.6%, 64.7% 24.5% of patients had more than two dose changes. In the everolimus treatment groups, the main reason for any dose change was to achieve the target level (67.5% for the 1.5 mg group and 70.6% for the 3.0 mg group).

An adverse event was the main reason for dose change in the Myfortic 1.44 gm group, and the second most frequent reason in the everolimus treatment groups (24.7%, 31.0% and 52.4% of dose-adjusted patients in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm treatment groups, respectively).

A dosing error was the reason for change in approximately 10% of any dose changes in any treatment group. Over 96% of any CsA dose changes (including interruptions) were as per the protocol. The majority of patients had more than two dose changes (96.0%, 95.3% and 95.6% in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm treatment groups, respectively).

In all treatment groups more than 80% of changes were to achieve the target level (83.2%, 86.2% and 81.9% of any changes in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm treatment groups, respectively). Adverse events were a reason for any dose change in fewer than 20% of patients in any treatment group.

7.2.1.3 *Average Daily Doses*

The average daily doses of everolimus and Myfortic are shown in Table 25 below. Mean values showed some variation for the everolimus groups, however median values remained constant.

Table 25. Average Daily Dose of Everolimus
(Source: Table 12-1, page 168, CSR):

Visit	Statistics	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 g N=273
Total	n	274	278	273
	Mean (SD)	2.64 (9.615)	5.81 (46.501)	1.344 (0.2104)
	Median (Range)	1.54 (0.3 – 149.6)	2.86 (1.1 – 776.5)	1.438 (0.70 – 2.23)
Day 1	n	274	278	273
	Mean (SD)	3.23 (22.600)	2.68 (0.452)	1.313 (0.1836)
	Median (Range)	1.50 (0.8 – 361.1)	3.00 (1.1 – 3.8)	1.440 (0.72 – 1.44)
Day 7	n	270	272	267
	Mean (SD)	2.72 (12.816)	2.90 (0.419)	1.419 (0.1216)
	Median (Range)	1.50 (0.4 – 150.0)	3.00 (1.1 – 4.5)	1.440 (0.67 – 2.16)
Month 1	n	257	257	257
	Mean (SD)	2.94 (13.065)	3.02 (1.133)	1.402 (0.1484)
	Median (Range)	1.50 (0.0 – 150.0)	3.00 (1.2 – 15.0)	1.440 (0.59 – 1.93)
Month 3	n	234	232	242
	Mean (SD)	3.06 (13.688)	9.02 (94.361)	1.361 (0.2190)
	Median (Range)	1.50 (0.4 – 150.0)	3.00 (0.5 – 1440.0)	1.440 (0.43 – 2.16)
Month 6	n	215	209	235
	Mean (SD)	2.50 (10.136)	2.69 (0.972)	1.334 (0.3064)
	Median (Range)	1.50 (0.5 – 150.0)	3.00 (1.0 – 7.3)	1.440 (0.00 – 2.88)
Month 9	n	206	198	225
	Mean (SD)	2.58 (10.354)	2.71 (0.967)	1.309 (0.2902)
	Median (Range)	1.50 (0.5 – 150.0)	3.00 (0.6 – 6.4)	1.440 (0.40 – 2.16)
Month 12	n	195	185	215
	Mean (SD)	2.64 (10.643)	3.38 (9.774)	1.314 (0.2880)
	Median (Range)	1.50 (0.5 – 150.0)	3.00 (0.8 – 135.0)	1.440 (0.54 – 2.16)

In calculating average daily doses, zero doses are used for periods of temporary interruption of study medication, regardless of whether this is due to safety reasons or non-compliance.
Source: [Table 14.3-1.3a](#)

The maximum values for everolimus groups in some cases were implausibly high and these were noted by the Applicant as likely erroneous (such as a maximum of 1.44 gm, which suggested the patient was switched to Myfortic). The analysis was repeated by the Applicant, and those doses of everolimus greater than 100 mg were replaced with a value of 0 based on the likelihood of a switch to Myfortic. Recorded doses of between 10 and 100 mg were divided by 10 to obtain a substitute value in Table 26 below.

Table 26. Average Daily Doses of Everolimus and Myfortic by Visit
 (Source: Table 12-2, page 168, CSR):

Visit	Statistics	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 g N=273
Total	n	274	278	273
	Mean (SD)	1.83 (1.060)	2.28 (0.844)	1.344 (0.2104)
	Median (Range)	1.54 (0.3 – 15.0)	2.85 (1.1 – 7.4)	1.438 (0.70 – 2.23)
Day 1	n	274	278	273
	Mean (SD)	1.42 (0.586)	2.68 (0.452)	1.313 (0.1836)
	Median (Range)	1.50 (0.8 – 7.0)	3.00 (1.1 – 3.8)	1.440 (0.72 – 1.44)
Day 7	n	270	272	267
	Mean (SD)	1.65 (1.190)	2.90 (0.419)	1.419 (0.1216)
	Median (Range)	1.50 (0.4 – 15.0)	3.00 (1.1 – 4.5)	1.440 (0.67 – 2.16)
Month 1	n	257	257	257
	Mean (SD)	1.89 (1.322)	3.02 (1.133)	1.402 (0.1484)
	Median (Range)	1.50 (0.0 – 15.0)	3.00 (1.2 – 15.0)	1.440 (0.59 – 1.93)
Month 3	n	234	232	242
	Mean (SD)	1.91 (1.388)	2.81 (1.080)	1.361 (0.2190)
	Median (Range)	1.50 (0.4 – 15.0)	3.00 (0.0 – 8.0)	1.440 (0.43 – 2.16)
Month 6	n	215	209	235
	Mean (SD)	1.87 (1.183)	2.69 (0.972)	1.334 (0.3064)
	Median (Range)	1.50 (0.5 – 15.0)	3.00 (1.0 – 7.3)	1.440 (0.00 – 2.88)
Month 9	n	206	198	225
	Mean (SD)	1.92 (1.230)	2.71 (0.967)	1.309 (0.2902)
	Median (Range)	1.50 (0.5 – 15.0)	3.00 (0.6 – 6.4)	1.440 (0.40 – 2.16)
Month 12	n	195	185	215
	Mean (SD)	1.95 (1.278)	2.71 (1.238)	1.314 (0.2880)
	Median (Range)	1.50 (0.5 – 15.0)	2.99 (0.8 – 13.8)	1.440 (0.54 – 2.16)

In calculating average daily doses, zero doses are used for periods of temporary interruption of study medication, regardless of whether this is due to safety reasons or non-compliance.
 Overall = from Day 1 to Month 12.
 Those records with Morning dose or Evening dose higher than 10 mg for RAD groups (everolimus 1.5 mg and everolimus 3.0 mg groups) are modified for this analysis; if dose >100 mg, then replaced by 0; if 0 < dose ≤ 100, then divided by 10.
 Source: [Table 14.3-1.3a1](#)

Mean and median doses decreased over the course of the study for all treatment groups, and were consistently lower in the everolimus treatment groups than the Myfortic group, as would be expected from the study design, with median Month 12 values of 1.36 mg/kg/day in the everolimus 1.5 mg group, and 2.93 mg/kg/day in the Myfortic 1.44 gm group.

7.2.1.3 Duration of Exposure

Median duration of treatment with everolimus or Myfortic was similar in all treatment groups, whilst mean duration of exposure was slightly longer in the Myfortic treatment group. Median exposure was at least 360 days, as shown in Table 27 below.

Table 27. Overall Exposure and Summary Statistics by Treatment Group (Safety population - 12 month analysis)

(Source: Table 12-4, page 171, CSR)

Table 12-4 Overall exposure and summary statistics by treatment group (Safety population - 12 month analysis)			
	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 g N=273
Exposure (days)			
Mean ± SD	288.7 ± 129.9	276.4 ± 134.6	310.3 ± 115.2
Median (range)	362.0 (2.0 – 408.0)	360.0 (1.0 – 391.0)	363.0 (2.0 – 426.0)
Categorical exposure duration (days) – n (%)			
≥ 1 day	274 (100.0)	278 (100.0)	273 (100.0)
≥ 5 days	270 (98.5)	272 (97.8)	267 (97.8)
≥ 12 days	261 (95.3)	263 (94.6)	261 (95.6)
≥ 22 days	257 (93.8)	257 (92.4)	257 (94.1)
≥ 45 days	243 (88.7)	248 (89.2)	250 (91.6)
≥ 76 days	234 (85.4)	231 (83.1)	242 (88.6)
≥ 106 days	225 (82.1)	221 (79.5)	238 (87.2)
≥ 151 days	216 (78.8)	209 (75.2)	234 (85.7)
≥ 196 days	211 (77.0)	201 (72.3)	231 (84.6)
≥ 241 days	207 (75.5)	198 (71.2)	225 (82.4)
≥ 316 days	196 (71.5)	186 (66.9)	215 (78.8)
Average daily dose during the study			
Mean ± SD	2.64 ± 9.615	5.81 ± 46.501	1.344 ± 0.2104

Source: [Table 14.3-1.1](#) and [14.3-1.3a](#)

7.2.2 Explorations for Dose Response

7.2.2.1 Exposure-Response for Efficacy

A whole blood trough concentration of 3 ng/mL was previously identified as the minimum target concentration to preserve efficacy in renal and heart transplantation from the exposure-response (ER) analyses from the renal transplantation studies B201 and B251, and heart transplantation study B253.

Both everolimus groups were pooled (one had target 3-8 and the other 6-12) for exposure-response analyses.

The efficacy results from Study A2309 were used to evaluate the robustness of this trough concentration of 3 ng/mL, as shown in Table 28. Consistent with the defined everolimus target ranges, a low number of patients had exposure lower than 3 ng/mL or higher than 12 ng/mL. The frequency of treated BPAR becomes progressively lower as everolimus trough concentrations increase. The risk of graft loss was higher at everolimus trough concentrations less than 3 ng/mL (11.4%) than between 3 and 8 ng/mL (3.7%). Above a minimum everolimus level of 3 ng/mL rates of treated BPAR are all numerically reduced compared to that with Myfortic. However, the risk of death was the highest (5.0%) at everolimus trough concentrations above 8 ng/mL, the upper limit of the sponsor proposed target therapeutic range. These results therefore support the 3 to 8 ng/mL target range for everolimus trough concentrations with regard to efficacy. Within these ranges BPAR, graft loss and death rates are comparable to those occurring with Myfortic.

Table 28. Association between Everolimus Target Trough levels and Efficacy

(Source: Pharmacometrics Review By Kevin Krudys, Ph.D.)

Everolimus trough levels	Treated BPAR	Graft Loss	Death
< 3 ng/mL	6/33 (18.2%)	4/35 (11.4%)	1/37 (2.7%)
3 – 8 ng/mL	64/415 (15.4%)	15/410 (3.7%)	9/411 (2.2%)
> 8 ng/mL	9/99 (9.1%)	3/101 (3.0%)	5/101 (5.0%)
Myfortic	47/277 (17%)	9/277 (3.2%)	6/277 (2.2%)

7.2.2.2 *Exposure-Response for Safety*

The relationship between whole blood everolimus trough concentrations and selected safety events up to 12 months post transplant in Study A3209 was established for the following:

- Proteinuria, defined as the urinary protein / urinary creatinine (UP/UC) ratio ≥ 0.3 g/g after Month 1

Reviewer's Comment: *According to NKF (National Kidney Foundation) the cut-off value is (UP/UC) ratio ≥ 0.2 .*

- Wound healing complications/events based on the applicant's analysis of all the relevant preferred terms
- Peripheral edema adverse events
- Hypercholesterolemia, defined as total cholesterol ≥ 6.2 mmol/L, or ≥ 240 mg/dL
- Hypertriglyceridemia, defined as triglycerides ≥ 5.6 mmol/L, or 500 mg/dL

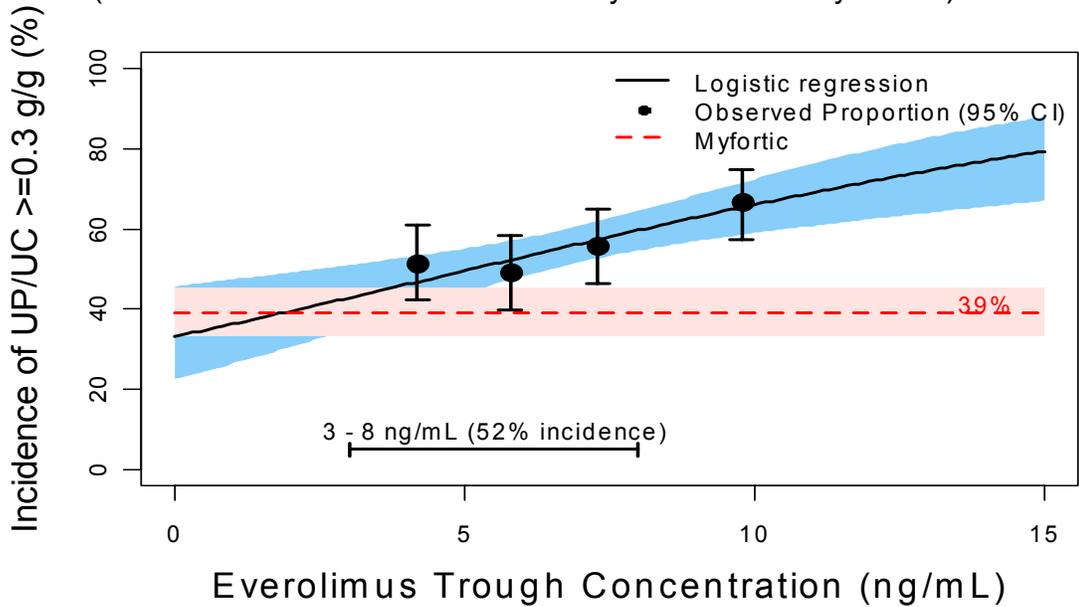
Reviewer's Comment: *These events were selected because they are associated with the M-TOR inhibitor class of drugs (i.e., sirolimus), were identified as clinically relevant, and were observed at higher rates in the everolimus treatment groups compared to the Myfortic control treatment group in Study A2309.*

Proteinuria

Incidence of proteinuria increases with higher everolimus concentrations (Figure 9).

Figure 9. Everolimus Trough Concentrations and Proteinuria.*

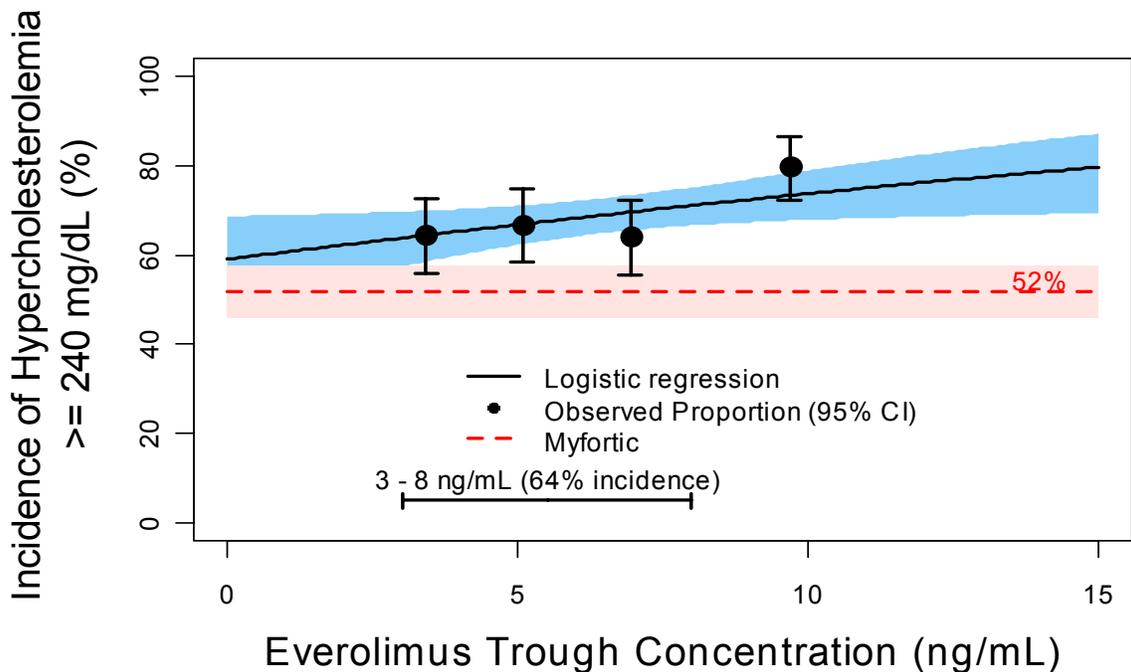
(Source: Pharmacometrics Review by Kevin M. Krudys Ph.D)



Hypercholesterolemia

Figure 10. Everolimus Trough Concentrations and Hypercholesterolemia.

(Source: Pharmacometrics Review by Kevin M. Krudys Ph.D)



Other Events

There was not a strong relationship between higher everolimus concentrations and the incidence of the following events:

- Peripheral edema adverse events
- Wound healing complications
- Hypertriglyceridemia (triglycerides >490 mg/dL)
- New onset diabetes mellitus

However, the incidence of these events was higher in the everolimus treatment groups.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to Section 4.3

7.2.4 Routine Clinical Testing

7.2.5 Metabolic, Clearance, and Interaction Workup

Everolimus pharmacokinetics has been characterized after oral administration of single and multiple doses to adult kidney transplant patients, hepatically-impaired patients, and healthy subjects.

From the label:

(b) (4)



(b) (4)



[Redacted] (b) (4)

[Redacted]

[Redacted]

[Redacted] (b) (4)

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The known M-TOR inhibitor class effects are:

- Hepatic artery thrombosis in liver transplantation and other Thromboembolic events
- Hyperlipidemia
- Proteinuria
- Wound healing problems like dehiscence, Incisional hernia, anastomotic separation (bronchial anastomotic dehiscence in lung transplantation)
- Peripheral edema

- Localized fluid collections like lymphocele, pericardial and pleural effusions, Ascites
- NODAT (New Onset Diabetes After Transplantation)
- Interstitial lung disease
- TMA/TTP/HUS
- Thrombocytopenia
- Angioedema
- Mouth ulcerations

7.3 Major Safety Results

7.3.1 Deaths

A total of 23 patients died during the first 12 months of the study, 7 (2.5%) in the everolimus 1.5 mg group, 10 (3.6%) in the 3.0 mg everolimus group, and 6 (2.2%) in the Myfortic control group. The most common causes of death across the study groups were related to cardiac conditions and infections. Table 26 through Table 28 for the everolimus and Myfortic groups, respectively; include relevant information regarding the patient's clinical course, along with the principal cause of death as assessed by the applicant and by FDA.

Four of the deaths occurred more than 30 days after discontinuation of study medication (one in the 1.5 mg everolimus group, two in the 3.0 mg everolimus group, and one in the Myfortic group).

One of the deaths in the everolimus 3.0 mg group (A2309-0168-00017) occurred in a patient who experienced multi-organ failure and died on Day 34. This patient was not included in the applicant's clinical database because the patient discontinued treatment and withdrew consent on Day 24.

Reviewer's Comment: *Although this patient (0168-00017) withdrew consent on Day 24 and died on Day 34, the chain of events that led to the demise of the patient (MI and pulmonary edema) started on Day 14 while he was still on treatment and there is only 10 days in between stopping the treatment medication and the death of the patient. This patient was included by FDA in their analysis of both the efficacy and safety populations.*

**Table 26. All Deaths Reported During the 12-month Study Period
 Everolimus 1.5 mg Group**
 (Source: Adapted by the Reviewer from Section 12.3 page 180 of the CSR)

Everolimus 1.5 mg					
(Investigator: 2 (3?) infectious, 3 cardiac, 1 PE, 1 malignancy = 7 deaths) (FDA: 2 (3?) infectious, 3 cardiac, 1 PE, 1 malignancy = 7 deaths)					
Patient	Day of Death	Day of D/C Study Medication	Relevant History	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
- 1 - 0125-00002 (F, 47, C)	31	30 (septic shock)	D16: lymphocele, UTI (rehospitalized) D22: cardiogenic shock and septic shock	Septic Shock	Septic Shock
- 2 - 0115-00020 (F, 43, C)	28	9 (Renal vein thrombosis)	D16: Transplant nephrectomy (renal vein thrombosis,) D23: re-laparotomy for evacuation of hematoma, abdominal sepsis D25: massive hemorrhage,	Abdominal sepsis	Abdominal sepsis
- 3 - 0100-00008 (F, 49, C)	148	76 (ureteral necrosis, urinoma nephrostomy)	D74: ureteral necrosis, urinoma, wound infection, cellulitis D77: nephrostomy, D87: psychosis	Poss ble pulmonary embolism	Pulmonary embolism? Multiple infections
- 4 - 0124-00076 (M, 39, C)	85 (sudden chest pain)	85 (death)	HTN Hypercholesterolemia after transplant Hypertensive cardiomyopathy	Myocardial infarction?	Myocardial infarction?
- 5 - 0516-00002 (M, 61, C)	156	156 (death)	D48: incisional hernia D 55: Hernia repair D102: edema, Lasix treatment CHF	Congestive heart failure (CHF)	Congestive heart failure (CHF)
- 6 - 0514-0003 (F, 51, O)	278	277 (sudden cardiac arrest at home)	On-study: intermittent reports of anemia, hypokalemia D277: cardiac arrest of unknown cause	Cardiac arrest (cause unknown)	Cardiac arrest (cause unknown)
- 7 - 0118-00012 (M, 52, C)	122	121 (melanoma)	D15: Lymphocele drainage D112: diagnosed with malignant melanoma D122: liver and brainstem metastases,	Metastatic melanoma	Metastatic melanoma

**Table 27. All Deaths Reported During the 12-month Study Period
 Everolimus 3.0 mg Group**

(Source: Adapted by the Reviewer from Section 12.3 of the CSR)

Everolimus 3.0 mg [Investigator: 3 infectious (2 pneumonia), 5 cardiac, 1 renal failure, 1 multiorgan failure = 10 deaths] [FDA: 5 infectious (6?) (3 pneumonia), 3 MI, 1 thrombocytopenia, 1 renal failure = 10 deaths]					
Patient	Day of Death	Day of D/C study Medication	Relevant History	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
- 1 - 0100-00002 (M, 56, C)	269	263 (pneumonia) <u>Everolimus dose reduced to 1.5 mg qd on D17 and to 1.25 mg on D34</u>	D16: perinephric collection-urinary fistula D30: recurrence urinary fistula D50 : recurrence urinary fistula D100: urolithiasis D263:pneumonia,	Septic Shock (Pneumonia)	Septic Shock (Pneumonia)
- 2 - 0114-0001 (M, 34, C)	243	45 (wound infection)	D2: coronary occlusion, angioplasty D30: wound infection D106: Bx. Rejection (methylprednisone, switch to tacrolimus) D140: graft loss, hemodialysis D243:X-Ray, pneumonia	Cardiac arrest (Pneumonia)	Pneumonia
- 3 - 0166-00025 (M, 30, C)	16	15 (cardio-pulmonary failure)	History: congestive cardiomyopathy, bronchopneumonia, pulmonary edema, f brotisans alveolitis Autopsy: Pneumonia	Cardiopulmonary failure (Autopsy: pneumonia)	Pneumonia
- 4 - 0507-0019 (M, 69, C)	234	230 (cardiac arrest)	History: coronary bypass, pulmonary HTN D56: Pneumonia D222: Myocardial infarction and staphylococcal pneumonitis D230: congestive heart failure, pulmonary edema,	Myocardial infarction	Pneumonia, Myocardial infarction
- 5 - 0532-0008 (F, 40, NA)	175	174 (death)	D175: severe renal abscess, pyelonephritis (autopsy: confirmed cardiomegaly – no further information)	Sudden death, Cardiomegaly	<u>Renal abscess, sepsis?</u> Congestive heart failure.
- 6 - 0553-0009 (F, 43, B)	322	316 (colitis)	D52: diarrhea (moderate) D 190-192: diarrhea (SAE, moderate) D265: culture of <i>Clostridium difficile</i> D308: <i>C.difficile</i> pancolitis. Fatal despite therapy, anemia	Colitis (<i>C. difficile</i>)	Colitis (<i>C. difficile</i>)
- 7 - 0168-00017	34	24 (withdrew consent)	D13: rejection, graft loss D14: pulmonary edema, non Q-wave MI-anticoagulation D23: Surgery for retroperitoneal	Multi-organ failure	Myocardial infarction Hemorrhagic shock

Everolimus 3.0 mg					
[Investigator: 3 infectious (2 pneumonia), 5 cardiac, 1 renal failure, 1 multiorgan failure = 10 deaths]					
[FDA: 5 infectious (6?) (3 pneumonia), 3 MI, 1 thrombocytopenia, 1 renal failure = 10 deaths]					
Patient	Day of Death	Day of D/C study Medication	Relevant History	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
(M, 59, C)			hematoma, hemorrhagic shock D24: Transplant nephrectomy		
- 8 - 0520-0009 (M, 65, C)	7	7 (death)	D6: MI, coronary occlusion by angiogram, stent placement D7: bradycardia with fatal cardiac arrest	Myocardial infarction	Myocardial infarction
- 9 - 0173-00003 (F, 52, B)	185	2 (TTP)	D3: thrombocytopenic purpura, hemolytic anemia D17: urine leak, infection D26: nephrotic syndrome, D89: purulent discharge in the wound D141:UTI, nephrotic syndrome	Renal failure, Fluid overload (No access to dialysis)	Renal failure, Fluid overload (No access to dialysis) Infection
- 10 - 0549-0001 (M, 55, C)	24	17 (Thrombocytopenia, sepsis)	History: aortic aneurism D16: Laparotomy: retroperitoneal hematoma, (No intestinal obstruction), D17 Platelets: 16,000 (Baseline: 165,000) Sepsis, Atrial fibrillation	Sepsis (Bowel obstruction)	Retroperitoneal bleeding, Thrombocytopenia, Sepsis

**Table 28. All Deaths Reported During the 12-month Study Period
 Myfortic Group**

(Source: Adapted by the Reviewer from Section 12.3 of the CSR)

Myfortic					
(Investigator: 2 cardiac, 1 stroke, 1 traffic accident, 1 natural = 6 deaths)					
(FDA: 2 MI, 1 stroke, 2 traffic accidents, 1 unknown = 6 deaths)					
Patient	Day of Death	Day of D/C Study Medication	Relevant History	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
- 1 - 0502-00016 (M, 58, B)	253	6 (rejection)	D4: Acute rejection D21: bacteremia Staph aureus D253: cardiac arrest at home. Also reported as acute myocardial infarction Switched to SIROLIMUS on D4	Cardiac Arrest (at home)	Myocardial infarction?
- 2 - 0544-00012 (M, 61, C)	34	33 (death)	Coronary bypass, asthma, diabetes hyperbilirubinemia D17: hypoglycemia (73 mg/dL)	Myocardial infarction	Myocardial infarction
- 3 - 0513-00010 (M, 64, C)	15	14 (stroke)	Bilateral femoral stent insertion D15: epistaxis, hyperglycemia (892), malignant HTN (226/100), hemorrhagic stroke) D16: no cerebral activity EEG	Hemorrhagic stroke	Hemorrhagic stroke
- 4 - 0521-00007 (M, 57, B)	356	356 (death)	D356: traffic accident, died instantaneously	Motor vehicle accident	Motor vehicle accident
- 5 - 0122-00003 (M, 62, C)	250	243 (sepsis)	D237: Motor vehicle accident, Multiple fractures, fever, hypotension D240: sepsis (<i>E. coli</i>)	Pulmonary embolism	Motor vehicle accident,
- 6 - 0553-00014 (M, 47, B)	55	55 (death)	History: heart murmur, obesity	"Natural cause" (no further information)	Unknown

Applicant's Assessment of Deaths

A difference was noted between the groups as regards to fatal infections (everolimus 1.5 mg: 2 cases, everolimus 3.0 mg: 4 cases, Myfortic 1.44 g: none). There were also a greater number of deaths ascribed to MI in the everolimus 3.0 mg group than in either of the other two treatment groups (everolimus 1.5 mg: 1 case; everolimus 3.0 mg: 3 cases; Myfortic 1.44 g: 1 case).

In the Applicant's review of deaths, 20 out of 22 were thought to be unrelated to study drug (not counting patient 0168-00017 who withdrew consent). The 2 deaths thought study drug-related were one case of late stage, metastatic melanoma in the 1.5 mg everolimus group and one case of cardiopulmonary failure with known congestive cardiomyopathy and hypertension in the 3.0 mg everolimus group.

In the everolimus 3 mg group, cardiac disorders and infections led to most deaths, none of which were considered drug-related except the case of cardiopulmonary failure mentioned above. The other deaths were randomly distributed across system organ classes and events.

Reviewer's Assessment of Deaths

A discussion of the deaths in each of the treatment groups follows along with an overall conclusion regarding the attributability of the deaths to the study medication.

Everolimus 1.5 mg Group:

Among the seven deaths in the everolimus 1.5 mg/d group, 3 are due to cardiac and 2 are due to infectious reasons and there is one case with possible pulmonary emboli in addition to co-existent infection and one malignancy associated death. The reviewer believes that there is an association between all the seven deaths reported in this group and the study medication (everolimus) including patient 0100-00008 who died more than 30 days after the discontinuation of the study medication.

Patients of special interest:

Patient 125-00002: This 47 year old female patient was rehospitalized on Day 13 after the transplant with the diagnosis of lymphocele and urinary tract infection (UTI). On Day 20 deep wound dehiscence with wound infection is also reported in the CRF. On Day 22 she had abdominal pain, anuria, nausea and was diagnosed with severe septic shock and severe cardiogenic shock secondary to propranolol intoxication. Her blood culture grew Acinetobacter species. Anasarca (generalized edema), is also described in the CRF during this period which lasted until the patient's death.

The events that started the decline of this patient are UTI, wound dehiscence, wound infection and lymphocele. UTI and wound infection which may be

associated with the study drug gave rise to septic shock. Wound healing problems and lymphocele are well described M-TOR class toxicities and probably also contributed to the death of this patient.

Patient 0115-00020: Graft thrombosis possibly related to the thrombogenic effects of everolimus (M-TOR inhibitors in general) led to intraabdominal infection which caused the death of this 43 year old female patient.

Patient 0100-00008: Although this patient died on Day 148, 70 days after stopping the study medication (everolimus) there is a highly possible association between the death of this patient and the study medication. This 49 year old female patient developed urethral necrosis followed by urinoma and nephrostomy placement for the treatment of this complication. At the same time this patient developed wound infection with cellulitis which altogether led to prolonged hospitalization and immobilization and also developed psychosis during this period. Wound related problems like delayed healing, dehiscence and infections are among the well characterized adverse effects of M-TOR inhibitors. It is very likely that the pulmonary emboli which is presented as the cause of death was caused by the preceding prolonged hospitalization and immobilization.

Patient 0124-00076: This 39 year old male patient whose death was attributed to acute myocardial infarction developed severe dyslipidemia (hypercholesterolemia) after the transplant which gradually worsened until his death on Day 85. His total cholesterol increased from 147 mg/dL to 432 mg/dL and his LDL cholesterol increased from 81 mg/dL to 212 mg/dL (normal levels: up to 129 mg/dL) during the course of the study. This 39 year old patient had a documented prior history of hypertensive cardiac disease (myocarditis).

Hypercholesterolemia is a well known class toxicity of M-TOR inhibitors and might have contributed to the death of this patient who had normal lipid levels before the start of the study treatment. Thrombogenicity of everolimus might have additionally contributed to this outcome by enhancing the coronary artery occlusion. It is also known from the non-clinical studies that everolimus has a potential to cause myocarditis which might have exacerbated the already existing hypertensive myocarditis.

Patient 0516-00002: This 61 year old male patient developed an incisional hernia after the transplant and had surgical hernia repair. He also had perinephric fluid collection. On Day 102, he was diagnosed to have edema and was put on furosemide treatment. On Day 156, he was diagnosed with severe congestive heart failure. The study medication was permanently discontinued due to the event. He died on the same day due to congestive cardiac failure.

This patient developed edema and other types of fluid collection like perinephric fluid followed by congestive heart failure which resulted in his death. Edema and other type of fluid collections in various compartments of the body are among the class toxicities of M-TOR inhibitors and hypervolemia may cause or enhance congestive heart failure.

Patient 0118-00012: A 52 year old male who had a biopsy of the bladder on Day 112 which revealed malignant melanoma. On Day 119, the patient experienced severe hematuria and on Day 121 a liver ultrasound revealed findings which were consistent with hepatic and brain stem metastases. The patient died subsequently due to metastatic malignant melanoma.

This is the only patient who died of cancer in the study. There may be an association with the study drug since it is known that systemic immunosuppression in general increases the incidence of malignancies.

Everolimus 3.0 mg Group:

The reviewer does not intend to give a detailed discussion of the deaths in this group since the applicant accepts the high incidence of adverse events in this treatment group and is not seeking approval of this dose. Details of the patients in this group will be given if there is an implication for the everolimus 1.5 mg group.

Among the 10 deaths in the everolimus 3.0 mg/day group, 5 are due to infectious reasons, 3 are due to myocardial infarction, one due to retroperitoneal bleeding associated with thrombocytopenia, and one is due to renal failure in a patient who did not have access to hemodialysis. It is important to note that of the five deaths caused by infections three were due to pneumonia.*

Patient 0100-00002: This 56 year old male patient was switched to 1.5 mg qd dosing on day 17 and the dose was further reduced down to 1.25 mg qd although he was in the everolimus 3.0 mg group. He stayed on the 1.25 mg qd dosing until his death on Day 263 due to pneumonia. Therefore the reviewer believes that this patient should be considered among the deaths in the everolimus 1.5 mg group for the evaluation of safety.

Patient 0549-0001: This 55 year old male patient died due to retroperitoneal bleeding which apparently started in association with severe thrombocytopenia which probably was drug induced. M-TOR inhibitors are known to cause thrombocytopenia. This patient had a laparotomy on Day 16 for suspected intestinal obstruction was found to have retroperitoneal hematoma. His baseline platelet count was 165,000. On Day 3 platelet count was down to 128,000, and on Day 14 it was down to 38,000. Between Day 7 and Day 14 his hemoglobin

level also dropped from 15.4 g/dL down to 11.4 g/dL. On Day 16 he had the laparotomy which disclosed the hematoma. On Day 18 his platelet count was 16,000 and everolimus was discontinued because of thrombocytopenia. The reviewer found this patient to be of special interest because of the association between the thrombocytopenia and this patient's death. It is not very common to see kidney transplant patients die due to hemorrhage which is associated with thrombocytopenia. Although other immunosuppressants like MPA derivatives may also cause thrombocytopenia it is very uncommon to see deaths and the thrombocytopenia due to MPA derivatives usually respond to dose reduction or discontinuation before resulting in a fatal outcome.

Myfortic Group

Among the 6 deaths in the control (Myfortic) group 3 are due to cardiovascular events. Two patients had myocardial infarctions and one patient had a hemorrhagic stroke. Of the remaining three two are due to motor vehicle accidents and one case of death on Day 55 in a 47 year old male patient reported as natural cause with no further information.

Patient 0502-00016: This 58 year old male patient died on Day 253 due to myocardial infarction. This patient was placed on Sirolimus (another M-TOR inhibitor) starting Day 4 and the study medication was discontinued starting Day 6 because of an acute rejection episode. Although this patient was in the control (Myfortic) group, he had been on Sirolimus treatment for 249 days when he died and he received the study medication only for 4 days after the transplant.

Although this patient (0502-00016) was randomized to the control group he received the study medication only for four days and he was on a different immunosuppressive regimen for the last 249 days that preceded his death. The reviewer believes that this incidence of death should not be counted among the deaths in the control group.

Patient 0122-00003: This 62 year old male patient died as a result of pulmonary emboli following a major motor vehicle accident on Day 237 of the study and sustained multiple fractures during the accident. He later developed E. coli sepsis and died on Day 250, 13 days after the accident. The cause of death for this patient is listed as pulmonary emboli by the sponsor.

Although the final event causing the death for this patient (0122-00003) might have been pulmonary emboli (no record of autopsy) this happened 13 days after a severe motor vehicle accident during which the patient sustained multiple fractures. It is very clear that this accident started the chain of events (sepsis and possible pulmonary emboli) that led to the death of this patient so the reviewer

believes that the real cause of death in this otherwise stable patient is the motor vehicle accident.

Patient 0521-00007: This patient also died due to a motor vehicle accident and expired instantly on the scene of the accident.

Reviewer's conclusion on the study medication attributability of mortality:

The total number of deaths reported during the study period is 23 including patient 0168-00017 (explained in more detail above) who withdrew consent on Day 24 and died on Day 34. After reviewing the narratives and CRFs, as an overall evaluation of mortality in Study A2309 the reviewer believes that the actual number of deaths which may have a causality association with the study drugs is 18. As stated above the reasons for excluding the possibility of any association between the study medication and the death event in 5 patients are:

In the Myfortic group, two patients (0122-00003 and 0521-00007) died as a result of motor vehicle accidents and the third patient (0502-00016) has been on a different immunosuppressive regimen (Sirolimus) almost for the whole duration of the study period until his death (249 days out of the total of 253 days).

In the everolimus 3.0 mg group, Patient 0173-00003 died 183 days after discontinuing the study medication. Patient 0114-0001 died on Day 243, 198 days after discontinuing the study medication.

After excluding these five cases of deaths because of lack of association between the death and the study medication the distribution of the number deaths with a probable association with the study medication across the study groups are as follows:

- 7 deaths in the 1.5 mg everolimus group*
- 8 deaths in the 3.0 mg everolimus group*
- 3 deaths in the Myfortic (control) group*

There is one patient (0100-00002) in the everolimus 3.0 mg group whose dose of everolimus was reduced down to 1.5 mg qd starting Day 17 and down to 1.25 mg qd starting Day 34 and stayed at this level until his death on Day 269. The reviewer believes that although this patient was assigned to the 3.0 mg group he has been on 1.25 mg everolimus qd for almost the whole duration of the study period (252 days) he should be included in the 1.5 mg qd group for purposes of safety evaluation. After the transfer of this patient to 1.5 mg everolimus group the final distribution of patient deaths with a probable attributability to the study medication:

- 8 deaths in the 1.5 mg everolimus group
- 7 deaths in the 3.0 mg everolimus group
- 3 deaths in the Myfortic (control) group

According to this final assessment of study drug attributability of patient deaths there are more than twice as many deaths in both of the everolimus groups compared to the Myfortic group that shows a probable association with the study medication.

This assessment is in line with mortality rates reported from another concentration controlled everolimus heart transplant study. In this heart transplant study (Study 2310), which utilized the same immunosuppressant regimens with same study design as in Study A2309, and utilized concentration controlled everolimus administration, the everolimus 3.0 mg group was terminated by the DMC due to excessive mortality in this group

In a study in de novo liver transplant patients, the use of Rapamune in combination with tacrolimus was associated with excess mortality and graft loss (22% in combination versus 9% on tacrolimus alone). Many of these patients had evidence of infection at or near the time of death.

In a clinical study in stable liver transplant patients 6-144 months post-liver transplantation and receiving a CNI-based regimen, an increased number of deaths was observed in the group converted to a sirolimus-based regimen compared to the group who was continued on a CNI-based regimen, although the difference was not statistically significant (3.8% versus 1.4%). This study was terminated by the Sponsor.

Although heart and liver transplants are different than de novo kidney transplant patients, the signal of increased mortality with everolimus 3.0 mg and sirolimus in combination with CsA or tacrolimus, observed in these other studies is consistent with Study A2309 and the known effects of the M-TOR inhibitors.

Another interesting observation in the assessment of the deaths was the high occurrence of wound complications among the patients who died in both of the everolimus groups. Although it is difficult to explain the association between this high occurrence of wound complications among the patients who died in both of the everolimus groups it is almost certain that there is a trend.

In the everolimus 1.5 mg group 5 of the 7 patients who died, in the everolimus 3.0 mg group 4 of the 10 patients who died developed wound related complications sometime after the transplant surgery compared to 1 out of 6 patients who died in the Myfortic group. Wound complications observed in the everolimus groups may be a surrogate for the patient's intolerance to the study drug. This association is

explained in more detail in the section of the review regarding wound complications.

** In another study of Sirolimus (M-TOR inhibitor) conversion in stable liver transplant patients, study 314 the applicant (Wyeth) found an association between the Cmin of Sirolimus and the occurrence of pneumonia. This study was terminated early due to excessive number of deaths in the Sirolimus conversion group.*

Deaths Reported Beyond the Initial 12 Month Analysis Period

The data in the NDA resubmission covers the period of April 24 through June 30, 2009 (12-month data analysis). However, the study is still ongoing and 5 additional deaths occurred beyond the 12 month analysis period. These deaths were included in the NDA resubmission, but not included as part of the 12-month analysis (patients 0304-00016, 0361-00002, 0517-00004, 0305-00004, and 553-00002). In addition after the NDA resubmission, there was one death (0181-00011) reported separately to FDA as a part of the applicant's commitment to provide periodic safety updates in this continuing study. These six additional deaths are summarized in Table 29.

Among these deaths of particular importance is the 47 year old male patient (0304-00016) in the everolimus 1.5 mg group who eventually died of pneumonia and septic shock on Day 436 after a series of events. This patient developed dyspnea starting day 316 and was diagnosed to have alveolar proteinosis by lung biopsy on Day 370. His condition gradually deteriorated until his death on Day 436. Alveolar proteinosis is a rare but potentially serious event associated with M-TOR inhibitors and is probably the primary cause of death in this patient. These deaths are summarized in Table 29 below:

**Table 29. Deaths Reported After the Initial 12 Month Study Period
 All Treatment Groups**

(Source: Adapted by the Reviewer from Section 12.3 of the CSR)

Patient	Day of Death	Day of D/C Study Medication	Relevant History	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
Everolimus 1.5 mg					
0304-00016 (M, 47, A)	436	435 (septic shock)	D316: dyspnea D370: Lung biopsy, alveolar proteinosis D434: pneumonia, septic shock	Septic shock	Alveolar proteinosis, pneumonia, septic shock
0181-00011 (M, 47, C)	602	496 (Presumptive acute rejection)	D434: Ao. valve incompetence: valve replacement. Warfarin D486: coronary by pass D494: Acute Rejection D499: Resp. failure, intubation, dialysis D505: mitral insufficiency. Valve replacement D600: endocarditis	Endocarditis Sepsis Circulatory Failure Mitral valve Failure	Endocarditis Sepsis Circulatory Failure Mitral valve Failure
Everolimus 3.0 mg					
0361-00002 (F, 39, C)	528	528 (death)	D366: hematuria after biopsy done for proteinuria (UP/UC: 79 mg/mmol) D528: malaise, death.	Presumed AMI	Presumed AMI
Myfortic					
0517-00004 (M, 67, B)	755 (After 24 month study period)	732 (completed study)	D570: suspected acute rejection D733: chest pain, nausea vomiting (feculent matter), cardiac arrest. ECG: A. fib., possible inferior and anterolateral subendocardial injury.	Cardiac arrest	Myocardial infarction?
0305-00004 (F, 32, A)	594	490 (Switched to Tacrolimus)	D420: Increased serum creatinine, acute rejection, treated with corticosteroids and Tacrolimus. According to the narrative tacrolimus was started without discontinuing CsA D 560: cough, chills pyrexia, hospitalized, diagnosed with Pneumocystis Jiroveci pneumonia	Pneumocystis Jiroveci pneumonia	Pneumocystis Jiroveci pneumonia
0553-00002 (M, 48, C)	535	522	D 503: peripheral neuropathy, acute renal failure D508: diarrhea, fever, dehydration, Myfortic dose increased, diarrhea worsened D522: double vision, nystagmus, encephalitis D525: positive for West Nile virus thought to contribute to kidney injury	West Nile virus infection	West Nile virus infection

Reviewer's Comment:

Although these deaths occurred beyond the 12 month study period and it is not possible to make a numerical comparison across the treatment groups with regard to these deaths still they are discussed to point to the causality association between everolimus and the death of especially patient 0304-00016 in the everolimus 1.5 mg group.

In the everolimus 1.5 mg group:

Patient 0304-00016: This 47 year old male patient died due to pneumonia and septic shock 60 days after a biopsy confirmed diagnosis of alveolar proteinosis which in the Reviewer's opinion caused the pneumonia and is the real cause of death. Alveolar proteinosis is a class effect of M-TOR inhibitors.

In the everolimus 3.0 mg group:

Patient 0181-00011 who had multiple cardiac problems also developed pancreatitis on Day 209 which was attributed to hyperparathyroidism but could also be related to everolimus since M-TOR inhibitors are known to cause pancreatitis. Novartis has reported an incidence of pancreatitis over 1% in their database.

Pancreatitis which developed on Day 209 in this patient (0181-0001) probably has little association with the death event if any, on Day 602 but may have contributed to the overall decline of the patient.

In the Myfortic group:

A total of 3 additional deaths were reported after the 12 month study period:

Patient 0517-00004 died on Day 755 after he has completed the 2 year study period and 23 days after the last dose of the study medication.

Patient 0305-00004 was switched to another CNI inhibitor, a generic formulation of tacrolimus 100 days before her death and there was a period of overlap approximately 1 month or longer in duration while the patient was receiving two different CNIs (CsA and tacrolimus) at the same time. The 100 day period between the discontinuation of the study medication and the death event and the fact that this patient two different CNIs at the same time for a considerable period makes it very difficult to find any causality or attributability association between the study medication and the death event.

Patient 0553-00002 who died of West Nile virus infection on D 535 started to have symptoms of this infection including peripheral neuropathy starting D 503 but the correct diagnosis was made on D 525, 22 days after the start of significant symptoms. During the delayed diagnosis period the dose of Myfortic was increased probably thinking that the symptoms were due to rejection which further deteriorated the condition of the patient. In this case although the study medication may have contributed to the patient's death the element of misdiagnosis and the consequent increase in immunosuppression must be taken into account. It is also important to note that the West Nile virus infection is not an opportunistic infection though it may have a more severe course in immunosuppressed patients and possibly transmitted by mosquitoes.

The overall conclusion for the deaths reported after the 12 month study period again in the Myfortic group we see less association between the deaths and the study medication and the Reviewer believes that it may not be justified to include patient 0517-00004 in the Myfortic group in this discussion since the death occurred after the 2 year study period was over.

7.3.2 Serious Adverse Events

Across the three groups, the highest incidence of SAEs, including fatal and non-fatal, are in the everolimus 3.0 mg group (60%) followed by the everolimus 1.5 mg group (57%) and the Myfortic group (54%). Most common SAEs are in the infections and infestations group in all three groups.

SAEs which had an incidence of $\geq 1.5\%$ and clinically important SAEs are included in Table 30 and discussed following the table. Adverse events which are known to be related to the M-TOR class of drugs are also included in the table and in the discussion, although they may not reach an incidence of 1.5% in any treatment group. These adverse events which are known to be related to the M-TOR class of drugs include:

- Thrombocytopenia, Thrombotic Thrombocytopenic Purpura (TTP), Thrombotic Microangiopathy (TMA), Hemolytic Uremic Syndrome (HUS)
- Ulcerative esophagitis
- All thrombotic events
- Edema and fluid collections/lymphocele
- Wound related events
- Hyperlipidemia
- Diabetes and related terms
- Focal glomerulosclerosis (FGS), focal segmental glomerulosclerosis (FSGS) and rapidly progressive glomerulonephritis (RPGN)
- Alveolar proteinosis and related terms (interstitial lung disease, lung infiltration)

In addition, equivalent and similar preferred terms for the same SAE are also included (i.e., acute myocardial infarction, myocardial infarction, acute coronary syndrome, coronary artery occlusion). General terms like “infection” which is not informative of the type and localization of the infection are not included. SAEs like appendicitis, tonsillitis, chronic sinusitis which occurred only in one patient have a very low probability of being drug related are not included.

In the infections and infestations section which has the highest occurrence of SAEs in all three groups all the sepsis and equivalent terms are included due to their clinical significance.

Within each System Organ Class (SOC) the related preferred terms (PTs) are grouped together for easy comparison and SAEs with less than 1.5% occurrence are in *italics*.

Table 30. Number (%) of Patients with SAEs ≥ 1.5% per Treatment Group and Clinically Important SAEs *

Source: Table 12-14 on page 189 of the Clinical Study Report

**(A patient with multiple occurrences of an event is counted only once in the SAE category. A patient with multiple events within a primary system organ class is counted only once in the total row)*

Within each System Organ Class (SOC) the related preferred terms are grouped together for easy comparison and SAEs with less than 1.5% occurrence are in italics.

Primary System Organ Class Preferred Term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
Any SAE	155 (56.6)	168 (60.4)	147 (53.8)
Blood and lymphatic system disorders (total)	11 (4.0)	10 (3.6)	8 (2.9)
Anemia	2 (0.7)	5 (1.8)	2 (0.7)
<i>Hemolysis</i>	<i>1 (0.4)</i>	<i>0 (0.0)</i>	<i>0 (0.0)</i>
<i>Hemolytic anemia</i>	<i>1 (0.4)</i>	<i>0 (0.0)</i>	<i>0 (0.0)</i>
<i>Hemolytic uremic syndrome</i>	<i>1 (0.4)</i>	<i>0 (0.0)</i>	<i>0 (0.0)</i>
<i>Thrombocytopenia</i>	<i>2 (0.7)</i>	<i>3 (1.1)</i>	<i>2 (0.7)</i>
<i>Thrombocytopenic purpura</i>	<i>0 (0.0)</i>	<i>1 (0.4)</i>	<i>0 (0.0)</i>
<i>TTP and TMA^s</i>	<i>2 (0.7)</i>	<i>1 (0.4)</i>	<i>0 (0.0)</i>
Cardiac disorders (total)	11 (4.0)	15 (5.4)	11 (4.0)
<i>Acute coronary syndrome</i>	<i>0 (0.0)</i>	<i>1 (0.4)</i>	<i>0 (0.0)</i>
<i>Acute myocardial infarction</i>	<i>0 (0.0)</i>	<i>2 (0.7)</i>	<i>0 (0.0)</i>
Myocardial infarction	0 (0.0)	5 (1.8)	2 (0.7)
<i>Angina Pectoris</i>	<i>2 (0.7)</i>	<i>0 (0.0)</i>	<i>0 (0.0)</i>
<i>Coronary artery occlusion</i>	<i>0 (0.0)</i>	<i>3 (1.1)</i>	<i>0 (0.0)</i>
Gastrointestinal disorders (total)	21 (7.7)	28 (10.1)	18 (6.6)
Diarrhea	1 (0.4)	6 (2.2)	1 (0.4)
Vomiting	2 (0.7)	7 (2.5)	4 (1.5)
<i>Esophagitis ulcerative</i>	<i>1 (0.4)</i>	<i>0 (0.0)</i>	<i>0 (0.0)</i>

Primary System Organ Class Preferred Term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
<i>Esophagitis hemorrhagic</i>	1 (0.4)	0 (0.0)	0 (0.0)
<i>Upper gastrointestinal hemorrhage</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Mesenteric vessel thrombosis</i>	0 (0.0)	1 (0.4)	0 (0.0)
General disorders and administration site conditions (total)	15 (5.5)	25 (9.0)	12 (4.4)
<i>Implant site effusion</i>	1 (0.4)	1 (0.4)	0 (0.0)
<i>Edema</i>	0 (0.0)	1 (0.4)	0 (0.0)
Edema peripheral	1 (0.4)	6 (2.2)	0 (0.0)
Pyrexia	7 (2.6)	12 (4.3)	10 (3.7)
Immune system disorders (total)	4 (1.5)	2 (0.7)	6 (2.2)
Kidney transplant rejection	3 (1.1)	2 (0.7)	4 (1.5)
Infections and infestations (total)	54 (19.7)	74 (26.6)	69 (25.3)
<i>Abdominal sepsis</i>	1 (0.4)	0 (0.0)	0 (0.0)
Sepsis	3 (1.1)	5 (1.8)	5 (1.8)
<i>Bacteremia</i>	3 (1.1)	3 (1.1)	1 (0.4)
<i>Septic shock</i>	1 (0.4)	1 (0.4)	0 (0.0)
Pyelonephritis	4 (1.5)	5 (1.8)	2 (0.7)
Urinary tract infection	18 (6.6)	16 (5.8)	19 (7.0)
Pneumonia	5 (1.8)	10 (3.6)	8 (2.9)
CMV infection	0 (0.0)	0 (0.0)	9 (3.3)
Herpes zoster	1 (0.4)	5 (1.8)	4 (1.5)
Upper resp. tract infection	2 (0.7)	2 (0.7)	6 (2.2)
Gastroenteritis	6 (2.2)	3 (1.1)	6 (2.2)
Injury, poisoning and procedural complications (total)	39 (14.2)	47 (16.9)	32 (11.7)
<i>Abdominal wound dehiscence</i>	0 (0.0)	1 (0.4)	1 (0.4)
<i>Wound complication</i>	1 (0.4)	1 (0.4)	0 (0.0)
<i>Wound dehiscence</i>	2 (0.7)	3 (1.1)	1 (0.4)
<i>Wound secretion</i>	1 (0.4)	1 (0.4)	0 (0.0)
<i>Incisional hernia</i>	2 (0.7)	1 (0.4)	0 (0.0)
<i>Incisional hernia, obstructive</i>	0 (0.0)	0 (0.0)	1 (0.4)
<i>Perinephric collection</i>	1 (0.4)	4 (1.4)	1 (0.4)
<i>Renal lymphocele</i>	0 (0.0)	1 (0.4)	1 (0.4)
<i>Seroma</i>	0 (0.0)	2 (0.7)	0 (0.0)
Perirenal hematoma	2 (0.7)	2 (0.7)	4 (1.5)
<i>Post procedural hemorrhage</i>	3 (1.1)	0 (0.0)	1 (0.4)
<i>Post procedural hematoma</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Renal hematoma</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Post procedural urine leak</i>	2 (0.7)	4 (1.4)	2 (0.7)
Complications of	8 (2.9)	4 (1.4)	5 (1.8)

Primary System Organ Class Preferred Term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
transplanted kidney			
<i>Renal graft loss*</i>	2 (0.7)	2 (0.7)	3 (1.1)
Graft loss*	5 (1.8)	8 (2.9)	3 (1.1)
Investigations (total)	23 (8.4)	21 (7.6)	22 (8.1)
Blood creatinine increased	19 (6.9)	18 (6.5)	18 (6.6)
Metabolism and nutrition disorders (total)	20 (7.3)	23 (8.3)	13 (4.8)
Dehydration	6 (2.2)	5 (1.8)	4 (1.5)
<i>Diabetes mellitus</i>	3 (1.1)	3 (1.1)	1 (0.4)
<i>Diabetic foot</i>	1 (0.4)	0 (0.0)	0 (0.0)
<i>Diabetic ketoacidosis</i>	0 (0.0)	0 (0.0)	1 (0.4)
<i>Hyperglycemia</i>	1 (0.4)	7 (2.5)	1 (0.4)
<i>Hypoglycemia</i>	0 (0.0)	1 (0.4)	1 (0.4)
<i>Hyperlipidemia</i>	1 (0.4)	0 (0.0)	0 (0.0)
<i>Malnutrition</i>	2 (0.7)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue Disorders (total)	5 (1.8)	3 (1.1)	1 (0.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps) (total)	4 (1.5)	3 (1.1)	5 (1.8)
Nervous system disorders (total)	6 (2.2)	7 (2.5)	5 (1.8)
Psychiatric disorders (total)	3 (1.1)	1 (0.4)	0 (0.0)
Renal and urinary disorders (total)	28 (10.2)	37 (13.7)	36 (13.2)
Hematuria	5 (1.8)	4 (1.4)	4 (1.5)
Hydronephrosis	2 (0.7)	2 (0.7)	6 (2.2)
Renal failure acute	6 (2.2)	4 (1.4)	5 (1.8)
Renal impairment	6 (2.2)	2 (0.7)	1 (0.4)
Ureteric obstruction	1 (0.4)	0 (0.0)	6 (2.2)
<i>Focal glomerulosclerosis</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Focal segmental glomerulosclerosis</i>	0 (0.0)	1 (0.4)	1 (0.4)
<i>Glomerulonephritis rapidly progressive</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Proteinuria</i>	2 (0.7)	4 (1.4)	0 (0.0)
<i>Nephrotic syndrome</i>	0 (0.0)	1 (0.4)	0 (0.0)
Reproductive system and breast disorders	3 (1.1)	1 (0.4)	0 (0.0)
Respiratory, thoracic and mediastinal disorders (total)	9 (3.3)	18 (6.5)	8 (2.9)

Primary System Organ Class Preferred Term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
<i>Alveolar proteinosis</i>	1 (0.4)	0 (0.0)	0 (0.0)
<i>Interstitial lung disease</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Lung infiltration</i>	0 (0.0)	1 (0.4)	0 (0.0)
Dyspnea	2 (0.7)	9 (3.2)	3 (1.1)
<i>Respiratory arrest</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Respiratory distress</i>	0 (0.0)	0 (0.0)	2 (0.7)
<i>Respiratory failure</i>	1 (0.4)	0 (0.0)	0 (0.0)
<i>Acute respiratory failure</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Pleural effusion</i>	2 (0.7)	1 (0.4)	0 (0.0)
<i>Pulmonary edema</i>	1 (0.4)	2 (0.7)	0 (0.0)
<i>Acute Pulmonary edema</i>	0 (0.0)	1 (0.4)	0 (0.0)
Vascular disorders (total)	26 (9.5)	28 (10.1)	20 (7.3)
Deep vein thrombosis	6 (2.2)	3 (1.1)	4 (1.5)
<i>Thrombosis</i>	1 (0.4)	0 (0.0)	0 (0.0)
<i>Venous thrombosis limb</i>	1 (0.4)	0 (0.0)	0 (0.0)
<i>Subclavian vein thrombosis</i>	0 (0.0)	1 (0.4)	0 (0.0)
Lymphocele	14 (5.1)	15 (5.4)	7 (2.6)
<i>Lymphorrhea</i>	2 (0.7)	0 (0.0)	0 (0.0)

* Not all of the graft loses are reported as SAEs. In the safety analysis of the ITT population there are 12 graft loses in the everolimus 1.5 mg group, 14 graft loses in the everolimus 3.0 mg group and 8 graft loses in the Myfortic group but only 7, 10 and 6 respectively are reported as SAEs.

SAEs in the following SOCs were reported at a higher rate in the everolimus 1.5 mg group compared to the Myfortic group:

- Blood and lymphatic system disorders, (4% vs. 2.9%)
- Gastrointestinal disorders (7.7% vs. 6.6%)
- General disorders and administration site conditions (5.5% vs. 4.4%)
- Injury, poisoning and procedural complications (14.2% vs. 11.7%)
- Investigations (8.4% vs. 8.1%)
- Metabolism and nutrition disorders (7.3% vs. 4.8%)
- Musculoskeletal and connective tissue disorders (1.8% vs. 0.4%)
- Nervous system disorders, psychiatric disorders (2.2% vs. 1.8%)
- Psychiatric disorders (1.1% vs. 0%)
- Reproductive system and breast disorders (1.1% vs. 0%)
- Respiratory, thoracic and mediastinal disorders (3.3% vs. 2.9%)
- Vascular disorders (9.5% vs. 7.3%)

The incidence of SAEs in the everolimus 3.0 mg group was higher than in the Myfortic group in all of the SOCs, except for Investigations and Neoplasms.

SAEs in the following SOCs were higher in the Myfortic group compared to the everolimus 1.5 mg group:

- Infections and infestations (25.3% vs.19.7%)
- Neoplasms (1.8% vs. 1.5%)
- Renal and urinary disorders (13.2% vs. 10.2%)

The higher incidence of SAEs in the renal and urinary disorders SOC in the Myfortic group is driven by the high incidence of hydronephrosis and ureteric obstruction (both 2.2%) in the Myfortic group, which may be related to surgical technique.

7.3.2.1 *Graft Losses*

According to the study protocol, graft loss was reported as a SAE.

The number of graft losses was 12 (4.3%) in the everolimus 1.5 mg group, 14 (5.0%) in the everolimus 3.0 mg group and 8 (2.9%) in the Myfortic group over the 12 month study period as shown in Table 31 through Table 33. One patient (0543-00007) with a graft loss in the Myfortic group never received the study drug and is not included in the safety population, but is included in the ITT population. As a consequence, there were nine graft losses in the Myfortic group in the efficacy analysis but only eight graft losses in the safety analysis. The most frequent cause of graft loss was renal artery thrombosis in the everolimus groups whereas the causes are more evenly distributed in the Myfortic group. Three patients died after they lost their grafts: one in the everolimus 1.5 mg group (0114-00001) and the other two in the everolimus 3.0 mg group (0115-00020 and 0168-00017).

Applicant's Analysis of Graft Losses

According to the applicant's analysis, using verbatim terms reported by the investigators, the number of graft losses due to renal artery thrombosis was four in the everolimus 1.5 mg group, one in the everolimus 3.0 mg group and one in the Myfortic group. Also one graft in the everolimus 1.5 mg group was lost due to renal vein thrombosis. The distribution of other causes like infarcted kidney, acute rejection and chronic rejection are listed in Table 31 through Table 33 for each of the treatment groups

Reviewer's Assessment of Graft Losses

According to FDA's analysis, one patient (0102-00005) in the everolimus 1.5 mg group whose cause of graft failure is listed as "other" by the investigator was presumed to have lost his graft due to renal vein thrombosis. Also three patients in the everolimus 3.0 mg group whose cause of graft loss was listed as infarcted kidney (0115-00006, and 0520-00019) or acute rejection (0166-00020) and one patient in the Myfortic group (0166-00008) were assessed to have lost their grafts due to renal artery thrombosis, according to the FDA's interpretation of the patient narratives. Another patient (0118-00009) in the Myfortic group who was listed with a diagnosis of infarcted kidney as the cause of graft loss as per the investigator was determined to have lost her graft due to renal artery rupture and consequent hematoma.

Despite these differences in use of terms, the Applicant and the FDA are in agreement regarding the number of graft losses in the study, as shown in Tables 31 through 33:

- 12 in the everolimus 1.5 mg group,
- 14 in the everolimus 3.0 mg group,
- 8 in the Myfortic group.

Table 31. Graft Loss by 12 Month Analysis Everolimus 1.5 mg Group
 (Source: Table 12-18, page 197 of CSR)

Everolimus 1.5 mg, 12 graft losses				
(Applicant: 4 renal artery thrombosis, 1 renal vein thrombosis, 1 other)				
(FDA: 4 renal artery thrombosis, 2 renal vein thrombosis)				
Patient No. (Age, sex)	Day of graft loss (Day of death)	Day of last dose of medication	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
0124-00048 (46, M)	4	4	Renal artery thrombosis	Renal artery thrombosis
0501-00020 (54, F)	11	11	Renal artery thrombosis	Renal artery thrombosis
0515-00004 (58, M)	55	55	Renal artery thrombosis	Renal artery thrombosis
0543-00014 (24, F)	8	9	Renal artery thrombosis	Renal artery thrombosis
0102-00005 (59, M)	4	4	Other (Renal vein thrombosis)	Renal vein thrombosis
0115-00020 (43, F)	7 (28)	9	Renal vein thrombosis	Renal vein thrombosis
0192-00002 (32, M)	116	116	Acute Rejection	Thrombotic thrombocytopenic purpura (TTP)
0511-00019 (67, M)	185	135	Other	Proliferative glomerulonephritis
0200-00008 (64, F)	54	54	Other	Acute rejection
0122-00004 42, M	215	12	Chronic rejection	Chronic rejection
0553-00016 (25, F)	366	206	Chronic rejection	Chronic rejection
0510-00001 (48, M)	31	31	Primary non-function	Primary non-function

Table 32. Graft Loss by 12 Month Analysis Everolimus 3.0 mg Group
 (Source: Table 12-18, page 197 of CSR)

Everolimus 3.0 mg, 14 graft losses				
(Applicant: 1 Renal artery thrombosis, 2 infarcted kidneys, 1 PNF)				
(FDA: 4 Renal artery thrombosis, 1 PNF/Renal artery thrombosis?)				
Patient No. (Age, sex)	Day of graft loss (Day of death)	Day of last dose of medication	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
0192-00003 (22, M)	7	8	Renal artery thrombosis	Renal artery thrombosis
0115-00006 (58, F)	7	7	Infarcted kidney	Renal artery thrombosis
0166-00020 (57, F)	14	19	Acute rejection	Renal artery thrombosis
0520-00019 (45, M)	5	25	Infarcted kidney	Renal artery thrombosis
0544-00005 (68, F)	4	4	Primary non-function	Renal artery thrombosis?
0168-00017 (59, M)	13 (34)	24	Acute rejection	Acute rejection
0114-00001 (34, M)	91 (243)	45	Acute rejection	Acute rejection
0161-00001 (52, M)	153	38	Chronic rejection	Chronic rejection
0519-00001 (55, F)	354		Non-compliance	Chronic rejection, UTI
0501-00019 (37, F)	161	161	Chronic rejection	Chronic rejection, pyelonephritis
0168-00015 (43, F)	34	34	Other	urine leak, septic shock,
0528-00008 (66, M)	213	213	Other	<i>E. coli</i> infection and cardiac arrest
0511-00017 (66, M)	50	50	Primary non-function	Primary non-function
0529-00002 (66, M)	108	108	Primary non-function	Primary non-function?

Table 33. Graft Loss by 12 Month Analysis Myfortic Group
 (Source: Table 12-18, page 197 of CSR)

Myfortic, 8 graft losses (Applicant: 1 Renal artery thrombosis, 1 infarcted kidney) (FDA: 2 Renal artery thrombosis)				
Patient No. (Age, sex)	Day of graft loss (Day of death)	Day of last dose of medication	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
0100-00011 (19, M)	1	4	Renal artery thrombosis	Renal artery thrombosis
0166-00008 (55, M)	14	14	Infarcted kidney	Renal artery thrombosis
0118-00009 (44, F)	4	4	Infarcted kidney (Renal artery rupture)	Renal artery rupture
0361-00003 (27, M)	34	34	Urological complications	Urological complications
0501-00008 (62, M)	217	217	Chronic rejection	Chronic rejection
0529-00006 (59, M)	25	28	Acute rejection	Primary non-function
0100-00004 (27, M)	132	132	Primary non-function	Primary non-function
0553-00012 (60, M)	164	153	Non-compliance	Non-compliance

Graft Losses Followed by Death of the Patient

One of the patients with renal vein thrombosis in the everolimus 1.5 mg group died later as a result of the events started by this complication (patient 0114-0001). Please refer to Section on mortality for details.

Graft Losses Caused by Renal Vascular Thrombosis:

FDA and the applicant agreed on the assessment of the number of patients who lost their grafts as a consequence of graft thrombosis (renal artery and renal vein):

- 6 graft thromboses (4 renal artery and 2 renal vein) in the everolimus 1.5 mg group,
- 4 graft thromboses (4 renal artery) with another probable 5th patient again with renal artery thrombosis according to the narrative in the everolimus 3.0 mg group
- 2 graft thromboses (2 renal artery) in the Myfortic group.

Reviewer's Comment: *In the Reviewer's assessment one of the patients (# 0114-0001) with renal vein thrombosis in the everolimus 1.5 mg group died later as a result of the events started by this complication. Thrombogenicity is a well known class effect of M-TOR inhibitors.*

Based on a comprehensive analysis taken from United Network for Organ Sharing/United States Renal Disease Study (UNOS/USRDS) data that includes over 84,000 renal transplants, graft thrombosis within 30 days occurs in 0.9% of transplants.⁸ In Study A2309 the incidence of graft thrombosis in the everolimus 1.5 mg group within 30 days of transplantation is 1.8% (5/274), and becomes 2.1% (6/274) if patient 0515-00004 who lost his graft on day 55 is included. The same incidences are 1.4% (4/278) in the everolimus 3.0 mg group and 0.7% (2/273) in the Myfortic group.

Graft Losses Caused by Acute or Chronic Rejection:

One patient in the everolimus 1.5 mg group and two patients, who later died, in the everolimus 3.0 mg group lost their grafts due to acute rejection compared to none in the Myfortic group. Two patients in the everolimus 1.5 mg group, three patients in the everolimus 3.0 mg group, and one patient in the Myfortic group lost their grafts due to chronic rejection.

One patient in the everolimus 1.5 mg group (0192-00002) lost his graft due to TTP, a known toxicity of M-TOR inhibitors.

Reviewer's assessment of graft losses:

The incidence of early graft thromboses (within 30 days of transplant) is 1.8% in the everolimus 1.5 mg group and 1.4% in the everolimus 3.0 mg group which are both above the national average of 0.9%⁸ and in line with the well known thrombogenic effect of M-TOR inhibitors. Sirolimus, another M-TOR inhibitor, contains a Boxed Warning for hepatic artery thrombosis (HAT).

This thrombogenic effect of M-TOR inhibitors may be partly due to their adverse effect on the vascular endothelial regeneration and this type of regeneration may be required most in the graft vasculature which is affected by the ischemic, surgical and the immunologic trauma due to the transplant procedure. From non-clinical studies everolimus is also known to increase fibrinogen levels which may be another reason for this thrombogenic effect. This high incidence of graft thrombosis in the everolimus groups is very concerning since it not only resulted in loss of the graft in all instances but also contributed to the death of one patient in the everolimus 1.5 mg group (patient 0115-00020).

Additionally more patients lost their grafts due to acute and chronic rejection in each of the everolimus groups compared to the Myfortic group which raises questions about efficacy although no significant differences between the treatment groups with regard to the incidence of BPAR was found in the efficacy analysis. Although the differences are not statistically significant, numerically

⁸ Ojo AO, Hanson JA, Wolfe RA, et al. Dialysis modality and the risk of allograft thrombosis in adult renal transplant recipients. *Kidney Int.* 1999;55:1952-1960

more kidney grafts were lost in each of the everolimus groups compared to the Myfortic group.

7.3.3 Dropouts and/or Discontinuations

During the study, information on study drug discontinuations due to AEs was collected on two different CRFs. The information from the first form (Treatment and Study Completion CRF) is summarized in Table 34. As noted in the table, the overall incidence of study drug discontinuations due to AEs according to this first data collection form were 18.1% in the everolimus 1.5 mg group, 20.4% in the everolimus 3.0 mg group, and 9.4% in the Myfortic group.

**Table 34 Patient disposition – n (%) of patients by treatment group*
(ITT population - 12 month analysis)**

(Source: Adapted from Table 10-, page 138, CSR)

(Discontinuations which are especially higher in the everolimus 1.5 mg group shown in light green)

	Everolimus 1.5 mg, n (%)	Everolimus 3.0 mg, n (%)	Myfortic 1.44 gm, n (%)
Total no. of patients	277 (100)	279 (100)	277 (100)
Completed study medication	194 (70.0)	184 (65.9)	217 (78.3)
Completed study phase	239 (86.3)	246 (88.2)	249 (89.9)
Discontinued study medication	83 (30.0)	95 (34.1)	60 (21.7)
Adverse events	50 (18.1)	57 (20.4)	26 (9.4)
Abnormal lab values	1 (0.4)	4 (1.4)	1 (0.4)
Abnormal test procedure	0 (0.0)	1 (0.4)	0 (0.0)
Unsatisfactory Therapeutic effect	11 (4.0)	14 (5.0)	13 (4.7)
Protocol deviation	2 (0.7)	5 (1.8)	2 (0.7)
Subject withdrew consent	11 (4.0)	4 (1.4)	5 (1.8)
Administrative problems	2 (0.7)	1 (0.4)	2 (0.7)
Death	3 (1.1)	3 (1.1)	4 (1.4)
Graft loss	3 (1.1)	6 (2.2)	6 (2.2)
Did not receive study drug	0 (0.0)	0 (0.0)	1 (0.4)
Discontinued study	38 (13.7)	33 (11.8)	28(10.1)
Subject withdrew consent	20 (7.2)	8 (2.9)	12 (4.3)
Death	7 (2.5)	9 (3.2)	6 (2.2)
Graft loss	9 (3.2)	10 (3.6)	7 (2.5)
Other	2 (0.7)	6 (2.2)	3 (1.1)

The information collected on the second form (AE/infections CRF) was more specific and contained information about the type of AE leading to study drug discontinuation. According to the second form, the rates of discontinuation were 23.4% in the everolimus 1.5 mg group, 28.4% in the everolimus 3.0 mg group and 15.8% in the Myfortic group. It was assumed that the information obtained from the second form would be more accurate and detailed; therefore this information is utilized for the analysis of AEs leading to drug discontinuation in Table 35. In the table, discontinuations $\geq 1\%$ per treatment group and clinically relevant SAEs related to class toxicities of M-TOR inhibitors and MPA are included.

Adverse events leading to study drug discontinuation in the following SOCs were more frequently reported in the everolimus 1.5 mg group than the Myfortic group:

- Blood and lymphatic system disorders
- Investigations (including the preferred term of increased blood creatinine and others);
- Injury, poisoning and procedural complications (including the preferred term of therapeutic agent toxicity, etc.);
- Renal and urinary disorders (proteinuria etc.); and
- Vascular disorders

Infections and infestations, and gastrointestinal disorders were the only SOCs where there were more discontinuations in the Myfortic group compared to the everolimus 1.5 mg group. However, the rate of discontinuation in both of these SOCs was higher in the everolimus 3.0 mg group than the Myfortic group.

Table 35. Number (%) of Patients with Adverse Events (AEs) Leading to Study Drug Discontinuation *

(Source: Table 12-5 on page 173 of CSR)

**(A patient with multiple occurrences of an AE/infection is counted only once in the AE category. A patient with multiple AEs/infections within a primary system organ class is counted only once in the total row.)*

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 gm N=273
	n (%)	n (%)	n (%)
Any AE leading to study drug discontinuation	64 (23.4)	79 (28.4)	43 (15.8)
Blood and lymphatic system disorders	7 (2.6)	2 (0.7)	3 (1.1)
Anemia	1 (0.4)	0 (0.0)	0 (0.0)
Leucopenia	1 (0.4)	0 (0.0)	2 (0.7)
Thrombocytopenia	0 (0.0)	1 (0.4)	1 (0.4)
TTP and TMA**	2 (0.7)	2 (0.7)	0 (0.0)
Cardiac disorders	2 (0.7)	4 (1.4)	1 (0.4)
Gastrointestinal disorders	3 (1.1)	7 (2.5)	6 (2.2)
Hemorrhagic esophagitis	1 (0.4)	0 (0.0)	0 (0.0)

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 gm N=273
	n (%)	n (%)	n (%)
Ulcerative esophagitis	1 (0.4)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	4 (1.5)	1 (0.4)	1 (0.4)
Death	0 (0.0)	0 (0.0)	1 (0.4)
Edema peripheral	3 (1.1)	1 (0.4)	0 (0.0)
Immune system disorders	3 (1.1)	0 (0.0)	3 (1.1)
Kidney transplant rejection	2 (0.7)	0 (0.0)	3 (1.1)
Infections and infestations	4 (1.5)	17 (6.1)	8 (2.9)
Pyelonephritis & renal abscess	0 (0.0)	3 (1.0)	0 (0.0)
Wound infection & abscess	0 (0.0)	6 (2.2)	0 (0.0)
Wound secretion	0 (0.0)	1 (0.4)	0 (0.0)
Injury, poisoning and procedural complications	14 (5.1)	20 (7.2)	6 (2.2)
Graft loss	2 (0.7)	6 (2.2)	3 (1.1)
Therapeutic agent toxicity	5 (1.8)	2 (0.7)	0 (0.0)
Wound dehiscence & impaired healing	1 (0.4)	6 (2.2)	0 (0.0)
Investigations	9 (3.3)	10 (3.6)	6 (2.2)
Blood creatinine increased	8 (2.9)	9 (3.2)	2 (0.7)
Metabolism and nutrition disorders	4 (1.5)	1 (0.4)	1 (0.4)
Musculoskeletal and connective tissue disorders	2 (0.7)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.4)	1 (0.4)	0 (0.0)
Nervous system disorders	0 (0.0)	2 (0.7)	1 (0.4)
Renal and urinary disorders	11 (4.0)	18 (6.5)	10 (3.7)
Focal segmental glomerulosclerosis	0 (0.0)	3 (1.1)	0 (0.0)
Nephropathy toxic	1 (0.4)	3 (1.1)	3 (1.1)
Proteinuria	2 (0.7)	4 (1.4)	0 (0.0)
Reproductive system and breast disorders	1 (0.4)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	2 (0.7)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	2 (0.7)	1 (0.4)
Vascular disorders	3 (1.1)	4 (1.4)	2 (0.7)
Lymphocele	3 (1.1)	4 (1.4)	0 (0.0)

** *Thrombotic thrombocytopenic purpura (TTP), Thrombotic microangiopathy (TMA)*

Since this is an open label study it is important to evaluate and compare rates of SAEs and study drug discontinuation due to those SAEs, as an indirect measure of whether there was any investigator bias for or against the investigational everolimus regimen compared to the approved control regimen, which may have resulted in differential discontinuations for the same type of event. To assess for this possible bias, FDA compared the drug discontinuation rates to SAE rates, since SAEs would be expected to result in drug discontinuations in many cases.

As seen in Table 36 below, while the incidence of SAEs by SOC for the everolimus 1.5 mg group or Myfortic group ranged from 2.9% to 25.3%, the rate of drug discontinuations for these events is noticeably lower, ranging from 0.4% to 5.1%. Thus, although there was a range of SAEs reported, some were managed with discontinuation of drug, while others were presumably managed by other measures, potentially including dose reduction. One can also compare that for some SAEs, close to half the patients reporting SAEs had drug discontinued (e.g., Blood and Lymphatic System Disorders), while for others SOCs about 1/10th of the patients with SAE had drug discontinued (e.g., Infections and Infestations). And finally, consistent with Table 30 and 34, for many of the SOC categories, proportionally more everolimus patients with SAE discontinued the study drug than Myfortic patients (e.g., Investigations/blood creatinine increased, Renal Urinary Disorders).

Table 36. Comparative Study Drug Discontinuation Rates Due to AEs in Relation to the Incidence of SAEs in the Same Category

System Organ Class Preferred Term resulting in Study Drug Discontinuation	Everolimus 1.5 mg		Myfortic	
	Drug Discontinuation (%)	Incidence of SAE (%)	Drug Discontinuation (%)	Incidence of SAE (%)
Blood and Lymphatic System Disorders	2.6	4.0	1.1	2.9
Cardiac Disorders	0.7	4.0	0.4	4.0
Gastrointestinal Disorders	1.1	7.7	2.2	6.6
General disorders and administration site conditions (total)	1.5	5.5	0.4	4.4
<i>Edema peripheral</i>	1.1	0.4	0.0	0.0
Infections and Infestations	1.5	19.7	2.9	25.3
Injury, Poisoning and Procedural Complications	5.1	14.2	2.2	11.7
Investigations	3.3	8.4	2.2	8.1
<i>Blood creatinine increased</i>	2.9	6.9	0.7	6.6
Metabolism and Nutrition Disorders	1.5	7.3	0.4	4.8
Renal and Urinary Disorders	4.0	10.2	3.7	13.2
Vascular Disorders	1.1	9.5	0.7	7.3

Reviewer's Comments: According to the analysis of patients with adverse events leading to study drug discontinuation again more patients in the everolimus 1.5 mg group discontinued the study medication because of adverse events compared to the Myfortic group (23.4% vs. 15.8%). Discontinuations were even higher in the everolimus 3.0 mg group (28.4).

Injury, poisoning and procedural complications which includes wound healing problems and investigations for blood creatinine increases were more common in both of the everolimus groups compared to the Myfortic group.

The incidence of infections as a cause for drug discontinuation in the 3.0 mg everolimus group was twice as high as in the Myfortic group while this incidence in the 1.5 mg group was lower compared to the Myfortic group. 6 patients in the

everolimus 3.0 mg discontinued the study drug due to wound abscess and wound infections while this number was "0" in the other two groups.

Graft loss, focal segmental glomerulosclerosis, toxic nephropathy and proteinuria were more frequently reported as a reason for discontinuation in the 3.0 mg group than the 1.5 mg group. Blood and lymphatic system disorders, increased blood creatinine, therapeutic agent toxicity, proteinuria peripheral edema, and lymphocele were more frequently reported as AEs leading to study drug discontinuation in the 1.5 mg everolimus treatment group than the Myfortic 1.44 gm group. Infections and infestations, leukopenia and gastrointestinal disorders were the only causes that resulted in more discontinuations in the Myfortic group compared to any of the everolimus groups.

Dose Adjustment or Interruptions:

In contrast, as stated in the following paragraphs and also as shown in Table 37 AEs requiring an adjustment or interruption to treatment were reported in 22.3% of patients in the everolimus 1.5 mg group, 27.0% of patients in the everolimus 3.0 mg group, and 34.8% of patients in the Myfortic group.

This higher incidence of dose adjustment/interruption in the Myfortic group was mainly due to the higher incidence of adjustment or interruption due to blood and lymphatic system disorders (11.4% in the Myfortic group vs. 3.6% in the everolimus 1.5 mg group and 4.3% in the everolimus 3.0 mg group), gastrointestinal disorders (11.0% in the Myfortic group vs. 2.6% in the everolimus 1.5 mg group and 2.9% in the everolimus 3.0 mg group) and infections and infestations (13.6% in the Myfortic group vs. 4.4% in the everolimus 1.5 mg group and 7.2% in the everolimus 3.0 mg group). This may partly be explained by the high incidence of gastrointestinal adverse events and leukopenia associated with MPA which usually requires frequent dose adjustments and interruptions in clinical practice.

Modification of study medication dose due to renal and urinary disorders and metabolism and nutrition disorders was more frequent in everolimus groups compared to Myfortic, with a dose response effect indicated.

Table 37. Number (%) of Patients with Adverse Events Leading to Study Drug Dose Adjustment/Interruption ($\geq 1\%$ per treatment group) (Safety population - 12 month analysis)

**(A patient with multiple occurrences of an AE/infection is counted only once in the AE category. A patient with multiple AEs/infections within a primary system organ class is counted only once in the total row)*

Reproduced from Table 12-6 on page 194 of the applicant's Clinical Study Report for Study A2309 in the NDA resubmission

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 gm N=273
	n (%)	n (%)	n (%)
Any AE leading to dose adjustment/interruption	61 (22.3)	75 (27.0)	95 (34.8)
Blood and lymphatic system disorders	10 (3.6)	12 (4.3)	31 (11.4)
Anemia	1 (0.4)	3 (1.1)	4 (1.5)
Leucopenia	4 (1.5)	4 (1.4)	23 (8.4)
Thrombocytopenia	3 (1.1)	5 (1.8)	3 (1.1)
Cardiac disorders	0 (0.0)	1 (0.4)	1 (0.4)
Ear and labyrinth disorders	1 (0.4)	0 (0.0)	0 (0.0)
Eye disorders	0 (0.0)	0 (0.0)	1 (0.4)
Gastrointestinal disorders	7 (2.6)	8 (2.9)	30 (11.0)
Abdominal pain	0 (0.0)	1 (0.4)	3 (1.1)
Diarrhea	1 (0.4)	1 (0.4)	14 (5.1)
Nausea	1 (0.4)	0 (0.0)	4 (1.5)
Vomiting	1 (0.4)	2 (0.7)	4 (1.5)
General disorders and administration site conditions	3 (1.1)	6 (2.2)	3 (1.1)
Impaired healing	0 (0.0)	3 (1.1)	0 (0.0)
Edema peripheral	3 (1.1)	0 (0.0)	0 (0.0)
Pyrexia	0 (0.0)	1 (0.4)	3 (1.1)
Hepatobiliary disorders	1 (0.4)	0 (0.0)	0 (0.0)
Immune system disorders	3 (1.1)	1 (0.4)	1 (0.4)
Infections and infestations	12 (4.4)	20 (7.2)	37 (13.6)
BK virus infection	0 (0.0)	1 (0.4)	3 (1.1)
Cytomegalovirus infection	0 (0.0)	0 (0.0)	7 (2.6)
Cytomegalovirus viremia	0 (0.0)	0 (0.0)	3 (1.1)
Herpes zoster	1 (0.4)	2 (0.7)	5 (1.8)
Sepsis	0 (0.0)	0 (0.0)	4 (1.5)
Upper respiratory tract infection	1 (0.4)	1 (0.4)	3 (1.1)
Urinary tract infection	5 (1.8)	4 (1.4)	3 (1.1)
Injury, poisoning and procedural complications	3 (1.1)	8 (2.9)	8 (2.9)
Therapeutic agent toxicity	0 (0.0)	2 (0.7)	4 (1.5)
Investigations	12 (4.4)	13 (4.7)	12 (4.4)

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 gm N=273
	n (%)	n (%)	n (%)
Blood creatinine increased	8 (2.9)	8 (2.9)	5 (1.8)
White blood cell count decreased	0 (0.0)	1 (0.4)	3 (1.1)
Metabolism and nutrition disorders	5 (1.8)	6 (2.2)	0 (0.0)
Dyslipidemia	2 (0.7)	4 (1.4)	0 (0.0)
Nervous system disorders	2 (0.7)	2 (0.7)	1 (0.4)
Renal and urinary disorders	6 (2.2)	13 (4.7)	4 (1.5)
Nephropathy toxic	0 (0.0)	4 (1.4)	1 (0.4)
Renal tubular necrosis	1 (0.4)	3 (1.1)	0 (0.0)
Reproductive system and breast disorders	1 (0.4)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	4 (1.4)	1 (0.4)
Skin and subcutaneous tissue disorders	2 (0.7)	3 (1.1)	0 (0.0)
Vascular disorders	5 (1.8)	4 (1.4)	2 (0.7)
Lymphocele	4 (1.5)	1 (0.4)	0 (0.0)

Reviewer's Comment:

As explained in detail above there have been more study drug discontinuations in both of the everolimus groups compared to the Myfortic group due to adverse events. On the contrary study drug dose adjustments and interruptions due to adverse events are more frequent in the Myfortic group compared to the everolimus groups. The Applicant is trying to put forward an argument based on this two different set of events which apparently go in the opposite direction.

The argument of the Applicant is both the everolimus groups and the Myfortic group have their own weaknesses with regard to tolerability of the study regimen such that everolimus groups have a higher rate of study drug discontinuations but Myfortic group has a higher rate of dose adjustments and interruptions due to adverse events.

The reviewer sees the higher rate of dose adjustments and interruptions due to AEs as strength of the Myfortic regimen not as a weakness, it proves the manageability of the Myfortic immunosuppressive regimen. The Reviewer, as a physician who has taken care of transplant patients knows that it is very common in clinical practice to adjust the dose or temporarily stop MPA derivatives because of decreases in leukocyte counts or gastrointestinal symptoms like diarrhea, nausea or vomiting which usually are not severe in nature and quickly respond to dose reduction partly due to the shorter half life of MPA (18 hrs). These symptoms almost serve as a surrogate for MPA TDM and obviate the need for

measuring trough levels of MPA derivatives and allow the physician to easily tailor the immunosuppressive regimen for each patient without checking the trough levels of MPA.

Since the AEs of leukopenia, nausea, vomiting and diarrhea are almost like surrogates for trough levels of MPA it may be justified to compare all of the dose adjustments and study drug discontinuations across the three study groups (Table 38):

In the Table 38 below another perspective about study drug adjustments or discontinuations is presented.

Table 38 Overall Dose Adjustments & Drug Discontinuations
 (Analysis performed by Clinical Pharmacology Reviewer Kevin M. Krudys Ph.D)

	Everolimus 1.5 mg, n (%)	Everolimus 3.0 mg, n (%)	Myfortic 1.44 gm, n (%)
More than 2 Dose Adjustments	52.6%,	64.7%	24.5%
All Discontinuations	103 (37.2%)	106 (38.0%)	84 (30.3%)

Reviewer's Comment: *In the table above when we look at all dose adjustments regardless of the cause (for TDM or due to AEs) the number of everolimus dose adjustments far exceed the number of dose adjustments for Myfortic.*

- In the reviewer's opinion the main reason that resulted in a higher rate of study drug discontinuations in the everolimus groups is the difficulty of managing the everolimus- low dose CsA immunosuppressive regimen. The reasons for this difficulty are:*
- The half-life of everolimus is around 31 hours (Cyclosporine has a half-life of 8 hours and MPA has a half life of 18 hours) and any trough level obtained sooner than 5 days after the dose change will not give an accurate estimate.*
- CsA exposure affects the everolimus exposure so every time CsA dosage is changed everolimus trough levels also need to be checked in addition to checking the CsA levels but this cannot be done earlier than 5 days after the change.*
- As a consequence of the above during times when a dose change is needed due to an adverse event like infection or wound healing problem the physician will not be able to see the result before a minimum of 5 days or sometimes longer with the everolimus regimen*

and if further adjustments are needed this will cause additional delays while the observed AE is still in progress.

- *In the Myfortic regimen there is no need for TDM for MPA and the trough levels come down quicker in case of dose reduction because of the shorter half life. Also the effect of CsA exposure on the MPA exposure is minimal (only thorough affecting the enterohepatic circulation of MPA) and unlike the additive effect between the CsA and the everolimus in terms of exposure, the interaction between the CsA and MPA is antagonistic such that CsA dose increases result in decreased exposure to MPA which in a way acts as a buffer mechanism.*

Because of the explained reasons investigators were probably more inclined to discontinue the everolimus treatment regimen rather than trying to adjust it.

7.3.4 Significant Adverse Events

In this section infections observed in Study A2309, class related effects of M-TOR inhibitors and MPA related adverse events will be discussed.

7.3.4.1 Infections

Rates of total infections, total fungal, and total bacterial infections were similar across all treatment groups. The lowest total rates were seen in the everolimus 1.5 mg group, which was due primarily to the low rates of viral infections [Cytomegalovirus (CMV) and BK virus] in this group.

As stated above in Sections 7.3.1 (Deaths) and 7.3.2.1 (Graft Loss), as per the FDA's assessment of attributability, infectious were the second most common primary cause of death in the study overall and appeared to be responsible for two deaths in the everolimus 1.5 mg group, five deaths in the everolimus 3.0 mg group (and appeared to contribute to the death in an additional patient), and appeared to contribute to four of the 14 graft losses in the everolimus 3.0 mg group.

The overall incidence of SAEs related to infectious causes are approximately 20% in the everolimus 1.5 mg group, 26% in the everolimus 3.0 mg group and 25% in the Myfortic group, as shown in Table 39, which includes all bacterial and viral infections are included to be able to make an accurate comparison across the study groups.

In Table 39, below, clinically relevant preferred terms for infections are grouped together, in order to make comparisons easier. Infection rates reported as SAEs in the following resulting groupings were compared:

- sepsis, bacteremia and septic shock
- musculoskeletal and extremity infections
- wound-related infections
- urinary system infections
- lung infections
- viral infections in general

The incidence of infections reported as SAEs is higher in the everolimus 1.5 mg group compared to the Myfortic group in the first four clinically relevant groupings, whereas the incidences are higher in the Myfortic group in the last three groupings. In the table below different colors are used for consecutive groupings for ease of following.

There were nine SAEs of CMV infections (including one case of CMV esophagitis) in the Myfortic group and none in the everolimus groups. According to the patient narratives, all of these CMV infections in the Myfortic group promptly responded to treatment with gancyclovir or valgancyclovir and resolved within a few days. In one patient Guillain-Barre syndrome presumed to be secondary to CMV infection developed after the CMV infection had resolved. The patient recovered from Guillan-Barre syndrome with treatment. CMV or any other type of viral infection did not cause any deaths or graft losses in any of the treatment groups.

There was one BK virus infection reported as SAE in the everolimus 1.5 mg group, no cases in the everolimus 3.0 mg group, and two cases in the Myfortic group.

Table 39. Number (%) of Patients with Infections Reported as SAEs *
 (Source: Table 12-8 on page 177 of CSR)

**(A patient with multiple occurrences of an event is counted only once in the SAE category. A patient with multiple events within a primary system organ class is counted only once in the total row.)*

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
Infections and infestations (total)	54 (19.7)	74 (26.6)	69 (25.3)
<i>Abdominal sepsis</i>	1 (0.4)	0 (0.0)	0 (0.0)
Sepsis	3 (1.1)	5 (1.8)	5 (1.8)
<i>Bacteremia</i>	3 (1.1)	3 (1.1)	1 (0.4)
<i>Septic shock</i>	1 (0.4)	1 (0.4)	0 (0.0)
<i>Abscess limb</i>	1 (0.4)	0 (0.0)	0 (0.0)
<i>A/V graft site infection</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Catheter site infection</i>	0 (0.0)	0 (0.0)	1 (0.4)
<i>Arthritis bacterial</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Osteomyelitis</i>	3 (1.1)	0 (0.0)	0 (0.0)
<i>Incision site infection</i>	0 (0.0)	4 (1.4)	1 (0.4)
<i>Postoperative wound</i>	1 (0.4)	3 (1.1)	2 (0.7)

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
<i>infection</i>			
Wound abscess	0 (0.0)	1 (0.4)	0 (0.0)
Wound infection	1 (0.4)	2 (0.7)	1 (0.4)
Wound infection staphylococcal	1 (0.4)	0 (0.0)	0 (0.0)
Cellulitis	3 (1.1)	2 (0.7)	1 (0.4)
Abdominal wall abscess	1 (0.4)	0 (0.0)	0 (0.0)
Subcutaneous abscess	1 (0.4)	0 (0.0)	0 (0.0)
Infected lymphocele	0 (0.0)	1 (0.4)	0 (0.0)
Perinephric abscess	1 (0.4)	1 (0.4)	0 (0.0)
Pyelonephritis	4 (1.5)	5 (1.8)	2 (0.7)
Pyelonephritis acute	0 (0.0)	4 (1.4)	1 (0.4)
Renal abscess	0 (0.0)	1 (0.4)	0 (0.0)
Stent related infection	1 (0.4)	0 (0.0)	0 (0.0)
Urosepsis	2 (0.7)	2 (0.7)	2 (0.7)
Urinary tract infection	18 (6.6)	16 (5.8)	19 (7.0)
Bronchopneumonia	2 (0.7)	1 (0.4)	0 (0.0)
Lobar pneumonia	0 (0.0)	1 (0.4)	1 (0.4)
Pneumonia	5 (1.8)	10 (3.6)	8 (2.9)
Pneumonia klebsiella	1 (0.4)	0 (0.0)	0 (0.0)
BK virus infection	1 (0.4)	0 (0.0)	2 (0.7)
CMV infection	0 (0.0)	0 (0.0)	9 (3.3)
CMV viremia	0 (0.0)	1 (0.4)	0 (0.0)
CMV esophagitis	0 (0.0)	0 (0.0)	1 (0.4)
Herpes simplex	1 (0.4)	0 (0.0)	2 (0.7)
Herpes virus infection	0 (0.0)	0 (0.0)	1 (0.4)
Herpes zoster	1 (0.4)	5 (1.8)	4 (1.5)
Herpes zoster disseminated	0 (0.0)	0 (0.0)	1 (0.4)
Upper resp. tract infection	2 (0.7)	2 (0.7)	6 (2.2)
Gastroenteritis	6 (2.2)	3 (1.1)	6 (2.2)
Fungal Infections	0 (0.0)	3 (1.1)	0 (0.0)
Tuberculosis	0 (0.0)	1 (0.4)	1 (0.4)

Infection data was coded with SNOMED (Systematized Nomenclature of Medicine) for micro-organism and type of infection (viral, bacterial, fungal and others). In addition to being analyzed similarly as AEs and SAEs, as described above, the incidence rate of infection by type and micro-organism was tabulated for each treatment group.

The incidences of all infections (bacterial, fungal, and viral) reported as AEs was 61.7% in the everolimus 1.5 mg group, 64% in the everolimus 3.0 mg group and 67.8% in the Myfortic group, as shown in Table 40. The causative organisms for viral infections with

an incidence of $\geq 1\%$ are included. Organisms causing bacterial fungal infections were not included, as they were similar across the study groups.

Table 40. Number of Patients (%) with Infections by Type of Organism

Source: Table 14.3.1-1.7 on page 1467 of CSR

Type of Infection	Everolimus 1.5 mg N=274, n (%)	Everolimus 3.0 mg N=278, n (%)	Myfortic 1.44 gm N=273, n (%)
All infections	169 (61.7)	178 (64.0)	185 (67.8)
Bacterial - Total	71 (25.9)	69 (24.8)	69 (25.3)
Fungal - Total	12 (4.4)	14 (5.0)	14 (5.1)
Viral - Total	27 (9.9)	20 (7.2)	57 (20.9)
<i>BK virus</i>	2 (0.7)	3 (1.1)	11 (4.0)
<i>Cytomegalovirus, nos</i>	3 (1.1)	1 (0.4)	23 (8.4)
<i>Human herpes simplex virus, nos</i>	7 (2.6)	11 (4.0)	14 (5.1)
<i>Human herpes virus 3</i>	4 (1.5)	2 (0.7)	7 (2.6)
<i>Polyomavirus, nos</i>	5 (1.8)	0 (0.0)	3 (1.1)
<i>Virus, nos</i>	4 (1.5)	3 (1.1)	0 (0.0)
Other - Total	135 (49.3)	135 (48.6)	129 (47.3)

nos = not otherwise specified

The incidence of CMV, herpes simplex and BK virus infections was higher in the Myfortic group compared to both of the everolimus groups and is the main cause of the difference in the overall rates of infections across the three groups. The incidence of CMV infections was 5.9% (16 patients) in the Myfortic group vs. 0.7% (2 patients) in the everolimus 1.5 mg group. Also, there were five cases of CMV viremia reported in the Myfortic group compared to one case in the everolimus 1.5 mg group, which brings the total number of CMV infections to 23 patients (8.4%) in the Myfortic group and 3 patients (1.1%) in the everolimus 1.5 mg group, as shown in Table 40.

In an analysis of CMV-related events according to the donor/recipient CMV status, the advantage in the everolimus groups over the Myfortic group in terms of the incidence of CMV related events disappears if the donor is seropositive and the recipient is seronegative for CMV. The incidences of CMV events in the donor (+)/recipient (-) combination are 10% in the everolimus 1.5 mg group, 21.4% in the everolimus 3.0 mg group, and 14.3% in the Myfortic group. According to the protocol, CMV prophylaxis was mandatory for all cases in which the donor tested positive and the recipient tested negative for CMV. All other cases were treated according to local practice.

CMV syndrome, defined as fever for two days, neutropenia, leukopenia viral syndrome, was more frequently reported in the Myfortic group (4.4%) compared to 1.5% or 1.4% in the everolimus 1.5 mg and 3.0 mg treatment groups but none of the CMV syndromes were reported as SAEs.

The incidence of infections reported as SAEs are higher in the Myfortic group compared to the everolimus 1.5 mg group (25.3% vs. 19.7%) whereas the incidence is highest of all in the everolimus 3.0 mg group (26.6%). The difference between the everolimus 1.5 mg group and the Myfortic group is mainly due to the higher incidence of viral infections (CMV, BK virus and Herpes virus) in the Myfortic group. The incidences of bacterial and fungal infections between these two groups are similar. A total of 9 CMV infections were reported as SAEs in the Myfortic group compared to none in the everolimus 1.5 mg group and 2 BK virus infections were reported as SAEs in the Myfortic group compared to 1 case in the everolimus 1.5 mg group. Also a total of 4 Herpes Zoster infections were reported as SAEs in the Myfortic group compared to 1 case in the everolimus 1.5 mg group.

All of the CMV infections reported as SAEs in the Myfortic group responded to treatment and all of the patients recovered.

BK virus infections did not result in any graft losses and apparently responded to medical management according to the narratives. One patient in the Myfortic group who according to the narrative developed herpes encephalitis and the event was continuing at the time of reporting, no further information was available but this patient was not reported among the deaths or graft losses after the 12 month study period.

Reviewer's Comment:

In the Reviewer's opinion having less viral infections mainly less CMV infections is an advantage of the everolimus treatment but CMV infections or other types of viral infections did not result in any deaths or graft losses in the Myfortic group although they appear to be more frequent. Infections caused or contributed to 2 deaths in the everolimus 1.5 mg group and 5 deaths in the everolimus 3.0 mg group during the 12 month study period. No deaths due to infection were reported in the Myfortic group during the same period.

The Reviewer's conclusion is, although everolimus-low dose CsA regimen results in lower numbers of CMV and other types of viral infections; bacterial infections tend to be more severe and appear as one of the main causes of death with this regimen.

7.3.4.2 Proteinuria

Proteinuria was assessed by the Applicant by evaluating the ratio of spot urine protein (measured in milligrams) to creatinine (measured in grams) (UP/UC ratio) based on an estimate of an average 24 hour excretion. According to the study protocol the UP/UC ratio was defined as:

- Normal (<30 mg/g);

- Mild proteinuria (30 – <300 mg/g);
- Sub-Nephrotic proteinuria (300 - <3000 mg/g);
- Nephrotic proteinuria (≥3000 mg/g).

According to the National Kidney Foundation (NKF) definition of proteinuria, as shown in Table 41, the normal range is defined as a UP/UC ≤ 200 mg/g and clinical proteinuria occurs at values > 200 mg/g.

In the FDA analysis of proteinuria, the UP/PC results are expressed in units of gm/gm or a unitless ration. The NKF definition and grading system was also utilized and various ranges of UP/UC were explored (≤ 0.2, > 0.2 to < 0.5, 0.5 to < 1, 1 to < 2, 2 to < 3 and ≥ 3) to have a better understanding of the distribution of patients at various ranges of proteinuria.

Table 41 NKF Definition of Proteinuria and Albuminuria
 (http://www.kidney.org/professionals/kdoqi/guidelines_bp/background.htm)

Table 28. Definitions of Proteinuria and Albuminuria				
	Urine Collection Method	Normal	Micro-albuminuria	Albuminuria or Clinical Proteinuria
Total Protein	24-Hour Excretion (varies with method)	<300 mg/d	NA	>300 mg/d
	Spot Urine Dipstick	<30 mg/dL	NA	>30 mg/dL
	Spot Urine Protein-to-Creatinine Ratio (varies with method)	<200 mg/g	NA	>200 mg/g
Albumin	24-Hour Excretion	<30 mg/d	30–300 mg/d	>300 mg/d
	Spot Urine Albumin-Specific Dipstick	<3 mg/dL	>3 mg/dL	NA
	Spot Urine Albumin-to-Creatinine Ratio	<30 mg/g	30-300 mg/g	>300 mg/g
	Spot Urine Albumin-to-Creatinine Ratio (gender-specific definition) ^a	<17 mg/g (men) <25 mg/g (women)	17–250 mg/g (men) 25–355 mg/g (women)	>250 mg/g (men) >355 mg/g (women)

^aUse of the same cut-off value for men and women leads to higher values of prevalence for women than men.¹ Gender-specific cut-off values are from two studies.^{18, 19}
 Note: There is no uniformly accepted conversion between urine albumin and total protein. In general, a spot urine total protein-to-creatinine ratio >200 mg/g corresponds approximately to a spot urine albumin-to-creatinine ratio of >120 mg/g.

Proteinuria was reported as a SAE in two (0.7%) patients in the everolimus 1.5 mg group, four (1.4%) patients in the everolimus 3.0 mg group and one (0.4%) patient in the Myfortic group. Also, two patients in the everolimus 1.5 mg group, 4 patients in the everolimus 3.0 mg group discontinued treatment due to proteinuria. No patient discontinued treatment due to proteinuria in the Myfortic group. Proteinuria was reported as an AE in 9.1% of the patients in the everolimus 1.5 mg group, 12.9% of the patients in the everolimus 3.0 mg group and 7.3% of the patients in the Myfortic group.

The following analyses were performed by Biostatistics Reviewer John S. Yap Ph.D. In the following tables “on treatment”** analyses of proteinuria are presented from three different perspectives:

- 1- Comparison of the average Proteinuria / Creatinuria ratio in the everolimus 1.5 mg group vs. Myfortic group at different time points over the 12 month study period.
- 2- Comparison of the percentage of patients in different severity ranges of proteinuria in the everolimus 1.5 mg group vs. Myfortic group at different time points over the 12 month study period.
- 3- Proteinuria levels of patients in different groups at the end of the study period in relation to their proteinuria level at month 1.

**** On treatment analysis:** Any assessment obtained no later than 2 days after discontinuation of study medication was considered an on-treatment value; the baseline value is represented by the last non-missing observation during the baseline period; for others, multiple assessments within a given visit-window for one patient were averaged.

Analyses of the data indicate that the UP/UC ratios distributions are skewed due to extreme outlying values such that the means were greater than the medians. To account for the lack of symmetry in the data, these data were analyzed by comparing medians at each visit window between treatment groups and using the nonparametric Wilcoxon rank-sum test to test for treatment differences.

Table 42 shows the mean and median UP/UC ratios in the everolimus 1.5 mg and Myfortic treatment groups in the safety on-treatment population, which was defined as the population of safety patients whose assessments were obtained on and after day 1 but no later than two days after the discontinuation of randomized study medication. Of note, ratios in the everolimus 3.0 mg group are not presented in the tables related to proteinuria for the ease of reviewing. however, the everolimus 3.0 mg group performed worse than everolimus 1.5 mg when compared to Myfortic. These data are also plotted in Figure 11 illustrating that the medians ratios in everolimus 1.5 mg group were consistently higher than those of Myfortic throughout the study including the Month 12 TEP (shown as Month 13).

**Table 42. UP/UC Ratios for Safety On-Treatment Population
 (in gm/gm; no unit)**

(Source: Safety Review by John S. Yap Ph.D)

Visit Window	Treatment Group	n (%)*	Mean (SD)	Median (Range)	p-value**
Day 14	Everolimus 1.5 mg	241(89)	0.60 (1.29)	0.33 (0.06-17.05)	0.1881
	Myfortic	244 (90)	0.62 (1.28)	0.29 (0.08-13.04)	
Month 1	Everolimus 1.5 mg	246 (91)	0.43 (0.76)	0.26 (0.06-8.51)	0.0025
	Myfortic	244 (90)	0.40 (0.85)	0.20 (0.06-9.51)	
Month 3	Everolimus 1.5 mg	219 (81)	0.28 (0.42)	0.17 (0.02-3.90)	0.0338
	Myfortic	224 (83)	0.27 (0.50)	0.13 (0.05-4.19)	
Month 6	Everolimus 1.5 mg	188 (69)	0.25 (0.43)	0.15 (0.00-4.96)	0.0292
	Myfortic	207 (77)	0.25 (0.50)	0.12 (0.00-4.65)	
Month 9	Everolimus 1.5 mg	188 (69)	0.25 (0.30)	0.15 (0.00-2.24)	<0.0001
	Myfortic	198 (73)	0.22 (0.42)	0.11 (0.03-3.88)	
Month 12	Everolimus 1.5 mg	183 (68)	0.31 (0.59)	0.15 (0.03-6.15)	<0.0001
	Myfortic	192 (71)	0.27 (0.61)	0.11 (0.00-5.12)	
Month 12 TEP***	Everolimus 1.5 mg	271	0.70 (3.64)	0.21 (0.03-58.00)	<0.0001
	Myfortic	270	0.49 (1.23)	0.12 (0.00-10.39)	

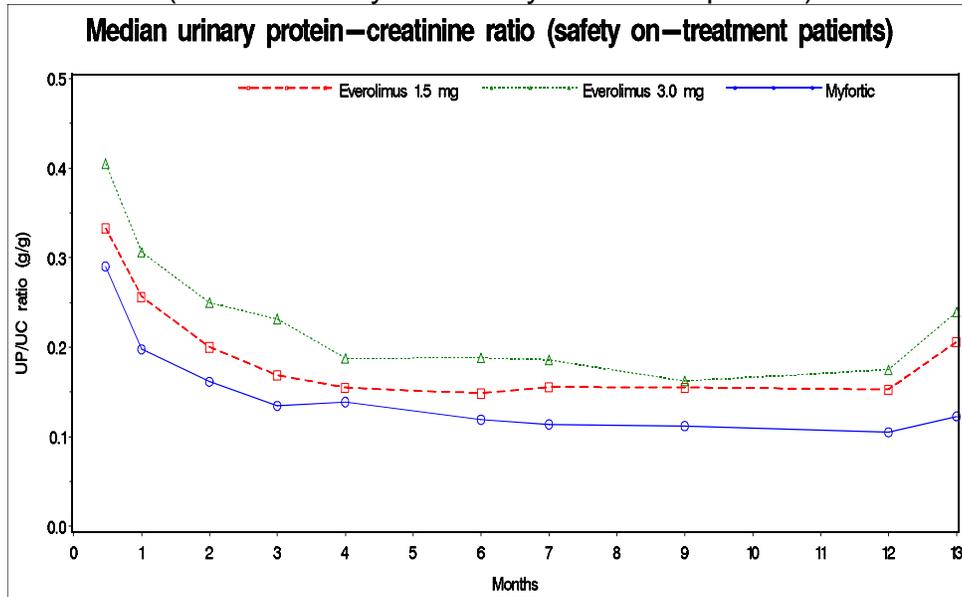
*% relative to Month 12 TEP; **Wilcoxon rank sum test; ***TEP=treatment endpoint (imputation by LOCF)
 No differences noted between treatment groups at baseline, days 1, 3, 7 and 14 (data omitted from table)

Reviewer's Comment: Although not shown in the Table 42 above Day 1 UP/UC values in the everolimus 1.5 mg group and the Myfortic group were similar to each other with no statistical difference in between. When we look at the values at M12 there is a 40 mg difference in between the everolimus 1.5 mg group and the Myfortic group both with regard to the mean or the median values.

When we look at the Month 12 TEP values which includes a higher number of patients due to the inclusion of the last on treatment value if the patient did not have a M12 value we notice that the gap between the everolimus 1.5 mg group and the Myfortic group increases and goes up to a difference of 100 mg when we look at the median values and increases even further when we look at the Month 12 TEP values (210 mg/g) and raises concerns about the further increases in this gap with longer follow-up.

As can be noticed starting Month 6 the differences between the two treatment groups become statistically significant. These differences become even higher when we consider the male patients only since the subset analysis (explained later in the text) shows that this higher level of proteinuria in the everolimus 1.5 mg group is driven by the male population.

Figure 11. Median Urinary Protein/Creatinine (Safety On-treatment Population)
 (Source: Safety Review by John S. Yap Ph.D)



Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

UP/UC ratios falling into clinically relevant categories at each visit window are presented in Table 43 below. These data suggest that there were more patients whose UP/UC ratios were less than 2.0 in the Myfortic group than the everolimus 1.5 mg group over time. This result is consistent with what was previously observed when assessing median ratios. *Note also, that there was an increasing number of missing data as study follow-up time increased. At Day 14, about 90% of data were collected compared to only about 70% at Month 12, as shown in Table 43.*

Table 43. Categorized UP/UC Ratios
(Source: Safety Review by John S. Yap Ph.D)

Visit Window	Treatment Group	n (%) [*]	UP/UC Ratio, n (%)					
			≤0.2	>0.2 to <0.5	0.5 to < 1	1 to < 2	2 to < 3	≥3
Baseline	Ever 1.5 mg	145 (54)	4 (3)	23 (16)	33 (23)	35 (24)	19 (13)	31 (21)
	Myfortic	134 (50)	3 (2)	18 (13)	27 (20)	42 (31)	16 (12)	28 (21)
Day 1	Ever 1.5 mg	235 (87)	7 (3)	56 (24)	80 (34)	56 (24)	14 (6)	22 (9)
	Myfortic	235 (87)	2 (1)	53 (23)	72 (31)	64 (27)	21 (9)	23 (10)
Day 14	Ever 1.5 mg	241 (89)	61 (25)	111 (46)	40 (17)	22 (9)	3 (1)	4 (2)
	Myfortic	244 (90)	78 (32)	104 (43)	34 (14)	16 (7)	5 (2)	7 (3)
Month 1	Ever 1.5 mg	246 (91)	87 (35)	109 (44)	34 (14)	11 (4)	3 (1)	2 (1)
	Myfortic	244 (90)	125 (51)	84 (34)	20 (8)	10 (4)	2 (1)	3 (1)
Month 3	Ever 1.5 mg	219 (81)	132 (60)	63 (29)	16 (7)	4 (2)	3 (1)	1 (0)
	Myfortic	224 (83)	146 (65)	59 (26)	11 (5)	4 (2)	1 (0)	3 (1)
Month 6	Ever 1.5 mg	188 (69)	124 (66)	48 (26)	12 (6)	2 (1)	1 (1)	1 (1)
	Myfortic	207 (77)	147 (71)	39 (19)	13 (6)	5 (2)	1 (0)	2 (1)
Month 9	Ever 1.5 mg	188 (69)	120 (64)	48 (26)	14 (7)	5 (3)	1 (1)	.
	Myfortic	198 (73)	149 (75)	34 (17)	8 (4)	5 (3)	1 (1)	1 (1)
Month 12	Ever 1.5 mg	183 (68)	110 (60)	49 (27)	16 (9)	4 (2)	2 (1)	2 (1)
	Myfortic	192 (71)	143 (74)	32 (17)	8 (4)	4 (2)	1 (1)	4 (2)
Month 12 TEP**	Ever 1.5 mg	271	135 (50)	80 (30)	31 (11)	11 (4)	6 (2)	8 (3)
	Myfortic	270	175 (65)	52 (19)	15 (6)	14 (5)	3 (1)	11 (4)

^{*}% relative to Month 12 TEP; ^{**}TEP=treatment endpoint (imputation by LOCF), Ever=everolimus

The proportions of patients with a UP/UC ratio falling into a specific range at month 12 according to the month 1 ratio are presented below in Table 44. These results show that at month 1, 88% of patients in the Myfortic group had a ratio < 0.5 compared to only 81% of patients in the everolimus 1.5 mg group. Of these patients, 40% and 56% in the everolimus 1.5 mg and Myfortic groups, respectively, had ratios below 0.2 at month 1 and about 76% and 85% of these maintained that level at month 12. For month 1, ratios in the > 0.2 to < 0.5 category, the month 12 levels were either maintained at that range or improved to the ≤ 0.2 category for 90% and 85% of the everolimus 1.5 mg and Myfortic patients respectively. In general, there were proportionately more patients in the Myfortic group with lower ratios at month 12 than in the everolimus 1.5 mg group. Note that Table 43 consists of data from patients who had both months 1 and 12 UP/UC measurements, representing only about 70% of the month 12 TEP sample size.

Table 44 Categorized UP/UC Ratios at Month 12
 (6 different grades of UP/UC ratios consolidated into 4 grades)
 (Source: Safety Review by John S. Yap Ph.D)

Visit Window	Treatment Group	Total #	Normal ≤ 0.2 n (%)	Mild > 0.2 to < 1.0 n (%)	Sub-nephrotic ≥ 1.0 to < 3.0 n (%)	Nephrotic ≥ 3.0 n (%)
Month 12	Eve. 1.5 mg Myfortic	183	110 (60)	65 (36)	6 (3)	2 (1)
		192	143 (74)	40 (21)	5 (3)	4 (2)
Month 12 TEP*	Eve. 1.5 mg Myfortic	271	135 (50)	111 (41)	17 (6)	8 (3)
		270	175 (65)	67 (25)	17 (6)	11 (4)

Reviewer's comment: In Table 44 above which gives the 12 Month values only, the 6 different ranges of proteinuria in Table 43 are consolidated into 4 consecutive ranges for easy interpretation. Regardless of the method utilized (M12 or M12 TEP) there are 15% more patients in the normal range in the Myfortic group compared to the everolimus 1.5 mg group. At the other end of the spectrum although we see an opposite trend, the number of patients are too small to make any meaningful comparisons at the nephrotic range. Also according to the Applicant's analysis which utilized a higher cut-off level, nephrotic range proteinuria (≥ 3.0 gm/gm) was reported for 0.7% of everolimus 1.5 mg treated patients, 1.4% of everolimus 3.0 mg treated patients, and by 0.4% of Myfortic treated patients during the 12 month study period.

Table 45 below shows the progression of patients at different ranges of proteinuria at month 1 to different stages of proteinuria at month 12.

Table 45. Categorized UP/UC Ratios (Months 1 and 12)
(Source: Safety Review by John S. Yap Ph.D)

Treatment	Proteinuria Range (Month 1)	n (%)	Proteinuria Range (Month 12), n (%)*					
			≤0.2	>0.2 to <0.5	0.5 to <1	1 to <2	2 to <3	≥3
Everolimus 1.5 mg (n=181)	≤0.2	72 (40)	55 (76)	14 (20)	2 (3)	1 (1)	0 (0)	0 (0)
	>0.2 to <0.5	75 (41)	45 (60)	22 (30)	4 (5)	1 (1)	1 (1)	2 (3)
	0.5 to <1	24 (13)	7 (29)	5 (21)	9 (38)	2 (8)	1 (4)	0 (0)
	1 to <2	7 (4)	2 (29)	4 (57)	1 (14)	0 (0)	0 (0)	0 (0)
	2 to <3	2 (1)	0 (0)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)
	≥3	1 (1)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Everolimus 3.0 mg (n=163)	≤0.2	46 (28)	36 (78)	7 (15)	0 (0)	2 (5)	1 (2)	0 (0)
	>0.2 to <0.5	82 (50)	43 (53)	28 (34)	3 (4)	5 (6)	2 (2)	1 (1)
	0.5 to <1	19 (12)	4 (21)	9 (47)	2 (11)	1 (5)	0 (0)	3 (16)
	1 to <2	13 (8)	6 (46)	6 (46)	0 (0)	0 (0)	0 (0)	1 (8)
	2 to <3	2 (1)	1 (50)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)
	≥3	1 (1)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Myfortic (n=187)	≤0.2	104 (56)	88 (85)	12 (11)	2 (2)	1 (1)	1 (1)	0 (0)
	>0.2 to <0.5	60 (32)	41 (68)	10 (17)	5 (8)	1 (2)	0 (0)	3 (5)
	0.5 to <1	14 (7)	6 (43)	7 (50)	0 (0)	1 (7)	0 (0)	0 (0)
	1 to <2	6 (3)	2 (33)	3 (50)	0 (0)	1 (17)	0 (0)	0 (0)
	2 to <3	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
	≥3	2 (1)	1 (50)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)

* % of row total

Table 46 below which is a simplified version of Table 45 shows the progression of patients at mild and subnephrotic ranges of proteinuria at month 1 to different stages of proteinuria at month 12.

Table 46 Shift Table of UP/UC Ratio Comparing Month 1 and 12
 (Simplified version of Table 45 with 6 ranges of UP/UC ratios consolidated into 4 ranges)
 (Source: Safety Review by John S. Yap Ph.D)

Treatment	UP/UC and Proteinuria Range at Month 1	n (%)	UP/UC and Proteinuria Range at Month 12			
			Normal ≤ 0.2 n (%)	Mild > 0.2 to < 1.0 n (%)	Sub-Nephrotic ≥ 1.0 to < 3.0 n (%)	Nephrotic ≥ 3.0 n (%)
Everolimus 1.5mg (N=274)	> 0.2 to < 1.0 Mild	99	52 (53)	40 (40)	5 (5)	2 (2)
	≥ 1.0 to < 3.0 Sub-nephrotic	9	2 (22)	7 (78)	0 (0)	0 (0)
Myfortic (N=273)	> 0.2 to < 1.0 Mild	74	47 (63)	22 (30)	2 (3)	3 (4)
	≥ 1.0 to < 3.0 Sub-nephrotic	7	2 (29)	3 (43)	1 (14)	1 (14)

Reviewer's comment:

One important point to consider before interpreting the results in Table 46 is the baseline stratification of the patients are done according to the month 1 values at which there already is a statistically significant difference between the everolimus groups and the Myfortic group with regard to proteinuria so month 1 values are not the baseline values. Nevertheless, this data may still give us an idea of the time course of development of proteinuria in these patients.

In Tables 45 and 46 above, of the patients who are initially in the mild proteinuria range (> 0.2 to < 1.0 gm/gm) approximately 10% more patients move down to the normal range in the Myfortic group compared to the everolimus 1.5 mg group.

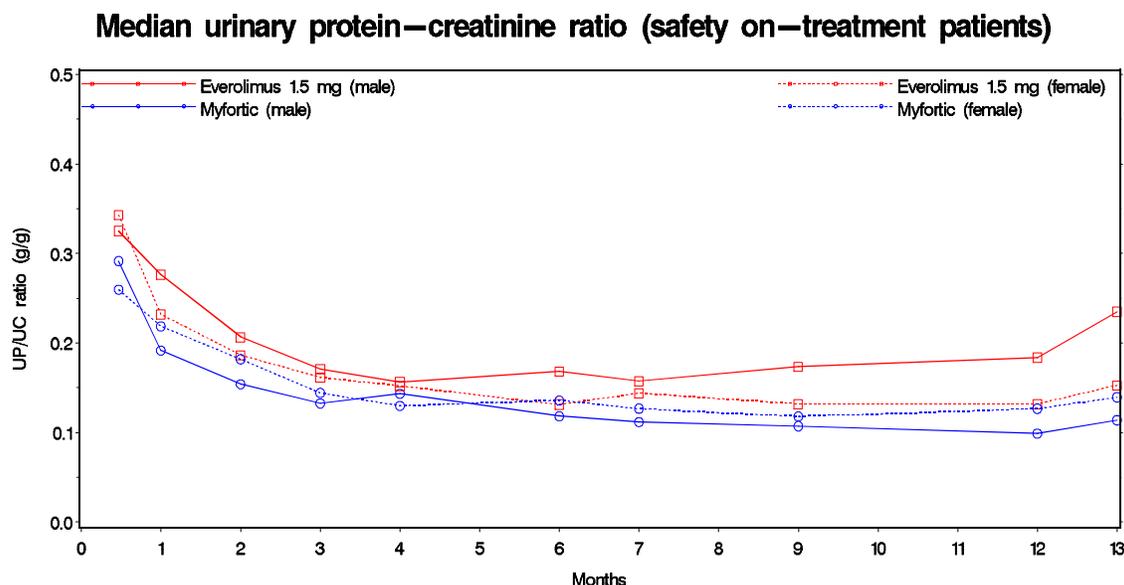
At the nephrotic range (≥ 3.0 gm/gm) we again see the opposite trend with numerically more patients moving up to this range (4 patients) in the Myfortic group compared to the everolimus 1.5 mg group (2 patients). Also at the nephrotic range the patient numbers are too small to make any meaningful comparisons. Also when we look at the total number of patients followed for this period it is only a fraction of the total: 108 patients in the everolimus 1.5 mg group and 81 patients in the Myfortic group.

Subgroup Analyses of Proteinuria by Gender, Race, Age and Diabetes Status
 (FDA analysis by John S. Yap Ph.D.)

Median UP/UC ratios among males in the everolimus 1.5 mg group were consistently higher than among males in the Myfortic group and the treatment groups were found to be statistically different at all time points except at baseline, days 7 and 14 and at month 4, as shown in Figure 12. These differences between the everolimus 1.5 mg and Myfortic groups were not observed among female patients. Thus, it appears that the differences that were seen earlier in the overall population between the everolimus 1.5 versus Myfortic groups may have been driven by the male population.

Reviewer’s Comment: *The fact that the proteinuria is driven by the male population (Figure 12) indicates that the magnitude of the proteinuria is larger for male patients. Also it is known from the literature that proteinuria is associated with worsened graft and patient survival and is a risk factor for cardiovascular morbidity. Also it is known from the literature that in general men are at increased risk for atherosclerotic heart disease compared to women. This differential effect across the gender will probably further increase the risk of graft failure and death in the male patients compared to female patients treated with everolimus.*

Figure 12 . Median Urinary Protein/Creatinine by Gender
 (Source: Safety Review by John S. Yap Ph.D)



Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

Use of ACEI/ARBs

An exploratory analysis was performed by the Applicant to examine the potential effect of the introduction of any angiotensin converting enzyme inhibitor (ACEI) or any angiotensin receptor blocker (ARB) on the level of proteinuria. ACEI or ARBs were used in approximately 50% of the patients across all groups in the new study. However, looking at the effect of the introduction of any ACEI or any ARB on proteinuria at least 30 days after the introduction was limited to approximately 20% of the entire study population. Nonetheless, there was a small yet similar reduction in the median urine protein to creatinine ratios for all groups (-38.9, -49.5 and -44.2 mg/g, respectively). In addition to the small number of patients, the analysis is also limited by the lack of data on the doses used of these agents, which is directly related to their known effect on proteinuria.

Clinical Significance

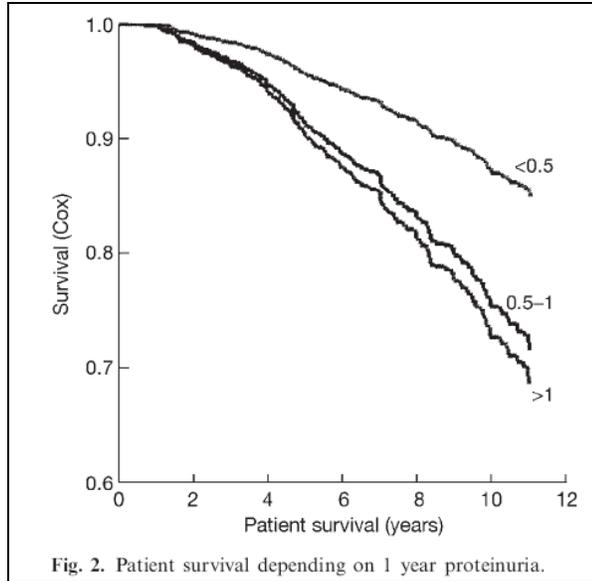
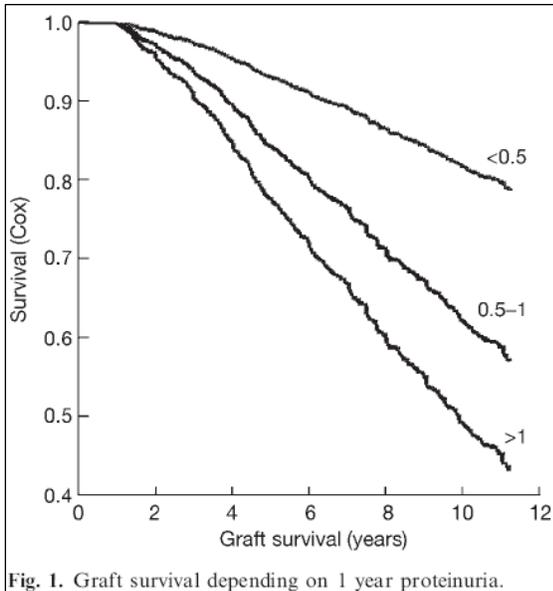
Proteinuria is not only a manifestation of renal disease, but is also a predictor of survival in most renal diseases. According to the published literature even low levels of proteinuria may adversely affect both the graft and patient survival in kidney transplant recipients.^{9,10} The following graphs (Figure 13) show the association between patient and graft survival by the level of proteinuria at one year.

9 Fernández-Fresnedo G, Plaza JJ, Sánchez-Plumed J, Sanz-Guajardo A, Palomar-Fontanet R, Arias M. Proteinuria: a new marker of long-term graft and patient survival in kidney transplantation. *Nephrol Dial Transplant*. 2004 Jun;19 Suppl 3:iii47-51.

10 Roodnat JI, Mulder PG, Rischen-Vos J, van Riemsdijk IC, van Gelder T, Zietse R, IJzermans JN, Weimar W. Proteinuria after renal transplantation affects not only graft survival but also patient survival. *Transplantation* 2001 Aug 15;72(3):438-44.

Figure 13. Patient and graft survival by the level of proteinuria

(Source: Reference No: 10)



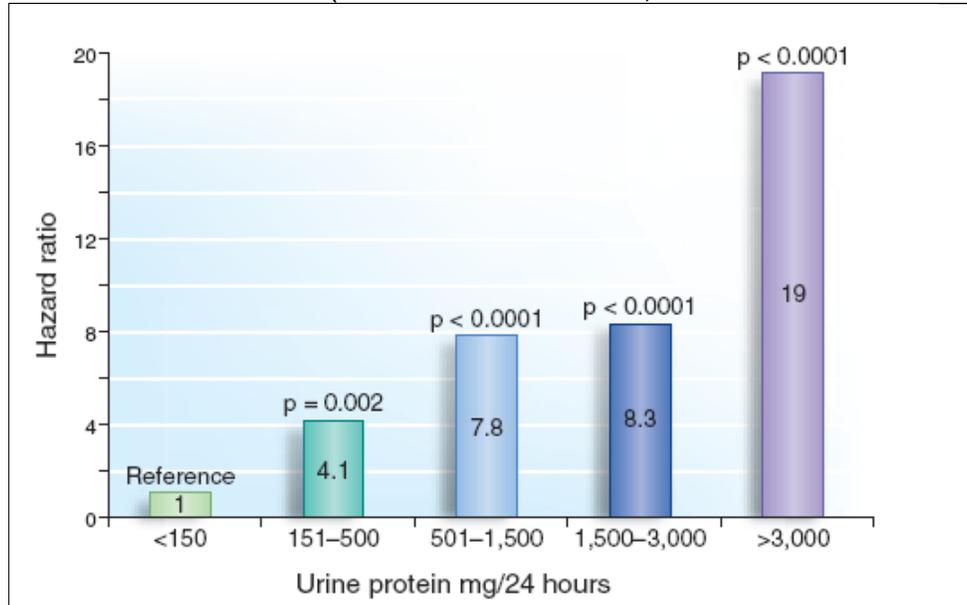
Some recently published data shows that even minimal proteinuria is a risk factor for graft survival.^{11,12} Figure 14 below shows the association between different levels of post-transplant proteinuria at 1 year and the risk of graft loss.

11 Kang NR, Lee JE, Huh W, Kim SJ, Kim YG, Kim DJ, Oh HY. 10. Minimal proteinuria one year after transplant is a risk factor for graft survival in kidney transplantation. J Korean Med Sci. 2009 Jan;24 Suppl:S129-34.

12 Amer H, Cosio FG. Significance and management of proteinuria in kidney transplant recipients. J Am Soc Nephrol. 2009 Oct 9. [Epub ahead of print]

Figure 14. Relationship between increasing levels of proteinuria at 1 year post-transplant and subsequent graft survival

(Source: Reference No: 11)



In absolute terms, 3.9%, 9.9%, 20%, 33.3%, and 41.2% of kidney allografts were lost during a period of 46 ± 20 mo of follow up in patients who at 1 yr had proteinuria <150 (n = 337), 151 to 500 (n= 182), 501 to 1500 (n= 50), 1500 to 3000 (n= 27), and >3000 (n= 17) mg/d, respectively.

Reviewer's comment: When the Month 12 TEP mean values are taken into consideration there is a difference of 210 mg/g between the everolimus 1.5 mg group and the Myfortic group in favor of the Myfortic group and this difference is even higher for the male patients since the overall higher levels of proteinuria in the everolimus 1.5 mg group is driven by the male patients. The fact that the differences between the two treatment groups became significant starting at Month 6 raises concerns that the gap may continue to widen in favor of the Myfortic group with longer follow-up and may be more severe for the male patients.

Proteinuria is a well known effect of M-TOR inhibitors. Currently a number of studies are being conducted to ameliorate the high levels of proteinuria associated with M-TOR inhibitors in transplant patients by use of concomitant usage of ACEIs/ARBs. Concomitant use of these medications may cause additional problems like chronic coughing and increased incidence of angioedema. Finally, ACEIs/ARBs may adversely affect the kidney graft function by reducing GFR and also by not clearly defined effects. It is also known that even small differences in the level of proteinuria may adversely affect kidney graft survival. Higher levels of proteinuria affect both the patient and graft survival (as explained above), as well as contributing to hyperlipidemia, which is already a

problem in transplant patients and was observed with higher severity in patients receiving everolimus, as will be discussed below.

7.3.4.3 Lipid Elevations

Earlier studies have shown an increased frequency of hyperlipidemia with M-TOR inhibitors and everolimus, predominantly associated with an increase in total cholesterol and triglycerides which can increase cardiovascular risk. Thus, the Applicant evaluated serum lipid profiles, rates of associated lipid-related events and use of lipid-lowering agents.

According to the study protocol patients who have severe hypercholesterolemia (> 350 mg/dL; > 9 mmol/L) or hypertriglyceridemia (> 500 mg/dL; > 8.5 mmol/L) were excluded from the study. Lipid lowering medications such as HMG CoA reductase inhibitors were to be administered according to local practice for the management of hyperlipidemia. According to the study protocol lovastatin and simvastatin were not allowed because of confirmed interaction between these drugs and CsA. Cerivastatin was also strongly discouraged because of insufficient data available. Lipid-lowering therapy was to be optimized before dose reduction of study medication was considered.

Hyperlipidemia was reported as a SAE was reported in only one patient in the study and was in the everolimus 1.5 mg group.

Dyslipidemia, (dyslipidemia, hypercholesterolemia and hyperlipidemia combined together) led to study drug discontinuations in two patients in each of the everolimus groups and one patient in the Myfortic group. Total numbers of patients with drug discontinuations or dose adjustments due to dyslipidemias are 4 (1.4%) patients in the everolimus 1.5 mg group, 7 (2.5%) patients in the everolimus 3.0 mg group compared to one (0.3%) patient in the Myfortic group.

Hyperlipidemia was reported as an AE in 57 (20.8%) patients in the everolimus 1.5 mg group, 60 (21.6%) patients in the everolimus 3.0 mg group, and 43 (15.8%) patients in the Myfortic group. Hypercholesterolemia was reported in 47 (17.2%) patients in the everolimus 1.5 mg group, 50 (18.0%) patients in the everolimus 3.0 mg group, and 34 (12.5%) patients in the Myfortic group as an AE in the 12 month safety population.

Lipid lowering agents were taken by a higher percentage of patients in the everolimus treatment groups (64.6%, 72.3% and 57.5% of patients in the everolimus 1.5 mg, 3.0 mg and Myfortic groups, respectively).

Among patients with high baseline cholesterol values before the statin treatment was initiated, 27.4% (17/62) in the everolimus 1.5 mg group compared to 13.9% (5/36) in the Myfortic group did not move down to the normal range despite the statin treatment. A

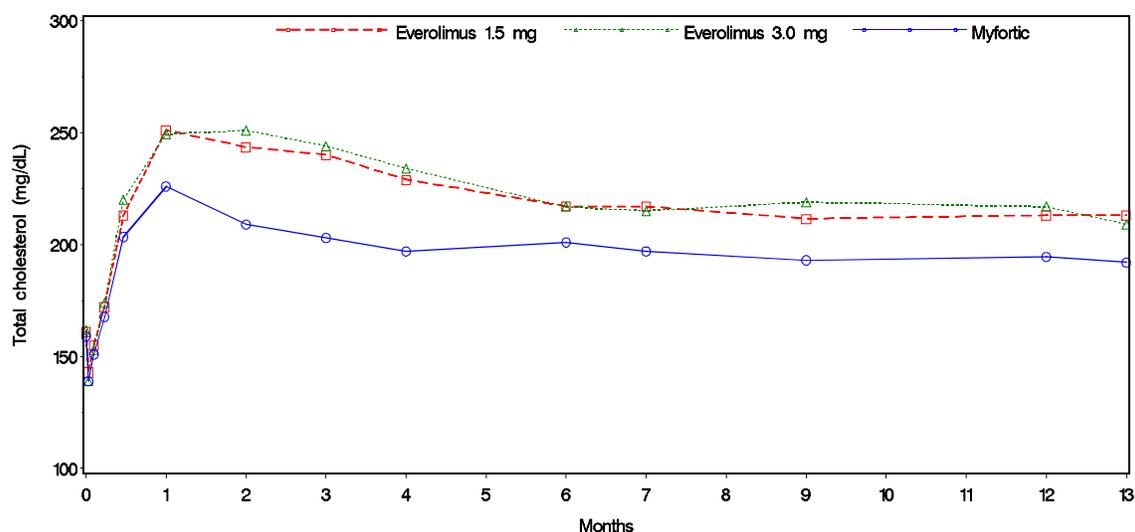
similar trend was also observed for triglycerides in a similar analysis. Among patients with high baseline triglyceride values before the statin treatment was initiated, 49% (22/45) in the everolimus 1.5 mg group compared to 26% (5/19) in the Myfortic group did not move down to the normal range despite the statin treatment.

Creatine kinase levels measured in both of the everolimus groups at all time points throughout the 12 month study period were significantly higher compared to the Myfortic group which may be an early sign of rhabdomyolysis although the mean and median levels in both groups stayed within the normal range.

Lipids were assessed in the safety on-treatment population focusing on the following clinical parameters: total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and total cholesterol-HDL ratio. The data presented in the figures below are given in mg/dL units. Since the distributions of the lipid measurements at each visit window are skewed, medians were plotted and the treatment groups were compared using the Wilcoxon rank-sum test.

As illustrated in Figure 15, the median total cholesterol was consistently higher in both everolimus groups compared to the Myfortic group and statistically significant differences were found from month 1 post-transplant through month 12 TEP (Month 13 in the figure).

Figure 15. Median Total Cholesterol
(Source: Safety Review by John S. Yap)
Median total cholesterol (safety on-treatment patients)

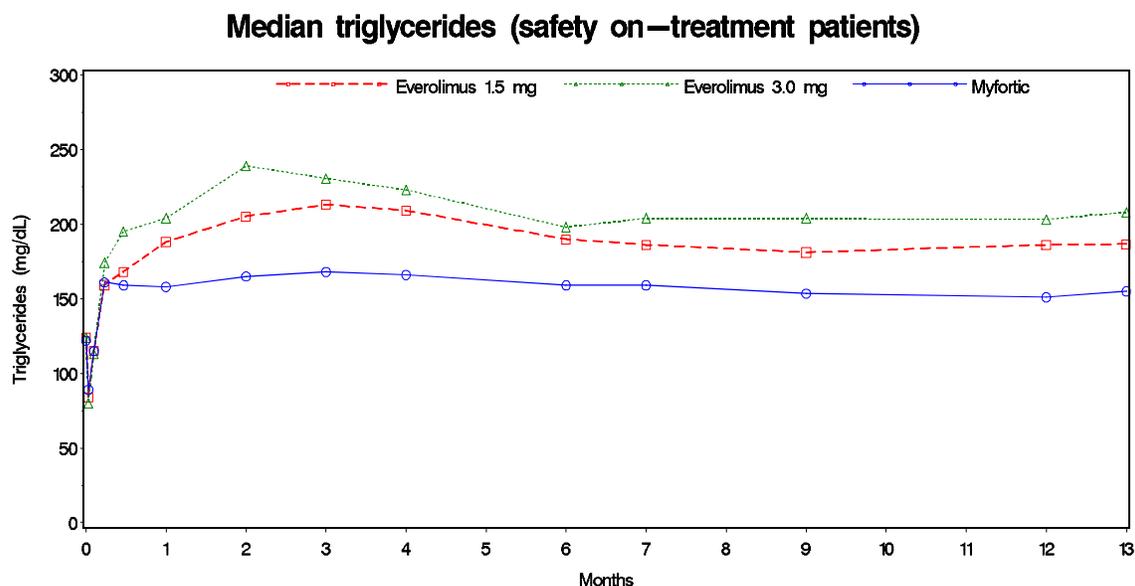


Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

Reviewer's Comment: As shown in Figure 15 above, starting at Month 9 the median values in the Myfortic group overlap with the upper bound of normal range (200 mg/dL) while the median values in both of the everolimus groups continue to stay well above the normal range. There is also a statistically significant difference in between the everolimus groups and the Myfortic group

Median triglycerides, shown in Figure 16, were consistently higher in both everolimus groups compared to the Myfortic group from month 1 through end of the 12 month follow-up period. Differences between the everolimus 1.5 mg and Myfortic groups were statistically significantly different at month 1 and onwards, including the month 12 TEP.

Figure 16. Median Triglycerides
(Source: Safety Review by John S. Yap Ph.D)

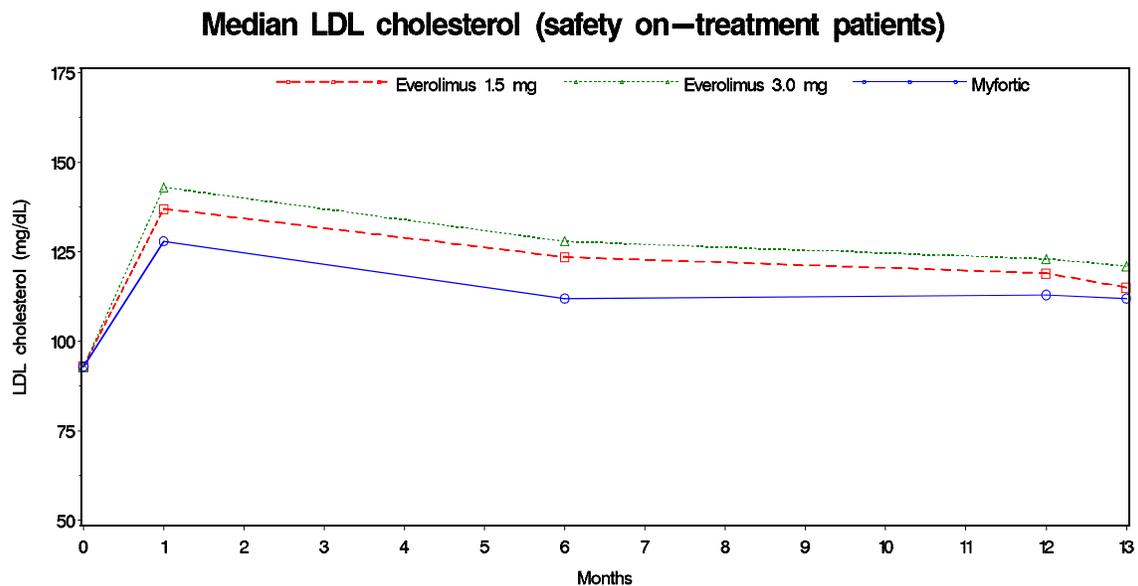


Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

Reviewer's Comment: We see a similar trend with triglyceride values to the trend we have seen with cholesterol values. As shown in Figure 16, starting at Month 9 the median values in the Myfortic group overlap with the upper bound of normal range (150 mg/dL) while the median values in both of the everolimus groups continue to stay well above the normal range. There is a statistically significant difference between both of the everolimus treatment groups and the Myfortic group.

LDL, HDL and total cholesterol to HDL ratio were assessed at baseline, months 1, 6 and 12. Few measurements were obtained at other study visits and were therefore excluded in the analysis. At baseline, no differences were noted among treatment groups. Post-baseline LDL and HDL levels were statistically significantly different between everolimus 1.5 mg and Myfortic at month 1 (p-value=0.0086) and at month 12 TEP (p-value=0.0158) for LDL (Figure 17) and month 6 (p-value=0.0013) and at month 12 TEP (p-value = 0.0002) for HDL (data not shown). Post-baseline total cholesterol to HDL ratio medians in the everolimus 1.5 mg group were greater than in the Myfortic group except at month 6, though treatment differences were not statistically significant.

Figure 17. Median LDL Cholesterol
(Source: Safety Review by John S. Yap Ph.D)



Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

Table 47 LDL Cholesterol Levels at Month 12 and Month 12 TEP (mmol/L)*
 (Source: Table 14.3-2.6a page 980, CSR)

Visit	Treatment Group	n	mean	s.d.	median	min	max	p-value of Wilcoxon Rank-Sum test	
								vs Myfortic	vs RAD 3.0mg
Month 12	RAD 1.5mg	185	3.20	1.089	3.08	0.9	7.2	0.143	0.095
	RAD 3.0mg	175	3.43	1.250	3.18	1.0	9.1	0.002	
	Myfortic	201	3.05	1.149	2.92	0.8	9.4		
Month 12 TEP	RAD 1.5mg	259	3.25	1.174	2.97	0.9	7.7	0.015	0.390
	RAD 3.0mg	259	3.36	1.283	3.13	0.7	9.1	0.001	
	Myfortic	260	2.98	1.186	2.90	0.6	9.4		

* mmol/L values need to be multiplied by 38.6 to convert into mg/dL values. Hence at M12 TEP mean LDL values are 125 mg/dL (3.25x38.6) in the everolimus 1.5 mg group and 115 mg/dL (2.98x38.6) in the Myfortic group.

Reviewer's Comment: According to the more recent research and KDIGO¹³ LDL is better correlated with cardiovascular risk compared to total cholesterol values. According to both the FDA's analysis and the Applicant's analysis, LDL values in the everolimus 1.5 mg group were significantly higher than the same values in the Myfortic group both at Month 12 and Month 12 TEP.*

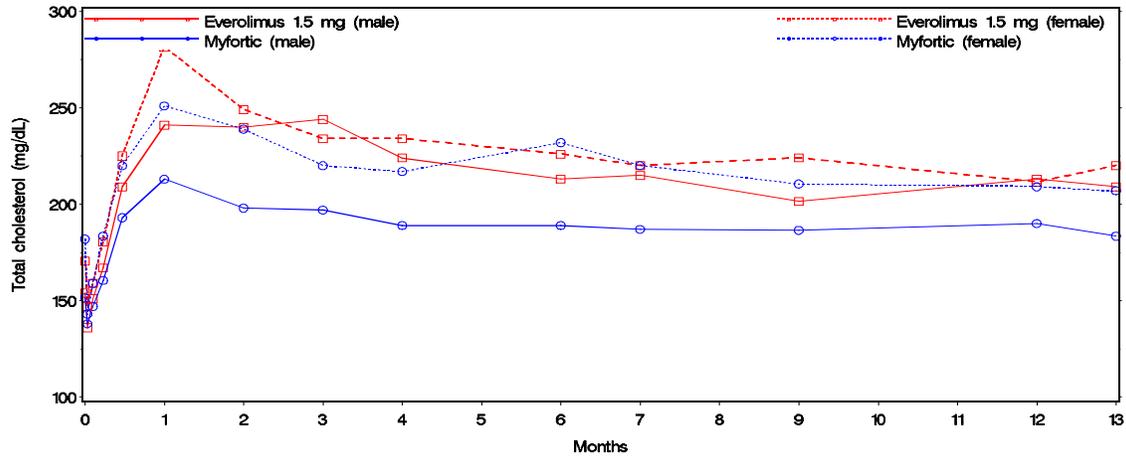
Subgroup Analyses of Hyperlipidemia by Gender, Race, Age and Diabetes Status

The following analyses were performed by John Yap PhD, FDA statistical Reviewer.

Median total cholesterol levels among males in the everolimus 1.5 mg group were consistently higher than those among males in the Myfortic group and the treatment groups were significantly different at all visit windows except at baseline and day 1 (Figure 18). Among females, differences between the everolimus 1.5 mg and Myfortic groups were only observed at months 1 (p-value 0.0449), 2 (p-value 0.0215) and 3 (p-value 0.0420), as shown in the same figure. Thus, it appears that the statistical differences that were seen earlier between the everolimus 1.5 versus Myfortic groups in regard to cholesterol levels may have been driven by the subset of male patients in the study. *Note: These comparisons are unadjusted.*

13 KDIGO, American Journal of Transplantation 2009; 9 (Suppl 3): S71–S79

Figure 18 Median Total Cholesterol by Gender
(Source: Safety Review by John S. Yap Ph.D)
Median total cholesterol (safety on—treatment patients)

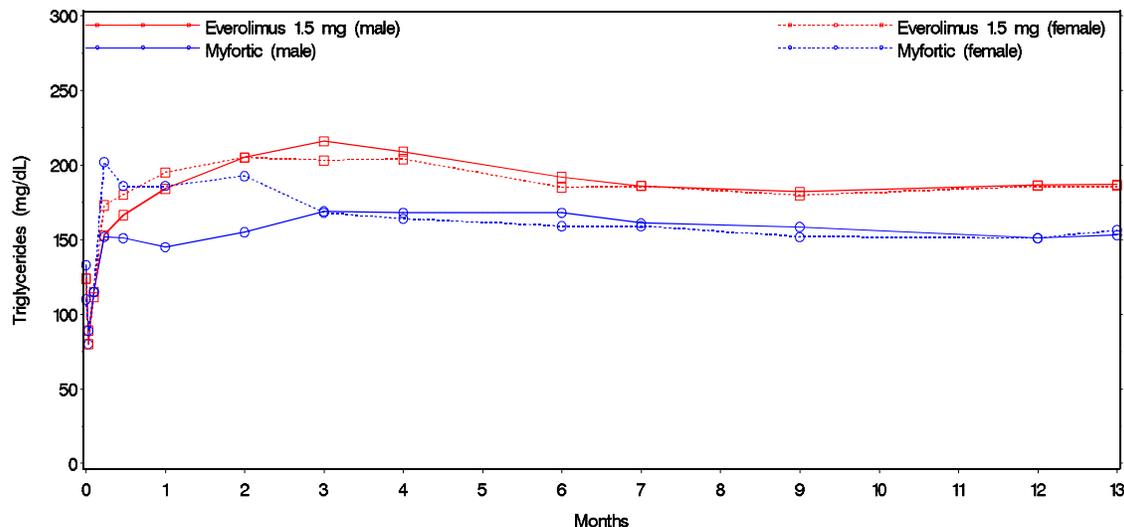


Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

Reviewer's Comment: As seen in seen Figure 18 above higher levels of total cholesterol in the everolimus 1.5 mg group compared to Myfortic group is primarily driven by male patients similar to what is observed with proteinuria (Figure 12).

Median triglyceride levels among males in the everolimus 1.5 mg group were consistently higher than among males in the Myfortic group. The differences between treatment groups were statistically significant at all visit windows except at baseline and days 1, 3, 7 and 14. A similar trend was found among females, with statistically significant differences noted between the everolimus 1.5 mg and Myfortic groups at months 3, 6, 7, 9 and 12, including the month 12 TEP (Figure 19). Thus, for triglyceride levels, it appears that the differences between the everolimus 1.5 versus Myfortic groups in the overall population are also seen when looking at each subgroup by gender.

Figure 19. Median Triglycerides by Gender
 (Source: Safety Review by John S. Yap Ph.D)
Median triglycerides (safety on-treatment patients)



Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

There were no notable treatment by gender effects or trends observed in subgroup analyses of LDL, HDL and total cholesterol to HDL ratio.

Table 48 showing the percentage of patients with notably high levels of cholesterol and triglyceride values and the patients with notably high Cholesterol/LDL ratios in the study. Notably high levels, as defined in the protocol by the Applicant, were < 350 mg/dL for cholesterol and 500 mg/dL for triglycerides. According to the 12 month on-treatment analysis, 15.7% of the patients in the everolimus 1.5 mg group have total cholesterol levels > 350 mg/dL compared to 6.3% of the patients in the Myfortic group. The same trend is seen for serum triglycerides.

Normal ranges in mmol/L:

Cholesterol (total): 2.2 - 5.2 (Notable Range: GT 9)

Cholesterol (LDL): 1.6 - 3.3

Cholesterol (HDL): 1 - 1.9

Triglycerides: 0.3 - 1.7 GT 8.4

Cholesterol/HDL (Ratio): 1 - 5 GE 5 and LE 7 or GT 7

Table 48 Patients with Notably High Lipid Values at Month 12*
 (Source Table 14.3-2.7, on page 1267 of CSR)

Table 14.3-2.7 (Page 6 of 8) Incidence Rates of Patients with Post-baseline Laboratory Abnormalities Based on Notable Criteria (Safety Population - 12 Month On-treatment Analysis)					
Variable	Notable Criteria	RAD 1.5mg N=274 n (%)	RAD 3.0mg N=278 n (%)	Myfortic 1.44g N=273 n (%)	Difference/95%CI for RAD 1.5mg-Myfortic RAD 3.0mg-Myfortic RAD 1.5mg-RAD 3mg
Lipids					
- Cholesterol (total) [mmol/L]	High: GT 9.0 mmol/L	43 / 274 (15.7%)	46 / 278 (16.5%)	17 / 272 (6.3%)	9.4% (4.3, 14.6)
					10.3% (5.1, 15.5) -0.9% (-7.0, 5.3)
- Triglycerides [mmol/L]	High: GT 8.4 mmol/L	12 / 274 (4.4%)	17 / 278 (6.1%)	7 / 272 (2.6%)	1.8% (-1.3, 4.9)
					3.5% (0.2, 6.9) -1.7% (-5.5, 2.0)
- Cholesterol/HDL (Ratio)	High: GE 5 but LE 7	68 / 259 (26.3%)	95 / 259 (36.7%)	81 / 261 (31.0%)	-4.8% (-12.5, 3.0)
					5.6% (-2.5, 13.8) -10.4% (-18.4, -2.5)
	Very High: GT 7	20 / 259 (7.7%)	13 / 259 (5.0%)	17 / 261 (6.5%)	1.2% (-3.2, 5.6) -1.5% (-5.5, 2.5) 2.7% (-1.5, 6.9)

* Values in the table are reported in mmol/L. A value of 9.0 mmol/L total cholesterol is approximately equal to 350 mg/dL of total cholesterol (conversion factor: multiply by 38.67 for total, HDL and LDL cholesterol: multiply by 88.57 for serum triglycerides).

Reviewer's Comment: In the everolimus 1.5 mg group almost three times as many patients (16% vs. 6%) have total cholesterol levels above 350 mg/dL and almost twice as many patients (4.4% vs. 2.6%) have triglyceride values above 500 mg/dL compared to the Myfortic group.

It is important to remember that the upper levels of normal range are 200 mg/dL for cholesterol and 150 mg/dL for triglycerides. Therefore the Applicant's notably high levels can be considered very high values, potentially with serious cardiovascular clinical consequences. This is a very concerning finding for the everolimus 1.5 mg group, especially in light of the 39 year old patient with normal pre-transplant lipid values who developed hyperlipidemia after the transplant and died on Day 85 due to myocardial infarction.

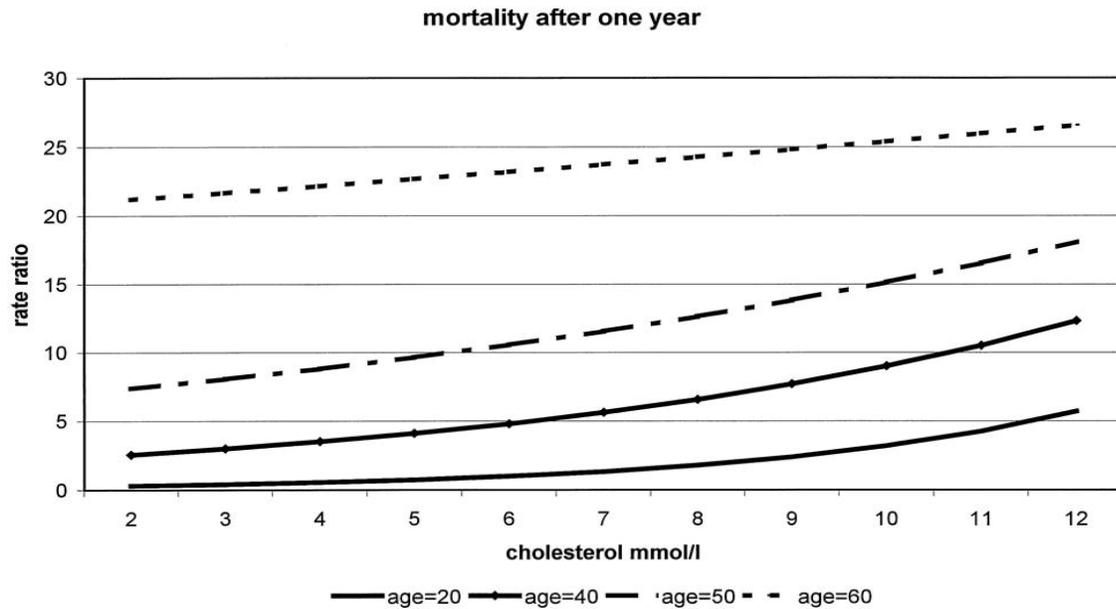
Clinical Significance

Hyperlipidemia is common in chronic kidney disease patients and the incidence increases after kidney transplantation. Various immunosuppressants, including CsA, corticosteroids, and M-TOR inhibitors, have been recognized as a major contributor to dyslipidemias seen after transplant.

Both serum cholesterol and recipient age are independent variables influencing the RR (relative risk) for patient death, adjusted for all other variables in the model.¹⁵ The

variables included in the study were cholesterol, creatinine, proteinuria, and hypertension at 1 year after transplantation, recipient and donor age and gender, HLA-mismatches on A and B locus, recipient race, original disease, and transplantation period. The simultaneous risk is defined as a continuous function of serum cholesterol for four ages (20, 40, 50, and 60 years). It is expressed relative to a cholesterol level of 6 mmol/L (240 mg/dL) and a 20-year-old patient. Figure 20 shows the influence of the interaction of cholesterol and recipient age relative to the rate of a 20-year-old with cholesterol of 6 mmol/L (240 mg/dL). The negative influence of high serum cholesterol is largest in the youngest patients. In the elderly, the rate increase caused by cholesterol is outweighed by the larger rate caused by other factors associated with advanced recipient age.¹⁴

Figure 20. Simultaneous Influence of Serum Cholesterol and Recipient Age on the Relative Risk of Death. (Source: Reference No.15)



The solid line is the regression line obtained with the regression equation when the RR for recipient age is 1. The influence of other recipient ages on the influence of cholesterol on the RR is plotted according to the regression equation.

Table 49 below compares the relative risk of developing ischemic heart disease in the kidney transplant recipients compared to the control group in relation to the presence of various known risk factors like hypercholesterolemia and diabetes. (Control subjects are from the Framingham Heart Study).

14 Roodnat JI, Mulder PG, Zietse R, Rischen-Vos J, van Riemsdijk IC, IJzermans JN, Weimar W. Cholesterol as an independent predictor of outcome after renal transplantation. *Transplantation* 2000 Apr 27;69(8):1704-10

Table 49. Relative Risk of Developing Ischemic Heart Disease in Kidney Transplant Recipients¹⁵
 (Source: Reference No.14)

TABLE 2. Relative risk for IHD among transplant recipients more than 1 year after kidney transplantation

Risk factor	Relative risk			
	Men		Women	
	Control	Transplant recipient	Control	Transplant recipient
Age	1.05	1.06 ^a	1.40	1.10
Cholesterol (mg/dL)				
<160	0.52	0.00 ^b	0.77	0.00 ^b
160–199	1.00 ^c	1.00 ^c	1.00 ^c	1.00 ^c
200–239	1.19	2.39	1.23	2.07
240–279	1.66	2.02	1.28	2.44
>280	1.93	2.25	1.71	1.84
Blood pressure (mm Hg)				
<120 and <80	1.00	0.25	0.59	0.56
120–129 or 80–84	1.00 ^c	1.00 ^c	1.00 ^c	1.00 ^c
130–139 or 85–89	1.33	1.05	0.93	1.26
140–159 or 90–99	1.68	1.19	1.30	1.63
≥160 or ≥100	1.86	1.47	1.59	0.31
Diabetes mellitus	1.53	2.78 ^a	1.82	5.40 ^a
Smoking	1.69	1.95 ^a	1.34	1.82

Reviewer’s Comment: As shown in Table 49 above even mild elevations in cholesterol levels may double the risk of developing ischemic heart disease in kidney transplant recipients unlike the milder increase of risk in the general population. Also as mentioned in the article by Roodnat published in *Transplantation*¹¹ the effect is even higher in younger patients.

The analysis shows that in Study A2309 the median values for both the total cholesterol and triglycerides are well above the upper bound of the normal range while the median values in the Myfortic group overlap or come down to the

15 Davidson J, Wilkinson A, Dantal J, et al. New-onset diabetes after transplantation: 2003 International Consensus Guidelines. *Transplantation* 2003; 75: SS3.

normal range especially towards the end of the 12 month study period. The differences between the Myfortic group and the everolimus groups are statistically significant.

Also the data shows that more patients fail to respond adequately to statin treatment in the everolimus 1.5 mg group compared to the Myfortic group with significantly higher CK values although the median and the mean CK values are within the normal range. High cholesterol and lipid values in general are well established risk factors for developing cardiovascular disease in the general population.

There are a substantial number of publications including the ones referenced in this review that shows that this adverse effect of high lipid levels is also valid for the transplant patients as well. Recently published Kidney Disease Guidelines (KDIGO) by the AST (American Society of Transplantation) also recommends lowering the serum lipid levels in kidney transplant patients for the same reasons⁷:

“Observational studies suggest that hypercholesterolemia and increased LDL-C are independently associated with CVD events in KTRs (Kidney Transplant Recipients)”
Chapter 16, page S76

In this study a 39 year old male patient (0124-00076) whose death was attributed to acute myocardial infarction developed severe dyslipidemia (hypercholesterolemia) after the transplant which gradually worsened until his death on Day 85. His total cholesterol increased from 147 mg/dL to 432 mg/dL and his LDL cholesterol increased from 81 mg/dL to 212 mg/dL (normal levels: up to 129 mg/dL) during the course of the study. Although this patient had a history of hypertensive heart disease the rapid rise of all lipid levels from normal range to very high values in a short period of time might have contributed to his death.

As mentioned above in the everolimus 1.5 mg group it is 2-3 times more likely to have cholesterol levels above 350 mg/dL and triglyceride levels above 500 mg/dL compared to the Myfortic group.

As explained in the text above LDL values (which is claimed to correlate better with cardiovascular risk in recent literature) in the everolimus 1.5 mg group are also significantly higher than the same values in the Myfortic group both at M12 and M12 TEP.

Hypertriglyceridemia observed in association with M-TOR inhibitors may also contribute to the already high incidence of pancreatitis observed in these patients (over 1% according to Novartis database).

7.3.4.4 Wound Healing

The applicant identified AEs related to wound healing events through a retrospective search of the AE and infectious events databases. Identified terms were reviewed by their clinical team to determine relevance and then paper CRFs were dispatched to the sites for further information regarding the events prior to database lock.

Based on the applicant's analysis of all the relevant preferred terms, including lymphocele, seroma, hematoma, dehiscence, incisional hernia and others; the overall incidence of wound events was 35% in the everolimus 1.5 mg group, 38.8% in the everolimus 3.0 mg group, and 25.6% in the Myfortic group.

As shown in Table 50, incisional wound complications were more frequent in the two everolimus groups compared to the Myfortic group with the highest number occurring in the 3.0 mg group. In each of the Dehiscence, Hernia and Infection categories, more patients required surgical intervention (i.e., intraoperative repair or debridement/drainage) in the everolimus groups compared to the Myfortic group. The total number of surgical interventions was nine in the everolimus 1.5 mg group, 22 in the everolimus 3.0 mg group, and nine surgical interventions in the Myfortic group. (See *shaded rows in the table*)

Wound dehiscence and impaired healing resulted in study drug discontinuations in one patient in the everolimus 1.5 mg group, six patients in the everolimus 3.0 mg group, and none in the Myfortic group.

Wound-related SAEs were reported in six patients in the everolimus 1.5 mg group, seven in the everolimus 3.0 mg group, and three in the Myfortic group. A higher incidence of wound-related SAEs in the everolimus groups is consistent with the known adverse effect of M-TOR inhibitors on the wound-healing process.

Table 50. Management for Patients with Any Incisional Wound Complications
(Source: Applicant's analysis submitted upon request)

Type of Incisional Wound Complication	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
Total Number of Patients	37 (13.5)	48 (17.3)	28 (10.3)
Dehiscence	19 (6.9)	27 (9.8)	13 (4.7)
Non-surgical observation	3 (1.1)	6 (2.2)	3 (1.1)
Intraoperative repair	6 (2.2)	7 (2.5)	3 (1.1)
Local wound care	10 (3.6)	16 (5.7)	7 (2.5)
Hernia	10 (3.6)	11 (3.9)	6 (2.2)
Non-surgical observation	3 (1.1)	5 (1.7)	4 (1.4)
Intraoperative repair	7 (2.5)	6 (2.2)	2 (0.7)
Infection	20 (7.2)	23 (8.2)	15 (5.4)
Intravenous antibiotics	10 (3.6)	12 (4.3)	7 (2.5)
Local wound care	13 (4.7)	17 (6.1)	12 (4.3)
Intraoperative debridement/drainage	6 (2.2)	9 (3.2)	4 (1.4)
Oral antibiotics	12 (4.3)	16 (5.7)	9 (3.2)
Other	1 (0.4)	3 (1.1)	3 (1.1)

Similar to the incidence of wound-related events, fluid collections (lymphoceles and seromas) were also more commonly reported in the everolimus groups compared to the Myfortic group, as shown in Table 51. Hematoma and urinomas are not included in this table since their mechanism is related to surgical technique, coagulation defects (hematomas); or distal ureteral necrosis or in some cases due to poor healing of the uretero-neocystostomy anastomosis (urinomas). On the other hand, seromas and lymphoceles have a common mechanism of development. Both usually develop as a result of excessive transudation of fluids across the membranes or due to failure of the transected lymphatics to heal following surgery.

Lymphocele led to drug discontinuations in three patients in the everolimus 1.5 mg group, four patients in the everolimus 3.0 mg group, and none in the Myfortic group. (See Table 50 above)

The number of surgical or percutaneous interventions (i.e., percutaneous drainage or intraoperative drainage) required for seromas and lymphoceles is also higher in the everolimus groups compared to the Myfortic group (24, 43, and 15 interventions, respectively). (See *shaded rows in the table*)

Table 51. Management of Fluid Collections
 (Source: Applicant's analysis submitted upon request)

Type of Fluid Collection	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic N=273 n (%)
Total Number of Patients	28 (10.2)	48 (17.2)	17 (6.2)
Seroma	8	13	3
Observation	3 (37.5)	4 (30.8)	2 (66.7)
Percutaneous drainage	5 (62.5)	6 (46.2)	1 (33.3)
Intraoperative drainage	1 (12.5)	2 (15.4)	0
Intravenous antibiotics	1 (12.5)	2 (15.4)	0
Other	1 (12.5)	4 (30.8)	0
Lymphocele	20	35	14
Observation	9 (45.0)	14 (40.0)	9 (64.3)
Percutaneous drainage	11 (55.0)	22 (62.9)	7 (50.0)
Intraoperative drainage	7 (35.0)	13 (37.1)	7 (50.0)
Intravenous antibiotics	6 (30.0)	4 (11.4)	6 (42.9)
Other	0	2 (5.7)	1 (7.1)

Reviewer's Comments:

As shown in Figure 21 and Figure 22 below in graphical form more patients required surgical and non surgical (mainly percutaneous drainage for fluid collections) interventions in the everolimus 1.5 mg group compared to the Myfortic group for the treatment of their wound related complications. This higher requirement of surgical and non-surgical interventions in the everolimus 1.5 mg group shows that not only the number of wound complications was higher in number but they were also more severe in nature in the everolimus 1.5 mg group.

Figure 21. Surgical Intervention Rates for the Treatment of Wound Complications

Source: Produced by the Clinical Reviewer from the data in Table 50

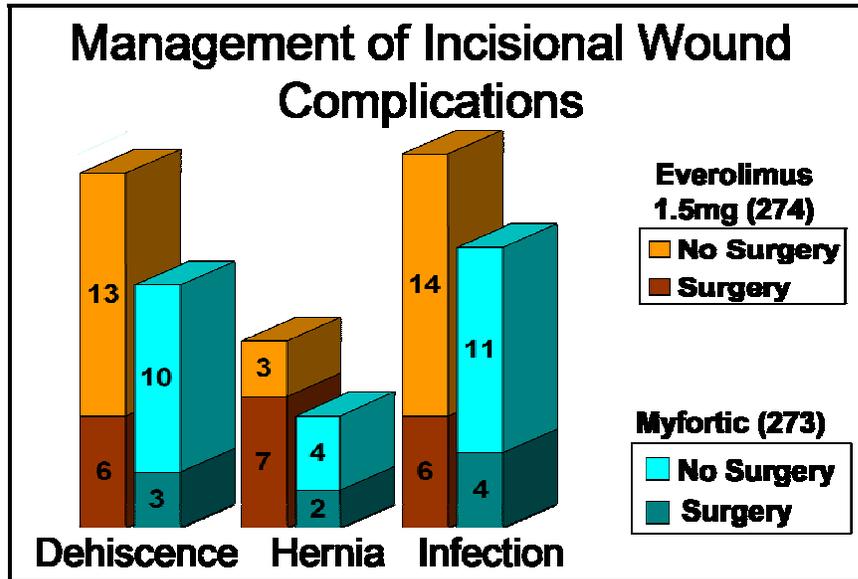
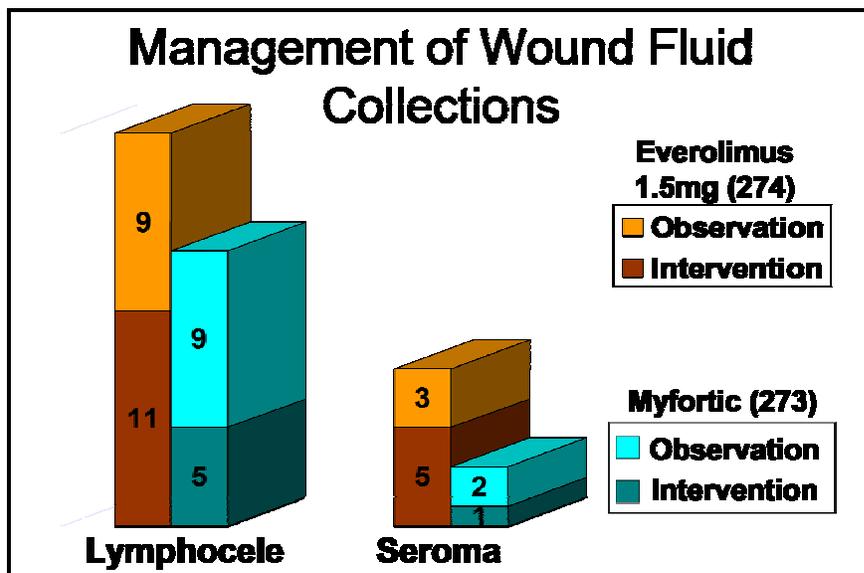


Figure 22. Intervention (Surgery and Percutaneous) Rates for the Treatment of Wound Fluid Collections

Source: Produced by the Clinical Reviewer from the data in Table 51



Reviewer's Comments: Analyses performed by the Applicant and summarized above show that there is an increased incidence and severity (as measured by the requirement for surgical and non-surgical interventions) of wound complications in the everolimus 1.5 mg group compared to the Myfortic group and the differences are statistically significant.

Lymphocele and lymphorrhoea led to drug discontinuations in 2.6% of the patients in the everolimus 1.5 mg group and in 2.2% of the patients in the everolimus 3.0 mg group while no patient discontinued the study drug due to wound events in the Myfortic group.

Among all the patients who died during the 12 month period wound related problems (mainly infections and dehiscences and lymphoceles) were noted in 5 patients in the everolimus 1.5 mg group, 4 patients in the everolimus 3.0 mg group and in 1 patient in the Myfortic group:

Everolimus 1.5 mg Group:

1-0125-00002: Lymphocele on Day 16, died on Day 22 due to septic shock

2-0115-00020: Day 16 graft nephrectomy, infection abdominal sepsis, died on Day 28

3-0100-00008: Day 74, ureteral necrosis, urinoma, wound infection, cellulitis, died on Day 148

4-0516-00002: Day 48 incisional hernia, Day 102 edema, died on Day 156

5-0118-00012: Day 15 lymphocele surgical debridement and drainage died due to malignant melanoma on Day 122

Everolimus 3.0 mg group:

1-0100-00002: Day 16: perinephric collection-urinary fistula, D30: recurrence urinary fistula, Day 50: recurrence urinary fistula, died on D269 due to septic shock

2-0114-00001: Day 30: wound infection, died on Day 243 due to pneumonia

3-0532-00008: Day 24: Wound dehiscence Day 175: severe renal abscess, died on day 175 due to renal abscess and heart failure

4-0173-00003: Day 17: urine leak, infection Day 89: purulent discharge in the wound, died on D185 due to fluid overload (no access to hemodialysis)

Myfortic group:

1-0521-00007: Lymphocele on Day 9 (treated with percutaneous drainage), died on day 356 due to road traffic accident on the scene.

It may not be always possible to show a clear association between the death of these patients and the wound complications they sustained especially in cases with a long interval between the wound complication and the death of the patient but still at least in three patients in the everolimus 1.5 mg group (0125-00002,

0115-00020 and 0100-00008) and one patient in the everolimus 3 mg group (0100-00002) such an association seems to be highly probable whereas in the single case in the Myfortic group we do not see such an association (died of traffic accident one year after lymphocele).

Despite the small number of patients mentioned here there seems to be a trend. In the everolimus 1.5 mg group, five of the 7 patients who died, in the everolimus 3.0 mg group 4 of the 10 patients who died developed wound related complications after the transplant surgery compared to 1 out of 6 patients who died in the Myfortic group. Wound complications observed in patients treated with everolimus are not only more severe compared to the wound complications observed in the Myfortic control group but may also contribute to the death of the patient.

7.3.4.5 *Fluid Accumulation, Including Peripheral Edema, Ascites, and Pleural Effusions*

At month 12, (Table 51) the incidence of edema related events was significantly higher in both everolimus groups than in the Myfortic group (55.5% and 54.7% versus 45.1%, p-value was 0.02 and 0.03 respectively, Fisher's exact test).

Table 52. Summary of Edema Related Event by Preferred Term and Treatment Group (Safety Population – 12 Month Analysis)

(Source: Applicant's analysis submitted upon request)

	Everolimus 1.5 mg (N=274)	Everolimus 3.0 mg (N=278)	Myfortic 1.44 gm (N=273)
Any edema related event	152 (55.5%)	152 (54.7%)	123 (45.1%)
Edema peripheral	123 (44.9%)	121 (43.5%)	108 (39.6%)
Fluid overload	20 (7.3%)	16 (5.8%)	17 (6.2%)
Edema	20 (7.3%)	16 (5.8%)	14 (5.1%)
Generalized edema	6 (2.2%)	6 (2.2%)	3 (1.1%)
Fluid retention	3 (1.1%)	7 (2.5%)	4 (1.5%)
Pitting edema	3 (1.1%)	2 (0.7%)	6 (2.2%)
Gravitational edema	1 (0.4%)	0 (0%)	0
Localized edema	1 (0.4%)	5 (1.8%)	3 (1.1%)
Edema due to renal disease	1 (0.4%)	0	0
Lymphedema	0	1 (0.4%)	0
95% CI (everolimus versus Myfortic) P-value*	(2.1%, 18.8%) p=0.02	(1.3%, 17.9%) p=0.03	N/A

Preferred terms were sorted by descending order of frequency in the everolimus 1.5 mg group

A patient with multiple occurrence of an event was counted only once in an event category.

* P-value for Fisher's exact test

Table 52 shows the incidence of AEs due to major fluid collections such as edema and other types of fluid collections was 44.9% in the 1.5 mg everolimus group, 43.2% in the 3.0 mg everolimus group and 39.6% in the Myfortic group. SAEs due to peripheral edema and pleural effusions were observed in three patients in the everolimus 1.5 mg group, six patients in the everolimus 3.0 mg group, and none in the Myfortic group. Fluid accumulation is a known effect of the class of M-TOR inhibitors and can cause an increased incidence of pleural and pericardial effusions and can also increase the permeability of serosal membranes in the body to proteins and fluids. Pericardial effusions and ascites were rarely reported.

Table 53. Types of Major Fluid Collections and Outcome
 (Source: Applicant's analysis submitted upon request)

Type of Fluid Collection	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
Peripheral edema (AE)	123 (44.9)	120 (43.2)	108 (39.6)
Severe peripheral edema	8 (2.9)	4 (1.4)	0
SAE	1 (0.4)	5 (1.8)	0
Drug discontinuation	3 (1.1)	1 (0.4)	0
Pleural effusions (AE)	7 (2.6)	5 (1.8)	5 (1.8)
SAE	2 (0.7)	1 (0.4)	0
Drug discontinuation	0	0	0
Pericardial effusions (AE)	1 (0.4)	1 (0.4)	1 (0.4)
SAE	0	0	0
Drug discontinuation	0	0	0
Ascites (AE)	1 (0.4)	0	0
SAE	0	0	0
Drug discontinuation	0	0	0

Reviewer's comment: *Peripheral edema possibly contributed to the death of one patient (0516-00002) in the everolimus 1.5 mg group. This patient was treated with furosemide because of edema on day 102 and died on day 156 due to congestive heart failure. This patient already had a history of congestive heart failure at the time of transplant but this might have worsened due to everolimus treatment.*

7.3.4.6 Major Cardiac Adverse Events

A specific case report form was designed in order to capture information on the occurrence of major cardiac events (MACE) in the study. The applicant collected information on the following AEs:

- acute myocardial infarction
- congestive heart failure
- percutaneous coronary intervention
- coronary artery bypass graft
- automatic internal cardiac defibrillator
- cerebrovascular accident
- peripheral vascular disease

The total number of patients with MACE was similar in the everolimus 1.5 mg group and the Myfortic groups (2.6% and 2.9%), but the incidence was higher in the everolimus 3.0 mg group (5.8%), as shown in Table 53. There were more patients with acute myocardial infarction, congestive heart failure and percutaneous cardiac intervention in the 3.0 mg group. The rates of drug discontinuations due to cardiac events were two in the everolimus 1.5 mg group, four in the everolimus 3.0 mg group and one in the Myfortic group.

Table 54. Number (%) of Patients with Major Cardiac Adverse Events (MACE)
 (Source: Table 12-30 on page 222 of CSR)

MACE Terms	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic N=273
Any MACE	7 (2.6)	16 (5.8)	8 (2.9)
Acute myocardial infarction	2 (0.7)	9 (3.2)	4 (1.5)
Congestive heart failure	3 (1.1)	6 (2.2)	2 (0.7)
Percutaneous cardiac intervention	1 (0.4)	3 (1.1)	0 (0.0)
Coronary artery bypass grafting	1 (0.4)	0 (0.0)	0 (0.0)
Automated implanted cardiac defibrillator	0 (0.0)	0 (0.0)	1 (0.4)
Cerebral vascular accident	1 (0.4)	0 (0.0)	0 (0.0)
Peripheral vascular disease	0 (0.0)	1 (0.4)	1 (0.4)

Reviewer's comment: Although the overall incidence of MACE events were much higher in the everolimus 3.0 mg group compared to the other two groups in the study, the everolimus 1.5 mg group and the Myfortic group look similar to each other except for the numerically higher number of MIs in the Myfortic group (4 vs. 2). This apparent discrepancy between the two everolimus groups when compared to the Myfortic group prompted a more detailed analysis of the MI events in Study A2309 focusing on the everolimus 1.5 mg and the Myfortic groups. Results of this analysis are shown in Table 55 below.

Table 55 Myocardial Infarctions Reported as MACE events

Source: Produced by the Clinical Reviewer from the information in Table 12-31 on page 223 of the CSR

Age, Sex	Day of MI	Day D/C Med	Outcome	Treatment Group
0532/0003 (49, M, C,)	326	46	Unknown	Everolimus 1.5 mg
0124-00076 (39, M, C)	85	85	Death (Hx. Of HTN)	Everolimus 1.5 mg
0544/00012 (61, M,C)	34	33	Death (Hx. of DM, quadruple bypass and MI)	Myfortic
0502/00016 (58, M, B,)	251	6	Death (On Sirolimus)	Myfortic (cardiac arrest at home)
0528/00014 (69, M,B)	2	4	Resolved (Hx. of DM, CAD, HTN, Gout)	Myfortic
0540/00007 (67M,B)	74	74	Resolved (Hx. of DM, HTN)	Myfortic (No MI on record?)

Reviewer's Comments: *The following is a more detailed discussion of the patients in Table 55 above.*

Everolimus 1.5 mg group:

Patient 0532/0003: This patient was lost to follow up after he had myocardial infarction, which raises doubts about his survival after the event. The MI is unlikely to be associated with the study medication (everolimus) since it occurred 278 days after stopping the study medication.

Patient 0124-00076: This 39 year old patient had very high lipid levels at the time of death as explained in Section 7.3.1., Deaths.

Myfortic group:

Patient 0544/00012: This patient had a history of quadruple coronary bypass, which was a very important risk factor for a subsequent MI

Patient 0502/00016: This patient was on Sirolimus (another M-TOR inhibitor) starting Day 4 until his death on Day 251 so it is not possible to associate the MI with the Myfortic control regimen.

Patient 0528/00014: This patient had the MI on the second day after transplant and had been on study medication for only one day. Therefore, due to the early occurrence of the MI, factors other than the study medication possibly contributed to the event.

Patient 0540/00007: In this patient's narrative there is no record of MI. On Day 73 this patient had surgery (resection of distal transplant ureter with neoureterocystostomy) and on Day 74 the patient had a cardiac arrest but according to the records the event resolved on the same day. There may be various other reasons which may possibly cause cardiac arrest including electrolyte abnormalities so it is not possible to attribute the event of cardiac arrest to myocardial infarction in this patient. This patient was probably reported as a mistake.

In the Reviewer's assessment among the cases with MI mentioned so far, in only one patient (0124-00076) 39 year old male in the everolimus 1.5 mg treatment group there is a probable association with the study medication (everolimus). This patient is explained in more detail in the section about the deaths.

It may also be relevant to note here that according to Novartis's assessment of relevant medical histories performed by standard MEDDRA query (SMQ) (narrow search) reported on page 1784 of the CSR, there were twice as many patients with a prior history of myocardial infarction in the Myfortic group compared to the everolimus 1.5 mg group, 18 (6.6%) vs. 9 (3.3%) which may be considered as an imbalance of the baseline characteristics in favor of the everolimus 1.5 mg group since having a prior MI increases the risk of having a second MI.

Considering the differences in baseline characteristics (twice as many prior MIs in the Myfortic group), the assessment of drug relatedness, the higher incidence of graft thromboses in the everolimus treatment groups (as discussed in Section 7,3,2,1), there seems to be a higher association between everolimus and the occurrence of MI compared to the possible association between Myfortic regimen and MI. Another confirmation of this trend is the unusually high incidence of MIs in the higher dose everolimus 3.0 mg group of 9 cases.

7.3.4.7 Other Thromboembolic Events

Thromboembolic events reported as AEs, other than graft thrombosis, are shown in Table 56. There were 13 (4.7%) in the 1.5 mg everolimus group, 16 (5.8%) in the 3.0 mg everolimus group and 9 (3.3%) in the Myfortic group. Two patients with HUS (Hemolytic Uremic Syndrome) and one each with TTP (Thrombotic Thrombocytopenic Purpura) and TMA (Thrombotic Microangiopathy) were reported in the everolimus 1.5 mg group.

The number of SAEs related to thrombotic events was: eight in the everolimus 1.5 mg group and four in each of the everolimus 3.0 mg and Myfortic groups. (Table 55)

Deep vein thrombosis (DVT) was reported in eight patients in the everolimus 1.5 mg group, seven patients in the everolimus 3.0 mg group, and five patients in the Myfortic group. Pulmonary embolism (PE) was reported in one, two, and two patients in the everolimus and Myfortic groups, respectively. Although there is a trend of increasing DVTs in the everolimus 1.5 mg and the 3.0 mg groups, there is no similar trend for PE. The trend seen with the DVTs is compatible with thrombogenic potential of the M-TOR inhibitor class of drugs.

Table 56. Incidence Rates of Thromboembolic Adverse Events
 (Source: Applicant's analysis submitted upon request)

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
Any Thromboembolic AE	13(4.7)	16(5.8)	9(3.3)
Blood and Lymphatic System Disorders -Total	4(1.5)	0	0
Hemolytic uremic syndrome	2(0.7)	0	0
Microangiopathic hemolytic anemia	0	0	0
Thrombotic microangiopathy	1(0.4)	0	0
Thrombotic thrombocytopenic purpura	1(0.4)	0	0
Acute myocardial infarction	2 (0.7)	9 (3.2)	4 (1.5)
Respiratory, Thoracic and Mediastinal Disorders - Total	1(0.4)	2(0.7)	2(0.7)
Pulmonary embolism	1(0.4)	2(0.7)	2(0.7)
Vascular Disorders - Total	8(2.9)	7(2.5)	5(1.8)
Deep vein thrombosis	8(2.9)	7(2.5)	5(1.8)

Reviewer's Comment: Thromboembolic events, other than MIs (which were discussed previously in Section 7.3.4.6), were primarily DVTs and were reported more frequently in both of the everolimus groups compared to the Myfortic group. This is in line with the known thrombogenic effects of M-TOR inhibitors.

Also TTP, TMA and HUS were only observed in the everolimus 1.5 mg group. These adverse events may be fatal although they are relatively uncommon. In the everolimus 1.5 mg group, TTP contributed to the graft loss in one patient (0192-00002) on Day 116.

TMA/TTP/HUS are also known to be associated with M-TOR inhibitors and the sirolimus label carries a warning regarding these AEs.

7.3.4.8 Hematologic Abnormalities, Including Thrombocytopenia, Neutropenia, and Anemia

Hematological events reported as AEs and SAEs are summarized in Table 57. The overall incidence of AEs was 33.9% in the 1.5 mg group, 40.3% in the 3.0 mg group, and 40.7% in the Myfortic group. SAEs were reported in eleven patients in the everolimus 1.5 mg group, ten in the everolimus 3.0 mg group, and eight patients in the Myfortic group.

One SAE each of hemolytic anemia, hemolysis, and HUS was seen in the everolimus 1.5 mg group. There were two cases of pancytopenia reported as SAEs in the Myfortic group while none were observed in the everolimus groups. Thrombocytopenia cases seem to be distributed equally across the three groups but potentially serious TTP and TMA were reported only in the everolimus group (Table 56 and 57). This is a class effect of immunosuppressants like M-TOR inhibitors and CsA as well.

Table 57. Incidence Rates of Selected Hematological Adverse Events
Source: Table 14.3.1-1.1 on page 1325 of CSR

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
Blood and Lymphatic System Disorders AEs	99 (33.9)	112 (40.3)	111 (40.7)
Anemia	70 (25.5)	86 (30.9)	68 (24.9)
Pancytopenia	2 (0.7)	4 (1.4)	4 (1.5)
Leucopenia	8 (2.9)	6 (2.2)	33 (12.1)
Neutropenia	1 (0.4)	3 (1.1)	6 (2.2)
Thrombocytopenia	3 (1.1)	10 (3.6)	6 (2.2)
Blood and Lymphatic System Disorders SAEs	11 (4.0)	10 (3.6)	8 (2.9)
Anemia	2 (0.7)	5 (1.8)	2 (0.7)
Pancytopenia	0	0	2 (0.7)
Leucopenia	2 (0.7)	1 (0.4)	3 (1.1)
Neutropenia	0	1 (0.4)	1 (0.4)
Thrombocytopenia	2 (0.7)	3 (1.1)	2 (0.7)
Blood and Lymphatic System Disorders AEs leading to Drug Discontinuations	7 (2.6)	2 (0.7)	3 (1.1)
Anemia	1 (0.4)	0	0
Pancytopenia	0	0	0
Leucopenia	1 (0.4)	0	2 (0.7)
Neutropenia	0	0	0
Thrombocytopenia	0	0	1 (0.4)
Blood and Lymphatic System Disorders AEs leading to Dose Adjustment/Interruption	10 (3.6)	12 (4.3)	31 (11.4)
Anemia	1 (0.4)	3 (1.1)	4 (1.5)
Pancytopenia	2 (0.7)	0	2 (0.7)
Leucopenia	4 (1.5)	4 (1.4)	23 (8.4)
Neutropenia	0	1 (0.4)	2 (0.7)
Thrombocytopenia	3 (1.1)	5 (1.8)	3 (1.1)

Thrombocytopenia

Thrombocytopenia was reported as an AE in three patients in the everolimus 1.5 mg group, ten in the everolimus 3.0 mg group, and six in the Myfortic group. Notably low platelet counts (defined as $< 50 \times 10^9 /L$ by the Applicant) were not reported for any patient in the everolimus 1.5 mg group, but were reported for three patients in the everolimus 3.0 mg group, and one in the Myfortic group.

Reviewer's Comment: *Thrombocytopenia is thought to contribute to one patient's death in the everolimus 3.0 mg group.*

Patient No. 0549-0001: *This 55 year old male had a laparotomy on Day 16 for suspected intestinal obstruction was found to have retroperitoneal hematoma. His*

baseline platelet count was 165,000. On Day 3 platelet count was down to 128,000, and on Day 14 it was down to 38,000. Between Day 7 and Day 14 his hemoglobin level also dropped from 15.4 gm/dL down to 11.4 gm/dL. On Day 16 he had a laparotomy which disclosed the retroperitoneal hematoma. On Day 18 his platelet count was 16,000 and everolimus was discontinued because of thrombocytopenia. In this patient who also had a history of abdominal aortic aneurysm, thrombocytopenia probably contributed to the retroperitoneal bleeding.

Neutropenia

Neutropenia reported as an AE was highest in the Myfortic group: one, three, and 6 patients in the everolimus 1.5 mg, 3.0 mg and Myfortic groups, respectively. In a systematic review of absolute neutrophil counts, notably low values (defined by the Applicant as segmented plus band forms totaling $< 1.1 \times 10^9$ cells/L) were reported by a higher percentage of patients in the Myfortic than everolimus groups: 1.8%, 3.6% and 6.3% of patients in the everolimus 1.5 mg, 3.0 mg and Myfortic groups, respectively.

Anemia

Anemia was reported as an AE at a similar rate in the everolimus 1.5 mg (25.5%) and Myfortic 1.44 gm groups (24.9%), but the incidence was higher in the everolimus 3.0 mg group (30.9%). Notably low values for hemoglobin (as defined by the applicant as < 60 g/L) were reported in the everolimus groups, but not the Myfortic group: four and one in the everolimus 1.5 mg and 3.0 mg groups, respectively.

Reviewer's Comment: *Although overall hematologic events reported as AEs were higher in number in the Myfortic group, the number of events reported as SAEs or events that led to drug discontinuations they are similar to each other. The main difference in the number of AEs between the two groups is due to the increased incidence of leukopenia observed in the Myfortic group which hardly rose to the level of SAE in Study A2309.*

There is only one death in the study associated with a hematologic event and that is the patient 0549-0001 in the everolimus 3.0 mg group who died because of hemorrhagic shock associated with severe thrombocytopenia.

7.3.4.9 *Interstitial Lung Disease, Lung Infiltration, and Pneumonitis*

A total of six patients were reported to have interstitial lung disease identified by the Applicant using the related preferred terms (*acute interstitial pneumonitis, allergic granulomatous angiitis, alveolar proteinosis, alveolitis, alveolitis allergic, alveolitis fibrosing, alveolitis, necrotizing bronchiolitis, diffuse alveolar damage, eosinophilia myalgia syndrome, eosinophilic pneumonia, eosinophilic pneumonia acute, eosinophilic pneumonia chronic, interstitial lung disease, lung infiltration, necrosis of bronchioli, obliterative bronchiolitis, pneumonitis, progressive massive fibrosis, pulmonary fibrosis,*

pulmonary necrosis, pulmonary radiation injury, pulmonary toxicity, pulmonary vasculitis, radiation alveolitis, radiation fibrosis – lung, radiation pneumonitis, transfusion-related acute lung injury). Two cases were in the everolimus 1.5 mg group, three in the everolimus 3.0 mg group, and one is in the Myfortic group.

According to the Applicant’s assessment, one of these six cases had a biopsy confirmed diagnosis of alveolar proteinosis in the everolimus 1.5 mg group. The investigator reduced the dosage of everolimus; however, the patient died of pneumonia and sepsis two months later (0304-00016). See Section 3.3 Deaths and Table 58 below.

Table 58 Patients Reported to Have Non-infectious Lung Infiltration According to the Applicant’s Assessment
 (Source: Produced by the Clinical Reviewer from patient narratives)

Patient	Diagnosis	Outcome	Treatment
47, M 0304-00016	Alveolar Proteinosis Sepsis	Died on Day 436	Everolimus 1.5 mg
21, F 0537-00008	Interstitial lung disease (Coding error?)	Resolved	Everolimus 1.5 mg
69, M 0507-00019	Pneumonitis , MI	Died on Day 243	Everolimus 3.0 mg
61, C 0124-00072	Pneumonitis (Staph. Coag. Neg.), PE	Resolved	Everolimus 3.0 mg
68, M 0136-00002	Lung infiltration, sepsis due to unknown virus	Resolved	Everolimus 3.0 mg
66, M 0537-00005	No record of lung related pathology in narrative	Completed study	Myfortic 1.44 gm

Non-infectious pneumonitis, including pulmonary alveolar proteinosis, is a rare but serious adverse event because of the mortality risk associated with it. It can be due to different etiologies and is listed among the adverse events associated with M-TOR inhibitors. Alveolar proteinosis is a diffuse lung disease that is characterized by the alveolar and interstitial accumulation of a periodic acid-Schiff (PAS) stain-positive phospholipoprotein that is derived from surfactant. The clinical course of the disease is variable, ranging from respiratory failure to spontaneous resolution. An important feature of the disease is susceptibility to pulmonary infections. Alveolar proteinosis is also among the class effects of M-TOR inhibitors and although observed rarely may have a fatal outcome. The suggested therapy is discontinuation of the M-TOR inhibitor and treatment of the superimposed infections.

Reviewer's Comment: A detailed discussion of the cases in Table 58 follows:

Everolimus 1.5 mg group:

Patient 0304-00016: This 47 year old male patient had a biopsy confirmed diagnosis of alveolar proteinosis and died due to pneumonia and septic shock 60 days after the diagnosis (see also Section 7.3.1, Deaths)

Patient 0537-00008: The Applicant claims that this patient was reported to have interstitial lung disease probably due to a coding error which replaced "renal interstitial fibrosis," with interstitial lung disease since the patient presented with an increased serum creatinine and was diagnosed with acute tubular necrosis.

Everolimus 3.0 mg group:

Patient 0507-00019: This 69-year-old Caucasian male who died on Day 243. According to the applicant the primary cause of death was myocardial infarction. However, the patient was also noted to have staphylococcal pneumonitis and according to the FDA's assessment, the pneumonia was felt to contribute to his death. (See also Section 7.3.1, Deaths).

Patient 0124-00072: This 61-year-old, Caucasian male who presented with fever and dyspnea and was hospitalized. A culture from the bronchoscopy grew coagulase negative staphylococcus and he was noted to have opacification and alveolar infiltration in the upper lobe of the right lung. He was treated with antibiotics and the dose of everolimus was also decreased. The patient developed a pulmonary embolism, which subsequently completely resolved along with the pneumonitis. In this case it may not be possible to completely rule out the possibility of interstitial lung disease, since this term is mentioned in the narrative and the bronchoscopy culture grew coagulase negative staphylococcus. Also, it is known from the published literature that interstitial lung disease may be superimposed by bacterial infection.

Patient 0136-00002: This 68 year old Asian male in the everolimus 3.0 mg group (0136-00002) was reported to have "sepsis due to unknown virus" in the narrative. The infiltration resolved, but it was not clear if the resolution was due to antibiotics or due to the dose reduction of everolimus or both.

Myfortic group:

Patient 0537-00005: In this 66 year old Caucasian male patients narrative there is no record of any type of lung infiltration or any other lung related pathology or suspicion of any lung or respiratory tract disease.

Five of the reported 6 cases with a possible interstitial lung disease are in the everolimus groups. The patient reported as having interstitial lung disease in the Myfortic group does not have any record of lung disease in the patient narrative.

The association between the M-TOR inhibitors and interstitial lung disease is well established and also mentioned in the Rapamune (Sirolimus) label. In study A2309 there is one death (patient 0304-00016) due to alveolar proteinosis and this patient was in the everolimus 1.5 mg group. This death was reported after the 12 month study period. This patient is explained in more detail in the section about deaths.

7.3.4.10 Benign and Malignant Neoplasms

Malignant neoplasms reported as AEs were uncommon and evenly distributed across treatments. Total neoplasms (which include non-malignant growths, such as cysts and polyps) were less frequent with both doses of everolimus than Myfortic, as shown in Table 59. The most frequently reported neoplasms in the Myfortic group were basal cell carcinoma, squamous cell carcinoma, skin papilloma and seborrhoeic keratosis, which are generally either benign or very slowly progressing tumors.

Only one patient died due to malignancy (metastatic melanoma) in the study and this was in the everolimus 1.5 mg group. There was one patient with Epstein-Barr virus-associated lymphoproliferative disorder in Study A2309, also known as post-transplant lymphoproliferative disorder (PTLD) which was in the everolimus 3.0 mg group.

The incidence of malignancies reported as SAEs are slightly higher in the Myfortic group (1.8%, n=11) compared to the everolimus 1.5 mg group (1.5%, n=8) and everolimus 3.0 mg group (1.1%, n=4). Types of tumors reported as SAEs:

Everolimus 1.5 mg group:

Basal cell carcinoma (3), Squamous cell carcinoma (3), metastatic melanoma,

Everolimus 3.0 mg group:

Basal cell carcinoma, Squamous cell carcinoma (2), Post-transplant lymphoproliferative disorder (PTLD)

Myfortic group:

Basal cell carcinoma (5), Squamous cell carcinoma (5), Transitional cell carcinoma

Two patients discontinued study medication due to a neoplasm, one in each of the everolimus groups: malignant melanoma in the everolimus 1.5 mg group and Epstein-Barr virus associated lymphoproliferative disorder (PTLD) in the everolimus 3.0 mg group. The absence of study medication discontinuations in other cases of neoplasms is partly indicative of the relative benign nature of these other tumors.

**Table 59. Number of Patients Reporting Neoplasms
 Safety Population 12 Month Analysis**
 (Source: Table 12-9 on page 178 of CSR)

Preferred Term	Everolimus 1.5 mg N=274, n (%)	Everolimus 3.0 mg N=278, n (%)	Myfortic 1.44 g N=273, n (%)
Total	9 (3.3)	8 (2.9)	16 (5.9)
Basal cell carcinoma	2 (0.7)	0 (0)	5 (1.8)
Benign breast neoplasm	1 (0.4)	0 (0)	0 (0)
Benign renal neoplasm	0 (0)	1 (0.4)	0 (0)
Dysplastic nevus syndrome	1 (0.4)	0 (0)	0 (0)
Epstein-Barr virus associated lymphoproliferative disorder	0 (0)	1 (0.4)	0 (0)
Fibrous histiocytoma	0 (0)	1 (0.4)	0 (0)
Hair follicle tumor benign	0 (0)	0 (0)	1 (0.4)
Lip neoplasm malignant	0 (0)	0 (0)	1 (0.4)
Lipoma	1 (0.4)	0 (0)	0 (0)
Malignant histiocytosis	0 (0)	1 (0.4)	0 (0)
Melanocytic nevus	2 (0.7)	0 (0)	2 (0.7)
Metastatic malignant melanoma	1 (0.4)	0 (0)	0 (0)
Myelodysplastic syndrome	0 (0)	1 (0.4)	0 (0)
Oral papilloma	0 (0)	0 (0)	1 (0.4)
Seborrheic keratosis	1 (0.4)	0 (0)	2 (0.7)
Skin papilloma	1 (0.4)	1 (0.4)	3 (1.1)
Squamous cell carcinoma	0 (0)	0 (0)	1 (0.4)
Squamous cell carcinoma of skin	1 (0.4)	3 (1.1)	3 (1.1)
Transitional cell carcinoma	0 (0)	0 (0)	1 (0.4)

Reviewer's comment: *The numerically higher occurrence of neoplasms in the Myfortic group compared to the everolimus groups are due to the higher incidence of basal cell, squamous cell carcinomas and benign conditions like skin papillomas and seborrheic keratosis in the Myfortic group.*

Most important tumors with regard to the associated mortality, one case of malignant melanoma (with a prior history of malignant melanoma) and one case of PTLD (Post Transplant Lymphoproliferative Disorder) listed as EBV associated lymphoproliferative disorder occurred in the everolimus groups. The patient with malignant melanoma died due to this malignancy. The Reviewer's conclusion is although the number of neoplasms in the Myfortic group are higher they are mostly benign and did not cause any deaths or graft losses.

7.3.4.10 New Onset Diabetes Mellitus

According to the study protocol, new onset diabetes (NODM) was defined as diabetes post-transplantation and identified by one of the following:

1. Diabetes was reported as an adverse event;
2. Glucose (random) \geq 11 mmol/L [198 mg/dL] post-transplantation;
3. Diabetes was recorded as reason for a medication given post-transplantation,
4. In patients who were not diabetic at the time of transplantation, identified by all of the following:
 - a. Reason for transplantation was not diabetes;
 - b. Diabetes was not included in medical history;
 - c. Glucose (random) $<$ 11 mmol/L at the time of transplantation;
 - d. Diabetes was not recorded as reason for any medication given prior to transplantation.

Reviewer's Comment: The standard definition of NODM, as defined by ADA (American Diabetes Association) and WHO (World Health Organization), includes another criterion in addition to the criteria mentioned above and that is having a fasting plasma glucose \geq 126 mg/dL (7.0 mmol/L)¹⁶ *Absence of this pivotal screening criterion for diabetes among the criteria utilized by the Applicant probably resulted in very low NODAT incidences in all of the treatment groups in Study A2309.*

The incidence of NODM was 9.1% in the everolimus 1.5 mg group, 12.2% in the everolimus 3.0 mg group, and 6.6% in the Myfortic group, as shown in Table 60. This trend is reflective of the known diabetogenic effects of M-TOR inhibitors. Although diabetes-related AEs were reported at similar rates in the everolimus 1.5 mg and the Myfortic groups, more events were reported as serious in both of the everolimus groups compared to the Myfortic group.

There were no discontinuations of study medication due to diabetes-related AEs in any of the treatment groups.

¹⁶ Davidson J, Wilkinson A, Dantal J, et al. New-onset diabetes after transplantation: 2003 International Consensus Guidelines. *Transplantation* 2003; 75: SS3.

Table 60. Disturbed Glucose Metabolism
 (Source: Table 5-24 on page 55 of the Clinical Overview)

	Everolimus 1.5 mg N=274 % (n)	Everolimus 3.0 mg N=278 % (n)	Myfortic 1.44 gm N=273 % (n)
New Onset Diabetes	9.1 (25)	12.2 (34)	6.6 (18)
SAEs			
diabetes mellitus	1.1 (3)	1.1 (3)	0.4 (1)
hyperglycemia	0.4 (1)	2.5 (7)	0.4 (1)
type 2 diabetes mellitus	0	0	0
AEs			
hyperglycemia	12.4 (34)	15.5 (43)	13.9 (38)
diabetes mellitus	5.1 (14)	7.9 (22)	7.0 (19)
type 2 diabetes mellitus	1.5 (4)	0.4 (1)	0.7 (2)
glucose tolerance impaired	0.4 (1)	0.4 (1)	0.4 (1)
impaired fasting glucose	0	0	0.4 (1)

Clinical Importance of NODAT:

According to one published article¹⁵, male kidney transplant recipients with diabetes have a risk factor of 2.78 and female kidney transplant recipients with diabetes have a risk factor of 5.4 for developing ischemic heart disease compared to a risk factor of 1.5 in male diabetic patients without a transplant and a risk factor of 1.8 female diabetic patients without a transplant.¹⁵ These numbers suggest that diabetes in kidney transplant patients may be associated with a higher risk of developing ischemic heart disease when compared to diabetic patients without an organ transplant. The following paragraph is excerpted from the KDIGO guidelines recently published in the American Journal of Transplantation¹³:

“A number of other risk factors for diabetes have not been rigorously studied in KTRs (Kidney Transplant Recipients), but there is little reason to believe that they would not also be risk factors after transplantation. These risk factors include: family history (type 2 diabetes), gestational diabetes, impaired fasting glucose, impaired glucose tolerance and dyslipidemia (high fasting triglycerides and/or low HDL-C. ...Data from observational studies have shown that NODAT (New Onset Diabetes After Transplantation is the new term for NODM= New Onset Diabetes Mellitus) is associated with worse outcomes, including increased graft failure, mortality and CVD)”⁷

As suggested in the paragraph above, hypertriglyceridemia may also increase the risk of developing NODAT in kidney transplant patients and NODAT is associated with poor graft and patient survival as expected according to the vast research data available from non-transplant patients with diabetes.

Reviewer's Comment: NODAT which is a major area of concern in transplant patients in general has not been assessed adequately in this study mainly because of omitting the pivotal criteria of FPG (Fasting Plasma Glucose) > 126 mg/dL in the screening criteria. This omission was probably the reason for the low incidence of NODM in all of the treatment groups when compared to the published literature related to NODAT. In the United States, the cumulative incidence of NODAT (all organs) among 11,659 patients is around 16%, at 12 months.¹⁶

In another recently published international, randomized trial NODAT or impaired fasting glucose at 6 months, occurred in 26.0% of the CsA treated patients and 33.6% of the tacrolimus treated patients.¹⁷ It is important to note that these are only six month incidences and the incidence of NODAT increases over time¹⁷.

The reviewer believes that the actual NODAT incidences in the treatment groups in Study A2309 should have been at least 3 times higher than reported (9.1% in the everolimus 1.5 mg group and 6.6% in the Myfortic group) if the NODAT screening had been performed according to the ADA guidelines and would be more compatible with the literature data.

As a crude estimate of the actual incidence of NODAT in this study we can multiply the reported 12 month incidences by 3 and have an incidence of 27.3% (9.1x3) for the everolimus 1.5 mg group and an incidence of 19.8% (6.6x3) for the Myfortic group. As we see the difference in between the two groups come up to 7.5% as opposed to the prior difference of 2.5%. Also it is known from the literature that M-TOR inhibitors have diabetogenic properties¹⁸ like tacrolimus and CsA. However, MPA derivatives are not associated with diabetes.

¹⁷ Vincenti F, Friman S, Scheuermann E, Rostaing L. et.al Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. Am J Transplant. 2007 Jun;7(6):1506-14

¹⁸ Fraenkel M, Ketzinel-Gilad M, Ariav Y, M-TOR inhibition by rapamycin prevents beta-cell adaptation to hyperglycemia and exacerbates the metabolic state in type 2 diabetes. Diabetes. 2008 Apr;57(4):945-57.

7.3.4.11 *Gastrointestinal Adverse Events and Oral Ulcers/Stomatitis*

Events in the gastrointestinal SOC were reported as SAEs most frequently in the everolimus 3.0 mg group (28 patients), followed by the 1.5 mg group (21 patients), and the Myfortic group (18 patients). The preferred terms of diarrhea and vomiting were more common in the everolimus 3.0 mg group compared to the other groups [diarrhea, six (2.2%) patients in the everolimus 3.0 mg group compared to one (0.4%) patient in each of the other groups; and vomiting in seven (2.5%) patients in the everolimus 3.0 mg group compared to two (0.7%) patients in the everolimus 1.5 mg group and four (1.5%) patients in the Myfortic group]. Two cases of hemorrhagic esophagitis in the everolimus 1.5 mg group and one case of mesenteric vessel thrombosis in the everolimus 3.0 mg group were reported as SAEs, which may be associated with the ulcerative and thrombogenic class effects of M-TOR inhibitors.

As shown in Table 61, ulcerations of the gastrointestinal (GI) tract were reported as AEs in three patients in the everolimus 3.0 mg group (one duodenal, one gastric, and one esophageal), two in the Myfortic group (one duodenal and one ileal) . No patient in the everolimus 1.5 mg group had GI ulcers reported. Regarding upper GI lesions, overall there was a higher incidence of aphthous stomatitis, stomatitis, mouth ulceration, tongue ulceration in both of the everolimus groups compared to the Myfortic group.

Aphthous stomatitis was reported as a SAE in six patients in the everolimus 1.5 mg group, five patients in the everolimus 3.0 mg group, and in two patients in the Myfortic group. There were additional three patients in the everolimus 1.5 mg group and two patients in the everolimus 3.0 mg group who reported as stomatitis compared to none in the Myfortic group. None of gastrointestinal ulcers, except for the ones shown in Table 61 below, were reported as SAEs.

One patient in the everolimus 3.0 mg group discontinued study medication due to stomatitis and another patient in the everolimus 1.5 mg group discontinued study medication because of esophageal ulceration (necrotic, ulcerative grade D reflux esophagitis on EGD).

Table 61. Gastrointestinal Lesions (Ulcers, Stomatitis)

Source : Table 5-21 on page 51 of the Clinical Overview

GI Disorders Preferred term	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 gm N=273
AE - % (n)			
aphthous stomatitis	2.2 (6)	1.8 (5)	0.7 (2)
stomatitis	1.1 (3)	0.7 (2)	0
mouth ulceration	3.3 (9)	5.0 (14)	1.8 (5)
lip ulceration	0	0	0.4 (1)
tongue ulceration	1.8 (5)	0	0
duodenal ulcer	0	0.4 (1)	0.4 (1)
peptic ulcer	0	0	0
esophageal ulcer	0	0.4 (1)	0
rectal ulcer	0	0	0
ileal ulcer	0	0	0.4 (1)
SAE - % (n)			
mesenteric vessel thrombosis	0	0.4 (1)	0
intestinal ulcer	0	0	0.4 (1)
esophagitis ulcerative	0.4 (1)	0	0
discontinued for AE			
aphthous stomatitis	0	0	0
mouth ulceration	0	0.4 (1)	0
esophagitis ulcerative	0.4 (1)	0	0

Reviewer's Comment: Mouth ulcerations and gastrointestinal tract ulcerations are among the AEs known to be associated with M-TOR inhibitors. In this study we see the same trend. These ulcers can be painful and may prevent patient's adequate food and liquid intake. The mechanism is thought to be the delayed healing of mucosal surface.

7.3.4.12 Endocrine Effects (Male Patients)

As a part of the study protocol FSH, LH and testosterone levels were checked in male patients, at baseline and periodically throughout the study. In the initial 12 months of the study, the latest time point of assessment was at month 9. For reference, normal testosterone levels in this study were reported to be < 10 nmol/L (if age < 50 years) and < 7 nmol/L (if age ≥ 50 years).

Tables 62 through 64 show the testosterone, LH, and FSH levels at baseline and again at month 9 for patients in the everolimus 1.5 mg and Myfortic groups. Data from the everolimus 3.0 mg group is not presented. At month 9 all three hormone levels

(testosterone, LH and FSH) in the everolimus 1.5 mg group were significantly different than the corresponding hormone levels in the Myfortic group, although the baseline values were similar in the two treatment groups. The everolimus 1.5 mg group had a lower mean testosterone level and higher mean LH and FSH levels than the Myfortic group. The difference between the testosterone levels across the two treatment groups at 9 months is thought to be caused by the decrease of testosterone levels in the everolimus 1.5 mg group throughout the study period. During this time period testosterone levels in the Myfortic group stayed the same. Month 9 mean testosterone levels are still within the normal range in both groups despite the significant decrease in the everolimus 1.5 mg group.

Table 62. Comparison of Testosterone Levels at Baseline and at Month 9 (Males Only)

(Source: Table 14.3-2.6.1b on page 1184 of CSR)

	Mean Testosterone, nmol/L	
	Baseline	Month 9
Everolimus 1.5 mg	15.1 ± 8	12.1 ± 5
Myfortic	15.6 ± 9	15.2 ± 6
p-value of Wilcoxon Rank-Sum test	0.949	0.000

Table 63. Comparison of LH Levels at Baseline and at Month 9 (Males Only)

Source: Table 14.3-2.6.1b on page 1184 of CSR)

	Mean LH, U/L	
	Baseline	Month 9
Everolimus 1.5 mg	10.3 ± 19	7.6 ± 11
Myfortic	9.0 ± 8	5.3 ± 4
p-value of Wilcoxon Rank-Sum test	0.29	0.025

Table 64. Comparison of FSH Levels at Baseline and at Month 9 (Males Only)

Source: Table 14.3-2.6.1b on page 1184 of CSR

	Mean FSH, U/L	
	Baseline	Month 9
Everolimus 1.5 mg	7.6 ± 9	11.1 ± 9
Myfortic	8.4 ± 8	7.9 ± 9
p-value of Wilcoxon Rank-Sum test	0.107	0.000

The mean FSH levels in the everolimus 1.5 mg group increased and rose up to the upper limit of the normal range (11.1 ± 9 U/L) at 9 months which may be indicative of decreased sperm production. (Table 64)).

Low testosterone as an AE was reported in 26/137 (19%) patients in the everolimus 1.5 mg group compared to 24/160 (15%) patients in the Myfortic group. Erectile dysfunction as an AE was reported in 9/137 (6.5%) patients in the everolimus 1.5 mg group compared to 4/160 (2.5%) patients in the Myfortic group (Source: Table 14.3.1-1.1 on page 1375 of CSR).

The baseline medical information for patients in the study indicates that twice as many patients in the Myfortic group had erectile dysfunction compared to the everolimus 1.5 mg group, as shown in Table 65 below. Despite this imbalance in the baseline characteristics in favor of the everolimus 1.5 mg group, there is almost a three times higher incidence of erectile dysfunction in the everolimus 1.5 mg group when compared to the Myfortic group during the 12 month study period (6.5% and 2.5%, respectively).

Reviewer's comment: *Male hypogonadism including azoospermia associated with M-TOR inhibitor usage is well established in the published literature¹⁹ The possible risk of male hypogonadism with everolimus treatment is also included in the foreign labels of everolimus. The findings in Study A2309 are consistent with the published literature.*

In general, gonadal function is expected to improve after renal transplantation parallel to a number of other endocrine and metabolic functions. In this study we see an opposite trend in the everolimus groups. At 9 months mean testosterone level in male patients decreased significantly in the everolimus 1.5 mg group whereas the mean testosterone level in the Myfortic group did not change during the same period. Despite these changes in the everolimus group, mean testosterone levels in both groups were still within the normal range at 9 months.

Although sperm counts were not included in this study protocol it has been reported in the published literature that M-TOR inhibitors adversely affect fertility by decreasing sperm production sometimes to the level of azospermia.

Maintaining normal levels of sperm counts and normal gonadal function is important for patients who plan on having children. Also maintaining normal levels of testosterone is important from a quality of life point of view. Testosterone plays important roles in maintaining bone density and erythropoiesis. It is important to remember that in study 2309 we only have the month 9 results and immunosuppressive therapy is a life long therapy.

There are also published articles recommending that male patients should be warned about this possible male hypogonadism associated with M-TOR inhibitors.²⁰

7.3.4.13 Delayed Graft Function

Delayed graft function (DGF) was defined by the Applicant as the need for dialysis within the first 7 days after transplantation. The frequency of DGF, which is important as it is known to be associated with a higher rate of efficacy failure, was only minimally higher in the everolimus groups compared to the Myfortic group: 10.2% (28/274) in the everolimus 1.5 mg group, 10.4% (29/278) in the everolimus 3.0 mg group, and 9.2% (25/273) in the Myfortic group.

¹⁹ Huyghe E, Zairi A, Nohra J, Kamar N, Gonadal impact of target of rapamycin inhibitors (sirolimus and everolimus) in male patients: an overview. *Transpl Int.* 2007;20(4):305-11

²⁰ Skrzypek J, Krause W. Azoospermia in a renal transplant recipient during sirolimus (rapamycin) treatment. *Andrologia.* 2007 Oct;39(5):198-9

The onset of DGF was categorized as occurring between 1-2, 3-4, or 5-8 days post-transplant and did not differ between treatments (data not shown). The duration of DGF was mostly <21 days, occasionally longer and only rarely continued, and did not appear to vary between everolimus and Myfortic groups.

The overall rate of efficacy failure in patients who experienced DGF was greater than in those who did not experience DGF, but equally so for all treatments, so that the rate of efficacy failure was similar across the treatment groups (data not shown).

7.3.4.14 *Biopsy Evaluation of Chronic Allograft Nephropathy*

Chronic allograft nephropathy (CAN), also known as chronic allograft injury (CAI), is the main cause of kidney graft loss in the long term and one of the main reasons for decreasing, or eliminating, the use of calcineurine inhibitors (CNIs) in immunosuppressive regimens. CNIs contribute to the development of CAN mainly by increasing graft fibrosis through TGF- β activation.

The main safety endpoint for Study A2309 was a comparison of GFR at 12 months between the treatment groups, which is also an indicator of the degree of CAN. Another, and possibly more important indicator of CAN, is tissue biopsy because GFR can be altered by other factors, like the reversible afferent arteriole vasoconstriction also caused by CNIs.

According to the study protocol, renal biopsies were to be performed at Month 12 in all patients with significant proteinuria (defined as > 0.5 g/day) or with suboptimal renal function (defined as estimated MDRD GFR of < 50 mL/min/1.72m²) to assess the frequency and severity of biopsy-proven chronic nephropathy and the rate of chronic sclerosing nephropathy. The data for all biopsies performed at 12 months are shown in Table 65 below. The percent of patients who met the protocol criteria for a biopsy was 37% in the everolimus 1.5 mg group, 43% in the everolimus 3.0 mg group, and 44% in the Myfortic group. However, it should be noted that the proportion of all patients who actually underwent this Month 12 biopsy is low in all groups (11 to 16% of the total population) and limits the interpretation of the findings.

The chronic allograft damage index (CADI) showed small, statistically insignificant differences in the mean and medians across the treatment groups. The rate of chronic sclerosing nephropathy also showed a small insignificant difference between the everolimus 1.5 mg group and the Myfortic group with the everolimus 3.0 mg group having the highest degree of sclerosis.

Table 65. Frequency of Biopsy and Rate and Severity of Chronic Allograft Nephropathy

(Source: Table 5-10, page 38, of Clinical Overview section of NDA resubmission)

Table 5-10	Frequency of biopsy and rate and severity of chronic nephropathy		
	Everolimus 1.5 mg N=277	Everolimus 3 mg N=279	Myfortic 1.44 g N=277
patients who met criteria for 12 month biopsy (n) (proteinuria >0.5 g/d or GFR <50 mL/min/1.72m ²)	102	119	121
patients in whom a biopsy was performed - % (n/N)	13.7 (38/277)	15.8 (44/279)	10.8 (30/277)
chronic allograft damage index - mean (SD)	4.4 (3.15)	4.4 (2.48)	4.9 (2.89)
chronic allograft damage index – median (range)	4.0 (0-13)	4.3 (0-12)	4.5 (0-10)
rate of chronic sclerosing nephropathy - % (n/N) ^a	8.5 (17/201)	13.9 (27/194)	9.0 (18/200)
^a Subgroup population for CAN: ITT patients with biopsy at baseline or Month 12 used for rate calculation (N=201, 194, 200 for 1.5 mg, 3 mg everolimus and Myfortic, respectively) Month 12 window covers Month 9 and Month 12 Source: [Study A2309 – Table 14.2-2.12 (chronic allograft damage index), [Study A2309 – Table 14.2-2.13] (incidence of chronic sclerosing nephropathy)			

The proportion of all patients who underwent this Month 12 biopsy, however, is low in all groups and limits any interpretation.

Biopsies were taken slightly more often with everolimus than Myfortic, with less difference to 1.5 mg everolimus. The chronic allograft damage index (CADI) showed small, statistically insignificant differences in the mean and medians across the treatment groups. The rate of chronic sclerosing nephropathy also showed a small insignificant difference between the everolimus 1.5 mg group and the Myfortic group with the everolimus 3.0 mg group having the highest degree of sclerosis.

Reviewer’s Comment: *Decreasing CAN or CAI is one of the most important goals in order to decrease the rates of long term graft loss and is the reason for decreasing, or even eliminating, the CNI component of immunosuppression over time.*

In Study A2309 it is not possible to make any solid conclusions about the comparison of the study groups with regard to CAN since the percentage of patients with available biopsy findings is very limited and the duration of follow-up is only 12 months, which is a relatively short time to see any outstanding differences. Nevertheless, with the available limited data, the everolimus 1.5 mg group did not appear to have any significant benefit in terms of CAN at 1 year. The relatively higher level of sclerosing nephropathy in the everolimus 3.0 mg group is concerning since it points to a trend as to what might happen if higher trough levels of everolimus is targeted for the purpose of increasing immunosuppression level such as in high immunologic risk patients.



7.3.5 Submission Specific Primary Safety Concerns

Submission specific safety concerns are already discussed in other sections

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events are shown by SOC in Table 66, and by PT (Preferred Term) for the most common events ($\geq 20\%$) in Table 67. Almost all patients experienced at least one AE in all treatment groups. The most frequently affected organ classes were metabolism and nutrition disorders, and gastrointestinal disorders. More than 70% of patients per treatment group reported AEs in these organ classes.

Generally the incidence of AEs by SOC between treatment groups was similar. SOC where there appeared to be a higher percentage of patients with AEs in the everolimus treatment groups were; general disorders and administration site conditions, metabolism and nutrition disorders, and reproductive system and breast disorders.

Reviewer's Comment: *In the evaluation of AEs according to SOCs the Reviewer refrains from making any comparisons across the treatment groups by SOC or placing too much emphasis on this type of comparisons unless there is a major difference. SOCs may include a variety of preferred terms which may not be always clinically related and may also fit under different SOCs.*

As an example: graft loss is a PT under Injury, Poisoning and Procedural complications, whereas a renal infarct, which may be the cause of graft loss, is a PT under Renal and Urinary Disorders.

Table 66 Number (%) of Patients Experiencing Adverse Events/infections by System Organ Class (SOC) and Treatment Group (Safety population – 12 Month Analysis)
(Source: Table 12-5, page 173, CSR)

System organ class	Everolimus 1.5 mg	Everolimus 3.0 mg	Myfortic 1.44 g
	N=274 n (%)	N=278 n (%)	N=273 n (%)
Any system organ class	271 (98.9)	276 (99.3)	270 (98.9)
Blood and lymphatic system disorders	93 (33.9)	112 (40.3)	111 (40.7)
Cardiac disorders	43 (15.7)	39 (14.0)	42 (15.4)
Congenital, familial and genetic disorders	7 (2.6)	4 (1.4)	2 (0.7)
Ear and labyrinth disorders	13 (4.7)	4 (1.4)	14 (5.1)
Endocrine disorders	11 (4.0)	10 (3.6)	20 (7.3)
Eye disorders	29 (10.6)	22 (7.9)	28 (10.3)
Gastrointestinal disorders	196 (71.5)	208 (74.8)	207 (75.8)
General disorders and administration site conditions	181 (66.1)	185 (66.5)	160 (58.6)
Hepatobiliary disorders	7 (2.6)	8 (2.9)	8 (2.9)
Immune system disorders	14 (5.1)	9 (3.2)	11 (4.0)
Infections and infestations	169 (61.7)	178 (64.0)	185 (67.8)
Injury, poisoning and procedural complications	163 (59.5)	174 (62.6)	163 (59.7)
Investigations	137 (50.0)	120 (43.2)	133 (48.7)
Metabolism and nutrition disorders	222 (81.0)	233 (83.8)	199 (72.9)
Musculoskeletal and connective tissue disorders	112 (40.9)	104 (37.4)	105 (38.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (3.3)	8 (2.9)	16 (5.9)
Nervous system disorders	92 (33.6)	96 (34.5)	109 (39.9)
Pregnancy, puerperium and perinatal conditions	1 (0.4)	0 (0.0)	0 (0.0)
Psychiatric disorders	90 (32.8)	76 (27.3)	72 (26.4)
Renal and urinary disorders	112 (40.9)	143 (51.4)	124 (45.4)
Reproductive system and breast disorders	50 (18.2)	51 (18.3)	23 (8.4)
Respiratory, thoracic and mediastinal disorders	86 (31.4)	108 (38.8)	93 (34.1)
Skin and subcutaneous tissue disorders	92 (33.6)	103 (37.1)	102 (37.4)
Social circumstances	0 (0.0)	1 (0.4)	1 (0.4)
Surgical and medical procedures	0 (0.0)	2 (0.7)	0 (0.0)
Vascular disorders	122 (44.5)	137 (49.3)	124 (45.4)

The most commonly reported PTs were constipation, nausea and anemia, as shown in Table 67. Nausea was reported by a similar percentage of patients in each treatment group. Anemia and constipation were most common in the 3.0 mg everolimus treatment group. Peripheral edema, hyperlipidemia and anemia were more frequent with everolimus than Myfortic, other AEs occurring at similar rates.

Hyperlipidemia was reported by at least 5% more patients in the everolimus groups than the Myfortic group.

Table 67 Incidence Rates of Most Frequent ($\geq 20\%$ in any Treatment Group) Adverse Events/Infections by Primary System Organ Class and Preferred Term (Safety population - 12 Month Analysis)
 (Source: Table 12-6, page 174, CSR)

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic N=273 n (%)
Any AE/Infection	271 (98.9)	276 (99.3)	270 (98.9)
Blood and lymphatic system disorders	99 (33.9)	112 (40.3)	111 (40.7)
Anemia	70 (25.5)	86 (30.9)	68 (24.9)
Gastrointestinal disorders	196 (71.5)	208 (74.8)	207 (75.8)
Constipation	105 (38.3)	122 (43.9)	117 (42.9)
Nausea	79 (28.8)	80 (28.8)	85 (31.1)
Vomiting	40 (14.6)	48 (17.3)	60 (22.0)
General disorders and administration site conditions	181 (66.1)	185 (66.5)	207 (75.8)
Edema peripheral	123 (44.9)	120 (43.2)	108 (39.6)
Infections and infestations	169 (61.7)	178 (64.0)	185 (67.8)
Urinary tract infection	60 (21.9)	57 (20.5)	63 (23.1)
Investigations	137 (50.0)	120 (43.2)	133 (48.7)
Blood creatinine increased	48 (17.5)	52 (18.7)	59 (21.6)
Metabolism and nutrition disorders	222 (81.0)	233 (83.8)	199 (72.9)
Hyperkalemia	49 (17.9)	58 (20.9)	48 (17.6)
Hyperlipidemia	57 (20.8)	60 (21.6)	43 (15.8)
Vascular disorders	122 (44.5)	137 (49.3)	124 (45.4)
Hypertension	81 (29.6)	76 (27.3)	82 (30.0)

Reviewer's comment: The preferred term of "blood creatinine increased" was reported more frequently in the Myfortic group (21.6%) compared to the everolimus 1.5 mg group (17.5%). During the review process the reviewer discovered that 5 patients in the Myfortic group who were reported to have blood creatinine increased or toxic nephropathy were actually receiving sirolimus (another M-TOR inhibitor) as a concomitant immunosuppressant in addition to the

study regimen which may affect the validity of the comparison in between the groups.

For the majority of PTs there was little difference in the incidence between treatment groups. Terms which were reported by at least 5% more patients in the everolimus 3.0 mg than 1.5 mg group were; anemia, constipation and acne. Where the incidence of preferred terms was at least 5% greater in the 1.5 mg everolimus group than in the 3.0 mg group was; tachycardia, abdominal pain, back pain, myalgia, pain in extremity and anxiety.

AEs reported with a 5% or more difference between the everolimus groups and the Myfortic group are shown in Table 68. PTs more common in the everolimus 1.5 mg compared to the Myfortic group were: peripheral edema, dyslipidemia, and hyperlipidemia. PTs more common in the everolimus 3.0 mg group than the Myfortic group were: anemia, dyslipidemia, hypercholesterolemia, hyperlipidemia, proteinuria, acne and lymphocele. In the Myfortic group, leukopenia, abdominal pain upper, dyspepsia, vomiting, CMV infection and tremor were more common than the everolimus 1.5 mg group. At least 5% more patients in the Myfortic group experienced leukopenia, abdominal pain, abdominal pain upper, CMV infection and tremor, than in the everolimus 3.0 mg group.

Table 68. Incidence Rates of Adverse Events/infections with a 5% or Greater Difference in Incidence Between Everolimus and Myfortic treatment Groups, by Preferred Term, Safety population – 12 month analysis
 (Source: Table 12-7, page 175, CSR)

Preferred term	Everolimus 1.5 mg	Everolimus 3.0 mg	Myfortic 1.44 g
	N=274 n (%)	N=278 n (%)	N=273 n (%)
Abdominal pain upper	9 (3.3)	14 (5.0)	30 (11.0)
Anaemia	70 (25.5)	86 (30.9)	68 (24.9)
Acne	26 (9.5)	41 (14.7)	23 (8.4)
Cytomegalovirus infection	2 (0.7)	0 (0.0)	16 (5.9)
Dyslipidemia	41 (15.0)	36 (12.9)	24 (8.8)
Hypercholesterolaemia	47 (17.2)	50 (18.0)	34 (12.5)
Hyperlipidaemia	57 (20.8)	60 (21.6)	43 (15.8)
Leucopenia	8 (2.9)	6 (2.2)	33 (12.1)
Lymphocele	21 (7.7)	34 (12.2)	16 (5.9)
Oedema peripheral	123 (44.9)	120 (43.2)	108 (39.6)
Proteinuria	25 (9.1)	36 (12.9)	20 (7.3)
Tremor	23 (8.4)	22 (7.9)	38 (13.9)

Severity

Investigators graded the severity of AEs as mild moderate or severe. The majority of AEs were reported as mild to moderate in severity by the investigators, with severe AEs reported for approximately one third of patients (32.1%, 39.9% and 35.9% of patients in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 groups, respectively)

There were few differences between treatment groups with regard to the proportion of patients for whom AEs were judged as being mild, moderate or severe. Infections and infestations was the only SOC where at least 10% of patients in any treatment group were reported as having experienced a severe AE (5.8%, 10.1% and 7.3% of patients in the everolimus 1.5 mg, 3.0 mg and Myfortic groups, respectively). There was no difference between treatment groups with regard to the severity of upper respiratory tract infections or urinary tract infections.

Peripheral edema, headache, and hyperlipidemia were reported as severe only for patients in the everolimus treatment groups (edema peripheral: 2.6% in the 1.5 mg group, and 1.4% in the 3.0 mg group; headache: 1.1% and 0.4% for the 1.5 mg and 3.0 mg groups, respectively; hyperlipidemia: 0.7% and 0% for the 1.5 mg and 3.0 mg groups, respectively). Lymphocele was reported as severe for 2.2% of patients in the everolimus 3.0 mg treatment group, and as severe for 0.7% in the 1.5 mg group and 0.4% in the Myfortic group.

Leukopenia was more frequently reported as moderate or severe in the Myfortic treatment group (1.1%, 1.4% and 8.1% of patients had moderate leukopenia in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm treatment groups, respectively). In the Myfortic treatment group, BK virus infections were more frequently severe (by at least 1.5%), while the proportion of patients experiencing mild, moderate and severe CMV infection, CMV viremia and HSV infection were similar across the treatment groups.

CsA-Associated AEs

Focusing on AEs commonly associated with CsA use, a reduction in these AEs was observed for both everolimus groups compared to the Myfortic group. However, the renal and urinary AEs were lower only for the everolimus 1.5 mg group as shown in Table 69.

Table 69. Frequency of CsA-associated AEs,
 (Source: Table 5-13, page 42, Clinical Overview section of NDA
 resubmission)

	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 g N=273
AEs - % (n)			
tremor	8.4 (23)	7.9 (22)	13.9 (38)
gingival hyperplasia	0.7 (2)	0.4 (1)	2.9 (8)
gingival hypertrophy	1.1 (3)	0.7 (2)	2.2 (6)
hirsutism	2.9 (8)	4.0 (11)	5.5 (15)
renal and urinary disorders	40.9 (112)	51.4 (143)	45.4 (124)
Notably high values % (n)			
notable high values for uric acid			
females	17.2 (17)	22.7 (20)	22.6 (19)
males	1.1 (2)	4.7 (9)	4.3 (8)
notably high values for blood pressure			
diastolic	6.6 (18)	6.1 (17)	8.4 (23)
systolic	2.9 (8)	3.2 (9)	4.4 (12)

Reviewer's Comment: As explained in more detail in Section 7.4.3, the reduction in systolic and diastolic blood pressure over the course of the study was higher in the Myfortic group compared to the everolimus 1.5 mg group and the differences with regard to the SBP were statistically significant (Table 71). Because of this significant difference in between the SBP changes in favor of the Myfortic group which is not supportive of the reverse finding of higher number of patients with notable values of systolic or diastolic BP in the same group (shown in Table 70), these results need to be interpreted with caution.

7.4.2 Laboratory Findings

7.4.2.1 Biochemistry

Amylase and lipase levels fell from baseline during the first week, after which there was no further change from baseline and mean and median values remained within the normal range.

Creatine kinase levels increased from baseline initially probably due to the effect of surgery, then decreased at Day 14. From Month 1 onwards mean and median levels fluctuated within the normal range although the levels were significantly higher in the everolimus groups compared to the Myfortic group.

Mean and median alkaline phosphatase levels remained within the normal range throughout the study period with an initial decrease from baseline, and subsequent increase from Day 14 to Month 4 after which the levels remained stable.

Bilirubin mean and median levels also remained within the normal range throughout the study period.

Apart from Day 7 and 14 where alanine aminotransferase (ALT) mean values were at or slightly above the upper limit of the normal range in all groups, mean and median aspartate aminotransferase (AST) levels remained within the normal range throughout the study period.

Lipid levels tended to increase from baseline, with the greatest change from baseline at Month 2 or Month 3. Absolute levels at Month 3 were unchanged to Month 12. The change from baseline and the absolute values were greater in the everolimus treatment groups than the Myfortic group, and greater in the everolimus 3.0 mg group than 1.5 mg. *LDL levels increased from baseline by more than HDL levels.* The cholesterol/HDL ratio showed no consistent changes for any treatment group.

Sodium, potassium, chloride, magnesium and calcium mean and median levels remained within the normal range throughout the study period. Inorganic phosphate mean and median values exceeded the normal range at baseline but remained within the normal range afterwards.

As expected, blood urea nitrogen (BUN) values were above the normal range at baseline, decreased during the first two months and remained stable afterwards, with mean and median values within normal range except for the Myfortic group in which the mean values were slightly above range throughout the entire study duration.

Uric acid levels decreased from baseline in all treatment groups. From Month 2 in the Myfortic group the change from baseline became positive and greater than in everolimus groups. This may be related to the higher CsA dose in Myfortic patients.

7.4.2.2 *Endocrinology*

Please refer to Section 7.3.4.12 *Endocrine Effects (Male Patients)*

7.4.2.3 *Hematology*

(Please also refer to section 7.3.4.8)

Total white cell counts increased in the perioperative period (Day 1 and 3), at which time mean and median values were at the upper limit of the normal range in all three groups. A similar pattern was observed for neutrophils. Lymphocyte counts followed an opposing path being low in the perioperative period and within normal range afterwards in all treatment groups.

Red blood cell (RBC) and hemoglobin levels followed a pattern that would be expected following surgery and blood loss. RBC and hemoglobin mean and median levels were low during the first month and normalized afterwards in all groups as expected after the kidney transplantation.

7.4.3 Vital Signs

Vital signs variables included measurements of systolic and diastolic blood pressures, pulse, and body weight.

Mean and median values for weight increased over the treatment period in all groups, with a median increase of 3.7-5.0 kg at Month 12 treatment endpoint.

Systolic blood pressure increased in the 14 days following surgery (the greatest rise was seen in the everolimus 1.5 mg treatment group), after which the change from baseline was negative. At the Month 12 treatment endpoint, median changes from baseline were -1.5, -6.5 and -8.0 mmHg for everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 g, respectively.

Diastolic blood pressure also showed a decrease from baseline from Month 4 onwards which was numerically but not significantly greater in the Myfortic group than everolimus 1.5 mg. At treatment endpoint median change from baseline was -1.0, -2.5 and -4.0 mmHg for the everolimus 1.5 mg, 3.0 mg and Myfortic groups, respectively.

Table 70 Blood Pressure Changes from Baseline

Source: Table 14.3-3.1 on page 1301 of CSR

Change From Baseline	Everolimus 1.5 mg N = 274 Median (mmHg)	Myfortic 1.44 gm N = 273 Median (mmHg)	p-value Wilcoxon Rank-Sum test (Everolimus 1.5 mg vs. Myfortic)
SBP (M 12, TEP)	-1.5	-8.0	0.054
DBP (M 12, TEP)	-1.0	-4.0	NS

Pulse rates increased slightly on Day 1, but showed no overall clinically meaningful trends.

Vital sign abnormalities were predominantly high values for systolic or diastolic blood pressure and were numerically higher in the Myfortic group (Table 71).

Table 71. Number (%) of patients with post-baseline vital sign abnormalities based on notable criteria by treatment group (Safety population - 12 month analysis)
 (Source: Table 12-22, page 205, CSR)

Notable Abnormality		Everolimus 1.5 mg	Everolimus 3.0 mg	Myfortic 1.44 g
		N=274 n (%)	N=278 n (%)	N=273 n (%)
Systolic BP	Low	0/274	2/278 (0.7)	0/273
	High	8/274 (2.9)	9/278 (3.2)	12/273 (4.4)
Diastolic BP	Low	1/274 (0.4)	0/278	0/273
	High	18/274 (6.6)	17/278 (6.1)	23/273 (8.4)

7.4.4 ECGs

ECG assessments were not included in the Assessment Schedule and no findings were reported.

7.4.5 Special Safety Studies/Clinical Trials

The following studies were not reviewed in detail by the Clinical Reviewer. Summaries, provided by the applicant, are included here.

Study No. RAD001A2420 (12 month analysis)

Title of study: A national, multicenter, randomized study comparing the early versus delayed administration of Certican® in de novo kidney transplant recipients at risk of delayed graft function

Study center(s): Seventeen centers in France

Study period

First patient enrolled: 10-Jun-2005

Last patient completed (12 months): 6-Jun-2008

Phase of development: IIIb

Objectives: The objective of this study was to evaluate if the delayed administration of Certican® could reduce the “anti-proliferative complications” (e.g. wound healing disorders) while maintaining efficacy in comparison with the immediate administration in de novo renal transplant patients.

The primary objective was to compare the incidence of the composite criteria combining biopsy proven acute rejection, graft loss, death, DGF and wound healing complications with immediate versus delayed administration of everolimus at 3 months. Secondary objectives were the comparison of immediate versus delayed administration of Certican® for further efficacy and safety variables.

Methodology: This was an open, randomized, parallel-group, multicenter study with two treatment groups, immediate everolimus and delayed everolimus. Patients randomized to immediate everolimus were treated with everolimus from transplantation on, while patients randomized to delayed everolimus were initially treated for one month with MPA and thereafter with everolimus.

Number of patients (planned and analyzed): It was planned to include 142 patients in this study. Actually, 139 patients were randomized, 65 to immediate and 74 to delayed everolimus. All 139 patients were analyzed for safety and efficacy.

Criteria for evaluation

Efficacy: The primary criterion for assessing efficacy was the primary failure endpoint at 3 months, defined as the occurrence of DGF, efficacy failure, or wound healing disorder related to initial transplant surgery within the first 3 months. Efficacy failure was defined as BPAR, graft loss, death, or loss to follow-up. Secondary efficacy endpoints included various components of the primary failure endpoint.

Safety: Main criteria for assessing safety were adverse events, renal function parameters, dialysis, clinical laboratory, and vital signs.

Efficacy results: At 12 months failure was observed for 42 patients (64.6%) in the immediate Certican® group and for 49 patients (66.2%) in the delayed Certican® group, (ITT population, $p=0.8599$, Fisher's exact test). Wound healing disorders had a similar frequency for immediate Certican® (26 patients, 40.0%) and for delayed Certican® (28 patients, 37.8%), and this was not statistically significant ($p=0.8622$). No major differences between treatment groups were seen for other efficacy parameters as well.

Safety results: Adverse events were reported for all patients. Five patients in the immediate everolimus group (7.7%) (two of them had lost the graft previously) and two patients (2.7%) in the delayed everolimus group died. In the immediate Certican® group 45 patients (69.2%) had a serious adverse event and 17 patients (26.2%) had an adverse event leading to discontinuation of study medication. In the delayed everolimus group 57 patients (77.0%) had a serious adverse event and 28 patients (37.8%) had an adverse event leading to discontinuation of study medication.

Conclusion:

1) In patients with risk to develop DGF, immediate vs. delayed introduction of Certican® in combination with reduced Neoral® dose showed a comparable failure rate in the composite primary failure endpoint at Month 12:

- Incidence of DGF as defined by dialysis within 7 days was identical between study groups and low for this patient population.
- Requirement for dialysis remained low until Month 12 and incidence of dialysis sessions was comparable between both groups.
- BPAR rates were similar in both treatment groups at 12 months.

- *Graft losses and deaths were slightly higher in the group with immediate introduction of everolimus (of the six patients with graft failure, two patients died).*

- Wound healing events related and unrelated to initial surgery were comparable and nearly unchanged from Month 3 onward.

Study No. RAD001A2421

Title of study: A prospective, open label, controlled, multicenter trial to assess the efficacy and safety of an induction regimen of Neoral®, Myfortic® and corticosteroids, followed by administration of Certican® together with withdrawal of Neoral® and Myfortic® or corticosteroids and Myfortic® in *de novo* kidney transplant recipients.

Study centre(s): TBA

Study No. RAD001A2426

Title of study:

A twelve-month, multicenter, open-label, randomized study of the safety, tolerability and efficacy of Certican® with Simulect®, corticosteroids and two different exposure levels of tacrolimus in *de novo* renal transplant recipients.

Study purpose:

This study is designed to evaluate whether tacrolimus dose reduction in *de novo* renal recipients receiving everolimus can preserve renal function while maintaining efficacy.

Primary objective

The primary objective is to determine whether tacrolimus dose reduction can preserve renal function in *de novo* renal recipients receiving tacrolimus in addition to everolimus Simulect®, and corticosteroids. This objective will be assessed by comparing renal function evaluated by calculated glomerular filtration rate (GFR) (MDRD formula) at 12 months post-transplant between two groups of patients receiving two different exposure levels of tacrolimus.

Study No. RAD001AES05

Title of study: A multicenter, randomized, open-label, 2-year follow-up study to evaluate the effect of calcineurin inhibitor withdrawal and early introduction of everolimus on graft function in patients with a kidney transplant.

Planned dates: first subject dosed: 01-Nov-2006 last subject completed: 01-Nov-2009

Primary objective(s):

The primary objective of the study is to investigate whether early introduction of everolimus combined with CNI withdrawal can improve renal function in recipients of a kidney transplant of at least 3 months duration. This objective, which will be compared between both groups in Month 15 post-transplant, will be evaluated by calculating creatinine clearance according to the MDRD formula.

Safety:

- Evaluation of safety parameters based on the following variables: physical examination, vital signs, including incidence of hypertension, laboratory test results for assessment of hyperlipidemia, diabetes mellitus/glucose intolerance, anemia, leukopenia, thrombocytopenia, as well as evaluation of adverse effects related to immunosuppression (infections, especially viral and fungal, and neoplasms) at 5, 6, 9, 15, 21 and 27 Months post-transplant.

Reviewer's Comment: *No results have been submitted for this study yet.*

Study No. RAD001ANL02

Title of study:

A prospective, open, randomized, multicenter study comparing the effects of everolimus versus mycophenolate sodium (MPS) as compared to cyclosporine as maintenance therapy in renal allograft recipients, on chronic allograft damage and cardiovascular parameters

Objectives: prospective, open randomized multicenter trial, in which we aim to achieve optimal immune suppression after renal transplantation with maximal reduction of side effects, especially of vascular injury.

Methodology: Induction therapy for renal transplant recipients will consist of quadruple immune suppression consisting of prednisolone, MPS, cyclosporine and basiliximab. After 6 months, patients will be randomized to one of three groups: in the first group MPS will be tapered and patients will continue on double therapy with prednisolone and cyclosporine, in the second group cyclosporine will be stopped and patients will continue on prednisolone and MPS and in the third group, cyclosporine and MPS will be stopped and everolimus will be started. In this group patients will continue on everolimus and prednisolone .

Number of centers & patients: Three of the seven transplant centers of the Netherlands will participate:

Amendment:

Based on the recommendations of the Study Safety Board, randomization to the experimental MPS prednisolone maintenance therapy group was stopped effective 1-Jul-2007, due to a late acute rejection rate of 22% in this group. The late acute rejection rate, at that time point in the Ciclosporin prednisolone group was 2 %, in the everolimus-prednisolone group 0%.

7.4.6 Immunogenicity

Everolimus is administered orally and is not expected to be immunogenic.

7.5 Other Safety Explorations

None.

7.5.1 Dose Dependency for Adverse Events

The Applicant performed analyses to describe the relationship between blood trough levels of everolimus and various safety events of special interest. Using the pooled data from both everolimus dose groups, these safety events were at various categories of everolimus blood trough levels.

Note: Pharmacometrics reviewer Kevin Krudys Ph.D did his own exposure/response analyses and these results are discussed in Section 7.2.2 and other relevant sections.

7.5.1.1 Metabolic changes, wound healing, stomatitis and oral ulcers, edema

Relationship between everolimus C_{min} and adverse events

The PK/safety population consisted of all safety patients who had either everolimus trough levels or CsA C0 levels post randomization.

The incidence of selected AEs, lipid profile and hormone changes, by everolimus C_{min} values is shown in Table 72 and Table 73. There was a tendency for higher everolimus dose levels (especially those greater than 9 ng/mL) to result in a higher percentage of patients reporting events, except for low testosterone. However, the low numbers of patients in the higher C_{min} categories hinder accurate analysis.

When combined dose groups were studied for the median effect there was no statistically significant relationship between C_{min} and the selected AEs. For diabetes and hypercholesterolemia the relationship (positive) approached significance (p=0.053 and p=0.083, respectively).

Everolimus C_{min} concentrations and low testosterone showed a significant (negative) relationship in the 1.5 mg and 3.0 mg treatment groups, but when the groups were combined the relationship was no longer significant (p=0.172).

Table 72. Selected Adverse Events by Average Everolimus Trough Concentration in Combined Everolimus Dose Groups; PK/safety Population
 (Source: Table 12-28, page 220, CSR)

Everolimus C _{min} *	Wound healing events	Peripheral edema	Stomatitis and oral ulcers	New onset diabetes ¹
RAD001	182/528 (34.5%)	242/504 (48.0%)	41/548 (7.5%)	52/543 (9.6%)
<3 ng/mL	20/45 (44.4%)	24/46 (52.2%)	2/38 (5.3%)	2/37 (5.4%)
3 – <4 ng/mL	23/73 (31.5%)	32/74 (43.2%)	5/74 (6.8%)	9/78 (11.5%)
4 – <5 ng/mL	30/102 (29.4%)	50/104 (48.1%)	7/113 (6.2%)	6/105 (5.7%)
5 – <6 ng/mL	26/84 (31.0%)	42/75 (56.0%)	8/87 (9.2%)	5/85 (5.9%)
6 – <7 ng/mL	18/63 (28.6%)	28/58 (48.3%)	6/72 (8.3%)	7/76 (9.2%)
7 – <8 ng/mL	17/56 (30.4%)	15/49 (30.6%)	5/60 (8.3%)	5/61 (8.2%)
8 – <9 ng/mL	14/40 (35.0%)	13/36 (36.1%)	3/48 (6.3%)	5/41 (12.2%)
9 – <10 ng/mL	11/24 (45.8%)	14/24 (58.3%)	4/24 (16.7%)	5/25 (20.0%)
10 – <11 ng/mL	5/13 (38.5%)	9/16 (56.3%)	0/12 (0.0%)	3/14 (21.4%)
11 – <12 ng/mL	9/13 (69.2%)	8/8 (100%)	1/7 (14.3%)	3/6 (50.0%)
12 – <13 ng/mL	3/4 (75.0%)	2/4 (50.0%)	0/3 (0.0%)	1/4 (25.0%)
≥13 ng/mL	6/11 (54.5%)	5/10 (50.0%)	0/10 (0.0%)	1/11 (9.1%)
3 – <6 ng/mL	79/259 (30.5%)	124/253 (49.0%)	20/274 (7.3%)	20/268 (7.5%)
6 – <8 ng/mL	35/119 (29.4%)	43/107 (40.2%)	11/132 (8.3%)	12/137 (8.8%)
8 – <12 ng/mL	39/90 (43.3%)	44/84 (52.4%)	8/91 (8.8%)	16/86 (18.6%)
≥12 ng/mL	9/15 (60.0%)	7/14 (50.0%)	0/13 (0.0%)	2/15 (13.3%)
Myfortic	70/273 (25.6%)	120/273 (44.0%)	8/273 (2.9%)	18/273 (6.6%)

* Average trough levels calculated up to event or censored at cut-off day

¹ Diabetes post-transplantation, identified by any of the following:

- a. Diabetes was reported as an adverse event;
- b. Glucose (random) ≥ 11 mmol/L (≥ 198 mg/dL) post-transplantation;
- c. Diabetes was recorded as reason for a medication given post-transplantation.

In patients who were not diabetic at the time of transplantation, identified by all of the following:

- a. Reason for transplantation was not diabetes;
- b. Diabetes was not included in medical history;

- c. Glucose (random) < 11 mmol/L at the time of transplantation;
 d. Diabetes was not recorded as reason for any medication given prior to transplantation.

Table 73. Lipid Profile and Hormone Changes by Average Everolimus Trough Concentration in Combined Everolimus Dose Groups; PK/safety Population

(Source: Table 12-29, page 221, CSR)

Everolimus C _{min} *	Hypercholesterolemia ₁	Hypertriglyceridemia ²	Low Testosterone ³ – male –
RAD001	375/544 (68.9%)	106/549 (19.3%)	63/287 (22.0%)
<3 ng/mL	39/55 (70.9%)	5/32 (15.6%)	2/8 (25.0%)
3 – <4 ng/mL	55/87 (63.2%)	16/70 (22.9%)	11/32 (34.4%)
4 – <5 ng/mL	66/94 (70.2%)	21/107 (19.6%)	10/59 (16.9%)
5 – <6 ng/mL	48/86 (55.8%)	13/91 (14.3%)	8/44 (18.2%)
6 – <7 ng/mL	40/58 (69.0%)	15/82 (18.3%)	14/40 (35.0%)
7 – <8 ng/mL	36/48 (75.0%)	9/59 (15.3%)	9/44 (20.5%)
8 – <9 ng/mL	35/48 (72.9%)	9/45 (20.0%)	4/26 (15.4%)
9 – <10 ng/mL	18/22 (81.8%)	5/21 (23.8%)	3/13 (23.1%)
10 – <11 ng/mL	15/17 (88.2%)	5/18 (27.8%)	1/9 (11.1%)
11 – <12 ng/mL	7/9 (77.8%)	5/8 (62.5%)	1/6 (16.7%)
12 – <13 ng/mL	5/6 (83.3%)	1/4 (25.0%)	0/1 (0.0%)
≥13 ng/mL	11/14 (78.6%)	2/12 (16.7%)	0/5 (0.0%)
3 – <6 ng/mL	169/267 (63.3%)	50/268 (18.7%)	29/135 (21.5%)
6 – <8 ng/mL	76/106 (71.7%)	24/141 (17.0%)	23/84 (27.4%)
8 – <12 ng/mL	75/96 (78.1%)	24/92 (26.1%)	9/54 (16.7%)
≥12 ng/mL	16/20 (80.0%)	3/16 (18.8%)	0/6 (0.0%)
Myfortic	141/272 (51.8%)	22/272 (8.1%)	24/160 (15.0%)

Metabolic alterations (hypercholesterolemia, hypertriglyceridemia, new onset diabetes) appeared to be more frequent with everolimus than Myfortic and rates increased as trough levels rose from <3 ng/mL to 8 to <12 ng/mL. For average everolimus troughs ≥12 ng/mL, the number of patients was too small for the incidence rates to be reliably estimated.

Wound healing events, stomatitis and oral ulcers were also more frequent with everolimus than Myfortic, with rates of stomatitis and oral ulcers (but not wound healing) also increased slightly as trough levels rose from <3 ng/mL to 8-<12 ng/mL.

Fluid retention from peripheral edema tended to be more common with everolimus than Myfortic and showed little relation to everolimus trough levels.

Table 74 Relation of Everolimus Trough Concentrations to Rates of Events,
(Source: Table 5-28, page 59, Clinical Overview section of NDA resubmission)

Table 5-28 Relation of everolimus trough levels to rates of events						
% (n/N)	Everolimus (ng/mL)					Myfortic (all)
	<3	3 – <6	6–<8	8–<12	≥12	
Metabolic changes:						
Hypercholest.	70.9 (39/55)	63.3 (169/267)	71.7 (76/106)	78.1 (75/96)	80.0 (16/20)	51.8 (141/272)
Hypertriglycer.	15.6 (5/32)	18.7 (50/268)	17.0 (24/141)	26.1 (24/92)	18.8 (3/16)	8.1 (22/272)
new onset diabetes	5.4 (2/37)	7.5 (20/268)	8.8 (12/137)	18.6 (16/86)	13.3 (2/15)	6.6 (18/273)
Wound healing and oral ulcers:						
wound healing	44.4 (20/45)	30.5(79/259)	29.4 (35/119)	43.3(39/90)	60.0 (9/15)	25.6(70/273)
stomatitis and oral ulcers	5.3 (2/38)	7.3 (20/274)	8.3 (11/132)	8.8 (8/91)	0 (0/13)	2.9 (8/273)
Fluid retention:						
peripheral edema	52.2 (24/46)	49.0 (124/253)	40.2 (43/107)	52.4 (44/84)	50.0 (7/14)	44.0 (120/273)

7.5.1.2 Renal function

The potential relationship between blood trough levels of everolimus and of CsA and the frequency of renal function related outcomes was explored. Using the pooled data from both everolimus dose groups, the frequencies of these events at various ranges of everolimus blood trough level are summarized in Table 75.

No consistent conclusions could be drawn for the relationship between everolimus exposure and all these events.

Table 75. Relation of everolimus trough levels to low renal function,
(Source: Table 5-29, page 60, Clinical Overview section of NDA resubmission)

% (n/N)	Everolimus (ng/mL)					Myfortic (all)
	<3	3 – <6	6–<8	8–<12	≥12	
Renal function:						
low GFR	42.9 (6/14)	12.4 (29/234)	18.3 (26/142)	15.0 (12/80)	16.7 (2/12)	15.4 (38/247)
decr. GFR (MDRD)	28.6 (4/14)	30.5 (73/239)	27.9 (38/136)	28.4 (23/81)	33.3 (4/12)	32.8 (81/247)
decr. GFR (Nankivell)	26.7 (4/15)	21.4 (50/234)	15.9 (21/132)	20.3 (16/79)	27.3 (3/11)	25.9 (63/243)
decr. creat. clearance	28.6 (4/14)	19.4 (46/237)	19.3 (27/140)	20.3 (16/79)	33.3 (4/12)	19.8 (49/247)
high creatinine	42.9 (6/14)	17.9 (42/234)	23.1 (33/143)	16.5 (13/79)	16.7 (2/12)	23.9 (59/247)
high UP/UC	66.7 (12/18)	51.7 (120/232)	53.0 (71/134)	63.9 (53/83)	92.3 (12/13)	39.0 (96/246)

7.5.1.3 Relationship between everolimus Trough Concentration and Renal Function

The PK/efficacy population was used for this analysis (those patients in the ITT population who had a post randomization everolimus trough or CsA C0 levels). The incidence of renal function impairment assessed using absolute GFR (MDRD), decrease in GFR (MDRD or Nankivell), decrease in creatinine clearance (Cockcroft-Gault), absolute creatinine levels or urinary protein-creatinine ratio by everolimus Cmin levels is shown in Table 76. The incidence of renal impairment did not show a statistical correlation with everolimus exposure when data across treatment groups were pooled.

Table 76. Renal Function Impairment by Average Everolimus Trough Concentration in Combined Everolimus Dose Groups; PK/Efficacy Population
(Source : Table 12-25, page 212, CSR)

Everolimus C _{min} *	Low GFR ¹	Decreased GFR (MDRD) ²	Decreased GFR (Nankivell) ²	Decreased creatinine clearance ³	High creatinine ⁴	High UP/UC ⁵
RAD001	75/482 (15.6%)	142/482 (29.5%)	94/471 (20.0%)	97/482 (20.1%)	96/482 (19.9%)	268/480 (55.8%)
<3 ng/mL	6/14 (42.9%)	4/14 (28.6%)	4/15 (26.7%)	4/14 (28.6%)	6/14 (42.9%)	12/18 (66.7%)
3–<4 ng/mL	8/48 (16.7%)	17/51 (33.3%)	8/45 (17.8%)	9/49 (18.4%)	15/50 (30.0%)	28/55 (50.9%)
4–<5 ng/mL	10/107 (9.3%)	31/104 (29.8%)	20/104 (19.2%)	19/106 (17.9%)	14/107 (13.1%)	52/101 (51.5%)
5–<6 ng/mL	11/79 (13.9%)	25/84 (29.8%)	22/85 (25.9%)	18/82 (22.0%)	13/77 (16.9%)	40/76 (52.6%)
6–<7 ng/mL	12/74 (16.2%)	20/74 (27.0%)	10/73 (13.7%)	10/73 (13.7%)	18/75 (24.0%)	43/81 (53.1%)
7–<8 ng/mL	14/68 (20.6%)	18/62 (29.0%)	11/59 (18.6%)	17/67 (25.4%)	15/68 (22.1%)	28/53 (52.8%)
8–<9 ng/mL	6/42 (14.3%)	12/40 (30.0%)	10/40 (25.0%)	8/40 (20.0%)	8/42 (19.0%)	21/38 (55.3%)
9–<10 ng/mL	3/18 (16.7%)	5/21 (23.8%)	3/19 (15.8%)	5/20 (25.0%)	3/19 (15.8%)	21/28 (75.0%)
10–<11 ng/mL	2/14 (14.3%)	5/15 (33.3%)	2/14 (14.3%)	2/14 (14.3%)	1/12 (8.3%)	6/10 (60.0%)
11–<12 ng/mL	1/6 (16.7%)	1/5 (20.0%)	1/6 (16.7%)	1/5 (20.0%)	1/6 (16.7%)	5/7 (71.4%)
12–<13 ng/mL	0/4 (0.0%)	0/4 (0.0%)	0/4 (0.0%)	0/4 (0.0%)	0/4 (0.0%)	1/1 (100%)
≥13 ng/mL	2/8 (25.0%)	4/8 (50.0%)	3/7 (42.9%)	4/8 (50.0%)	2/8 (25.0%)	11/12 (91.7%)
3 – <6 ng/mL	29/234 (12.4%)	73/239 (30.5%)	50/234 (21.4%)	46/237 (19.4%)	42/234 (17.9%)	120/232 (51.7%)
6 – <8 ng/mL	26/142 (18.3%)	38/136 (27.9%)	21/132 (15.9%)	27/140 (19.3%)	33/143 (23.1%)	71/134 (53.0%)
8 – <12 ng/mL	12/80 (15.0%)	23/81 (28.4%)	16/79 (20.3%)	16/79 (20.3%)	13/79 (16.5%)	53/83 (63.9%)
≥12 ng/mL	2/12 (16.7%)	4/12 (33.3%)	3/11 (27.3%)	4/12 (33.3%)	2/12 (16.7%)	12/13 (92.3%)
Myfortic	38/247 (15.4%)	81/247 (32.8%)	63/243 (25.9%)	49/247 (19.8%)	59/247 (23.9%)	96/246 (39.0%)

* Average trough levels calculated up to event or censored at date of last dose + 2 days

1 GFR (MDRD) < 30 mL/min/1.73m²

2 Decrease in GFR (MDRD or Nankivell) > 30% from Month 1

3 Decrease in creatinine clearance (Cockcroft Gault) > 30% from Month 1

4 Creatinine ≥ 200 μmol/L

5 Urine protein-creatinine ratio ≥ 300 mg/g

7.5.2 Time Dependency for Adverse Events

Not applicable due to various reasons including the fact that immunosuppression is a life-long treatment and some of the adverse events are related to the extent of immunosuppression hence to the level of drug exposure rather than the duration of

treatment. In transplant patients some adverse events like CMV infections show a time dependency but this may be more related to the general course of the transplant patients rather than the type of immunosuppression. Multitude and etiological diversity of adverse events may not always permit a time dependency analysis or yield meaningful results.

7.5.3 Drug-Demographic Interactions

The drug-demographic interactions in this study are mentioned in relevant sections such as the differential severity of proteinuria in relation to gender.

7.5.4 Drug-Disease Interactions

Please refer to Ike Lee's Clinical Pharmacology Review with original NDA submission.

The half-life estimates from 12 maintenance renal transplant patients who received single doses of everolimus capsules at 0.75 mg or 2.5 mg with their maintenance cyclosporine regimen indicated that the pharmacokinetics of everolimus are linear over the clinically-relevant dose range. Results indicate the half-life of everolimus in maintenance renal transplant patients receiving single doses of 0.75 mg or 2.5 mg everolimus during steady-state cyclosporine treatment was 30 ± 11 hours (range 19-53 hours).

7.5.5 Drug-Drug Interactions

Please refer to 7.2.5. for a listing of the DDI studies conducted for Clinical Pharmacology.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable

7.6.2 Human Reproduction and Pregnancy Data

Cumulatively, until March 31, 2009, 21 reports of drug exposure during pregnancy were received by the Applicant, including 9 reports of drug exposure to the father. This included 18 prospective cases and 3 retrospective.

An abnormal outcome was reported in 3 cases: 2 reports of spontaneous abortions/intrauterine death (PHHO2004AU16391, PHHO2004US09505, both retrospective, and PHHO2008MX08628, prospective) and 1 prospective report of a live birth with congenital anomalies. The anomaly was described as follows: reduced amniotic fluid consistent with "preterm premature rupture of fetal membranes", dilatation of cerebral ventricles inferiorly without midline falx, kidney abnormalities and two vessel cords. The newborn died shortly after delivery. The investigator suspected a relationship between this event and the study medication (PHHO2005AU08081 baby case, PHHO2004AU16391 mother case, clinical trial).

7.6.3 Pediatrics and Assessment of Effects on Growth

(b) (4)

Given that the application is being issued a CR letter, a final decision on the pediatric plan has not been made. The Division is considering a deferral or waiver for the development pediatric program but due to the CR action, consensus was not reached within the Division and with the Pediatrics and Maternal Health Staff. Once the labeling and REMS program for everolimus in adult patients is addressed, a decision about the information needed in pediatric patients, and whether the studies conducted to date by Novartis are adequate, will be determined, in consultation with the Pediatric and Maternal Health Staff.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is very little information on overdose. During clinical development, single doses of up to 25 mg given to transplant recipients and multiple weekly doses of up to 70 mg given to oncology patients resulted in no major acute tolerability issues.

7.7 Additional Submissions / Safety Issues

None.

7.8 Safety Summary

Primary Safety Endpoint – Renal Function:

At the end of 12 month study period the calculated GFR with the MDRD formula was similar in the everolimus 1.5 mg and the Myfortic (control) groups

Deaths

A total of 23 patients died during the first 12 months of the study, 7 (2.5%) in the everolimus 1.5 mg group, 10 (3.6%) in the 3.0 mg everolimus group, and 6 (2.2%) in the Myfortic control group. The most common causes of death across the study groups were related to cardiac conditions and infections. The reviewer evaluated the narratives and Case Report Forms (CRFs) for the patients who died in this study and, after excluding five deaths because of lack of any discernable association between the cause of death and the study medication, concluded a probable association between the other 18 deaths and the study medication as follows:

- 7 deaths in the 1.5 mg everolimus group
- 8 deaths in the 3.0 mg everolimus group
- 3 deaths in the Myfortic (control) group

According to this final assessment of study drug attributability of patient deaths there are more than twice as many deaths in both of the everolimus groups compared to the Myfortic group that shows a probable association with the study medication.

Although a direct comparison is not possible because of the differences in the study designs and treatment regimens, it may be relevant to mention that in both of the previous studies of fixed dose everolimus with standard dose CsA (Studies B201 and B251) there were numerically more deaths in both of the everolimus groups compared to the MMF control group.

Serious Adverse Events (SAEs)

SAEs in the following MedDRA System Organ Classes (SOCs) were reported at a higher rate in the everolimus 1.5 mg group compared to the Myfortic group:

- Blood and lymphatic system disorders, (4% vs. 2.9%)
- Gastrointestinal disorders (7.7% vs. 6.6%)
- General disorders and administration site conditions (5.5% vs. 4.4%)
- Injury, poisoning and procedural complications (14.2% vs. 11.7%)
- Investigations (8.4% vs. 8.1%)
- Metabolism and nutrition disorders (7.3% vs. 4.8%)
- Musculoskeletal and connective tissue disorders (1.8% vs. 0.4%)
- Nervous system disorders, psychiatric disorders (2.2% vs. 1.8%)
- Psychiatric disorders (1.1% vs. 0%)
- Reproductive system and breast disorders (1.1% vs. 0%)

- Respiratory, thoracic and mediastinal disorders (3.3% vs. 2.9%)
- Vascular disorders (9.5% vs. 7.3%)

SAEs in the following SOCs were higher in the Myfortic group compared to the everolimus 1.5 mg group:

- Infections and infestations (25.3% vs. 19.7%)
- Neoplasms (1.8% vs. 1.5%)
- Renal and urinary disorders (13.2% vs. 10.2%)

The higher incidence in the Myfortic group is mainly due to the higher number of cases with hydronephrosis and ureteric obstruction which are usually due to poor surgical technique. Also 5 patients who were reported to have toxic nephropathy or blood creatinine increase in the Myfortic group were concomitantly receiving sirolimus in addition to the Myfortic study regimen

Graft Losses and Graft Thromboses

Another M-TOR inhibitor, sirolimus, has a Boxed Warning regarding the increased incidence of hepatic artery thromboses in liver transplant patients, so this is a recognized class effect. The number of graft losses was 12 (4.3%) in the everolimus 1.5 mg group, 14 (5.0%) in the everolimus 3.0 mg group and 8 (2.9%) in the Myfortic group over the 12 month study period. One of the patients with renal vein thrombosis in the everolimus 1.5 mg group died later as a result of the events started by this complication (patient 0114-0001).

The Reviewer and the applicant agreed on the assessment of the number of patients who developed graft thrombosis (artery and vein) and consequently lost their grafts:

- 6 graft thromboses (4 renal artery and 2 renal vein) in the everolimus 1.5 mg group
- 4 graft thromboses (4 renal artery) with another probable 5th patient again with renal artery thrombosis according to the narrative in the everolimus 3.0 mg group
- 2 graft thromboses (2 renal artery) in the Myfortic group.

In the everolimus 1.5 mg group the incidence of early graft thromboses (within 30 days of transplant) is 1.8% and we see the same trend in the everolimus 3.0 mg group with an incidence of 1.4% which are both above the national average of 0.9% and in line with the well known thrombogenic effect of M-TOR inhibitors.

Dropouts and/or Discontinuations

Significantly more patients prematurely discontinued study medication due to adverse events in the everolimus group (18.1%) compared to the Myfortic group (9.4%) (p-value=0.004). This difference was primarily driven by significant differences between treatment groups among female patients.

Significant Adverse Events

Infections reported as AEs had a lower incidence in the everolimus 1.5 mg group compared to the Myfortic group (62% vs. 68%) which is mainly due to the more frequent CMV, BK virus and other herpes virus infections in the Myfortic group. When we look at the infections reported as SAEs the only notable differences between the two groups are 9 CMV infections and 4 herpes zoster infections in the Myfortic group vs. no CMV infection and 1 herpes zoster infection in the everolimus 1.5 mg group. All the CMV and herpes zoster infections reported as SAEs were successfully treated without any patient or graft losses.

There are no deaths due to infections in the Myfortic group whereas 2 deaths in the everolimus 1.5 mg group and 5 deaths in the everolimus 3.0 mg group are due to infections. Although numerically there were more infections in the Myfortic group the infections in the everolimus group were more serious and resulted in at least two deaths.

Proteinuria

The median UP/UC ratios over the 12 months of the study in the safety on-treatment population, which was defined as the population of safety patients whose assessments were obtained on and after day 1 but no later than two days after the discontinuation of randomized study medication. The median ratios in the everolimus 1.5 mg group were consistently higher than those of Myfortic throughout the study including the Month 12 TEP²¹, as shown as Month 13. The differences between the groups became significant starting at Month 6 onwards.

There is a difference of 210 mg/g between the everolimus 1.5 mg group and the Myfortic group in favor of the Myfortic group using the Month 12 TEP values and this difference is even higher for the male patients since higher levels of proteinuria in the everolimus 1.5 mg group is driven by the male patients. The biological mechanism for higher levels of proteinuria in males is not known. Therefore, the Reviewer believes there is an augmented risk for the male patients over female patients. The fact that the differences between the two treatment groups became significant starting Month 6 raises concerns that the gap may continue to widen in favor of the Myfortic group with longer follow-up and may be more severe for the male patients. Proteinuria is a known risk factor for

21 TEP=treatment endpoint (imputation by LOCF)

cardiovascular disease, diabetes and may contribute to hyperlipidemia at high levels. It has also been shown to decrease patient and graft survival in kidney transplantation.

Hypertriglyceredemia, diabetes and proteinuria (at the microalbuminuria level) are all components of the metabolic syndrome, which is linked to adverse patient and graft outcomes^{22,23} and they occur with higher incidence and severity in both of the everolimus treatment groups compared to the Myfortic group. It is not unreasonable to assume that this coexistence of hyperlipidemia, NODAT and proteinuria with higher severity or higher incidence compared to the control group will result in higher cardiovascular morbidity and mortality in this high cardiac risk population in the long term if not during shorter periods of follow-up like one year.

Hyperlipidemia

Hyperlipidemia was reported as an AE in 57 (20.8%) patients in the everolimus 1.5 mg group, 60 (21.6%) patients in the everolimus 3.0 mg group, and 43 (15.8%) patients in the Myfortic group.

All through the 12 month study period mean total cholesterol and triglyceride values were significantly higher in both of the everolimus groups compared to the Myfortic group. Generally, after the 9 month time point, the mean values of both total cholesterol and triglycerides came down to the normal range in the Myfortic group, whereas the mean values in both of the everolimus groups stayed above the upper limit of normal ranges. LDL values in the everolimus groups were also significantly higher in the everolimus groups compared to the Myfortic group.

In the everolimus 1.5 mg group almost three times as many patients (16% vs. 6%) have total cholesterol levels above 350 mg/dL and almost twice as many patients (4.4% vs. 2.6%) have triglyceride values above 500 mg/dL compared to the Myfortic group.

Lipid lowering agents were taken by a higher percentage of patients in the everolimus treatment groups (64.6%, 72.3% and 57.5% of patients in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm treatment groups, respectively).

Among patients with high baseline cholesterol values before the statin treatment was initiated, 27.4% (17/62) in the everolimus 1.5 mg group compared to 13.9% (5/36) in the Myfortic group did not move down to the normal range despite the statin treatment. A similar trend was also observed for triglycerides in a similar analysis. Among patients with high baseline triglyceride values before the statin treatment was initiated, 49% (22/45) in the everolimus 1.5 mg group compared to 26% (5/19) in the Myfortic group did not move down to the normal range despite the statin treatment.

22 de Vries et al. Metabolic Syndrome Is Associated with Impaired Long-term Renal Allograft Function; Not All Component criteria Contribute Equally. *American Journal of Transplantation* 2004; 4: 1675–1683
23 Sharif. Metabolic Syndrome and Solid-Organ Transplantation. *American Journal of Transplantation* 2009; 9: 1–6

Usage of statins in the everolimus groups also resulted in significantly higher levels of CK (Creatine kinase) levels which may indicate excessive muscle tissue breakdown despite the mean levels stayed within the normal range.

A 39 year old male patient (0124-00076), whose death was attributed to acute myocardial infarction, developed severe dyslipidemia (hypercholesterolemia) after the transplant which gradually worsened until his death on Day 85. His total cholesterol increased from 147 mg/dL to 432 mg/dL and his LDL cholesterol increased from 81 mg/dL to 212 mg/dL (normal levels: up to 129 mg/dL) during the course of the study. Although this patient had a history of hypertensive heart disease the rapid rise of all lipid levels from normal range to very high values in a short period of time might have contributed to his death.

Hyperlipidemia is common in chronic kidney disease patients and the incidence increases after kidney transplantation. Various immunosuppressants, including CsA, corticosteroids, and M-TOR inhibitors, have been recognized as a major contributor to dyslipidemias seen after transplant. According to published research above even mild elevations in cholesterol levels may double the risk of developing ischemic heart disease in kidney transplant recipients unlike the milder increase of risk in the general population and the associated increase in mortality affects the younger recipients more than the older recipients.

Wound Healing and Wound Fluid Collections

Incisional wound complications were more frequent in the two everolimus groups compared to the Myfortic group with the highest number occurring in the 3.0 mg group. In each of the Dehiscence, Hernia and Infection categories, more patients required surgical intervention (i.e., intraoperative repair or debridement/ drainage) in the everolimus groups compared to the Myfortic group. The total number of surgical interventions was 19 in the everolimus 1.5 mg group, 22 in the everolimus 3.0 mg group, and 9 in the Myfortic group.

Similar to the incidence of wound-related events, fluid collections (lymphoceles and seromas) were also more commonly reported in the everolimus groups compared to the Myfortic group

Among all the patients who died during the 12 month period wound related problems (mainly infections and dehiscences and lymphoceles) were noted in 5 patients in the everolimus 1.5 mg group, 4 patients in the everolimus 3.0 mg group and in 1 patient in the Myfortic group. Although it is difficult to explain the association between this high occurrence of wound complications among the patients who died in both of the everolimus groups it is almost certain that there is a trend.

Fluid Accumulation, Including Peripheral Edema, Ascites, and Pleural Effusions;

At Month 12 the incidence of edema related events was statistically significantly higher in both everolimus groups than in the Myfortic group (55.5% and 54.7% versus 45.1%). Peripheral edema possibly contributed to the death of 1 patient in study 2309 who was in the everolimus 1.5 mg group. This patient (0516-00002) was treated with furosemide because of edema on day 102 and died on day 156 due to congestive heart failure.

MACE (Major Cardiac Adverse Events)

Although the overall incidence of MACE events are much higher in the everolimus 3.0 mg group compared to the other two groups in the study, everolimus 1.5 mg group and the Myfortic group look similar to each other except for the numerical increase in myocardial infarctions in the Myfortic group (2 vs 4). When those cases with myocardial infarctions are analyzed in the reviewer's assessment only one case, 39 year old male patient (0124-00076) in the everolimus 1.5 mg treatment group can be associated with the study medication (everolimus).

Hematologic Adverse Events including Thrombocytopenia

The overall incidence of hematologic AEs was 33.9% in the 1.5 mg group, 40.3% in the 3.0 mg group, and 40.7% in the Myfortic group. The higher incidence in the Myfortic group was mainly driven by the higher incidence of leucopenia. Leucopenia associated with mycophenolic-acid (MPA) is very common in clinical practice and is usually responsive to dose reductions or interruptions. Hematologic events reported as SAEs were reported in eleven patients in the everolimus 1.5 mg group, ten in the everolimus 3.0 mg group, and eight patients in the Myfortic group.

Thrombocytopenia contributed to one patient's death in the everolimus 3.0 mg group (patient 0549-0001).

Other Thromboembolic Events

There were 13 (4.7%) in the 1.5 mg everolimus group, 16 (5.8%) in the 3.0 mg everolimus group and 9 (3.3%) in the Myfortic group. Two patients with HUS and one each with TTP and TMA were reported in the everolimus 1.5 mg group. The number of SAEs related to thrombotic events was: eight in the everolimus 1.5 mg group and four in each of the everolimus 3.0 mg and Myfortic groups.

TMA/TTP/HUS

Thrombotic microangiopathies [TMA (Thrombotic Microangiopathy), TTP (Thrombotic Thrombocytopenic Purpura) and HUS (Hemolytic Uremic Syndrome)] are rare events traditionally associated with calcineurin inhibitors (CNIs), like CsA, until the recent discovery that they are also associated with M-TOR immunosuppression and the combined usage of M-TOR inhibitors and CNIs may increase the incidence. In Study A2309 a total of 4 TMA cases (1 TMA, 1 TTP and 2 cases of HUS) were reported all in the everolimus 1.5 mg group. TTP reported in the everolimus 1.5 mg group also contributed to one graft loss (patient 0192-00002).

Non Infectious Pneumonitis, Including Alveolar Proteinosis

Non infectious pneumonitis, including alveolar proteinosis, is a class effect of M-TOR inhibitors. It is relatively rare but may have a fatal outcome, especially if it is not recognized or treated appropriately. The diagnosis must be considered in every patient who develops dyspnea especially if they are on an M-TOR inhibitor. Infectious pneumonia is also commonly superimposed. Treatment includes discontinuation of the M-TOR inhibitor and steroids.

A total of six patients were reported to have interstitial lung disease identified by the applicant. Two cases were in the everolimus 1.5 mg group, three in the everolimus 3.0 mg group, and one is in the Myfortic group. The patient in the Myfortic group had no record of lung related pathology in narrative.

One patient developed alveolar proteinosis (0304-00016) in the everolimus 1.5 mg group following the initial 12 months of the study and died due to pneumonia and septic shock 60 days after the diagnosis.

Neoplasms

Neoplasms, benign and malignant, were reported at a lower incidence in the everolimus 1.5 mg group compared to the Myfortic group (9 patients compared to 16 patients, respectively) but the only malignancy death in the study (malignant melanoma) was also reported in the everolimus 1.5 mg group and the only lymphoma (PTLD) was observed in the everolimus 3.0 mg group.

New Onset Diabetes after Transplantation (NODAT)

Fasting plasma glucose \geq 126 mg/dL (7.0 mmol/L), which is part of the standard definition for NODAT by the ADA (American Diabetes Association) was not included as part of the other screening criteria for NODAT in this study. Therefore, the Reviewer believes the resulting estimation of NODAT in all three study groups is lower than anticipated. The incidence of NODAT was 9.1% in the everolimus 1.5 mg group, 12.2% in the everolimus 3.0 mg group, and 6.6% in the Myfortic group.

The reported incidence of NODAT among kidney transplant recipients with standard immunosuppression in the literature is around 30% though it may be higher depending on the type of CNI inhibitor utilized and in some publications it is reported to be as high as 50%. The numbers reported in Study A2309 are not compatible with the published literature. If the screening criteria had been more stringent (ADA recommended criteria) the incidences would be higher in all treatment groups with a possible increase of the difference between the everolimus group and the Myfortic group in favor of the Myfortic group.

Gastrointestinal Adverse Events

Gastrointestinal adverse events like nausea vomiting and diarrhea are commonly observed with MPA treatment. However, in the study gastrointestinal adverse events overall had a similar incidence in the everolimus 1.5 mg and the Myfortic groups (72% compared to 76%, respectively).

Gastrointestinal events reported as SAEs were more frequent and tended to be more severe, as described below, in the everolimus 1.5 mg group. The everolimus 3.0 mg group had the highest incidence of SAEs in the SOC of Gastrointestinal Disorders (28 patients) followed by the 1.5 mg group (21 patients) and the Myfortic group (18 patients), respectively.

Two cases of hemorrhagic esophagitis in the everolimus 1.5 mg group and one case of mesenteric vessel thrombosis in the everolimus 3.0 mg group were reported as SAEs, which may be associated with the ulcerative and thrombogenic class effects of M-TOR inhibitors.

Male Endocrine Effects

At 9 months patients in the everolimus 1.5 mg group displayed a lower mean testosterone level and higher mean LH and FSH levels when compared to the Myfortic group. The mean values for all three hormones were still within the normal ranges with FSH level in the everolimus 1.5 mg group being at the upper level of normal. The difference between the testosterone levels across the two treatment groups at 9 months appeared to be caused by a decrease of testosterone levels in the everolimus 1.5 mg group throughout the 9 month period during which the testosterone levels in the Myfortic group stayed the same. Month 9 mean testosterone levels are still within the normal range in both groups despite the significant decrease in the everolimus 1.5 mg group.

The mean FSH levels in the everolimus 1.5 mg group increased and rose up to the upper limit of the normal range (11.1 ± 9 U/L) at 9 months which may be indicative of decreased sperm production. Sperm counts were not performed as part of the protocol in Study A2309. However, oligospermia or azospermia, which is usually reversible, is reported in the literature for other M-TOR inhibitors and documented in the non-clinical

studies for everolimus. The effect is partly due to the anti-proliferative effects of M-TOR inhibitors.

Other Concerns: Drug-Drug Interactions

Both everolimus and CsA are metabolized through the CYP3A4 enzyme system in the liver. On the other hand, MPA is mainly metabolized through glucuronidation.

For both everolimus and CsA, concurrent treatment with strong 3A4 inhibitors, such as azole antifungals (ketoconazole, itraconazole, voriconazole) and macrolide antibiotics (clarithromycin, telithromycin) gives rise to significant increases in the concentrations of these drugs and concurrent use is not recommended. In addition, CsA also has a significant drug interaction with some of the HMG-CoA reductase inhibitors and use with lovastatin and simvastatin is also not recommended.

In addition, co-administration of CsA with everolimus significantly increases the concentrations of everolimus. Therefore, if the dose of CsA is increased, everolimus toxicity is possible if everolimus concentrations are not carefully monitored and the dose of everolimus adjusted. Another difficulty with the TDM regulation of the everolimus is the relatively long plasma half life which is around 30 hours in kidney transplant recipients. At least 5 days need to elapse before a meaningful trough concentration can be obtained every time either the everolimus or the CsA dose is changed

On the other hand, there is no CYP3A4 interaction between MPA and CsA. In fact, there is a small effect of CsA on the enterohepatic circulation of MPA such that an increase in CsA exposure decreases MPA exposure and reduces the possibility of increased toxicity due to this interaction.

Non-Clinical Findings and Possible Risk of Cataracts

Eye examinations were not included in the study protocol so it is not known if there is an increased incidence with everolimus treatment but in non-clinical studies (in rats) everolimus at clinically relevant doses caused fibrillar degeneration in the lens (see section 4.3).

Conclusion

The efficacy results from Study A2309 showed that both everolimus treatment regimens were non-inferior to the Myfortic control regimen at 12 months with regard to the primary efficacy composite endpoint consisting of the first occurrence of treated BPAR, graft loss, death or loss to follow-up. Although the incidence rate of death, graft loss and loss to follow-up was similar between both everolimus groups and Myfortic group, numerically these events were more frequent in the everolimus groups and displayed a clear association with everolimus treatment.

In terms of GFR, there were no statistically significant differences between any of the treatment groups at month 12.

However, there were significant safety findings in the everolimus 1.5 mg group compared to the Myfortic control specifically:

- Numerically increased mortality with more causality associations,
- Numerically increased graft losses with an increased incidence of graft thromboses one of which resulted in death.
- More hyperlipidemia
- More NODAT
- More proteinuria
- More wound healing problems with more patients requiring surgical or non-surgical interventions for treatment
- Interstitial lung disease which contributed to the death of one patient
- TMA/TTP/HUS one of which contributed to the graft loss in one patient
- Severe thrombocytopenia which contributed to the death of one patient in the everolimus 3.0 mg group. It is not known if this adverse effect is exposure dependent. Thrombocytopenia has been frequently associated with M-TOR inhibition in the literature; although it may also be encountered with MPA treatment it is usually milder in nature.
- Adverse effects on the male gonadal function.
- -More study drug discontinuations due to adverse events which may partly due to the difficulty of managing the regimen.

Therefore, it is the Reviewer's opinion that the safety findings with the everolimus 1.5 mg regimen far outweigh the benefits of the regimen and probably will result in increased mortality both in the short term and the long term when compared to the comparator Myfortic regimen or other similar immunosuppressive regimens currently being used. The higher morbidity and mortality associated with everolimus may become more noticeable in the long term since some of the associated risks like hyperlipidemia, NODAT and proteinuria continue to exert their effects over the course of the years and immunosuppression is a life long treatment unlike many other treatments.

8 Postmarket Experience

The following post-marketing experience is a summary of the Applicant's Post-Marketing Periodic Safety Updates with details of labeling changes from the NDA resubmission:

The post-marketing experience is derived from the periodic safety update reviews (PSURs) and updates to the Company Core Data Sheet (CDS), this being the document prepared by the pharmaceutical manufacturer, containing among other things all relevant safety information, such as adverse drug reactions, which are required to be

listed for the drug in all countries where the drug is marketed (CIOMS 1996). The CDS for Certican is identical to the Summary of Product Characteristics (SmPC) used in the European Union.

Adverse drug reactions (ADRs) were attributed to Certican in the SmPC based on an imbalance in their frequency relative to active, non-everolimus CsA-based controls, as seen in the initial phase 3 studies and the frequencies quoted are the absolute frequencies for the combination of everolimus and CsA.

Safety issues previously subject to close monitoring, now the subject of routine pharmacovigilance without change

ADRs included in initial SmPC

The following disorders, included as ADRs in the initial SmPC and subject to cumulative reviews in successive PSURs after approval, have since reverted to routine pharmacovigilance without change to their initial characterization in the SmPC: *acute tubular necrosis* (uncommon ADR), *biliary disorders/hepatotoxicity disorders* (uncommon ADR), *lymphocele* (common ADR), *malignancies* (warning), *myotoxicity* (myalgia is uncommon ADR), *thromboembolic events* (venous thromboembolism common ADR), *thrombotic thrombocytopenic purpura* (common ADR).

ADRs not included in SmPC

The following disorders have been the subject of cumulative reviews in past PSURs and have reverted to routine pharmacovigilance without their inclusion into the SmPC: *bronchial/vascular dehiscence*, *hemorrhagic events*, *toxicoderma*, *urinary leak*, *right heart failure*, *pulmonary hypertension*, *cardiac failure*, *pancytopenia*.

ADRs added to SmPC since the Initial Approval in Mexico in 2003

The following disorders related to use in kidney transplant were not included in the initial SmPC but have been added subsequently as a result of later experience:

Angioneurotic edema was the subject of an assessment in November 2005 after receipt of literature reports of tongue swelling in Certican²⁴-treated patients with subsequent inclusion of the disorder in the Certican SmPC as a common disorder reported predominantly in patients receiving concomitant therapy with ACE inhibitors. A cumulative search until the period of PSUR 6 identified 25 reports (described as angioedema or as edema/swelling evoking the diagnosis) in the Novartis safety database. In all but three cases patients were receiving concomitant therapy with an ACE inhibitor or angiotensin receptor blocker. When outcome was documented, complete recovery was apparent in all cases after treatment (steroids, antihistamines and, in one case, tracheostomy). Negative rechallenge was reported in two patients with reintroduction of everolimus following withdrawal of the ACE inhibitor. The experience

²⁴ Certican is the applicant's trade name for everolimus in the countries in which the drug is approved.

during the review period being compatible with the description of this adverse reaction in the SmPC, it was concluded that the disorder should be subject to routine pharmacovigilance procedures.

Pancreatitis was reviewed in PSURs 1-2. The topic was re-assessed during the period of PSUR 6. It was noted that although the incidence in the initial phase 3, double-blind clinical trials had not been more elevated than that in the control groups (azathioprine, mycophenolate mofetil) pancreatitis was included as drug-related disorder in the labels of both these drugs. With one case rechallenge positive among those documented, the disorder was included into the Certican SmPC (common disorder, frequency just above 1%).

Safety issues currently subject to close monitoring

Interstitial lung disease (ILD)

Included as an uncommon adverse drug reaction (ADR) in the first SmPC, ILD has been continuously monitored since PSUR 1.

In May-2007, the topic was the subject of a cumulative review (PSUR 6 - Appendix 4) which resulted in modification of the SmPC with further description of the disorder including the existence of fatal cases, the insertion of a warning into the SmPC and the identification also of *pulmonary alveolar proteinosis* as a distinct but rare ADR.

Among transplant recipients, the frequency of ILD appears to be 3 times more frequent in heart transplant patients than in renal transplant patients (1.6% v. 0.5% in clinical trial patients, PSUR 7). Until 31-Mar-2009, there had been 11 reports of ILD with fatal outcome. In only 1 case (spontaneous report in a heart transplant recipient) did this occur in a patient with no evidence of confounding lung disorders. Otherwise, in almost all cases, outcome has been favorable after discontinuation of everolimus with or without steroids.

Rhabdomyolysis/creatinine kinase increase

The accumulated data on reports of rhabdomyolysis and elevated CPK does not suggest Certican to be a causal agent. Rather, the limited number of cases observed appear to be essentially an extension of the known effect of statins prescribed to oppose the lipid-raising effects of everolimus and calcineurin inhibitors including cyclosporine. A small number of cases accompany infectious episodes. Warnings are carried already on the labels of statins, cyclosporine, everolimus and strong 3A4 inhibitors such as itraconazole which can interact with those statins which are 3A4 substrates.

Safety issues identified as requiring review and possible inclusion in the SmPC but pending completion of Study A2309

Stomatitis

There have been numerous reports of stomatitis in everolimus patients in both transplant and oncology indications. A dose-relationship was established for everolimus as regards the incidence and severity of stomatitis in studies in cancer patients (which employ everolimus as monotherapy with significantly higher exposures than in transplant patients). It remains to be assessed whether this disorder is related to everolimus therapy when administered at the lower exposures employed post-transplantation.

Polyomavirus infections

With recent requests from health authorities to include information on the risk of polyomavirus infections in transplant recipients receiving immunosuppressant drugs, the Novartis safety database was searched for evidence of polyomavirus infections in everolimus treated patients. BK virus (BKV) had been reported only in clinical trial patients, almost exclusively in renal transplant recipients, with a crude overall reporting frequency of 0.29%. The reporting of proven BKV-associated nephropathy (BKVAN) in renal transplant recipients is 0.14%. No reports of progressive multifocal leukoencephalopathy (PML) were found.

9 Appendices

9.1 Literature Review/References

Relevant references are given in the text as footnotes.

9.2 Labeling Recommendations

Below are portions of the revised package insert which was attached to the CR letter. The Medication Guide as part of REMS

8 Page(s) of Draft Labeling has been withheld in full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	Zortress (EVEROLIMUS) TABLETS

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/s/

HUSEYIN E VELIDEDEOGLU
04/20/2010
ZORTRESS CLINICAL REVIEW

JOETTE M MEYER
04/20/2010

Reviewer is recommending non-approval. See CDTL and Clinical Team Leader Review.

**DIVISION OF SPECIAL PATHOGEN AND TRANSPLANT PRODUCTS
MEDICAL OFFICER REVIEW**

Date: April 15, 2010
To: NDA 21-560
From: Marc W. Cavallé-Coll, M.D., Ph.D.
Lead Medical Officer, DSPT
Subject: Pediatric Research Equity Act Waiver Request

General Information:

Application: NDA 21-560
Applicant: Novartis Pharmaceutical Corporation
Drug Product: Zortress® (everolimus) tablet
Indication: Prophylaxis of organ rejection in patients at low to moderate immunologic risk receiving a renal transplant.
Materials Reviewed: Pediatric Research Equity Act Waiver Request - Pediatric Investigation Plan – NDA 21-560/SN 0034 (November 10, 2009)

Introduction:

Novartis Pharmaceuticals Corporation is seeking the approval of Zortress® (everolimus) tablet for the indication of prophylaxis of organ rejection in patients at low to moderate immunologic risk receiving a renal transplant. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. This review will briefly summarize the issues and basis for granting a waiver for the requirement of pediatric studies in patients from birth to 16 years of age.

Background:

A Pediatric Written Request (PWR), which has now expired, was issued on April 25, 2000 for Certican® (everolimus) Tablets, now known as Zortress®, to obtain needed pediatric information on the active moiety, everolimus (RAD001), in pediatric transplant patients for the prophylaxis of acute rejection in allogeneic kidney and liver transplantation. (b) (4)



(b) (4)



(b) (4)



(b) (4)



Anticipated use in pediatric patients

¹ <http://optn.transplant.hrsa.gov>

Everolimus is a member of a new class of immunosuppressants called the mTOR² inhibitors, which includes sirolimus, marketed in the U.S. under the trade name Rapamune®³ for the prevention of rejection in kidney transplantation. Although when the Written Request was issued in 2000 it was felt that everolimus would provide a potential health benefit to the pediatric population, since that time, other therapies have eclipsed mTOR inhibitors as the standard of care. Regimens that may have been in favor five or ten years ago are currently less frequently used, and new regimens that were still infrequently used five or ten years ago have become increasingly favored. These trends and the clinical experience with them must be taken into consideration as one thinks about pediatric use of everolimus, another mTOR inhibitor, in kidney transplantation. In particular, Rapamune® (sirolimus), an mTOR inhibitor, does not currently have substantial use in adult or pediatric renal transplant recipients in the U.S. Rapamune® was originally approved for use in renal transplant recipients on September 15, 1999, and approved for use in pediatric renal transplant recipients 13 years and older on March 11, 2005. As of 2006, the use of Rapamune® for maintenance immunosuppression between hospital discharge and one year following transplantation in kidney recipients of all ages was only about 14% and declining from a peak of 21.5% in 2001⁴. Thus, it is not anticipated that everolimus would be used in a substantial number of pediatric patients age 2 to 16 years.

Potential therapeutic benefit in pediatric patients

Everolimus is not expected to represent a meaningful therapeutic benefit over existing therapies, for pediatric renal transplant recipients aged 2 to 16 years. Numerous toxicities are associated with available immunosuppressive products used to prevent or treat rejection in kidney transplantation. It is acknowledged that such toxicities represent the inevitable price of achieving adequate protection against graft rejection; however, there is no credible evidence to support that everolimus may have a safety benefit over existing immunosuppressive therapies, including sirolimus, another mTOR inhibitor to which it is closely related in structure and function. In particular, mTOR inhibitors, such as sirolimus or everolimus, possess anti-proliferative, anti-hemangiogenesis, and anti-lymphangiogenesis properties, which may account for the increased risk of lymphocele and other wound healing complications, associated with the use of this class of drugs in solid organ transplantation. In addition, the use of mTOR inhibitors appears to be associated with an increased rate of hyperlipidemia, a contributor to risk of cardiovascular complications.

Evolving understanding of the functional consequences of mTOR inhibition

As new roles of mTOR and the signaling pathways it is involved in are explored, the understanding of the functional consequences of mTOR inhibition is constantly evolving. Such new information may need to be integrated in any future assessment of the use of mTOR inhibitors for immunosuppression in children. The mTOR protein complex

² mTOR stands for the mammalian target of rapamycin.

³ See NDAs 21-083 and 21-110.

⁴ OPTN/SRTR 2008 Annual Report: http://optn.transplant.hrsa.gov/ar2008/data_tables.htm

functions as an integration center for various intracellular signaling pathways involving cell cycle progression, proliferation, and angiogenesis^{5,6}. Since 2003, more information has come to light on the antiproliferative effect of mTOR inhibitors and related effects on hemangiogenesis, lymphangiogenesis and bone growth that have potential implications in growing children. In addition, new roles of mTOR that raise questions about other potential effects of mTOR inhibitors continue to be discovered. For example, recent findings on the role of mTOR in the immune system indicate that sirolimus, in contrast to its immunosuppressive properties in helper T cells, has the potential to foster inflammation via activating innate immune cells⁷.

Pediatric Research Committee review and recommendations

The proposed waiver for the requirement of pediatric studies for Zortress® (everolimus) was reviewed by the Pediatric Research Committee's PREA Subcommittee on January 27, 2010.

(b) (4)

After discussion of the issues, the Pediatric Research Committee recommended that the Division grant a full waiver for this product from 0-16 years because product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups.

Conclusion and recommendations:

A waiver for the requirement of pediatric studies in patients from birth to 16 years of age should be granted, and the following wording should be used to communicate this to the Applicant in the regulatory correspondence:

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

⁵ Gibbons JJ, Abraham RT, Yu K. Mammalian target of rapamycin: discovery of rapamycin reveals a signaling pathway important for normal and cancer cell growth. *Semin Oncol*. 2009 Dec;36 Suppl 3:S3-S17.

⁶ Foster KG, Fingar DC. mTOR: Conducting the cellular signaling symphony. *J Biol Chem*. 2010 Mar 15. [Epub ahead of print]

⁷ Säemann MD, Haidinger H, Hecking M, Hörl WH, Weichhart T. The Multifunctional Role of mTOR in Innate Immunity: Implications for Transplant Immunity. *Am J of Transplantation*, Volume 9 Issue 12 (December 2009), pp 2655-2661

We are waiving the pediatric study requirement for patients from birth to 16 years of age because the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric patients in this group.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	GI-1	NOVARTIS PHARMACEUTICA LS CORP	Zortress (EVEROLIMUS) TABLETS

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/s/

MARC W CAVAILLE COLL
04/15/2010

Cross-Discipline Team Leader Review

Date	December 23, 2009
-From	Ozlem Belen, MD, MPH Deputy Director for Safety Joette Meyer, Pharm.D. Clinical Team Leader
Subject	Cross-Discipline Team Leader Review
Division	Division of Special Pathogen and Transplant Products
NDA/BLA # Supplement#	NDA 22-268
Applicant	Novartis Pharmaceuticals Corporation
Date of Submission	June 30, 2009
PDUFA Goal Date	December 30, 2009
Date Review Completed	December 23, 2009
Proprietary Name / Established (USAN) names	Zortress (everolimus) Tablets
Dosage forms / Strength	0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg
Proposed Indication(s)	Everolimus is indicated for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant. Everolimus is to be administered concurrently with reduced doses of Neoral (cyclosporine) and corticosteroids. Everolimus has been administered in combination with basiliximab in kidney transplantation.
Proposed Dosing Regimen	An initial everolimus dose of 0.75 mg b.i.d. is recommended for the general kidney transplant population, administered as soon as possible after transplantation. The daily dose of everolimus should be given orally in two divided doses (b.i.d.), consistently either with or without food and at the same time as Neoral (cyclosporine). The dose of Neoral (cyclosporine) should be reduced to optimize renal function.
Recommended:	Complete Response based on REMS and Labeling

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1 Introduction

Everolimus (40-O-(2-hydroxyethyl)-rapamycin) is a macrolide immunosuppressant and has a stable 2-hydroxyethyl chain substitution at position 40 on the sirolimus (rapamycin) as apparent from the chemical formula.

The mechanism of action of everolimus is similar to sirolimus. Everolimus, like sirolimus, binds to FKBP12 (FK506-binding protein), forming a complex that binds to mammalian target of rapamycin (mTOR), a key regulatory kinase. The mTOR protein is a serine-threonine kinase that is pivotal for a number of important processes such as cell growth and proliferation, cellular metabolism, autophagy, and angiogenesis. The FKBP12-everolimus-mTOR complex dephosphorylates and inhibits p70S6 kinase which, when activated, stimulates the ribosomes for protein synthesis and cell-cycle progression. This blockade by everolimus inhibits:

- T cell activation and proliferation that occurs in response to antigenic and cytokine (IL-2 and IL-15) stimulation;
- IL-6 stimulated B cell activation, proliferation, and antibody production;
- Proliferation of non-immune cells like smooth muscle cells.

Everolimus is being developed for the prophylaxis of acute rejection in adult patients receiving a *de novo* renal transplant, in combination with basiliximab, reduced dose cyclosporine (Neoral®) and corticosteroids.

The proposed regimen is an initial dose of everolimus 0.75 mg orally twice daily (i.e., 1.5 mg/day) starting within 24 hours of transplantation. The dose should be adjusted to achieve a target trough concentration of 3 to 8 ng/mL. Cyclosporine (CsA) should be initiated at the same time and the dose should be adjusted over time to maintain trough concentrations (ng/mL) of: 100 to 200 (until Month 2), 75 to 150 (Months 2-4), 50 to 100 (Months 4-6) and 25 to 50 (after Month 6).

2 Background

An initial New Drug Application (NDA 21-560) supporting the use of fixed-dose everolimus with standard dose CsA compared to mycophenolate mofetil (MMF; CellCept®) with standard dose CsA for the prophylaxis of organ rejection in allogeneic kidney and heart transplant patients was submitted to the FDA on December 19, 2002 by the applicant, Novartis. The submission contained the results from two Phase 3 trials (Studies B201 and B251) in *de novo* renal transplant recipients and one study in *de novo* heart transplant recipients (Study B253).

Both studies compared two fixed-dose regimens of everolimus, 1.5 mg per day and 3 mg per day given in two divided doses twice daily, to the approved dose of MMF 1g twice daily and standard CsA plus corticosteroid regimens. Induction therapy was not given in these trials. A total of 193 and 194 subjects were randomly assigned to the 1.5 mg total dose of everolimus, while an additional 194 and 198 subjects were assigned to the 3.0 mg total dose of everolimus, in studies B201 and B251, respectively.

Both studies were double-blind for the first 12 months following transplantation and were extended as open-label studies for an additional two years. The 12 month analysis of GFR showed increased rate of renal impairment in the everolimus groups compared to the MMF control group in both studies.

Efficacy of everolimus was demonstrated in Studies B201 and B251; however, interpretation of the results was complicated by the premature treatment discontinuations due to reduced graft function and higher serum creatinine concentrations seen in the everolimus groups compared to the MMF control groups.

Due to these observed renal toxicities, the NDA was not approved and the applicant was asked to establish a safe and effective dosing regimen for everolimus and CsA that minimizes renal function impairment while maintaining efficacy, such as concentration-controlled regimens of everolimus and cyclosporine using therapeutic dose monitoring (TDM).

Data from two additional open-label, non-comparative kidney transplant trials (A2306 and A2307), along with some exposure-response analyses, were submitted to the NDA as a Complete Response by the applicant on February 27, 2004. Studies A2306 (without basiliximab) and A2307 (with basiliximab) were conducted, using concentration-controlled everolimus dosing (initial doses of 1.5 mg and 3.0 mg per day adjusted to trough concentrations above 3 ng/mL) and reduced-dose CsA. As these studies were designed to compare the 1.5 mg and 3.0 mg doses of everolimus and did not include an active control group, the analyses in the submission were based primarily on cross-study comparisons between A2306 and A2307 and studies in the original submission. FDA noted these and other limitations in the studies' design, therefore the applicant was asked to provide additional information to establish a safe and effective dosing regimen for everolimus and CsA.

On November 16, 2005 the Cardiovascular and Renal Drugs Advisory Committee met to discuss the use of everolimus for prophylaxis of rejection in heart transplantation.¹ While the committee agreed that a fixed-dose regimen of everolimus with standard-dose CsA in Study B253 should not be used in heart transplant due to short-term and long-term loss of renal function, they also commented that additional data were needed to characterize the safety and efficacy of everolimus using TDM regimens to maintain everolimus concentrations while rapidly tapering CsA to minimize renal toxicity.

Subsequently Novartis designed a new study of concentration-controlled everolimus with low dose CsA both adjusted using TDM in *de novo* kidney transplant recipients, and the protocol was discussed with FDA. Study A2309 is a 24-month, multicenter, randomized, open-label, three-arm trial that enrolled 833 *de novo* adult renal transplant recipients in Africa, Asia, Australia, Europe, North and South America. Patients were randomized to one of three groups: everolimus starting at either 1.5 or 3.0 mg per day combined with reduced dose CsA, or mycophenolic acid (MPA; Myfortic®) 1.44 gm per day with standard dose CsA. The starting dose of everolimus in this study was the same as used in the initial studies B201 and B251. However, in this study everolimus doses were adjusted to achieve blood trough concentrations

¹ <http://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4183M1.pdf>

of 3 to 8 ng/mL (low dose group, starting at 1.5 mg/day) and 6 to 12 ng/mL (high dose group starting at 3.0 mg/day) combined with reduced exposure to CsA, which was tapered over time. Both drug concentrations were guided by TDM. The upper limit of the CsA target range for everolimus groups at Day 3 was 200 ng/mL compared to 300 ng/mL in the control group. At Month 2, CsA target concentrations were a maximum of 150 ng/mL in the everolimus groups, while in the control group, the target CsA maximum was 250 ng/mL. The target trough concentrations for CsA were lower in the everolimus groups compared to the everolimus groups in studies B201 and B251, while exposure to CsA in the control groups was similar in all 3 studies and higher than in the everolimus groups in this study. The control regimen in studies B201 and B251 was MMF, while in this study it was MPA. The dose of MPA was selected to provide the same molar dose as 1 gm of MMF (720 mg Myfortic is the molar equivalent of 1 gm MMF) and is the approved dose for use in combination with cyclosporine. All patients were given basiliximab as induction therapy and maintained on concomitant corticosteroids, which were dosed based on local practice. The current submission contains data from the first 12-months of the study.

Table 1. Dose and Target Concentrations for Everolimus and CsA across Studies

Study Treatment Group	Drug	Study B201	Study B251	Study A2309
Everolimus 1.5 mg/day group	Everolimus	0.75 mg bid	0.75 mg bid	Target trough 3-8 ng/mL
	CsA	Full Dose: 150 to 400 ng/mL (Weeks 1-4), 100 to 300 ng/mL (Months 2-12), 50 to 75 ng/mL (after Month 12)	Full Dose: 200 to 350 ng/mL (Weeks 1-4), 100 to 300 ng/mL (Months 2-12), 50 to 75 ng/mL (after Month 12)	Reduced Dose:* 100 to 200 ng/mL (until Month 2), 75 to 150 ng/mL (Months 2-4), 50 to 100 ng/mL (Months 4-6) and 25 to 50 ng/mL (after Month 6)
Everolimus 3.0 mg/day group	Everolimus	1.5 mg bid	1.5 mg bid	Target trough 6-12 ng/mL
	CsA	Full Dose – same as above	Full Dose – same as above	Reduced Dose:* same as above
Control group	MMF or MPA	MMF 1gm bid	MMF 1 mg	MPA 720 mg bid per day
	CsA	Full Dose – same as above	Full Dose – same as above	Standard:* 200 to 300 ng/mL (Month 1), 100 to 250 ng/mL (Month 2-12)

* Pages 113 and 5772 of 14,328 from Study Report RAD001A2309, submitted June 30, 2009.

2.1 Study Design and Efficacy Endpoints

Design

Study A2309, “A 24-month, multicenter, randomized, open-label non-inferiority study of efficacy and safety comparing two regimens of concentration-controlled everolimus in two doses (1.5 and 3.0 mg/day starting doses) with reduced Neoral versus 1.44 g Myfortic with standard dose Neoral in *de novo* renal transplant recipients”, was conducted to compare two regimens of concentration-controlled everolimus with reduced dose Neoral (cyclosporine; CsA) versus 1.44 gm Myfortic with standard dose Neoral (CsA) in *de novo* renal transplant recipients.

As shown in the Figure below, Study A2309 was a prospective, 24-month, multicenter, randomized, open-label, non-inferiority study. Across 79 centers located in 16 countries and regions throughout the world, 833 male or female primary renal transplant patients, between the age of 18 and 70, were randomized to study regimens containing a 1.5 mg/day starting dose everolimus (which was then adjusted to reach target blood trough concentrations of 3 to 8 ng/mL), a 3.0 mg/day starting dose of everolimus (adjusted to reach target concentrations of 6 to 12 ng/mL), or a 1.44 gm/day dose of Myfortic. All patients received basiliximab induction, CsA and steroids.

Figure 1: Study Design of A2309

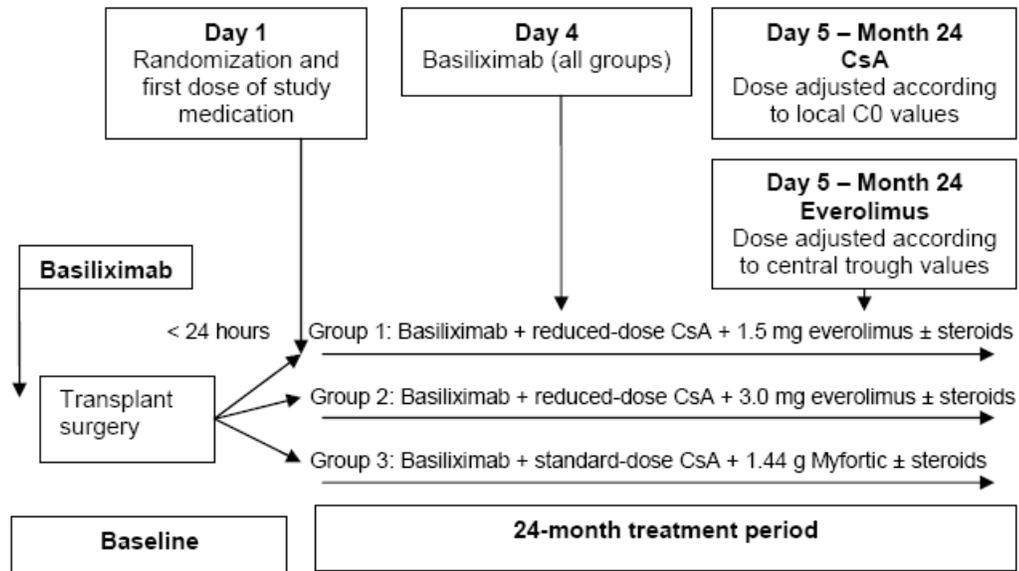


Figure from the Applicant’s Clinical Study Report of Study A2309

The primary efficacy analysis was performed when all randomized patients completed 12 months of the study, and is included in the current submission. A secondary analysis is planned and will be performed when all randomized patients complete the full 24-month of study follow-up. The primary objective was to demonstrate that one or both everolimus groups are non-inferior with respect to the primary efficacy endpoint to Myfortic control, based on a 10% non-inferiority margin. The Hochberg’s procedure was used to maintain the overall type I

error rate at $\alpha = 0.05$ level. The primary efficacy analysis was based on the intent-to-treat (ITT) population, defined as all randomized patients.

Primary Endpoint

The primary efficacy endpoint was efficacy failure at 12 months post transplantation, where efficacy failure was defined as the composite endpoint of treated biopsy-proven acute rejection (BPAR), graft loss, death, or loss to follow-up. Each of these components is further defined below.

Treated Biopsy-Proven Acute Rejection (BPAR)

Biopsies were read by the local pathologist according to the 1997 updated Banff criteria. Determination of the need for treatment was made according to the local pathologist's findings and the overall clinical presentation of rejection. The local pathologist was blinded to patient treatment. A BPAR episode was defined as a biopsy graded IA, IB, IIA, IIB, or III that was treated with anti-rejection therapy.

Death

Death was recorded at either study completion, follow-up, or as the outcome of an adverse event, if it occurred.

Graft loss

Graft loss was defined as any of the following:

- Loss of the graft. The allograft was presumed to be lost on the day the patient started dialysis and was not able to be subsequently removed from dialysis.
- Re-transplant

Loss to Follow-up

A patient who did not experience treated BPAR, graft loss or death and whose last day of contact was prior to study Day 316, which is the protocol defined lower limit of Month 12 visit window, was considered lost to follow-up.

Note: Loss to follow-up in the analysis of death, graft loss and loss to follow-up was defined as any patient who did not experience a graft loss or death and whose last day of contact was prior to Day 316.

Secondary Endpoints

The main secondary endpoint was the incidence rate of the composite endpoint of graft loss, death or loss to follow up at 12 months. Other secondary endpoints included efficacy failure (as defined for the primary endpoint) at 6 months, treated BPAR at 6 and 12 months, graft loss at 6 and 12 months, death at 6 and 12 months, biopsy proven chronic allograft nephropathy (CAN) at 12 months, graft loss or death at 6 and 12 months, graft loss, death or loss to follow up at 6 months, and antibody treated BPAR at 12 months.

2.2 Justification of the Non-Inferiority (NI) Margin

For confirmatory non-inferiority trials, the applicant is required to provide a detailed justification of the proposed NI margin using information from historical trials. For Study

A2309, the applicant submitted a justification for the primary efficacy endpoint (i.e. efficacy failure: a composite of treated BPAR, death, graft loss or loss to follow-up at 12 months), which is acceptable. Additionally, a margin for the endpoint of death, graft loss or loss to follow-up was not able to be justified due to a lack of sufficient information on these endpoints from historical information. It should be noted that while the primary endpoint includes components of death, graft loss, and loss to follow-up; proof of efficacy is mainly driven by the treated BPAR component of the composite endpoint in trials of *de novo* kidney transplantation.

Details of the justification of the 10% non-Inferiority margin for study A2309 can be found in the statistical review for this submission.

2.3 Population Studied

The protocol called for the inclusion of patients with low to moderate immunologic risk into the study. Low to moderate immunologic risk was defined in the study as an ABO blood type compatible first time organ or tissue transplant recipient with anti-HLA Class I PRA < 20% by a complement dependant cytotoxicity-based assay, or < 50% by a flow cytometry or ELISA-based assay, and with a negative T-cell cross match.

Eight hundred and thirty-three (833) patients were randomized after transplantation; 277 randomized to the everolimus 1.5 mg per day group, 279 to the everolimus 3.0 mg per day group and 277 to the Myfortic 1.44 gm per day group. The study was conducted at 79 renal transplant centers across Europe, South Africa, North and South America, and Asia-Pacific. There were no major baseline differences between treatment groups with regard to recipient or donor disease characteristics. The majority of transplant recipients in all groups (67-76%) had three or more HLA mismatches; mean percentage of panel reactive antibodies ranged from 0.9% to 4.3%.

The population was between 18 and 70 years; more than 43% were 50 years of age or older. More than 63% of all recipients were male and more than 64% were Caucasian. Demographic characteristics were comparable between treatment groups. The most frequent diseases leading to transplantation were balanced between groups and included hypertension/nephrosclerosis, glomerulonephritis/glomerular disease and diabetes mellitus.

2.4 Approved mTOR Inhibitors

The first drug to be approved in the mTOR inhibitor class of immunosuppressants for the indication of prevention of rejection in renal transplant patients was sirolimus (Rapamune®, NDA 21-083), oral solution, in September, 1999. Later, a 1 mg tablet (in August 2001) and a 2 mg tablet (August 2002) were approved under NDA 21-110. The information on the adverse reactions associated with the use of sirolimus, the first approved drug in the mTOR class, has been evolving since its approval, based on the data obtained from additional studies in renal, hepatic, lung transplantation and from post-marketing reports.

On March 30, 2009 the applicant received approval for everolimus (marketed as Afinitor®) for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib (Sutent®) or sorafenib (Nexavar®). The approved dose for this indication is 10 mg once daily, which is higher than the proposed starting dose for the renal transplant indication. As summarized in the package insert, management of severe and/or intolerable adverse

reactions may require temporarily dose reduction, to a suggested dose of 5 mg per day, or interruption of therapy.²

3 CMC/Device

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. However, it was noted by the CMC reviewer Mark R. Seggel of ONDQA that labeling issues, including package insert, blister/carton labels, and REMS were still pending as of the date of this review dated December 22, 2009. Therefore, from the CMC perspective, this NDA is not recommended for approval until the labeling issues are resolved.

3.1 General Product Quality Considerations

Everolimus is a semisynthetic macrolide immunosuppressant derived from sirolimus. Sirolimus, also known as rapamycin, is the active ingredient in Wyeth's approved Rapamune drug products, and is obtained by fermentation with a strain of *Streptomyces hygroscopicus*. The manufacture of sirolimus by Novartis subsidiary Biochemie G.m.b.H. (now Sandoz) is described in Drug Master File 15720. Everolimus is obtained through a short synthetic sequence in which a hydroxyethyl group is coupled to the hydroxyl group of the cyclohexyl side chain of sirolimus. Everolimus is poorly water-soluble. Like sirolimus, everolimus is susceptible to oxidation. (b) (4) butylated hydroxytoluene (BHT), a commonly used antioxidant. The material (sometimes referred to as RAD n BHT) is isolated as an amorphous powder. The drug product is an immediate-release compressed tablet containing everolimus in four strengths, 0.25-, 0.50, 0.75-, and 1.0-mg. The stability of the drug product in blister packaging has been evaluated through 60 months at 25°C/60% relative humidity (RH). The product exhibits good stability under these conditions. Adequate stability was also observed at 40°C/75% RH. The proposed expiration dating period of 36 months for product stored in the proposed blister at 25°C/60% RH (excursions to 15°C and 30°C) is acceptable.

Drug substance and drug product CMC has been previously reviewed (see NDA 21-560 Chemistry Reviews #1, #2, #3 and #4; also see NDA 22-334 for information regarding Afinitor (everolimus) Tablets, 5 mg and 10 mg). On the basis of Reviews #1 and #2, a recommendation for approval of NDA 21-560 from the CMC perspective was made. However, the application was not approved because of clinical deficiencies. Review #3 covered drug substance CMC in support of NDA 21-560 and NDA 22-334. Review #4 covered drug product CMC.

The sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability

² http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022334lbl.pdf

information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

3.2 Facilities Review/Inspection

All drug substance and drug product facilities have been found acceptable. An overall site recommendation of “Acceptable” was issued by the Office of Compliance (07-DEC-2009). Reference is made to CMC review by Mark R. Seggel of ONDQA, Division of Pre-Marketing Assessment II, dated December 03, 2009.

4 Nonclinical Pharmacology/Toxicology

The original Pharmacology/Toxicology reviewer for this application, Dr. Steven Kunder, indicated approval for this application in his 2003 review:

The New Drug Application 21-560 for Certican is approvable based on the preclinical pharmacology and toxicology submission. Toxicities demonstrated in preclinical studies may be monitored or be superseded by the benefit/risk ratio determined by the clinical studies supporting kidney and heart transplant indications.

The clinical pharmacology team leader Dr. William Taylor agrees with Dr. Kunder’s assessment and conclusions in his review dated December 22, 2009.

4.1 General Nonclinical Pharmacology/Toxicology Considerations

Everolimus was studied in mice, rats, minipigs and cynomolgus monkeys to evaluate its toxicities and in rats and rabbits to determine its reproductive toxicity potential. Everolimus causes toxicities in animal studies both by its pharmacologic mechanism of action, immunosuppression, as well as by direct toxicity. Immunosuppression by everolimus resulted in atrophy of the lymphoid organs (thymus, spleen, lymph nodes) as well decreased circulating lymphocytes and total leukocytes.

Toxicities affected by immunosuppression included myocardial degeneration/myocarditis in monkeys and rats at 1.5 mg/kg (1.7-4.5x human exposure); this is likely related to viral infection emerging under immunosuppression. Other toxicities included reproductive organ toxicity in all species tested including testicular atrophy in monkeys at 0.3 mg/kg (0.9x human exposure) and uterine atrophy and reduced follicular development in mice and monkeys at doses of 1.5 mg/kg (4.5-18x human exposure); renal toxicity in rats with tubular degeneration at doses of 5.0 mg/kg (55x human exposure); pancreatic toxicity was seen in monkeys with islet cell degeneration at 5.0 mg/kg (4.5x human exposure) and vacuolation of the exocrine pancreas in minipigs at 5.0 mg/kg (23x human exposure); lung toxicity in mice at 1.5 mg/kg (15x human exposure) and rats at 0.5 mg/kg (0.1x human exposure); and toxicity to the eye as swelling and disruption of cortical fibers of the lens at a dose of 0.9 mg/kg in rats (0.4 x human exposure).

CDTL Comment: Foreign post-marketing experience of pancreatitis was recently re-assessed. This evaluation led to inclusion of information regarding pancreatitis in the post-marketing section of the proposed labeling (see Section 8.8).

Toxicities affecting the male fertility in rats, similar to described above is in Section 13.1 "Carcinogenesis, Mutagenesis, Impairment of Fertility" of the proposed PI. Effects of everolimus on male fertility in humans were added in Section 5.15 "Warnings and Precautions".

4.2 Reproductive Toxicology

4.2.1 Impairment of Fertility

Animal reproductive toxicology studies showed effects in rats and rabbits. In a 13-week fertility study in male rats, testicular morphology was altered at a dose of 0.5 mg/kg/day (providing a systemic exposure approximately 0.2x that of the maximum clinical dose). Marked effects on male fertility occurred at 5.0 mg/kg (providing a systemic exposure approximately 1.0x that of maximum clinical dose) including inability to impregnate females as well as testicular atrophy, oligospermia, aspermia and vacuolation of duct epithelium of the epididymides. Sperm motility, testicular sperm head count and plasma testosterone levels were reduced. In the reproductive toxicity studies in female rats, everolimus did not affect fertility at doses up to 0.9 mg/kg (providing approximately 0.2 x the systemic exposure of the maximum clinical dose).

4.2.2 Reproductive Toxicity

In the reproductive toxicity studies in female rats, everolimus crossed the placenta. At all doses, toxicity to fetus was observed. Increased pre- and postimplantation losses and an increased incidence in skeletal retardations occurred at all doses. An increase in the incidence of spontaneously occurring malformations was seen at doses of 0.3 and 0.9 mg/kg (providing an exposure approximately 0.9 x that of the maximum clinical dose based exposure comparisons). In rabbits no effects on the embryo-fetal development were observed other than those attributable to maternal toxicity up to the highest dose tested, 0.8 mg/kg (yielding a systemic exposure approximately 5.0x that of the maximum clinical dose based on body surface area comparisons). In a pre- and postnatal developmental study in rats, effects of everolimus included slightly reduced body weight and survival of the F1 generation at doses 0.1 mg/kg. No effects were observed on morphological development, motor activity, learning ability or fertility assessment of the F1 generation at doses up to 0.3 mg/kg.

There are no data on the use of everolimus in pregnant women. The potential risk for humans is unknown. Therefore, Dr. Steven Kunder concluded in his review that everolimus should only be given to pregnant women if the potential benefit outweighs potential risk for the fetus. Women of childbearing potential should be advised to use effective contraception methods while they are receiving Certican and up to 8 weeks after treatment has been stopped.

4.3 Carcinogenicity and Mutagenesis

Everolimus was not carcinogenic in mice or rats when administered daily by oral gavage for 2 years at doses of 0.9 mg/kg. In these studies, AUCs in mice were much higher (at least 20

times) than those in humans receiving 0.75 mg b.i.d., and AUCs in rats were in the same range as those in humans receiving 0.75 mg b.i.d.

Everolimus was not mutagenic in the bacterial reverse mutation assay, the mouse lymphoma thymidine kinase assay, or the chromosome aberration assay using V79 Chinese hamster cells, or in vivo following two daily doses of 500 mg/kg in the mouse micronucleus assay.

4.4 Other Notable Pharmacology/Toxicology Issues

4.4.1 Labeling

There are two principal differences between the Pharm/Tox portions of the label for Zortress, and the Pharm/Tox portions of the approved label for Afinitor[®]. The first difference is that the comparison of animal exposures to human exposures (for the transplant indication) is based on human AUC data from kidney transplant trials. The doses (and clinical exposures) for the oncology indication are considerably higher than those for the prophylaxis of kidney rejection. The consequence is that some animal toxicity seen only at higher doses in animals may be appropriate for inclusion in the oncology label, but not in the label for the transplant indication. Additionally, in the oncology Division, human doses are generally expressed in units of mg/m², which are not appropriate, in this case, for this transplant indication.

Secondly, the Afinitor label Pregnancy Category (Section 8.1) is a “D”, whereas the Zortress Pregnancy Category is a “C”. John K. Leighton, Ph.D., DABT, Associate Director for Oncology Pharmacology/Toxicology responded to an email request to clarify why the Afinitor label has a “D” Pregnancy Category. Dr. Leighton provided the following explanation to Dr. Taylor in an email on November 17, 2009:

Because when ODAC [Oncology Drug Advisory Committee] reviewed this topic (pregnancy categories) they determined that the mechanism of action (investigational data) was likely relevant to humans, and thus merited D. We have discussed this numerous times with maternal health, and the clinicians in DDOP wanted to stick with what works (the D).

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Specifically, there are no human data to support the “D” label. After discussing this issue with Abby Jacobs, Ph.D., Associate Director for Pharmacology/ Toxicology, Office of New Drugs, Dr. Taylor selected the “C” Pregnancy Category for Zortress based on (1) the data from animal studies, (2) the lack of human pregnancy data supporting a “D” category, and (3) the “C” Pregnancy Category for the same-class drug, Rapamune[®] (sirolimus/rapamycin).

<p><i>CDTL and Clinical Team Leader Comment: There is agreement with the conclusions made by Dr. Taylor regarding the pregnancy category “C” for Zortress.</i></p>
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5 Clinical Pharmacology/Biopharmaceutics

Reference is made to the review by pharmacometrics reviewer, Kevin Krudys, Ph.D., dated December 18, 2009. Dr. Krudys concluded that the data from Study A2309 support a 3 to 8 ng/mL target range for everolimus trough concentrations for prophylaxis of organ rejection in adult patients at low to moderate immunologic risk receiving a kidney transplant and labeling should clearly reflect the everolimus and cyclosporine trough concentrations observed in Study A2309.

5.1 General Clinical /Pharmacology/Biopharmaceutics Considerations

Steady-state is reached by day 4 with an accumulation in blood concentrations of 2- to 3-fold compared with the exposure after the first dose. The half-life estimates from 12 maintenance renal transplant patients in study W101 who received single doses of everolimus capsules at 0.75 mg or 2.5 mg with their maintenance cyclosporine regimen indicate that the pharmacokinetics of everolimus are linear over the clinically-relevant dose range. Results indicate the half-life of everolimus in maintenance renal transplant patients receiving single doses of 0.75 mg or 2.5 mg everolimus during steady-state cyclosporine treatment was 30 ± 11 hours (range 19-53 hours).

5.1.1 Exposure-Response for Efficacy

The exposure-response relationship for efficacy derived from Study A2309 supports a minimum everolimus trough concentration of 3 ng/mL to achieve adequate efficacy. The risk of treated biopsy-proven acute rejection (BPAR) was higher at everolimus trough concentrations less than 3 ng/mL (18.2%) than within 3 and 8 ng/mL (15.4%).

The difference in event rate was more pronounced for graft loss, where the proportion of patients in Study A2309 with graft loss was substantially higher at everolimus trough concentrations less than 3 ng/mL (11.4%) than within 3 and 8 ng/mL (3.7%). Further support of the 3 to 8 ng/mL target range is provided by the observation that the incidence of treated BPAR, graft loss and death in patients in Study A2309 with everolimus trough concentrations within the proposed target range were numerically similar to incidences in the Myfortic treatment group as seen in the table below.

Table 2. Efficacy Events by Time Averaged Everolimus Trough Concentrations through Day 195 Post-Transplant (Approximately Month 6)

Everolimus trough levels	Treated BPAR	Graft Loss	Death
< 3 ng/mL	6/33 (18.2%)	4/35 (11.4%)	1/37 (2.7%)
3 – 8 ng/mL	64/415 (15.4%)	15/410 (3.7%)	9/411 (2.2%)
> 8 ng/mL	9/99 (9.1%)	3/101 (3.0%)	5/101 (5.0%)
Myfortic	47/277 (17%)	9/277 (3.2%)	6/277 (2.2%)

*Table 1 from Dr. Krudys pharmacometrics review.

During the course of the review it was noted that among female patients, higher incidence of efficacy failure was observed compared to the Myfortic group. Everolimus trough concentrations over time were plotted separately for female and male (see Figures below) patients by the pharmacometrics reviewer as seen below. Although men had lower everolimus trough concentrations on Day 3 on average, the differences between female and male patients were minor over the 12 months of Study A2309 (reference is made to Dr. Krudys pharmacometrics review for further details). These minor differences in concentrations did not explain the differences in efficacy outcomes noted above. This difference in efficacy failure between the genders will be further discussed in this review below in Section 7.2.3.

5.1.2 Exposure-Response for Safety

In Studies B201 and B251, the 12 month analysis of GFR showed an increased rate of renal impairment in the everolimus groups compared to the MMF control group. Therefore, Study A2309 with therapeutic drug monitoring of everolimus and reduced dose cyclosporine was conducted. Although 12 month GFR in Study A2309 in the 1.5 mg/day group was now similar to the Myfortic group, the relationship between everolimus and cyclosporine and GFR was still evaluated in the context of the 3 to 8 ng/mL target.

For the purpose of exposure-response analysis, a GFR value less than 30 mL/min/1.73m² after Month 1 was categorized as a safety event. The relationship between everolimus and cyclosporine trough concentrations and GFR < 30 mL/min/1.73m² in Study A2309 is presented in Table below. For each level of cyclosporine concentrations (0-100 ng/mL, 100-200 ng/mL and >200 ng/mL), an increase in everolimus trough concentration > 8 ng/mL does not result in an increased incidence of GFR < 30 mL/min/1.73m² compared to the proposed target range (3 to 8 ng/mL). Within the target everolimus trough range, however, higher cyclosporine concentrations correspond to higher incidences of GFR < 30 mL/min/1.73m². These data suggest that the occurrence of renal dysfunction manifested as a decrease in GFR is driven primarily by cyclosporine exposure, not everolimus exposure.

Table 3: Relationship between Everolimus and Cyclosporine Trough Concentrations and GFR < 30 mL/min/1.73m²

Everolimus trough levels	Cyclosporine trough 0-100 ng/mL	Cyclosporine trough 100-200 ng/mL	Cyclosporine trough >200 ng/mL
3 – 8 ng/mL	10/171 (5.8%)	35/183 (19.0%)	10/19 (52.6%)
> 8 ng/mL	1/34 (2.9%)	6/43 (14%)	7/15 (48.7%)

*Table 4 from Dr. Krudys pharmacometrics review.

CDTL and Clinical Team Leader Comments: Interpretation of the results from Studies B201 and B251 were complicated by the premature treatment discontinuations due to reduced graft function and higher serum creatinine concentrations seen in the everolimus groups compared to the MMF control groups. The applicant was asked to establish a safe and effective dosing regimen for everolimus and CsA that minimizes renal function impairment while maintaining efficacy, such as concentration-controlled regimens of everolimus and cyclosporine using therapeutic dose monitoring (TDM). Therefore, it is important to assess how the nephrotoxicity in the previous studies was overcome through CsA reduction.

5.1.3 Drug-Drug Interactions

Everolimus is known to be a substrate for both cytochrome CYP3A4 and P-gp. Cyclosporine (CYP3A4/P-gp inhibitor and CYP3A4 substrate): Everolimus should be taken concomitantly with cyclosporine. Everolimus concentrations may decrease when doses of cyclosporine are reduced, unless the everolimus dose is increased.

In a single-dose study in 12 healthy subjects, Neoral administered at a dose of 175 mg increased everolimus AUC by 168% (range, 46% to 365%) and Cmax by 82% (range, 25% to 158%) when administered with 2 mg everolimus compared with administration of everolimus alone.

The following excerpt is from the proposed PI to the applicant at the time of CR action. Reference is made to clinical pharmacology reviews by Jang-Ik Lee, Pharm.D., Ph.D. dated October 17, 2003 and August 17, 2004 with concurrence from Dr. Phil Colangelo.

(b) (4)



(b) (4)



(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

5.2 Whole Blood Trough Concentrations Observed in Kidney Transplant Patients

5.2.1 Everolimus Whole Blood Trough Concentrations Observed in A2309

In the Study A2309, everolimus whole blood trough concentrations were measured at Days 3, 7 and 14 and Months 1, 2, 3, 4, 6, 7, 9 and 12.

The proportion of patients receiving the 0.75 mg twice daily everolimus treatment regimen who had everolimus whole blood trough concentrations within the protocol specified target range of 3 to 8 ng/mL at Days 3, 7 and 14 were 55%, 71% and 69%, respectively.

Approximately 80% of patients had everolimus whole blood trough concentrations within the 3 to 8 ng/mL target range by Month 1 and remained stable within range through Month 2. The median everolimus trough concentration for the 0.75 mg twice daily treatment group was between 3 and 8 ng/mL throughout the study duration (see Figure below).

Figure 2. Everolimus trough concentrations over time for everolimus 1.5 mg group in Study A2309.

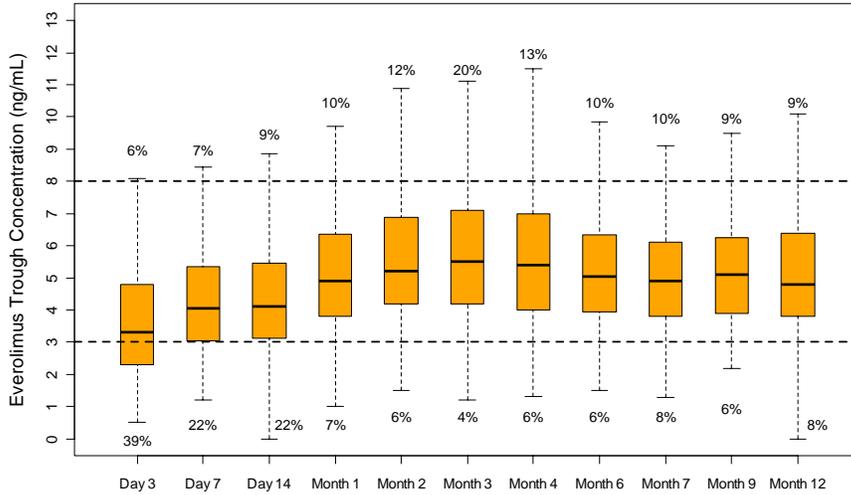


Figure 1 from Dr. Krudys review.

The dashed lines indicate the target range.

The percentages above and below the boxes represent the percentage of subjects whose everolimus trough concentration fell above and below the target range, respectively.

5.2.2 Cyclosporine Whole Blood Trough Concentrations Observed in A2309

In the clinical trial, the target cyclosporine whole blood trough concentrations for the everolimus treatment arm of 0.75 mg twice daily were 100 to 200 ng/mL through Month 1 post-transplant, 75 to 150 ng/mL at Months 2 and 3 posttransplant, 50 to 100 ng/mL at Month 4 post-transplant, and 25 to 50 ng/mL from Month 6 through Month 12 post-transplant. Cyclosporine whole blood trough concentrations tended to exceed the protocol-specified targets throughout the 12 months of Study A2309. Cyclosporine trough concentrations in Study A2309 from Month 4 to Month 12 were more likely to exceed the protocol-specified target range, where 41% to 82% of trough concentrations observed at these time intervals exceeded the upper limit of the target range (see Figure below).

Figure 3. Cyclosporine trough concentrations over time for everolimus 1.5 mg group in Study A2309.

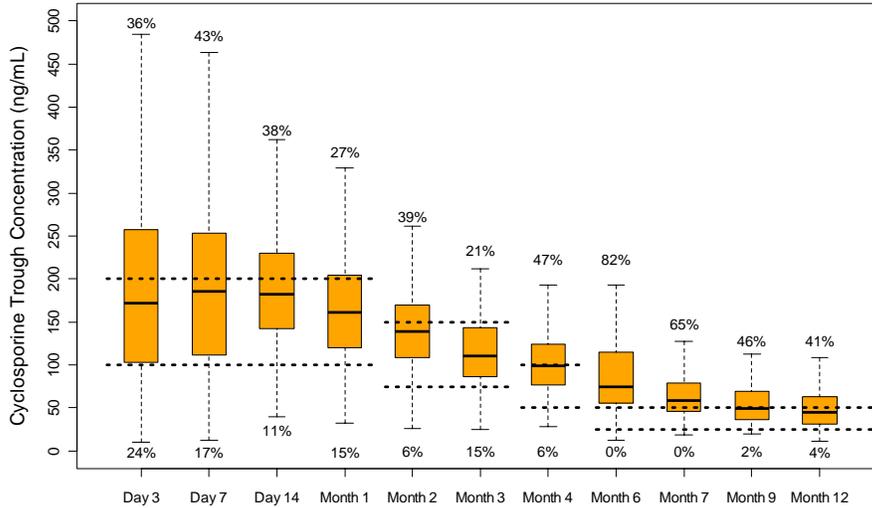


Figure 2 from Dr. Krudys review.

The dashed lines indicate the target range. The percentages above and below the boxes represent the percentage of subjects whose everolimus trough concentration fell above and below the target range, respectively.

5.3 Therapeutic Drug Monitoring

The following sections are in line with the proposed labeling.

5.3.1 Therapeutic Drug Monitoring – Everolimus

Routine everolimus whole blood therapeutic drug concentration monitoring is recommended for all patients using (b) (4) assay methodology. The recommended everolimus therapeutic range is 3-8 ng/mL.

It is important to monitor everolimus whole blood trough concentrations in patients with hepatic impairment, during concomitant administration of CYP3A4 inducers or inhibitors, when switching formulations and/or when cyclosporine dosing is reduced according to recommended target concentrations.

Optimally, dose adjustments of everolimus should be based on whole blood trough concentrations obtained 4 or 5 days after a previous dosing change. There is an interaction of cyclosporine on everolimus, and consequently, everolimus concentrations may decrease if cyclosporine exposure is reduced.

5.3.2 Therapeutic Drug Monitoring – Cyclosporine

(b) (4)

Cyclosporine, Modified USP, is to be administered as oral capsules twice daily unless cyclosporine oral solution or i.v. administration of cyclosporine cannot be avoided.

Cyclosporine, Modified USP should be initiated as soon as possible – and no later than 48 hours - after reperfusion of the graft and dose adjusted (b) (4)

If impairment of renal function is progressive the treatment regimen should be adjusted. In renal transplant patients, the cyclosporine dose should be based on cyclosporine whole blood trough concentrations. In renal transplantation, there are limited data regarding dosing everolimus with reduced cyclosporine trough concentrations of 25-50 ng/mL after 12 months. Everolimus has not been evaluated in clinical trials with other formulations of cyclosporine. Prior to dose reduction of cyclosporine it should be ascertained that the steady-state everolimus whole blood trough concentration is at least 3 ng/mL. There is an interaction of cyclosporine on everolimus, and consequently, everolimus concentrations may decrease if cyclosporine exposure is reduced.

5.4 Notable Safety Events: Exposure-Response Analyses

These events were selected because they are associated with the mTOR inhibitor class of drugs (i.e., sirolimus), were identified by the Clinical Reviewer, Dr. Velidedeoglu as clinically relevant, and were observed at higher rates in the everolimus treatment groups compared to the Myfortic control treatment group in Study A2309.

5.4.1 Proteinuria

The exposure-response analysis revealed a significantly increased incidence of proteinuria (urinary protein/urinary creatinine (UP/UC) ratio ≥ 0.3 g/g) with higher concentrations of everolimus throughout the 3 to 8 ng/mL target range (see Figure below). The model-predicted incidence of the UP/UC ratio ≥ 0.3 g/g is 43% at 3 ng/ml and 60% at 8 ng/mL. The observed incidence between 3 and 8 ng/mL was 52% as compared to 39% observed in the Myfortic group in Study A2309.

Figure 4. Relationship between Everolimus Trough Concentration and Incidence of UP/UC ≥ 0.3 g/g.

Solid black symbols represent the observed percentage of patients with UP/UC ≥ 0.3 g/g in each everolimus trough concentration quartile. The solid line represents the mean logistic regression prediction. The blue shaded area represents the 95% confidence interval of the prediction. The red dotted line represents the incidence observed in the Myfortic treatment arm. The red shaded area represents the 95% confidence interval of this observation. The horizontal bar represents the 3 – 8 ng/ml target range and the observed incidence of UP/UC ≥ 0.3 g/g in patients within this range in Study A2309.

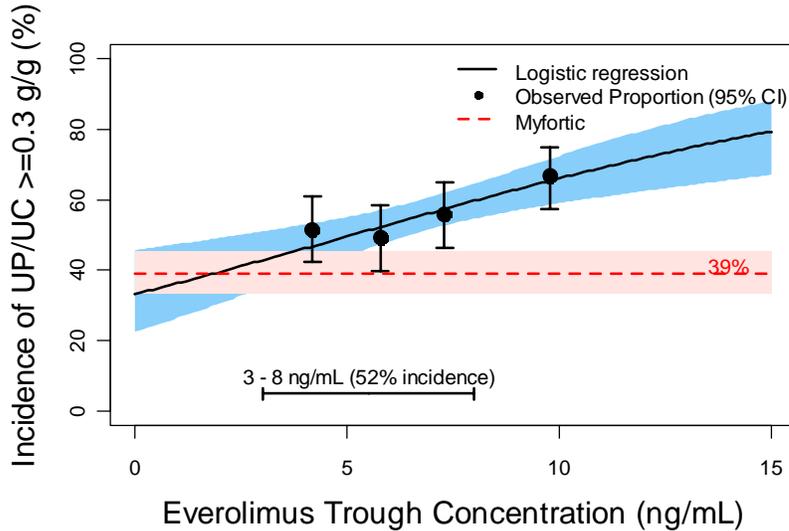


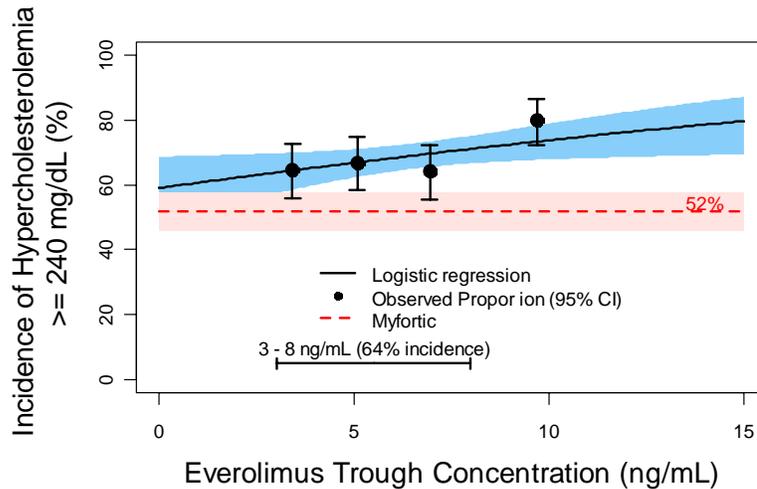
Figure 3 from Dr. Krudys review.

An exposure-response analysis was also performed using everolimus trough concentrations from the 1.5 mg/day treatment group only. The incidence of UP/UC ≥ 0.3 g/g in patients in the 3 to 8 ng/mL everolimus trough target is still higher (47%) than the Myfortic group (39%). A positive relationship between everolimus trough concentrations and incidence of proteinuria was not observed, however most likely due to the narrow everolimus concentrations range in the 1.5 mg/day group and relatively small sample size.

5.4.2 Hypercholesterolemia

The exposure-response analysis revealed a significantly increased incidence of hypercholesterolemia (≥ 240 mg/dL) (Figure 5) with higher concentrations of everolimus throughout the 3 to 8 ng/mL target range. The model-predicted incidence of hypercholesterolemia is 64% at 3 ng/mL and 71% at 8 ng/mL. The observed incidence between 3 and 8 ng/mL was 64% compared to the observed rate of 52% in the Myfortic treatment group.

Figure 5. Relationship between Everolimus Trough Concentration and Incidence of Hypercholesterolemia.



*Figure 4 from Dr. Krudys review.

5.4.3 Wound Healing/Peripheral Edema/Hypertriglyceridemia/New Onset Diabetes

Increasing everolimus trough concentrations did not show a strong relationship with an increased incidence of wound healing complications/events, peripheral edema, hypertriglyceridemia or new onset diabetes, even though the incidence of these events was higher in the 1.5 mg/day everolimus treatment group compared to the Myfortic group.

There is some evidence, however, to suggest a relationship between higher everolimus concentrations and incidences of wound healing complications/events and new onset diabetes mellitus. Patients in the highest quartile of everolimus time-normalized concentrations (8.11 to 36.4 ng/mL) had a higher incidence of new onset diabetes (14.0%) than patients within the 3 to 8 ng/mL target (8.1%).

Patients in the highest quartile of everolimus time-normalized concentrations had a higher incidence of wound healing complications/events (43.9%) than patients within the proposed target range (26%). It was noted that the everolimus concentrations in the highest quartile lie beyond the proposed target range of 3 to 8 ng/mL. Within the 3 to 8 ng/mL range, the relationship between everolimus concentrations and wound healing complications/events and new onset diabetes was not as striking as that for proteinuria and hypercholesterolemia. These results, however, provided further support for an upper target concentration of 8 ng/mL.

6 Clinical Microbiology

This NDA was found approvable with respect to Microbiology pending an accepted version of the labeling. The Microbiology Reviewers were Avery Goodwin, Ph.D. (dated December 1, 2003) and Simone Shurland, Ph.D (dated November 24, 2009). The following summary is excerpted from their reviews. Reference is made to Dr. Shurland's review for labeling recommendations.

6.1 Mechanism of Action

On a cellular level everolimus inhibits growth factor-stimulated cell proliferation irrespective of the cell lineage or growth factor involved. This inhibition is reversible, that is, everolimus is not a cytotoxic compound. On a molecular level, growth factor-stimulated phosphorylation of p70 S6 ribosomal protein kinase (p70S6K) is inhibited in the presence of everolimus. To exert its activity everolimus needs to form a complex with a cytoplasmic binding protein, FKBP-12; this everolimus/FKBP-12 complex in turn is thought to bind to and disable mTOR. p70S6K is a key translational regulator which controls protein synthesis, in particular that of pivotal proteins involved in cell growth and cell cycle regulation. p70S6K is a downstream effector of mTOR, it gets activated by mTOR-catalyzed phosphorylation. Inhibiting the activation of p70S6K by interfering with mTOR eventually results in cell cycle arrest and inhibition of cell proliferation.

6.2 Activity In Vitro

The *in vitro* immunosuppressive effect of RAD (everolimus) was compared with rapamycin in the MLR, using mouse and human derived mononuclear cells. RAD, like rapamycin, was capable of dose dependently inhibiting T cell proliferation in both mouse and human mononuclear cells. The immunosuppressive activity of RAD appears to be comparable to that of rapamycin. Therefore, the different mechanism of action of the two compounds suggests a potential for synergy. In mouse mixed lymphocyte immune response assay RAD and CysA (Neoral) effectively showed improved activity as measured by an *in vitro* cell proliferation assay.

RAD, like rapamycin was also capable of dose dependently inhibiting (1) IL-6 dependent proliferation of a B-cell hybridoma subclone and (2) IL-2 and IL-15 dependent T cell proliferation. IL-2 (produced by CD 4+ and CD 8+ T cells) and IL-15 (produced by activated macrophages, muscle and epithelial cells) receptors are thought to be closely related since both are known to utilize β and γ chains of the IL-2 receptor. However, other studies show that IL-15 is pleiotropically expressed and this expression pattern plays a unique role in both innate and adaptive immune cell homeostasis (Lodolce *et al.*, 2002).

RAD dose dependently inhibits *in vitro* and *in vivo* mouse humoral immune responses against T cell-independent and T cell-dependent antigens. When rapamycin was used as a comparator, RAD demonstrated 5 to 7 fold less activity in responses against DAGG-Ficoll and SRBC but not for responses to TNP-LPS. In comparison to CysA, RAD, like rapamycin, inhibited *in vitro* T-independent immune response against TNP-LPS.

6.3 Activity In Vivo

RAD, when compared with rapamycin, was effective at improving heterotropic heart and orthotopic kidney grafts in rats and primates. In the heart and kidney transplantation models, RAD and rapamycin demonstrated increased activity with CysA (Neoral) in prolonging graft survival.

In the rat lung transplant model, the administration of RAD in combination with CysA showed a slight increase in the ability to suppress severe acute lung rejection. However, neither monotherapy with RAD, nor cyclosporine prevented severe acute rejection in unilateral lung transplant animals.

RAD was shown to dose dependently inhibit intima thickening (80% inhibition) in rat allogeneic aorta transplantation. However, complete inhibition was not demonstrated. In studies involving CysA, only 28% inhibition was demonstrated. In drug combination studies, CysA and RAD showed increased activity in preventing intima thickening.

RAD, like rapamycin, was effective at inhibiting some of the immune responses *in vivo* such as (1) localized graft-versus-host reaction, (2) antibody responses to T-dependent and T-independent antigens, and (3) antibody responses to hepatitis A and B antigens.

6.4 Effect of RAD plus Neoral on Renal Transplantation

The effect of combination of oral formulation of RAD, or rapamycin, and Neoral was evaluated in the BN/Lewis rat orthotopic kidney transplant model. Graft survival was measured by the survival of the recipient animals. RAD, in combination with Neoral, achieved long-term survival without histological signs of rejection. The minimal effective dose was determined to be 1.0 mg/kg for RAD and 1.0 mg/kg for Neoral or 0.5 mg/kg for RAD and 2.0 mg/kg Neoral. A combination of low doses of RAD plus CsA was more effective in prolonging graft survival than either drug alone.

7 Clinical/Statistical - Efficacy

In general, the clinical and statistical reviewers agreed with the applicant's efficacy endpoints and analyses. There were no major issues of disagreement between the reviewers, the CDTL, or the applicant on the analyses of the data and interpretation of outcomes in the NDA.

The Clinical Efficacy review was performed by was conducted by Xiao Ding, Ph.D. statistical reviewer and concurrence was obtained from LaRee Tracy, Ph.D. and Karen Higgins, Sc.D in a review dated December 11, 2009.

7.1 Clinical/Statistical Efficacy Conclusions

The primary efficacy endpoint of study A2309 was a composite endpoint consisting of treated BPAR episode, graft loss, death, or loss to follow-up at 12 months post-transplant. Using the protocol-defined Hochberg's procedure for multiple comparison adjustment, the study demonstrated that both of the everolimus treatment regimens were non-inferior to the Myfortic treatment regimen in preventing the incidence of efficacy failure at 12 months. Rates of graft loss, death and loss to follow-up were deemed acceptable in both everolimus treatment regimens although the rates were numerically higher than that observed in the Myfortic group. Similar results between the everolimus and Myfortic groups were shown for other secondary efficacy endpoints (note: there is no justified non-inferiority margin for these endpoints).

The primary safety endpoint of study A2309 was estimated GFR using the MDRD formula at 12 months following the kidney transplantation. Similar values of estimated GFR at month 12 were achieved in each of the everolimus regimens compared to the Myfortic regimen.

Based on the protocol defined and justified non-inferiority margin of 10%, and using the Hochberg's procedure to adjust for multiple comparisons, non-inferiority of both everolimus groups to Myfortic with respect to the primary efficacy endpoint was achieved. This was

demonstrated by the fact that the upper limits of both 95% confidence intervals of the difference were less than the 10% non-inferiority margin, as show in bold in the Table below.

Table 4. Primary Efficacy Endpoint Analysis by Treatment Group (ITT Population -12 Month Analysis) *

	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 gm (N=277)
Efficacy Failure	70 (25.3%)	61 (21.9%)	67 (24.2%)
Treated BPAR	45 (16.3%)	37 (13.3%)	47 (17.0%)
Graft Loss	12 (4.3%)	13 (4.7%)	9 (3.3%)
Death	7 (2.5%)	10 (3.6%)*	6 (2.2%)
Loss to follow-up	12 (4.3%)	8 (2.9%)**	9 (3.3%)
95% CI (everolimus-Myfortic)	(-6.1%, 8.3%)	(-9.3%, 4.7%)	N/A
97.5% CI (everolimus-Myfortic)	(-7.1%, 9.3%)	(-10.3%, 5.7%)	N/A

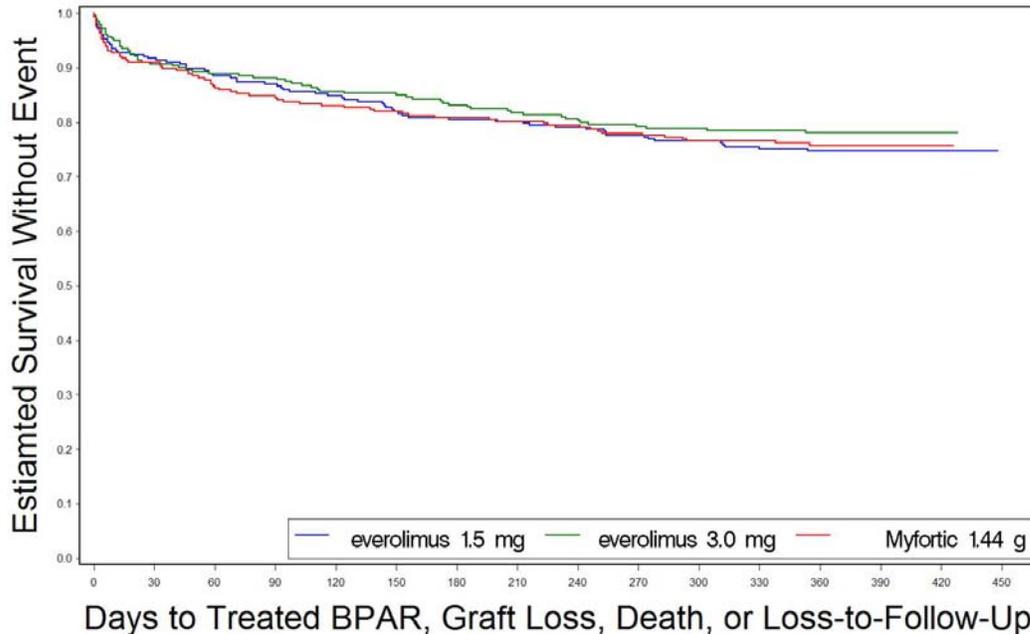
*One patient who had graft loss before the randomization was considered as loss to follow-up

**One patient who died 10 days after withdrew consent was included

Table 3 from statistical review from statistical review by Drs. Ding and Tracy dated December 11, 2009.

A Kaplan Meier plot for the primary efficacy endpoint within 12 months is provided in Figure below. Based on the log-rank test, median time to event was not statistically significantly different between the everolimus 1.5 mg (p-value=0.83), everolimus 3.0 mg (p-value=0.49), and Myfortic groups. In addition, no statistically significantly difference in time to event was shown between the two everolimus groups (p-value=0.37).

Figure 6. Kaplan-Meier Estimates for the Primal Efficacy Endpoint by Treatment Group (ITT population -12 Month Analysis)



*Figure 3 from statistical review by Drs. Ding and Tracy.

The main secondary efficacy objective was to compare the incidence rate of the composite endpoint of death, graft loss, or loss to follow-up between the everolimus and Myfortic treatment groups at 12 months post-transplantation.

As presented in the Table below, the incidence of death, graft loss or loss to follow up was similar between the two everolimus groups (11.6% and 11.1% respectively), and was 9.4% in the Myfortic group. It was noted in the statistical review that a non-inferiority margin for the endpoint of death, graft loss or loss to follow-up was not able to be justified due to a lack of sufficient data from historical information. However, the applicant stated that a 10% margin would be used and as shown in bold in the Table, both 95% confidence intervals for the everolimus groups compared to Myfortic excluded this margin based on the upper bound.

**Table 5. Main Secondary Efficacy Endpoint Analysis by Treatment Group
(ITT Population -12 Month Analysis)**

	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 gm (N=277)
Graft loss, death or loss to follow up	32 (11.6%)	31 (11.1%)	26 (9.4%)
Graft Loss	12 (4.3%)	13 (4.7%)	9 (3.3%)
Death	7 (2.5%)	10 (3.6%)	6 (2.2%)
Loss to follow-up **	14 (5.1%)	10 (3.6%)*	11 (4.0%)
95% CI (Everolimus-Myfortic)	(-2.9%, 7.3%)	(-3.3%, 6.8%)	N/A
97.5% CI (Everolimus-Myfortic)	(-3.7%, 8.0%)	(-4.0%, 7.5%)	N/A

* One patient who died 10 days after withdrew consent was included

** A loss to follow-up patient is a patient who did not experience graft loss or death and whose last day of contact is prior to study Day 316

Treated BPAR at 12 months was also a secondary endpoint of the study. The tables below present the grade and the number of treated BPAR episodes which were similar between the two everolimus groups and the Myfortic group. In all three treatment groups, more than 85% of patients who experienced treated BPAR had only one treated BPAR event during the first 12 months of the study.

**Table 6. Grade of Treated BPAR by Treatment Group
(ITT Population -12 Month Analysis)**

N (%) of patient with any grade of treated BPAR	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 gm (N=277)
Total episodes	45 (16.3%)	37 (13.3%)	47 (17.0%)
Banff Type IA	21 (7.6%)	16 (5.7%)	22 (7.9%)
Banff Type IB	7 (2.5%)	9 (3.2%)	6 (2.2%)
Banff Type IIA	7 (2.5%)	9 (3.2%)	15 (5.4%)
Banff Type IIB	1 (0.4%)	3 (1.1%)	2 (0.7%)
Banff Type III	1 (0.4%)	0 (0%)	1 (0.4%)
Missing grade	6 (2.2%)	4 (1.4%)	3 (1.1%)

*Based on the local pathology assessment

Table 6 of the statistical review.

**Table 7. Number of Treated BPAR Episodes by Treatment Group
(ITT Population -12 Month Analysis)**

N (%) of patient with treated BPAR by number of BPAR	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 gm (N=277)
0 treated BPAR	232 (83.8%)	242 (86.7%)	230 (83.0%)
1 treated BPAR	39 (14.1%)	32 (11.5%)	41 (14.8%)
2 treated BPAR	5 (1.8%)	5 (1.8%)	5 (1.8%)
3 treated BPAR	0 (0%)	0 (0%)	0 (0%)
4 treated BPAR	1 (0.4%)	0 (0%)	0 (0%)

*Based on the local pathology assessment

Table 6 of the statistical review.

In addition, the statistical reviewer noted that there were no significant differences between the everolimus groups and the Myfortic group in other secondary efficacy endpoints, including the incidence of efficacy failure within 6 months, graft loss or death at 6 and 12 months, graft loss, death or loss to follow-up at 6 months, and antibody treated BPAR at 12 months.

Subgroup analyses showed that efficacy results of Study A2309 were not consistent across gender. There was a significant interaction noted between the everolimus 3.0 mg group and Myfortic by gender. The efficacy failure rate was lower in both everolimus groups than in the Myfortic group in male patients. Among female patients, the efficacy failure rate was higher in both everolimus groups than Myfortic. Furthermore, for female patients, incidence of premature treatment discontinuation was significantly higher in each of the everolimus groups than in the Myfortic group. Statistical reviewer was particularly concerned with the higher rates of graft loss and death in the everolimus subjects compared to Myfortic.

7.2 Notable Efficacy Issues

7.2.1 Premature Study Medication Discontinuation

Premature treatment discontinuation, primarily due to adverse events, was frequent and statistically significantly higher in each of the everolimus groups, as compared to the Myfortic

group. The imbalanced incidence of treatment discontinuation should be of concern when interpreting the safety and efficacy outcomes of Study A2309. Both the patient and the investigator were unblinded to the treatment regimen a patient received, because of the open-label design of study A2309. This should be taken into consideration in the interpretation of the study results, since unblinded study is more subject to bias.

The incidence rate of premature treatment discontinuation was 30.0%, 34.7% and 21.7% in the everolimus 1.5 mg, 3.0 mg and Myfortic groups respectively. The rates were statistically significantly higher in both everolimus groups (p=0.03, everolimus 1.5 mg, p=0.001 everolimus 3.0 mg) compared to the Myfortic group. The statistical reviewer noted that the imbalanced incidence of treatment discontinuation should be considered, when interpreting the safety and efficacy outcomes of Study A2309.

To assess the impact of the disproportionate rates of premature treatment discontinuation on the primary efficacy endpoint, treatment discontinuation was treated as failure along with the other components of the primary efficacy composite endpoint. In this sensitivity analysis, both everolimus groups failed to demonstrate non-inferiority to Myfortic, given that the upper limits of both 95% confidence intervals exceeded 10%, as shown in Table below.

Table 8. Primary Efficacy Endpoint with Premature Treatment Discontinuation as Failure by Treatment Group (ITT Population -12 Month Analysis)

	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 gm (N=277)
Efficacy Failure or Premature Treatment Discontinuation	103 (37.2%)	106 (38.0%)	84 (30.3%)
95% CI (everolimus - Myfortic)	(-1.0%, 14.7%)	(-0.2%, 15.5%)	N/A
97.5% CI (everolimus - Myfortic)	(-2.1%, 15.8%)	(-1.3%, 16.7%)	N/A

Table 4 of the statistical review.

There did not appear to be one primary reason for premature study discontinuation occurring in the everolimus groups compared to the Myfortic group.

Table 9: Premature Study Medication or Study Phase Discontinuation by Treatment Group (ITT Population - 12 Month Analysis)

Number of patients (%)	everolimus 1.5 mg (N=277)	everolimus 3.0 mg (N=279)	Myfortic 1.44 g (N=277)
Discontinued study medication	83 (30.0)	95 (34.1)	60 (21.7)
Adverse event(s)	50 (18.1)	57 (20.4)	26 (9.4)
Unsatisfactory therapeutic effect	11 (4.0)	14 (5.0)	13 (4.7)
Subject withdrew consent	11 (4.0)	4 (1.4)	5 (1.8)
Graft loss	3 (1.1)	6 (2.2)	6 (2.2)
Death	3 (1.1)	3 (1.1)	4 (1.4)
Protocol deviation	2 (0.7)	5 (1.8)	2 (0.7)
Abnormal lab value	1 (0.4)	4 (1.4)	1 (0.4)
Administrative problems	2 (0.7)	1 (0.4)	2 (0.7)
Abnormal test procedure	0 (0)	1 (0.4)	0 (0)
Unknown	0 (0)	0 (0)	1 (0.4)
Discontinued study phase	38 (13.7)	33 (11.8)	28 (10.1)
Subject withdrew consent	20 (7.2)	8 (2.9)	12 (4.3)
Graft loss	9 (3.3)	10 (3.6)	7 (2.5)
Death	7 (2.5)	9 (3.2)	6 (2.2)
Unknown	2 (0.7)	6 (2.2)	3 (1.1)

Table 2 of the statistical review by Drs. Ding and Tracy.

7.2.2 Age and Race

Subgroup analyses of the primary efficacy endpoint by recipient age and race were adequately addressed in the statistical review. No significant differences were seen among treatments within the different age categories (i.e. ≤ 50 and > 50). Among Black patients, the observed incidence of efficacy failure was lower in both everolimus groups than in the Myfortic group (29.4% and 35.0% versus 38.5%); however, no statistically significant differences were found ($p=0.47$ and 0.82 respectively). It was noted in the statistical review that Black patients represent only 13.5% of the total study population and therefore use of caution was suggested when interpreting findings in this small subgroup by the reviewer.

7.2.3 Gender

Among male patients, the efficacy failure rate at 12 months post-transplantation was 28.4%, 21.5%, and 29.6%, in the everolimus 1.5 mg, everolimus 3.0 mg and Myfortic groups respectively. Compared to the Myfortic group, the everolimus 1.5 mg group had slightly lower incidence of efficacy failure with risk difference (RD) of -1.2% (95% CI: -10.5%, 8.1%). The incidence was marginally significantly lower in the everolimus 3.0 mg group than in the Myfortic group [RD=-8.1% (-16.9%, 0.6%), p -value=0.08].

In contrast, the primary efficacy failure among female patients was more frequent in both everolimus groups than in the Myfortic group. The incidence rate in the everolimus 1.5 mg, everolimus 3.0 mg and Myfortic groups were 19.0%, 22.7%, and 12.5% respectively. The

difference between everolimus 1.5 mg and Myfortic was 6.5% [(-3.8%, 16.8%), p=0.24], and difference between everolimus 3.0 mg and Myfortic was 10.2% [(-0.9 %, 21.4%), p=0.11].

Analysis by gender revealed that among female patients, rates of premature treatment discontinuation, primary efficacy failure and graft loss and death were considerably higher in both everolimus groups compared to the Myfortic group.

Table 10. Primary Efficacy Endpoint Analysis by Gender and Treatment Group (ITT Population -12 Month Analysis) *

	Males Total =556			Females Total =276		
	Everolimus 1.5 mg (N=176)	Everolimus 3.0 mg (N=191)	Myfortic 1.44 gm (N=189)	Everolimus 1.5 mg (N=100)	Everolimus 3.0 mg (N=88)	Myfortic 1.44 gm (N=88)
Efficacy Failure*	50 (28.4%)	41 (21.5%)	56 (29.6%)	19 (19.0%)	20 (22.7%)	11 (12.5%)
Treated BPAR	33 (18.8%)	25 (13.1%)	39 (20.6%)	12 (12.0%)	12 (13.6%)	8 (9.1%)
Graft Loss	7 (4.0%)	7 (3.7%)	7 (3.7%)	5 (5.0%)	6 (6.8%)	2 (2.3%)
Death	3 (1.7%)	7 (3.7%)**	6 (3.2%)	4 (4.0%)	3 (3.4%)	0 (0%)
Loss to follow-up	10 (5.7%)	7 (3.7%)	8 (4.2%)	1 (1.0%)	1 (1.1%)	1 (1.1%)
95% CI (everolimus – Myfortic)	(-10.5%, 8.1%)	(-16.9%, 0.6%)	N/A	(-3.8%, 16.8%)	(-0.9 %, 21.4%)	N/A
P-value***	p=0.82	p=0.08		p=0.24	p=0.11	

* One subject's gender was unknown and is excluded from this analysis

** One patient who died 10 days after withdrew consent was included

*** P-value for the Fisher's exact test

Table 18 of the statistical review.

The observed incidence of graft loss, death, or loss to follow-up was similar across all three treatment groups (11.9% and 10.5% in the everolimus groups versus 12.2% in the Myfortic group) in male patients. Among female patients, the rate of graft loss, death, or loss to follow-up was 10.0%, 12.5%, 3.4% in the everolimus 1.5 mg, 3.0 mg and Myfortic groups respectively (p-value = 0.09 and 0.05 respectively, for everolimus 1.5 mg and 3.0 mg compared to Myfortic). These differences in females were driven by higher rates of both death and graft loss in both everolimus groups compared to Myfortic. Specifically, graft loss occurred in 5.0%, 6.8% and 2.3% and death in 4.0%, 3.4% and 0% in the everolimus 1.5 mg, 3.0 mg and Myfortic groups respectively (see Table below).

Table 11. Graft Loss, Death, or Loss to Follow-up by Gender and Treatment Group (ITT Population -12 Month Analysis) *

	Males Total =556			Females Total =276		
	Everolimus 1.5 mg (N=176)	Everolimus 3.0 mg (N=191)	Myfortic 1.44 gm (N=189)	Everolimus 1.5 mg (N=100)	Everolimus 3.0 mg (N=88)	Myfortic 1.44 gm (N=88)
Graft Loss, Death or Loss to follow-up	21 (11.9%)	20 (10.5%)	23 (12.2%)	10 (10.0%)	11 (12.5%)	3 (3.4%)
Graft Loss	7 (4.0%)	7 (3.7%)	7 (3.7%)	5 (5.0%)	6 (6.8%)	2 (2.3%)
Death	3 (1.7%)	7 (3.7%) ^{**}	6 (3.2%)	4 (4.0%)	3 (3.4%)	0 (0%)
Loss to follow-up	11 (6.3%)	8 (4.2%)	10 (5.3%)	2 (2.0%)	2 (2.3%)	1 (1.1%)
95% CI (everolimus – Myfortic)	(-6.9%, 6.5%)	(-8.1%, 4.7%)	N/A	(-0.4%, 13.6%)	(1.2 %, 17.0%)	N/A
P-value^{**}	p=1.0	p=0.63		p=0.09	p=0.05	

* One subject's gender was unknown (in the everolimus 1.5 mg group) and is excluded from this analysis

** One patient who died 10 days after withdrew consent was included

*** P-value for the Fisher's exact test

Table 19 of the statistical review.

In female patients, the incidence of premature treatment discontinuation in the everolimus 1.5 mg, everolimus 3.0 mg and Myfortic groups was 32.0% (32/100), 38.6% (34/88), and 15.9% (14/88) respectively, resulting in a p-value of 0.01 (everolimus 1.5 mg – Myfortic) and a p-value of 0.001 (everolimus 3.0 mg – Myfortic). Furthermore, in the everolimus 1.5mg group, approximately 22% of the female patients prematurely discontinued treatment due to adverse events, which was statistically significantly higher (p-value= 0.004) than the Myfortic group (6.8%). Similarly, the incidence of premature treatment discontinuation due to adverse events in female patients in the everolimus 3.0 mg group was statistically significantly higher compared to the Myfortic group (21.6% versus 6.8%, with p-value=0.009). These differences were not observed among male patients in the study. Specifically, the incidence of premature treatment discontinuation among male patients in the everolimus 1.5 mg, everolimus 3.0 mg and Myfortic groups was 29.0% (51/176), 31.9% (61/191), and 24.3% (46/189) respectively (p-value=0.34 for everolimus 1.5 mg versus Myfortic and p-value=0.11 for everolimus 3.0 mg versus Myfortic). Analysis results for premature discontinuation by gender are presented in the Table below.

Table 12. Premature Study Medication Discontinuation by Gender and Treatment Group (ITT Population- 12 month analysis) *

	Males Total =556			Females Total =276		
	Everolimus 1.5 mg N=176 (%)	Everolimus 3.0 mg N=191 (%)	Myfortic 1.44 gm N=189 (%)	Everolimus 1.5 mg N=100 (%)	Everolimus 3.0 mg N=88 (%)	Myfortic 1.44 gm N=88(%)
Discontinued study medication	51 (29.0)	61 (31.9)	46 (24.3)	32 (32.0)[#]	34 (38.6)[#]	14 (15.9)
Adverse event(s)	28 (15.9)	38 (19.9)	20 (10.6)	22 (22.0) [#]	19 (21.6) [#]	6 (6.8)
Unsatisfactory therapeutic effect	8 (4.6)	9 (4.7)	9 (4.8)	3 (3.0)	5 (5.7)	4 (4.6)
Others	15 (8.5)	14 (7.3)	17 (9.0)	7 (7.0)	10 (11.4)	4 (4.5)

* One subject's gender was unknown (in the everolimus 1.5 mg group) and is excluded from this analysis

[#] p<0.05 compared to Myfortic for Fisher's exact test

Derived from Table 21 of the statistical review.

The statistical reviewer commented:

When interpreting these subgroup analysis results, one must take into account that multiple comparisons according to various subgroups are unadjusted.

8 Safety

The Medical Officer is recommending Non-Approval of this application due to safety concerns: a numerically higher mortality rate and various safety signals, including graft loss, proteinuria, hyperlipidemia, and impaired wound healing. Given these safety concerns, and the lack of a demonstration of an efficacy advantage (i.e., superiority) over currently approved products, he believes the everolimus 1.5 mg regimen should not be approved.

The Clinical Safety Review was conducted by Ergun Velidedeoglu, M.D, Medical Officer in DSPTP. John Yap, Ph.D. from the Quantitative Safety and Pharmacoepidemiology Group (QSPG), Office of Biostatistics did the statistical review of the primary safety endpoint, as well as the analysis of proteinuria and hyperlipidemia. The following summary is excerpted from their reviews.

8.1 Safety Database

The safety population in Study A2309 consisted of 277 patients in the 1.5 mg everolimus group, 279 patients in the 3.0 mg everolimus group and 277 patients in the Myfortic group.

8.2 Primary Safety Endpoint – Renal Function

The main safety endpoint of Study A2309 was serum creatinine at month 12 by calculated glomerular filtration rate (GFR) using the MDRD (Modification of Diet in Renal Disease) formula. The main safety objective was to show that the mean GFR of either everolimus 1.5 mg or 3.0 mg group was no worse than (non-inferior to) the Myfortic group by 8 mL/min/1.73m² at month 12 using t-test based, two-sided 95% and 97.5% confidence

intervals. The Division did not agree to the proposed non-inferiority margin; therefore, the results of this endpoint were assessed for clinical importance only.

The results for everolimus 1.5 mg and Myfortic, using a Last Observation Carried Forward (LOCF) approach for missing data, were comparable at Month 12 in the ITT population (see Table below).

Table 13. Calculated Glomerular Filtration Rates (mL/min) by MDRD At 12 Months Post-Transplant

	Everolimus 1.5 mg/day n=275 (%)	Myfortic 1.44 gm/day n=277 (%)
Month 12 GFR (MDRD)		
Mean (SD)	54.6 (21.7)	52.3 (26.5)
Median (Range)	55.0 (0 - 140.9)	50.1 (0 - 366.4)

Figure below shows the mean GFR over time using data with no imputation.

Figure 7. Mean GFR (MDRD) Over Time

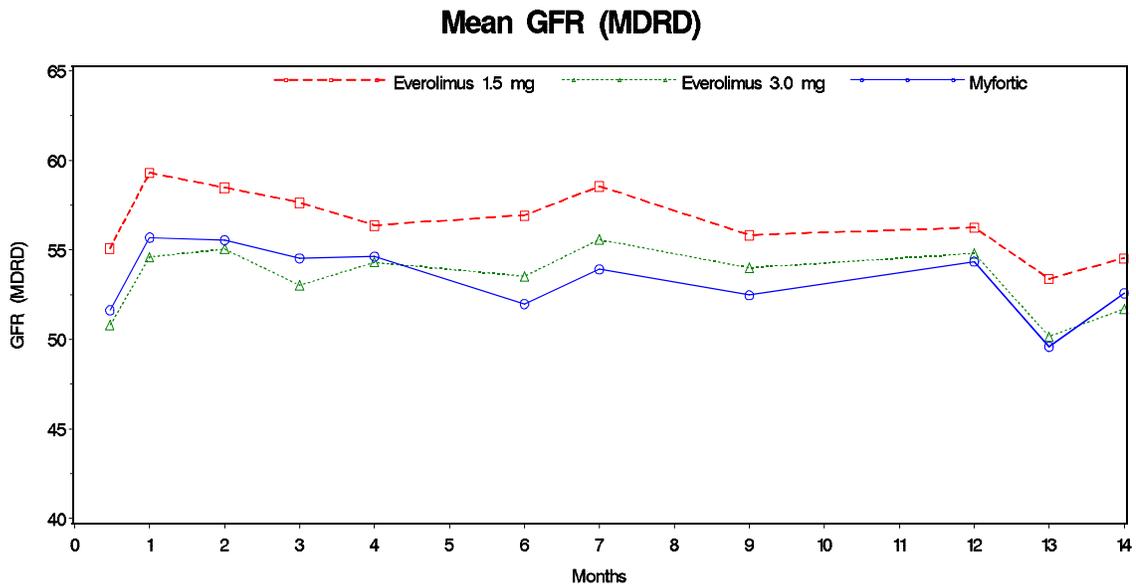


Figure 2 from Dr. Yap’s review.

Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit. Month 14 represents the month 12 study endpoint consisting of the last post-baseline observation up to and including the month 12 visit.

The Clinical Reviewer agrees that there is no difference in GFR between the groups and that the Applicant has overcome the previous safety concerns of decreased renal function in the original NDA using fixed dose everolimus and standard dose CsA. However, he also notes that since the CsA exposure in the Myfortic group is higher compared to the everolimus

groups, the fact that the everolimus groups were able to show a similar GFR is less meaningful than if the Myfortic control group contained an equivalent CsA exposure.

CDTL Comment: There is general agreement that the results of the GFR analysis demonstrate that the Applicant has overcome the renal toxicity noted in Studies B201 and B251 with the everolimus fixed dose regimen.

8.3 Deaths

A total of 23 patients died during the first 12 months of the study, 7 (2.5%) in the everolimus 1.5 mg group, 10 (3.6%) in the 3.0 mg everolimus group, and 6 (2.2%) in the Myfortic control group. The most common causes of death across the study groups were related to cardiac conditions and infections.

Applicant's Assessment of Deaths

According to the applicant's assessment, the most common primary cause of death across the treatment groups was cardiac related (8 total): three in the everolimus 1.5 mg group (myocardial infarction, congestive heart failure, and cardiac arrest), three in the everolimus 3.0 mg group [myocardial infarction (n=2), and sudden death/cardiomegaly], and two in the Myfortic group (cardiac arrest and myocardial infarction). An additional two deaths in the everolimus 3.0 mg group were related to both cardiac and infectious etiologies (cardiac arrest/pneumonia and cardiopulmonary failure pneumonia).

The second most common primary cause of death overall was related to infections (5 total): two in the everolimus 1.5 mg group (septic shock and abdominal sepsis), three in the everolimus 3.0 mg group (septic shock/pneumonia, *C. difficile* colitis, and sepsis/bowel obstruction), and none in the Myfortic group. As noted above, an additional two deaths in the everolimus 3.0 mg group were related to both cardiac and infectious etiologies (cardiac arrest/pneumonia and cardiopulmonary failure, pneumonia).

Clinical Reviewer's Assessment of Deaths

After reviewing the narratives and CRFs, as an overall evaluation of mortality in Study A2309 the Reviewer believes that the actual number of deaths which may have been associated with study drug is 18: all 7 deaths in the everolimus 1.5 mg group, 8 out of 10 deaths in the everolimus 3.0 mg group (all except 0114-0001 and 0173-00003), and 3 of the 6 deaths in the Myfortic group (all except 0502-00016, 0521-00007, and 0122-00003). For tables and narratives of the deaths, see the Clinical Safety Review.

Fatalities Occurring Beyond the 12-month Analysis Period

The data in the NDA resubmission covers the period of April 24 through June 30, 2009 (12-month data analysis). However, the study is still ongoing and 6 additional deaths occurred beyond the 12 month analysis period. Among these deaths of particular importance is a 47 year old male patient (0304-00016) in the everolimus 1.5 mg group who eventually died of pneumonia and septic shock. This patient initially developed dyspnea and was diagnosed to have alveolar proteinosis by lung biopsy. His condition gradually deteriorated until his death. Alveolar proteinosis is a rare but serious event associated with the mTOR inhibitor class of

drugs and was probably the primary cause of death in this patient, according to the Clinical Reviewer.

The Clinical Reviewer concludes that there are twice as many deaths in both of the everolimus groups compared to the Myfortic group (based on the 12-month analysis) that appear to be associated with study medication. In addition, he also notes the imbalance in deaths that appear related to everolimus is consistent with the adverse event profile of sirolimus, another approved M-TOR inhibitor, which contains a Boxed Warning regarding excess mortality seen in liver transplant.

CDTL and Clinical Team Leader Comments: It should be noted that there is no overall imbalance in the number of deaths between the everolimus 1.5 mg and Myfortic groups and attributability of death to study medication is a subjective assessment. While the CDTL may not agree with the Clinical Reviewer on attributability in all cases, there is general agreement that patients in the everolimus groups appeared to have more infectious and thrombotic processes associated with their deaths.

8.4 Serious Adverse Events

It should be noted that reports of Adverse Events (AEs) and Serious Adverse Events (SAEs) were not systemically collected after 8 days and 30 days, respectively, following discontinuation of treatment. Given that there was a higher rate of discontinuation due to AEs in the everolimus group, this practice may have biased the study in favor of the Myfortic group.

SAEs in the following MedDRA System Organ Classes (SOCs) were reported at a higher rate in the everolimus 1.5 mg group compared to the Myfortic group:

- Blood and lymphatic system disorders, (4% vs. 2.9%)
- Gastrointestinal disorders (7.7% vs. 6.6%)
- General disorders and administration site conditions (5.5% vs. 4.4%)
- Injury, poisoning and procedural complications (14.2% vs. 11.7%)
- Investigations (8.4% vs. 8.1%)
- Metabolism and nutrition disorders (7.3% vs. 4.8%)
- Musculoskeletal and connective tissue disorders (1.8% vs. 0.4%)
- Nervous system disorders, psychiatric disorders (2.2% vs. 1.8%)
- Psychiatric disorders (1.1% vs. 0%)
- Reproductive system and breast disorders (1.1% vs. 0%)
- Respiratory, thoracic and mediastinal disorders (3.3% vs. 2.9%)
- Vascular disorders (9.5% vs. 7.3%)

The incidence of SAEs in the everolimus 3.0 mg group was higher than in the Myfortic group in all of the SOCs, except for Investigations and Neoplasms.

SAEs in the following SOCs were higher in the Myfortic group compared to the everolimus 1.5 mg group:

- Infections and infestations (25.3% vs. 19.7%)
- Neoplasms (1.8% vs. 1.5%)

- Renal and urinary disorders (13.2% vs. 10.2%)

The higher incidence of SAEs in the renal and urinary disorders SOC in the Myfortic group is driven by the high incidence of hydronephrosis and ureteric obstruction (both 2.2%) in the Myfortic group, which may be related to surgical technique.

8.4.1 *Graft Loss*

According to the study protocol, graft loss was reported as a SAE.

The number of graft losses was 12 (4.3%) in the everolimus 1.5 mg group, 14 (5.0%) in the everolimus 3.0 mg group and 8 (2.9%) in the Myfortic group over the 12 month study period. One patient (0543-00007) with a graft loss in the Myfortic group never received the study drug and is not included in the safety population, but is included in the ITT population. As a consequence, there were nine graft losses in the Myfortic group in the efficacy analysis but only eight graft losses in the safety analysis. The most frequent cause of graft loss was renal artery thrombosis in the everolimus groups whereas the causes are more evenly distributed in the Myfortic group. Three patients died after they lost their grafts: one in the everolimus 1.5 mg group (0114-00001) and the other two in the everolimus 3.0 mg group (0115-00020 and 0168-00017).

The Applicant and the Clinical Reviewer were in agreement regarding the number of graft losses in the study: 12 in the everolimus 1.5 mg group, 14 in the everolimus 3.0 mg group, and 8 in the Myfortic group. There was also agreement on the number of graft losses due to thrombosis: 6 in the everolimus 1.5 mg group, 4 in the everolimus 3.0 mg group, and 2 in the Myfortic group.

One patient in the everolimus 1.5 mg group and two patients, who later died, in the everolimus 3.0 mg group lost their grafts due to acute rejection compared to none in the Myfortic group. Two patients in the everolimus 1.5 mg group, three patients in the everolimus 3.0 mg group, and one patient in the Myfortic group lost their grafts due to chronic rejection.

One patient in the everolimus 1.5 mg group (0192-00002) lost his graft due to Thrombotic Thrombocytopenic Purpura (TTP), which is also a known toxicity of mTOR inhibitors.

The Clinical Reviewer notes that the national average rate of graft thrombosis within 30 days following transplantation is 0.9% of renal transplant, based on a data from the United Network for Organ Sharing/United States Renal Disease Study (UNOS/USRDS).³ The incidence of graft thrombosis within 30 days following transplantation in Study A2309 was 1.8% (5/274) in the everolimus 1.5 mg group [2.1% (6/274) if patient 0515-00004 who lost his graft on day 55 is included], 1.4% (4/278) in the everolimus 3.0 mg group, and 0.7% (2/273) in the Myfortic group. He concludes that the graft thrombosis rate in the everolimus groups is above the national average and consistent with the thrombogenic effect of the M-TOR inhibitor class of drugs.

³ Ojo AO, Hanson JA, Wolfe RA, et al. Dialysis modality and the risk of allograft thrombosis in adult renal transplant recipients. *Kidney Int.* 1999;55:1952-1960

CDTL and Clinical Team Leader Comments: There is agreement that the rate of graft thrombosis was higher in the everolimus 1.5 mg group compared to the Myfortic group (6 and 2, respectively). If approved, everolimus should carry a Boxed Warning regarding graft thrombosis, similar to the sirolimus (Rapamune) package insert.

8.5 Significant Adverse Events

The following safety summary and discussion is structured to cover adverse events (AEs) known to occur with all immunosuppressants (e.g., infections and neoplasms), as well as AEs known to occur with M-TOR inhibitors (e.g., interstitial lung disease and wound healing problems).

8.5.1 Infections

Rates of total infections, total fungal, and total bacterial infections were similar across all treatment groups. The lowest total rates were seen in the everolimus 1.5 mg group, which was due primarily to the low rates of viral infections [Cytomegalovirus (CMV) and BK virus] in this group.

As stated above in Sections 8.3 (Deaths) and 8.4.1 (Graft Loss), as per the Clinical Reviewer's assessment of attributability, infectious were the second most common primary cause of death in the study overall and appeared to be responsible for two deaths in the everolimus 1.5 mg group, five deaths in the everolimus 3.0 mg group (and appeared to contribute to the death in an additional patient), and appeared to contribute to four of the 14 graft losses in the everolimus 3.0 mg group.

The overall incidence of SAEs related to infectious causes were approximately 20% in the everolimus 1.5 mg group, 26% in the everolimus 3.0 mg group and 25% in the Myfortic group.

There were nine SAEs of CMV infections and an additional SAE of CMV esophagitis in the Myfortic group and none in the everolimus groups. According to the patient narratives, all of these CMV infections in the Myfortic group promptly responded to treatment with gancyclovir or valgancyclovir and resolved within a few days. In one patient Guillain-Barre syndrome secondary to CMV infection developed after the CMV infection had resolved. The patient also recovered from Guillan-Barre syndrome with treatment. CMV or any other type of viral infection did not cause any deaths or graft losses in any of the treatment groups.

There was one BK virus infection reported as SAE in the everolimus 1.5 mg group, no cases in the everolimus 3.0 mg group, and two cases in the Myfortic group.

The incidences of infections reported as AEs was 61.7% in the everolimus 1.5 mg group, 64 % in the everolimus 3.0 mg group and 67.8 % in the Myfortic group, as shown in the Table below. The causative organisms for viral infections with an incidence of $\geq 1\%$ are included.

Organisms causing bacterial fungal infections were not included, as they were similar across the study groups.

Table 14. Number of Patients (%) with Infections by Type of Organism

Type of Infection	Everolimus 1.5 mg N=274, n (%)	Everolimus 3.0 mg N=278, n (%)	Myfortic 1.44 gm N=273, n (%)
All infections	169 (61.7)	178 (64.0)	185 (67.8)
Bacterial - Total	71 (25.9)	69 (24.8)	69 (25.3)
Fungal - Total	12 (4.4)	14 (5.0)	14 (5.1)
Viral - Total	27 (9.9)	20 (7.2)	57 (20.9)
<i>BK virus</i>	2 (0.7)	3 (1.1)	11 (4.0)
<i>Cytomegalovirus, nos</i>	3 (1.1)	1 (0.4)	23 (8.4)
<i>Human herpes simplex virus, nos</i>	7 (2.6)	11 (4.0)	14 (5.1)
<i>Human herpes virus 3</i>	4 (1.5)	2 (0.7)	7 (2.6)
<i>Polyomavirus, nos</i>	5 (1.8)	0 (0.0)	3 (1.1)
<i>Virus, nos</i>	4 (1.5)	3 (1.1)	0 (0.0)
Other - Total	135 (49.3)	135 (48.6)	129 (47.3)

nos = not otherwise specified

The incidence of CMV, herpes simplex and BK virus infections was higher in the Myfortic group compared to both of the everolimus groups and is the main cause of the difference in the overall rates of infections across the three groups.

In the Clinical Reviewer's opinion having less viral infections (mainly less CMV infections) is an advantage of the everolimus regimen. However, more CMV infections and other types of viral infections in the Myfortic group did not result in death or graft loss. The Reviewer's conclusion is although the everolimus 1.5 mg regimen results in less CMV and other types of viral infections; the bacterial infections which occurred in this group, while similar in overall incidence, tended to be more severe and appeared to result in several deaths.

CDTL and Clinical Team Leader Comments: There is agreement that there were less viral infections in the everolimus 1.5 mg group compared to the Myfortic group and that bacterial infections may have played a role in several deaths in the everolimus 1.5 mg group.

8.5.2 Proteinuria

Proteinuria was reported as a SAE in two (0.7%) patients in the everolimus 1.5 mg group, four (1.4%) patients in the everolimus 3.0 mg group and one (0.4%) patient in the Myfortic group. Also two patients in the everolimus 1.5 mg group, four patients in the everolimus 3.0 mg group discontinued treatment due to proteinuria. No patient discontinued treatment due to proteinuria in the Myfortic group. Proteinuria as an AE was reported in 9.1% of the patients in the everolimus 1.5 mg group, 12.9% of the patients in the everolimus 3.0 mg group and 7.3% of the patients in the Myfortic group.

Proteinuria was assessed by evaluating the ratio of spot urine protein (measured in grams) to creatinine (measured in grams) (UP/UC ratio) based on an estimate of an average 24 hour excretion. According to the study protocol the UP/UC ratio was defined as:

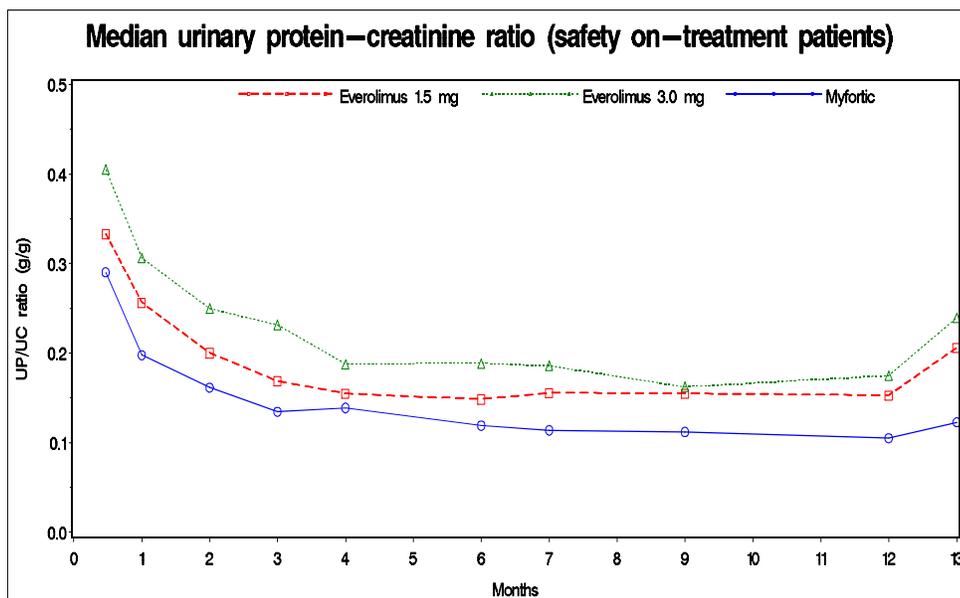
- Normal (<30 mg/g);
- Mild proteinuria (30 – <300 mg/g);
- Sub-Nephrotic proteinuria (300 - <3000 mg/g);
- Nephrotic proteinuria (\geq 3000 mg/g).

Analyses of the data indicate that the UP/UC ratios distributions are skewed due to extreme outlying values such that the means were greater than the medians. To account for the lack of symmetry in the data, these data were analyzed by comparing medians at each visit window between treatment groups and using the nonparametric Wilcoxon rank-sum test to test for treatment differences.

Figure 8 below shows the median UP/UC ratios over the 12 months of the study in the safety on-treatment population, which was defined as the population of safety patients whose assessments were obtained on and after day 1 but no later than two days after the discontinuation of randomized study medication. The Figure shows that the median ratios in the everolimus 1.5 mg group were consistently higher than those of Myfortic throughout the study including the Month 12 TEP⁴, as shown as Month 13.

Of note, that there was an increasing number of missing data as study follow-up time increased. At Day 14, about 90% of data were collected compared to only about 70% at Month 12.

⁴ TEP=treatment endpoint (imputation by LOCF)

Figure 8. Median Urinary Protein/Creatinine (Safety On-treatment Population)

Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

Figure 4 from Dr. Yap's review.

The Clinical Reviewer states that when the Month 12 TEP mean values are taken into consideration, there is a difference of 210 mg/g between the everolimus 1.5 mg group and the Myfortic group in favor of the Myfortic group and this difference is even higher for the male patients since the overall higher levels of proteinuria in the everolimus 1.5 mg group is driven by the male patients [data not shown]. The fact that the differences between the two treatment groups became significant starting at Month 6 raises concerns that the gap may continue to widen in favor of the Myfortic group with longer follow-up and may be more severe for the male patients.

CDTL and Clinical Team Leader Comments: There is agreement that the median UP/UC ratios for the everolimus 1.5 mg group are higher than the Myfortic group. From the 12 month results it is not possible to determine whether this difference between the groups will continue to widen over time, although it is suspected that proteinuria will continue to increase in the everolimus group, due to the known effects on proteinuria of the M-TOR inhibitor class. Despite the statistically significance difference between the everolimus and Myfortic groups, there were very few SAEs, AEs, or AEs leading to drug discontinuation in the everolimus 1.5 mg group. The biological significance of more proteinuria in male patients compared to in female patients is not clear.

The exposure-response analysis performed by the Pharmacometric Reviewer, Kevin Krudys, Ph.D., found a relationship between everolimus trough concentrations and proteinuria, as discussed in Section 5.4.1.

8.5.3 Lipid Elevations

According to the study protocol patients who have severe hypercholesterolemia (> 350 mg/dL; > 9 mmol/L) or hypertriglyceridemia (> 500 mg/dL; > 8.5 mmol/L) were excluded from the study. Lipid lowering medications such as HMG CoA reductase inhibitors were to be administered according to local practice for the management of hyperlipidemia. Patients requiring treatment with this class of medications, especially lovastatin, were to be monitored closely for signs of rhabdomyolysis. Lipid-lowering therapy was to be optimized before dose reduction of study medication was considered.

Hyperlipidemia as a SAE was reported in only one patient in the study and was in the everolimus 1.5 mg group.

Dyslipidemia, hypercholesterolemia and hyperlipidemia combined together led to study drug discontinuations in two patients in each of the everolimus groups and one patient in the Myfortic group.

Hyperlipidemia was reported as an AE in 57 (20.8%) patients in the everolimus 1.5 mg group, 60 (21.6%) patients in the everolimus 3.0 mg group, and 43 (15.8%) patients in the Myfortic group. Hypercholesterolemia is reported in 47 (17.2%) patients in the everolimus 1.5 mg group, 50 (18.0%) patients in the everolimus 3.0 mg group, and 34 (12.5%) patients in the Myfortic group as an AE in the 12 month safety population.

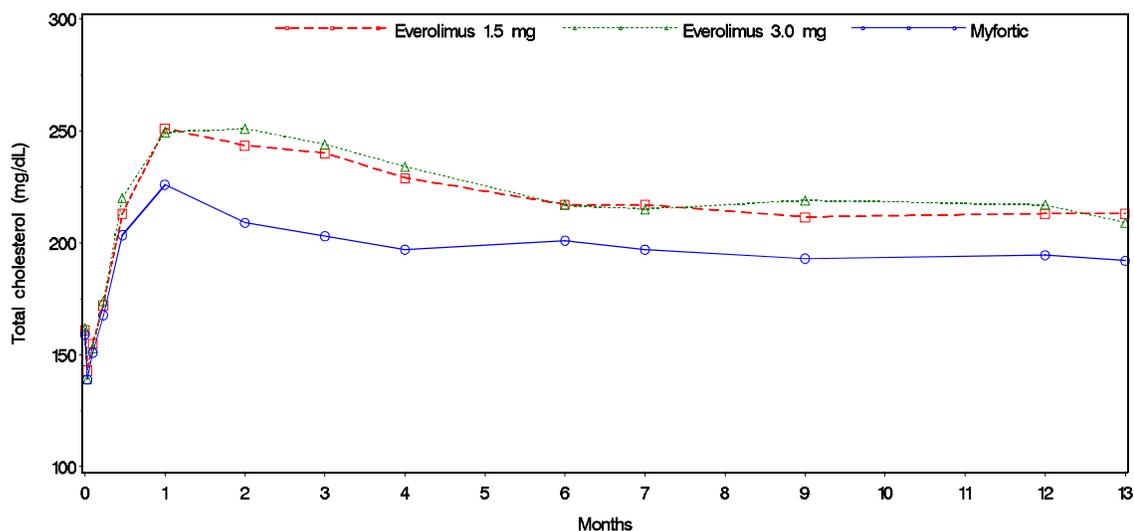
Lipid lowering agents were taken by a higher percentage of patients in the everolimus treatment groups (64.6%, 72.3% and 57.5% of patients in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm treatment groups, respectively).

Among patients with high baseline cholesterol values before the statin treatment was initiated, 27.4% in the everolimus 1.5 mg group and 34.4% in the everolimus 3.0 mg group compared to 13.9% in the Myfortic group did not move down to the normal range despite the statin treatment. A similar trend was also observed for triglycerides in a similar analysis.

Lipids were assessed in the safety on-treatment population focusing on the following clinical parameters: total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and total cholesterol-HDL ratio. Only the results for total cholesterol are shown below (the results of the other analysis show a similar trend). Note that data presented in the figures below are given in mg/dL units. Since the distributions of the lipid measurements at each visit window are skewed, medians were plotted and the treatment groups were compared using the Wilcoxon rank-sum test.

As illustrated in Figure below, the median total cholesterol was consistently higher in both everolimus groups compared to the Myfortic group and statistically significant differences were found from month 1 post-transplant through month 12 TEP (Month 13 in the Figure).

Figure 9. Median Total Cholesterol
Median total cholesterol (safety on-treatment patients)



Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.
 Figure 5 from Dr.Yap's review.

The Clinical Reviewer states that the median values for both the total cholesterol and triglycerides are well above the upper bound of the normal range while the median values in the Myfortic group overlap or come down to the normal range, especially towards the end of the 12 month study period. The differences between the Myfortic group and the everolimus groups are statistically significant. Also the data shows that more patients fail to respond adequately to statin treatment in the everolimus 1.5 mg group compared to the Myfortic. High cholesterol and lipid values in general are well established risk factors for developing cardiovascular disease in the general population.

CDTL and Clinical Team Leader Comments: There is agreement that lipid elevations were more significant in the everolimus 1.5 mg group compared to Myfortic and were less likely to respond to anti-lipid therapy. In addition, the death of one patient in the everolimus 1.5 mg group with high levels of proteinuria (0124-00076) is concerning. The impact of these lipid elevations on long-term cardiovascular outcomes can not be predicted from the relatively short 1 year period of follow-up in the study.

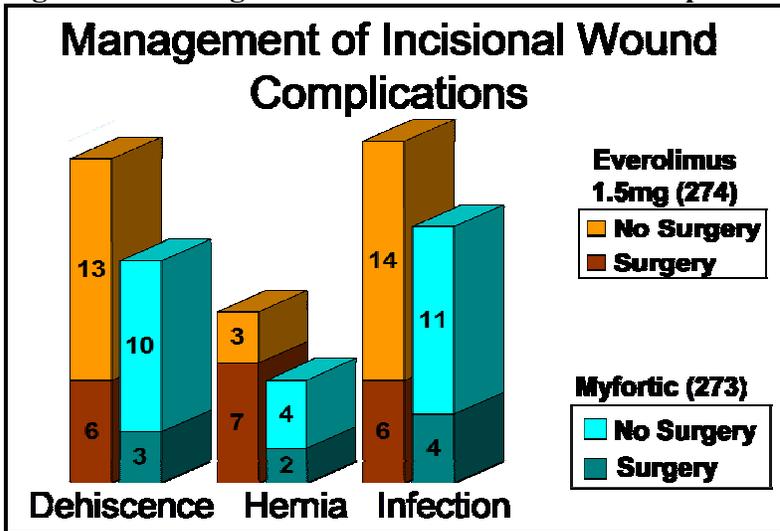
The exposure-response analysis performed by the Pharmacometric Reviewer, Kevin Krudys, Ph.D., found a relationship between hypercholesterolemia and proteinuria, as discussed in Section 5.4.2.

8.5.4 Wound Healing and Fluid Collections

The applicant identified AEs related to wound healing events through a retrospective search of the AE and infectious events databases. Identified terms were reviewed by their clinical team to determine relevance and then paper CRFs were dispatched to the sites for further information regarding the events prior to database lock.

Based on the Applicant’s analysis of all the relevant preferred terms, including lymphocele, seroma, hematoma, dehiscence, incisional hernia and others; the overall incidence of wound events was 35% in the everolimus 1.5 mg group, 38.8% in the everolimus 3.0 mg group, and 25.6% in the Myfortic group. Incisional wound complications were more frequent in the two everolimus groups compared to the Myfortic group with the highest number occurring in the 3.0 mg group. In each of the Dehiscence, Hernia and Infection categories, more patients required surgical intervention (i.e., intraoperative repair or debridement/ drainage) in the everolimus 1.5 mg group compared to the Myfortic group, as shown in the graph below.

Figure 10. Management of Incisional Wound Complications



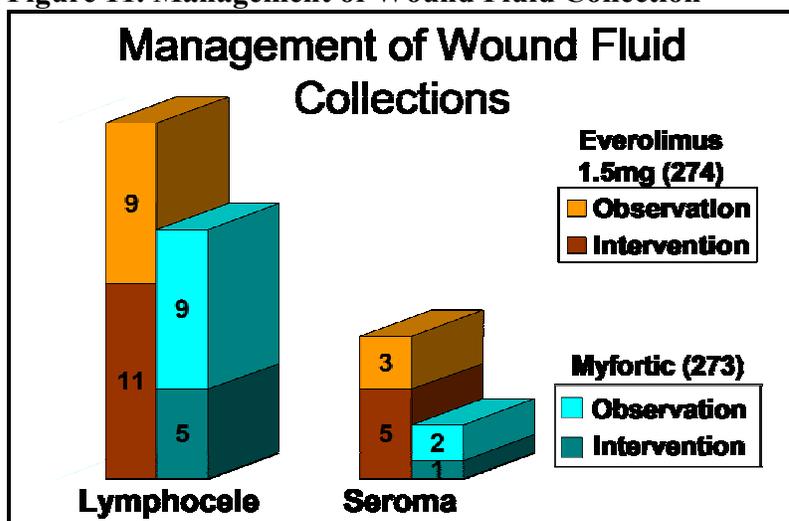
Presented Dr. Velidedeoglu at the Advisory Committee Meeting on December 7, 2009.

Wound dehiscence and impaired healing resulted in study drug discontinuations in one patient in the everolimus 1.5 mg group, six patients in the everolimus 3.0 mg group, and none in the Myfortic group.

Wound-related SAEs were reported in six patients in the everolimus 1.5 mg group, seven in the everolimus 3.0 mg group, and three in the Myfortic group. A higher incidence of wound-related SAEs in the everolimus groups is consistent with the known adverse effect of mTOR inhibitors on the wound-healing process.

Similar to the incidence of wound-related events, fluid collections (lymphoceles and seromas) were also more commonly reported in the everolimus groups compared to the Myfortic group, as shown in the graph below.

Figure 11. Management of Wound Fluid Collection



Presented by Dr. Velidedeoglu at the Advisory Committee Meeting on December 7, 2009.

Lymphocele led to drug discontinuations in three patients in the everolimus 1.5 mg group, four patients in the everolimus 3.0 mg group, and none in the Myfortic group.

The Clinical Reviewer concludes that in the everolimus 1.5 mg group there is an increased incidence and severity of overall wound-related complications, as measured by the requirement for surgical and non-surgical interventions, compared to the Myfortic group, which is also statistically significant. In addition, there were more lymphoceles and seromas overall and more that required intervention in the everolimus 1.5 mg group compared to the Myfortic group. In addition, he states that among all the patients who died during the 12 month period, wound related problems (mainly infections and dehiscences and lymphoceles) were noted in five patients in the everolimus 1.5 mg group, four patients in the everolimus 3.0 mg group, and in one patient in the Myfortic group.

CDTL and Clinical Team Leader Comments: There is agreement that wound-related complications and wound-related fluid collections were more common and required more interventions in the everolimus 1.5 mg group compared to the Myfortic group. However, the number of SAEs, and AEs leading to discontinuation of study medication due to these complications were low. It is not possible to comment on the role wound-related problems played in patients who died.

8.5.5 Fluid Accumulation, Including Peripheral Edema, Ascites, and Pleural Effusions

At month 12, the incidence of edema-related AEs was statistically significantly higher in both everolimus groups than in the Myfortic group (55.5% and 54.7% versus 45.1%, p-value was 0.02 and 0.03 respectively, Fisher's exact test).

The incidence major fluid collections, such as edema, reported as AEs is show in Table below. SAEs due to peripheral edema and pleural effusions were observed in three patients in the

everolimus 1.5 mg group, six patients in the everolimus 3.0 mg group, and none in the Myfortic group. Pericardial effusions and ascites were rarely reported.

The Clinical Reviewer notes that fluid accumulation is a known effect of the class of mTOR inhibitors and can cause an increased incidence of pleural and pericardial effusions and can also increase the permeability of serosal membranes in the body to proteins and fluids.

CDTL and Clinical Team Leader Comments: There is agreement that fluid collections were more common and required more interventions in the everolimus 1.5 mg group compared to the Myfortic group. However, the number of SAEs, and AEs leading to discontinuation of study medication due to these complications were low.

Table 15. Types of Major Fluid Collections and Outcome

Type of Fluid Collection	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
Peripheral edema (AE)	123 (44.9)	120 (43.2)	108 (39.6)
Severe peripheral edema	8 (2.9)	4 (1.4)	0
SAE	1 (0.4)	5 (1.8)	0
Drug discontinuation	3 (1.1)	1 (0.4)	0
Pleural effusions (AE)	7 (2.6)	5 (1.8)	5 (1.8)
SAE	2 (0.7)	1 (0.4)	0
Drug discontinuation	0	0	0
Pericardial effusions (AE)	1 (0.4)	1 (0.4)	1 (0.4)
SAE	0	0	0
Drug discontinuation	0	0	0
Ascites (AE)	1 (0.4)	0	0
SAE	0	0	0
Drug discontinuation	0	0	0

8.5.6 Major Cardiac Adverse Events

A specific case report form was designed in order to capture information on the occurrence of major cardiac events (MACE) in the study. The applicant collected information on the following AEs:

- acute myocardial infarction
- congestive heart failure
- percutaneous coronary intervention
- coronary artery bypass graft
- automatic internal cardiac defibrillator
- cerebrovascular accident
- peripheral vascular disease

The total number of patients with MACE was similar in the everolimus 1.5 mg group and the Myfortic groups (2.6% and 2.9%), but the incidence was higher in the everolimus 3.0 mg group (5.8%), as shown in Table below. The rates of drug discontinuations due to cardiac events were two in the everolimus 1.5 mg group, four in the everolimus 3.0 mg group and one in the Myfortic group.

Table 16. Number (%) of Patients with Major Cardiac Adverse Events (MACE)

MACE Terms	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic N=273
Any MACE	7 (2.6)	16 (5.8)	8 (2.9)
Acute myocardial infarction	2 (0.7)	9 (3.2)	4 (1.5)
Congestive heart failure	3 (1.1)	6 (2.2)	2 (0.7)
Percutaneous cardiac intervention	1 (0.4)	3 (1.1)	0 (0.0)
Coronary artery bypass grafting	1 (0.4)	0 (0.0)	0 (0.0)
Automated implanted cardiac defibrillator	0 (0.0)	0 (0.0)	1 (0.4)
Cerebral vascular accident	1 (0.4)	0 (0.0)	0 (0.0)
Peripheral vascular disease	0 (0.0)	1 (0.4)	1 (0.4)

The Clinical Reviewer states that although the overall incidence of MACE events were much higher in the everolimus 3.0 mg group compared to the other two groups in the study, the everolimus 1.5 mg group and the Myfortic group look similar to each other except for the numerically higher number of MIs in the Myfortic group (4 vs. 2). The reviewer looked into the MI events occurring during the study more closely. He concluded that considering the differences in baseline characteristics (twice as many prior MIs in the Myfortic group compared to the everolimus 1.5 mg group), the assessment of drug relatedness and the higher incidence of graft thromboses in the everolimus treatment groups (as discussed in Section 8.4.1), there appears to be a higher association between everolimus and MI as compared Myfortic, which is also supported by the unusually high incidence of nine MIs in the higher dose everolimus 3.0 mg group.

CDTL and Clinical Team Leader Comments: The number of MACE events is low and similar between the everolimus 1.5 mg group and the Myfortic group. One patient in each of these groups had an MI which was implicated in their death. Any further assessment of the relationship between study medication and the occurrence of MI is confounded, since information on prior cardiac history was not systematically collected and transplant patients are known to have multiple risk factors for MI. Finally, the Applicant is not seeking approval of the everolimus 3.0 mg regimen.

8.5.7 Other Thromboembolic Events

Thromboembolic events, other than graft thrombosis, are reported in Table below. There were 13 (4.7%) in the 1.5 mg everolimus group, 16 (5.8%) in the 3.0 mg everolimus group and 9

(3.3%) in the Myfortic group. Two patients with HUS and one each with TTP and TMA were reported in the everolimus 1.5 mg group.

The number of SAEs related to thrombotic events was: eight in the everolimus 1.5 mg group and four in each of the everolimus 3.0 mg and Myfortic groups.

Deep vein thrombosis (DVT) was reported in eight patients in the everolimus 1.5 mg group, seven patients in the everolimus 3.0 mg group, and five patients in the Myfortic group. Pulmonary embolism (PE) was reported in one, two, and two patients in the everolimus and Myfortic groups, respectively. Although there is a trend of increasing DVTs in the everolimus 1.5 mg and the 3.0 mg groups, there is no similar trend for PE. The trend seen with the DVTs is compatible with thrombogenic potential of the class of mTOR inhibitors.

Table 17. Incidence Rates of Thromboembolic Adverse Events

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
Any Thromboembolic AE	13(4.7)	16(5.8)	9(3.3)
Blood and Lymphatic System Disorders -Total	4(1.5)	0	0
Hemolytic uremic syndrome	2(0.7)	0	0
Microangiopathic hemolytic anemia	0	0	0
Thrombotic microangiopathy	1(0.4)	0	0
Thrombotic thrombocytopenic purpura	1(0.4)	0	0
Acute myocardial infarction	2 (0.7)	9 (3.2)	4 (1.5)
Respiratory, Thoracic and Mediastinal Disorders - Total	1(0.4)	2(0.7)	2(0.7)
Pulmonary embolism	1(0.4)	2(0.7)	2(0.7)
Vascular Disorders - Total	8(2.9)	7(2.5)	5(1.8)
Deep vein thrombosis	8(2.9)	7(2.5)	5(1.8)

The Clinical Reviewer concludes that thromboembolic events, other than MIs (which were discussed previously in Section 8.5.6 above), were primarily DVTs, were reported more frequently in both of the everolimus groups compared to the Myfortic group, and that thromboembolic complications are known effects of the M-TOR class of drugs. Also TTP, TMA and HUS, also known to be associated with M-TOR inhibitors, were only observed in the everolimus 1.5 mg group. In the everolimus 1.5 mg group, TTP contributed to the graft loss in one patient (0192-00002).

CDTL and Clinical Team Leader Comments: The overall incidence of thromboembolic AEs was slightly higher in the everolimus 1.5 mg group (13 patients) compared to the Myfortic group (9 patients), and there were more DVTs, but fewer MIs, in the everolimus group. Both thromboembolic complications and TMA/TTP/HUS are associated with M-TOR inhibitors. However, the frequency of these events in this study was low. The sirolimus package insert carries a specific warning regarding TMA/TTP/HUS.

8.5.8 Hematologic Abnormalities, Including Thrombocytopenia, Neutropenia, and Anemia

The overall incidence of hematologic events reported as AEs was 33.9% in the 1.5 mg group, 40.3% in the 3.0 mg group, and 40.7% in the Myfortic group, as shown in Table below. SAEs were reported in eleven patients in the everolimus 1.5 mg group, ten in the everolimus 3.0 mg group, and eight patients in the Myfortic group.

One SAE each of hemolytic anemia, hemolysis, and HUS was seen in the everolimus 1.5 mg group. There were two cases of pancytopenia reported as SAEs in the Myfortic group while none were observed in the everolimus groups.

Table 18. Incidence Rates of Selected Hematological Adverse Events

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
Blood and Lymphatic System Disorders AEs	99 (33.9)	112 (40.3)	111 (40.7)
Anemia	70 (25.5)	86 (30.9)	68 (24.9)
Pancytopenia	2 (0.7)	4 (1.4)	4 (1.5)
Leucopenia	8 (2.9)	6 (2.2)	33 (12.1)
Neutropenia	1 (0.4)	3 (1.1)	6 (2.2)
Thrombocytopenia	3 (1.1)	10 (3.6)	6 (2.2)
Blood and Lymphatic System Disorders SAEs	11 (4.0)	10 (3.6)	8 (2.9)
Anemia	2 (0.7)	5 (1.8)	2 (0.7)
Pancytopenia	0	0	2 (0.7)
Leucopenia	2 (0.7)	1 (0.4)	3 (1.1)
Neutropenia	0	1 (0.4)	1 (0.4)
Thrombocytopenia	2 (0.7)	3 (1.1)	2 (0.7)
Blood and Lymphatic System Disorders AEs leading to Drug Discontinuations	7 (2.6)	2 (0.7)	3 (1.1)
Anemia	1 (0.4)	0	0
Pancytopenia	0	0	0
Leucopenia	1 (0.4)	0	2 (0.7)
Neutropenia	0	0	0
Thrombocytopenia	0	0	1 (0.4)
Blood and Lymphatic System Disorders AEs leading to Dose Adjustment/Interruption	10 (3.6)	12 (4.3)	31 (11.4)
Anemia	1 (0.4)	3 (1.1)	4 (1.5)
Pancytopenia	2 (0.7)	0	2 (0.7)
Leucopenia	4 (1.5)	4 (1.4)	23 (8.4)
Neutropenia	0	1 (0.4)	2 (0.7)
Thrombocytopenia	3 (1.1)	5 (1.8)	3 (1.1)

Thrombocytopenia

Thrombocytopenia was reported as an AE in three patients in the everolimus 1.5 mg group, ten in the everolimus 3.0 mg group, and six in the Myfortic group. Notably low platelet counts (defined as $< 50 \times 10^9$ /L by the Applicant) were not reported for any patient in the everolimus

1.5 mg group, but were reported for 3 patients in the everolimus 3.0 mg group, and one patient in the Myfortic group.

Thrombocytopenia may have contributed to one patient's death in the everolimus 3.0 mg group (0549-0001).

Neutropenia

Neutropenia reported as an AE was highest in the Myfortic group: one, three, and six patients in the everolimus 1.5 mg, 3.0 mg and Myfortic groups, respectively. In a systematic review of absolute neutrophil counts, notably low values (defined by the Applicant as segmented plus band forms totaling $< 1.1 \times 10^9$ cells/L) were reported by a higher percentage of patients in the Myfortic than everolimus groups: 1.8%, 3.6% and 6.3% of patients in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm groups, respectively.

Anemia

Anemia was reported as an AE at a similar rate in the everolimus 1.5 mg (25.5%) and Myfortic 1.44 gm groups (24.9%), but the incidence was higher in the everolimus 3.0 mg group (30.9%). Notably low values for hemoglobin (as defined by the Applicant as < 60 g/L) were reported in the everolimus groups, but not the Myfortic group: 1.5%, 0.4% and 0% of patients in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm groups, respectively.

The Clinical Reviewer concluded that although overall hematologic events reported as AEs were higher in number in the Myfortic group, the number of events reported as SAEs or AEs leading to drug discontinuations are similar between the groups. The main difference in the number of AEs between the two groups is due to the increased incidence of leucopenia observed in the Myfortic group.

CDTL and Clinical Team Leader Comments: The overall rate of hematologic AEs was higher in the Myfortic group than the everolimus 1.5 mg group (40.7% and 33.9%, respectively), which was primarily driven by the much higher incidence of leucopenia in the Myfortic group (12.1% and 2.9%, respectively). SAEs and AEs leading to drug discontinuation were higher in the everolimus 1.5 mg group (4% and 2.6%) compared to the Myfortic group (2.9% and 1.1%), while AEs leading to dose adjustment/interruption were 11.4% in the Myfortic group compared to 3.6% in the everolimus 1.5 mg group.

8.5.9 Interstitial Lung Disease, Lung Infiltration, and Pneumonitis

A total of six patients were reported to have interstitial lung disease (ILD) identified by the applicant using the various related preferred terms: two patients the everolimus 1.5 mg group, three in the everolimus 3.0 mg group, and one in the Myfortic group.

One of the two patients in the everolimus 1.5 mg group had a biopsy confirmed diagnosis of alveolar proteinosis (0304-00016), as discussed in Section 5.3 "Deaths" above. The other patient in the everolimus 1.5 mg group was reported to have ILD, which was probably a coding error instead of "renal interstitial fibrosis," according to the applicant, since the patient

presented with an increased serum creatinine and was diagnosed with acute tubular necrosis (0537-00008).

The preferred term of “lung infiltration” was reported for two patients: one patient in the everolimus 3.0 mg group (0136-00002) and the other in the Myfortic group (0537-00005).

There were also two reports of pneumonitis, both in the everolimus 3.0 mg group, both likely to be related to infectious causes: patient 0507-00019 who died (See Section 5.3 “Deaths) and patient 0124-00072.

The Clinical Reviewer states that five of the reported six cases of possible ILD are in the everolimus groups and the association between the M-TOR inhibitors and ILD is well established and mentioned in the package insert for sirolimus.

CDTL and Clinical Team Leader Comments: There was only one case of interstitial lung disease (alveolar proteinosis) in the everolimus 1.5 mg group. The other patient reported to have ILD was considered to be a coding error. The one patient with lung infiltration in the Myfortic group is also suspect, as the narrative supplied by the Applicant did not discuss any lung-related pathology. Alveolar proteinosis is a rare event associated with mTOR inhibitors and the sirolimus label mentions this AE in the post-marketing section.

8.5.10 Benign and Malignant Neoplasms

Adverse events due to malignant neoplasms were uncommon and evenly distributed across treatments. Total neoplasms (which include non-malignant growths, such as cysts and polyps) were less frequent with both doses of everolimus than Myfortic. The most frequently reported neoplasms in the Myfortic group were basal cell carcinoma, squamous cell carcinoma, skin papilloma and seborrheic keratosis, which are generally either benign or very slowly progressing tumors.

Only one patient died due to malignancy (metastatic melanoma) in the study and occurred in the everolimus 1.5 mg group. There was one patient with Epstein-Barr virus-associated lymphoproliferative disorder, also known as post-transplant lymphoproliferative disorder (PTLD) in the everolimus 3.0 mg group and a B-cell non-Hodgkins lymphoma in the everolimus 1.5 mg group.

The incidence of malignancies reported as SAEs are slightly higher in the Myfortic group (1.8%, n=11) compared to the everolimus 1.5 mg group (1.5%, n=8) and everolimus 3.0 mg group (1.1%, n=4). Types of tumors reported as SAEs:

Everolimus 1.5 mg group:

Basal cell carcinoma (3), Squamous cell carcinoma (3), metastatic melanoma, B-cell non-hodgkin lymphoma

Everolimus 3.0 mg group:

Basal cell carcinoma, Squamous cell carcinoma (2), Post-transplant lymphoproliferative disorder (PTLD)

Myfortic group:

Basal cell carcinoma (5), Squamous cell carcinoma (5), Transitional cell carcinoma

Two patients discontinued study medication due to a neoplasm, one in each of the everolimus groups: malignant melanoma in the everolimus 1.5 mg group and Epstein-Barr virus associated lymphoproliferative disorder (PTLD) in the everolimus 3.0 mg group. The absence of discontinuations in other cases of neoplasms is partly indicative of the relative benign nature of these other tumors.

The Clinical Reviewer concludes the numerically higher occurrence of neoplasms in the Myfortic group compared to the everolimus groups are due to the higher incidence of basal cell, squamous cell carcinomas and benign conditions like skin papillomas and seborrheic keratosis in the Myfortic group.

More important malignancies, with regard to the associated mortality, include one case of malignant melanoma and one case of PTLD (Post Transplant Lymphoproliferative Disorder) listed as EBV-associated lymphoproliferative disorder in the everolimus groups. The patient with malignant melanoma died due to the malignancy. The Reviewer's conclusion is although the number of neoplasms in the Myfortic group are higher the type of neoplasms in the everolimus groups are more serious in nature and resulted in the death of one patient in the everolimus 1.5 mg group.

CDTL and Clinical Team Leader Comments: The Applicant should not have combined malignant and benign neoplasms together, due to the difference in the clinical importance of PTLD and malignant or benign skin lesions. The number of malignancies was low in both the everolimus 1.5 mg group and the Myfortic group. The patient who died of malignant melanoma had a past medical history of skin neoplasm excision before the transplant. During the study he was diagnosed with metastatic malignant melanoma when metastases were found in the bladder, liver, and brain stem. While everolimus did not induce the malignancy in this patient, his overall degree of immunosuppression probably contributed to an accelerated course of the disease. There was one case of non-Hodgkins B-cell lymphoma and no cases of PTLD in the everolimus 1.5 mg group. Malignancies, including PTLD, are associated with all immunosuppressants and the package inserts for these products contain a standard Boxed Warning regarding the risk of lymphoma and other malignancies, particularly of the skin.

8.5.11 New Onset Diabetes Mellitus

According to the study protocol, new onset diabetes (NODM), defined as diabetes post-transplantation which is identified by one of the following:

1. Diabetes was reported as an adverse event;
2. Glucose (random) ≥ 11 mmol/L [198 mg/dL] post-transplantation;
3. Diabetes was recorded as reason for a medication given post-transplantation,

4. In patients who were not diabetic at the time of transplantation, identified by all of the following:
 - a. Reason for transplantation was not diabetes;
 - b. Diabetes was not included in medical history;
 - c. Glucose (random) < 11 mmol/L at the time of transplantation;
 - d. Diabetes was not recorded as reason for any medication given prior to transplantation.

The Applicant's definition of NODM is similar to the standard definition of new onset diabetes after transplant (NODAT) except that it is missing the important criterion of fasting plasma glucose > 126 mg/dL.⁵

The incidence of NODM was 9.1% in the everolimus 1.5 mg group, 12.2% in the everolimus 3.0 mg group, and 6.6% in the Myfortic group. This trend is reflective of the known diabetogenic effects of mTOR inhibitors. Diabetes mellitus or hyperglycemia were infrequent cause of SAEs and there were no discontinuations of study medication due to diabetes-related AEs in any of the treatment groups.

The Clinical Reviewer states that NODAT is a major concern in transplant patients and has not been assessed adequately in this study, mainly because of omitting fasting plasma glucose in the screening criteria. The Reviewer concludes this omission was probably the reason for the low incidence of NODM in all of the treatment groups in this study, when compared to published cumulative incidence of NODAT (all organs) of approximately 16%, at 12 months.⁹ The Reviewer believes that the actual NODAT incidences in the treatment groups in Study A2309 should have been at least 3 times higher than reported (9.1% in the everolimus 1.5 mg group and 6.6% in the Myfortic group) if the NODAT screening had been performed according to the American Diabetes Association (ADA) guidelines and would be more compatible with the literature data

CDTL and Clinical Team Leader Comments: The protocol for this study was discussed with the Division and agreed upon prior to the Applicant starting the study. The definition of NODAT has been evolving over time. It is not clear how the Reviewer arrived at a multiplication factor of 3 and it is not appropriate to recalculate the rates of NODM in this study using this factor. While the incidence of NODM, as defined by the protocol, was slightly higher in the everolimus 1.5 mg group, there was no corresponding increase in the reports of SAEs or discontinuations due to AEs.

8.5.12 Gastrointestinal Adverse Events and Oral Ulcers/Stomatitis

The highest incidence of SAEs in the SOC of Gastrointestinal Disorders was in the everolimus 3.0 mg group (28 patients) followed by the 1.5 mg group (21 patients) and the Myfortic group (18 patients). Diarrhea and vomiting as SAEs were more common in the everolimus 3.0 mg

⁵ Davidson J, Wilkinson A, Dantal J, et al. New-onset diabetes after transplantation: 2003 International Consensus Guidelines. *Transplantation* 2003; 75: SS3.

group compared to the other groups. Two cases of hemorrhagic esophagitis in the everolimus 1.5 mg group and one case of mesenteric vessel thrombosis in the everolimus 3.0 mg group were reported as SAEs, which may be associated with the ulcerative and thrombogenic class effects of mTOR inhibitors.

Ulcerations of the gastrointestinal (GI) tract were reported as AEs in three patients in the everolimus 3.0 mg group (one duodenal, one gastric, and one esophageal), two in the Myfortic 1.44 gm group (one duodenal and one ileal). No patient in the everolimus 1.5 mg group had GI ulcers reported. Regarding upper GI lesions, overall there was a higher incidence of aphthous stomatitis, stomatitis, mouth ulceration, tongue ulceration in both of the everolimus groups compared to the Myfortic group.

Aphthous stomatitis was reported as a SAE in six patients in the everolimus 1.5 mg group, five patients in the everolimus 3.0 mg group, and in two patients in the Myfortic group. There are additional three patients in the everolimus 1.5 mg group and two patients in the everolimus 3.0 mg group who reported as stomatitis compared to none in the Myfortic group.

One patient in the everolimus 3.0 mg group discontinued study medication due to stomatitis and another patient in the everolimus 1.5 mg group discontinued the study medication because of esophageal ulceration (necrotic, ulcerative grade D reflux esophagitis on EGD).

The Clinical Reviewer concludes that mouth ulcerations and gastrointestinal tract ulcerations are among the AEs known to be associated with M-TOR inhibitors. The mechanism is thought to be delayed healing prevention of mucosal regeneration. Ulcerations can be painful and may prevent adequate food and liquid intake by the patient.

CDTL and Clinical Team Leader Comments: There was a low rate of SAEs and discontinuations due to mucosal ulcerations in this study; therefore, it is difficult to conclude that these ulcerations impacted patients' ability to eat and drink.

8.6 Adverse Events Leading to Study Drug Discontinuation (DAE)

During the study, information on study drug discontinuations due to AEs was collected on two different CRFs. The information from the first form (Treatment and Study Completion CRF) is summarized in the Table titled "Premature Study Medication or Study Phase Discontinuation by Treatment Group (ITT Population – 12 Month Analysis) in Section 7.2.1. "Premature Study Medication Discontinuation" above. As noted in the Table, the overall incidence of study drug discontinuations due to AEs according to this first data collection form were 18.1% in the everolimus 1.5 mg group, 20.4% in the everolimus 3.0 mg group, and 9.4% in the Myfortic group. The difference was statistically significant between the everolimus 1.5 mg group (18.1%) compared to the Myfortic group (9.4%) (p-value=0.004) and was primarily driven by significant differences between treatment groups among female patients.

The information collected on the second form (AE/Infections CRF) was more specific and contained information about the type of AE leading to study drug discontinuation. According to the second form, the rates of discontinuation were 23.4% in the everolimus 1.5 mg group,

28.4% in the everolimus 3.0 mg group and 15.8% in the Myfortic group. It was assumed that the information obtained from the second form would be more accurate and detailed; therefore this information is utilized for the analysis of AEs leading to drug discontinuation, as discussed and shown in Table 19 below.

Adverse events leading to study drug discontinuation in the following SOCs were more frequently reported in the everolimus 1.5 mg group than the Myfortic group:

- Blood and Lymphatic System Disorders
- Investigations
- Injury, Poisoning and Procedural Complications
- Renal and Urinary Disorders
- Vascular Disorders

Infections and Infestations, and Gastrointestinal Disorders were the only SOCs where there were more discontinuations in the Myfortic group compared to the everolimus 1.5 mg group. However, the rate of discontinuation in both of these SOCs was higher in the everolimus 3.0 mg group than the Myfortic group.

Table 19. Number (%) of Patients with Adverse Events (AEs) Leading to Study Drug Discontinuation *

**(A patient with multiple occurrences of an AE/infection is counted only once in the AE category. A patient with multiple AEs/infections within a primary system organ class is counted only once in the total row. (Reproduced from the applicant's clinical study report of Study A2309)*

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 gm N=273
	n (%)	n (%)	n (%)
Any AE leading to study drug discontinuation	64 (23.4)	79 (28.4)	43 (15.8)
Blood and lymphatic system disorders	7 (2.6)	2 (0.7)	3 (1.1)
Anemia	1 (0.4)	0 (0.0)	0 (0.0)
Leucopenia	1 (0.4)	0 (0.0)	2 (0.7)
Thrombocytopenia	0 (0.0)	1 (0.4)	1 (0.4)
TTP and TMA**	2 (0.7)	2 (0.7)	0 (0.0)
Cardiac disorders	2 (0.7)	4 (1.4)	1 (0.4)
Gastrointestinal disorders	3 (1.1)	7 (2.5)	6 (2.2)
Hemorrhagic esophagitis	1 (0.4)	0 (0.0)	0 (0.0)
Ulcerative esophagitis	1 (0.4)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	4 (1.5)	1 (0.4)	1 (0.4)
Death	0 (0.0)	0 (0.0)	1 (0.4)
Edema peripheral	3 (1.1)	1 (0.4)	0 (0.0)
Immune system disorders	3 (1.1)	0 (0.0)	3 (1.1)
Kidney transplant rejection	2 (0.7)	0 (0.0)	3 (1.1)
Infections and infestations	4 (1.5)	17 (6.1)	8 (2.9)
Pyelonephritis & renal abscess	0 (0.0)	3 (1.0)	0 (0.0)
Wound infection & abscess	0 (0.0)	6 (2.2)	0 (0.0)
Wound secretion	0 (0.0)	1 (0.4)	0 (0.0)

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 gm N=273
	n (%)	n (%)	n (%)
	Injury, poisoning and procedural complications	14 (5.1)	20 (7.2)
Graft loss	2 (0.7)	6 (2.2)	3 (1.1)
Therapeutic agent toxicity	5 (1.8)	2 (0.7)	0 (0.0)
Wound dehiscence & impaired healing	1 (0.4)	6 (2.2)	0 (0.0)
Investigations	9 (3.3)	10 (3.6)	6 (2.2)
Blood creatinine increased	8 (2.9)	9 (3.2)	2 (0.7)
Metabolism and nutrition disorders	4 (1.5)	1 (0.4)	1 (0.4)
Musculoskeletal and connective tissue disorders	2 (0.7)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.4)	1 (0.4)	0 (0.0)
Nervous system disorders	0 (0.0)	2 (0.7)	1 (0.4)
Renal and urinary disorders	11 (4.0)	18 (6.5)	10 (3.7)
Focal segmental glomerulosclerosis	0 (0.0)	3 (1.1)	0 (0.0)
Nephropathy toxic	1 (0.4)	3 (1.1)	3 (1.1)
Proteinuria	2 (0.7)	4 (1.4)	0 (0.0)
Reproductive system and breast disorders	1 (0.4)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	2 (0.7)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	2 (0.7)	1 (0.4)
Vascular disorders	3 (1.1)	4 (1.4)	2 (0.7)
Lymphocele	3 (1.1)	4 (1.4)	0 (0.0)

***Thrombotic thrombocytopenic purpura (TTP), Thrombotic microangiopathy (TMA)*

The Clinical Reviewer concluded that AEs leading to discontinuation in the SOC of Injury, Poisoning and Procedural Complications, which includes wound healing problems and investigations for blood creatinine increases, were more common in both of the everolimus groups compared to the Myfortic group. AEs in the SOC of Infections and Infestations were reported twice as frequently in the 3.0 mg everolimus group as in the Myfortic group. The AEs of wound abscess and wound infection were reported for six patients in the everolimus 3.0 mg group compared to none in the other two groups.

The Preferred Terms (PTs) of graft loss, focal segmental glomerulosclerosis, toxic nephropathy and proteinuria were more frequently reported as a reason for discontinuation in the everolimus 3.0 mg group than the 1.5 mg group. The SOC of Blood and Lymphatic System Disorders and the PTs of increased blood creatinine, therapeutic agent toxicity, proteinuria, peripheral edema, and lymphocele had more reports of AEs leading to study drug discontinuation in the 1.5 mg everolimus treatment group than the Myfortic group. Therapeutic agent toxicity was always related to CsA according to the investigators' recording of adverse events. AEs in the SOC of Infections and Infestations and the PTs of leukopenia and gastrointestinal disorders were more common in the Myfortic group compared to either of the everolimus groups.

The Applicant also reported AEs requiring an adjustment or interruption to treatment were reported in 22.3% of patients in the everolimus 1.5 mg group, 27.0% of patients in the everolimus 3.0 mg group, and 34.8% of patients in the Myfortic group. This higher incidence of dose adjustment/interruption in the Myfortic group was mainly due to the higher incidence of adjustment or interruption in Blood and Lymphatic System Disorders, Gastrointestinal Disorders, and Infections and Infestations. This may partly be explained by the high incidence of gastrointestinal adverse effects and leukopenia associated with mycophenolic acid (MPA)-containing products.

The Clinical Reviewer noted that the higher rate of dose adjustments and interruptions due to AEs is strength of the Myfortic regimen, not as a weakness, since it proves the manageability of the Myfortic immunosuppressive regimen. He views these symptoms as a “surrogate” for MPA trough levels, which are not routinely done in clinical practice. In the Reviewer’s opinion, the main reason for the higher rate of study drug discontinuations in the everolimus groups was the difficulty of managing the everolimus-low dose CsA immunosuppressive regimen due to the long-half life of everolimus and the interdependence of adjusting everolimus and CsA doses due to a interaction between the two drugs.

CDTL and Clinical Team Leader Comments: There is agreement that AEs leading to study drug discontinuation are not the same as dose adjustments/interruptions. The fact that the everolimus 1.5 mg group had a higher rate of discontinuations compared to Myfortic may have reflected, in part, the fact that Study A2309 is an open-label study and investigators may not have had much experience in adjusting everolimus trough concentrations. As a result, they may have preferred to discontinue patients rather than adjust the dose. In contrast, clinicians are well versed in reducing Myfortic doses based on toxicities. It should also be noted that patients were discontinued from the everolimus regimens for a variety of AEs and it is not possible to identify one or several main causes of discontinuations.

8.7 Common AEs

The most common AEs were reported in the following SOCs for all treatment groups: Metabolism and Nutrition Disorders, Gastrointestinal Disorders, and General Disorders and Administration Site Conditions. As shown in the Table below, the most common preferred terms are consistent with AEs discussed in earlier sections and reflect the known AE profile of the mTOR inhibitors and Myfortic.

Table 20. Incidence Rates of Most Frequent ($\geq 20\%$ in any Treatment Group) Adverse events/Infections by Primary System Organ Class and Preferred Term (Safety population - 12 month analysis)

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic N=273 n (%)
Any AE/Infection	271 (98.9)	276 (99.3)	270 (98.9)
Blood and lymphatic system disorders	99 (33.9)	112 (40.3)	111 (40.7)
Anemia	70 (25.5)	86 (30.9)	68 (24.9)
Gastrointestinal disorders	196 (71.5)	208 (74.8)	207 (75.8)
Constipation	105 (38.3)	122 (43.9)	117 (42.9)
Nausea	79 (28.8)	80 (28.8)	85 (31.1)
Vomiting	40 (14.6)	48 (17.3)	60 (22.0)
General disorders and administration site conditions	181 (66.1)	185 (66.5)	207 (75.8)
Edema peripheral	123 (44.9)	120 (43.2)	108 (39.6)
Infections and infestations	169 (61.7)	178 (64.0)	185 (67.8)
Urinary tract infection	60 (21.9)	57 (20.5)	63 (23.1)
Investigations	137 (50.0)	120 (43.2)	133 (48.7)
Blood creatinine increased	48 (17.5)	52 (18.7)	59 (21.6)
Metabolism and nutrition disorders	222 (81.0)	233 (83.8)	199 (72.9)
Hyperkalemia	49 (17.9)	58 (20.9)	48 (17.6)
Hyperlipidemia	57 (20.8)	60 (21.6)	43 (15.8)
Vascular disorders	122 (44.5)	137 (49.3)	124 (45.4)
Hypertension	81 (29.6)	76 (27.3)	82 (30.0)

8.8 Foreign Post-Marketing Experience

Everolimus in combination with CsA first received marketing authorization, as Certican®, for the prophylaxis of organ rejection in *de novo* renal and heart transplant recipients, in Mexico, on July 8, 2003. Currently, everolimus as Certican is marketed by Novartis in 70 countries worldwide.

AEs of angioneurotic edema and pancreatitis, not included in the Company Core Data Sheet (also referred to as the Summary of Product Characteristics) prepared at the time of initial approval, but have been added based on post-marketing reports.

Angioneurotic edema was the subject of an assessment in November 2005 after receipt of literature reports of tongue swelling and was included in the document as a common disorder reported predominantly in patients receiving concomitant therapy with ACE inhibitors. A cumulative search identified 25 reports (described as angioedema or as edema/swelling evoking the diagnosis) in the Applicant's safety database. In all but three cases patients were receiving concomitant therapy with an ACE inhibitor or angiotensin receptor blocker. When outcome was documented, complete recovery was apparent in all cases after treatment

(steroids, antihistamines and, in one case, tracheostomy). Negative rechallenge was reported in two patients with reintroduction of everolimus following withdrawal of the ACE inhibitor.

Pancreatitis was recently re-assessed. It was noted that although the incidence in the initial phase 3, double-blind clinical trials was not elevated above that in the control groups (azathioprine, mycophenolate mofetil), it was included as drug-related disorder in the labels of both these drugs. One case of positive re-challenge among the documented cases was noted.

9 Advisory Committee Meeting

A meeting of the Anti-Infectives Advisory Committee to discuss NDA 22-268 was held on December 7, 2009. The following is a Quick Minutes summary prepared by Elaine Ferguson from the Advisors and Consultants Staff.

3 Page(s) has been withheld in full immediately following this page as duplicative – see the Advisory Committee Meeting Information located at the FDA website.

10 Pediatrics

A Pediatric Written Request (which has now expired) was issued on April 25, 2000 for Certican® (everolimus) Tablets to obtain needed pediatric information on the active moiety, everolimus (RAD001), in pediatric transplant patients for the prophylaxis of acute rejection in allogeneic kidney and liver transplantation.

The April 25, 2000 written request was issued to obtain needed information on safety, tolerability, and basic pharmacokinetics to select an adequate dosing regimen for pediatric transplant patients. Study 3 (Study B351), which is the primary focus of this pediatric exclusivity denial, was set forth in the April 25, 2000 written request. The April 25, 2000 written request included for Study 3 the following endpoint criteria: the collection of information on longer-term safety (i.e., infections, serious adverse events, vital signs, physical examinations, electrocardiogram, safety laboratory evaluations, and concomitant medications), incidence of biopsy-proven acute rejection, graft loss or death, and chronic graft dysfunction at 6 and 12 months post-transplantation. (b) (4)

[Redacted]

[Redacted] (b) (4)

Given that the application is being issued a CR letter, a final decision on the pediatric plan has not been made. The Division is considering a deferral or waiver for the development pediatric program but due to the CR action, consensus was not reached within the Division and with the Pediatrics and Maternal Health Staff. Once the labeling and a REMS program for everolimus in adult patients is addressed, a decision about the information needed in pediatric patients, and whether the studies conducted to date by Novartis are adequate, will be determined, in consultation with the Pediatric and Maternal Health Staff.

11 Other Relevant Regulatory Issues

11.1 DSI Inspections

DSPTP discussed the need for inspections with DSI. The DSI reviewer Susan Thompson, MD, informed the division that DSI inspections were not necessary. Inspections were conducted during the review cycle of Afinitor®, NDA 22-334.

11.2 DRISK Consult and REMS

The Division consulted DRISK of OSE for the review of the proposed REMS by Novartis and worked very closely with the DRISK review team consisted of Kathryn O’Connell, MD, PhD, (scientific lead) Suzanne Berkman Robottom, Pharm.D (Team Leader).

The applicant submitted a REMS proposal (in the June 30, 2009) submission without request from FDA. The goals they targeted were education about drug level monitoring and the risk of wound healing complications. To achieve these educational goals, they proposed a patient Medication Guide and a Communication Plan (CP) for healthcare professionals (HCP), with a timetable for assessments consistent with FDAAA minimum requirements of 18 months, 3 years, and 7 years post-approval. Novartis did not submit any of the Communication Plan materials. During the NDA review, the applicant was offered interim advice about the goals in the event that FDA did request a REMS which was sent on October 28, 2009. Specifically, they were advised of the 3 safety issues noted at the time by the clinical reviewer (proteinuria, wound healing, lipid abnormalities) that the REMS should address, and that if a CP became necessary, mock-ups of all materials and the specifics of distribution would need to be submitted for review (in consult with DRISK). These safety issues were raised as a concern based on the review of the safety data from study A2309. On November 9, 2009, Novartis submitted revised materials to their proposed REMS.

On December 7, 2009 the Advisory Committee (AC) voted almost unanimously for approval (with one no vote based on efficacy). In the safety discussion, the AC focused mainly on the lack of long-term cardiovascular outcomes data. They voiced concern about proteinuria and hyperlipidemia, which are risk factors associated with poor cardiovascular outcomes. The AC members were also asked to vote on whether they thought a REMS was necessary. The committee voted in the affirmative, but did not provide detailed advice, with no clear consensus about what the Communication Plan should consist of (the goals) or who should be targeted for education/communication. One member voiced concerns about off-label use. The AC members placed emphasis on post-marketing studies and trials, which are separate from REMS.⁶ The committee did note that the safety issues identified for everolimus are not significantly different from the risks of other mTOR inhibitors in the class, specifically sirolimus which is indicated for prophylaxis if organ rejection in renal transplant recipients.

Following excerpts are taken from the DRISK review:

⁶ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>

...Management of organ transplant recipients involves teams of highly experienced healthcare practitioners well versed in therapeutic drug monitoring and the plethora of potentially serious side effects of currently available drugs for rejection prevention...

...The risks identified during the course of the everolimus application review are recognized mTOR class effects and are not specific to this moiety. In the absence of information that the risks of everolimus are different or more severe than for sirolimus, additional measures beyond labeling and pharmacovigilance do not appear necessary to ensure that the benefits of the drug outweigh the risks...

Therefore the DRISK consultants did not recommend a Communication Plan or Elements to Assure Safe Use if everolimus is approved. The DRISK team also concluded that a Medication Guide was a consideration, since the product does have serious risks that could affect a patient's decision to use or continue to use the drug. Furthermore, the DRISK team commented that if a Medication Guide is required for everolimus at the time of approval; it should be required for sirolimus as well. In conclusion, the DRISK review team recommended a Medication Guide-only REMS for everolimus.

CDTL and Clinical Team Leader Comments: During the review process several adverse events emerged warranting a Medication Guide to communicate these risks to kidney transplant patients in order to ensure the benefits outweigh the risks associated with everolimus. In addition, the Communication Plan, as it is envisioned by the Division, will take advantage of the product launch period in order to communicate these important risks to the healthcare professionals (physicians, nurses, pharmacists etc.) and the healthcare professional societies. The risks of wound healing complications, hyperlipidemia, proteinuria, and graft thromboses, as well as nephrotoxicity when co-administered with standard doses of cyclosporine were identified as the goals of a REMS by the review team based on the review of the safety data in the submission.

It is generally agreed that these risks are not unique to everolimus but rather mTOR inhibitor class effects. However, the experience with the only approved mTOR inhibitor for the same indication (sirolimus), has shown us that the risk profile for mTOR inhibitor class has slowly emerged over the last 10 years of its marketing. Therefore, with a better understanding of this safety profile and the limitations of its use, the Division can make the most informed decision in trying to mitigate these risks. The AC members were not able to specifically identify the goals for such a REMS program. However, they did underline the need for communicating cardiovascular related risks (i.e. hyperlipidemia and proteinuria) to healthcare professionals. The Division agrees with the DRISK review team, that with the approval of everolimus with a Medication Guide, it will be logically required for sirolimus as well; this recommendation was also supported by the AC members. The Review Division will take advantage of authority to require a REMS given by the 2007 Food and Drug Administration Amendments Act (FDAAA) to require a similar REMS program if feasible.

On a final note, since REMS program as proposed by the applicant (goals and the CP materials) are not ready for approval, the application will be given a Complete Response, pending submission of these materials.

12 Labeling

12.1 *Proprietary name*

DSPTP requested a consult for the review of the proprietary name [REDACTED] (b) (4) [REDACTED] from the Division of Medication Error Prevention and Analysis (DMEPA) and DDMAC. [REDACTED] (b) (4)

(b) (4) [REDACTED]

On November 23, 2009 Novartis submitted draft examples of cartons, container labels, and blister foils for all Tablet strengths 0.25mg, 0.5mg, 0.75mg and 1.0mg along with the proposed name of Zortress. In an e-mail dated DMEPA sent notification e-mail to DSPTP email is that the DMEPA has reached the midpoint of their review and determined the proposed proprietary name Zortress (everolimus) is acceptable. Their decision was based upon the information submitted by the Applicant, DDMAC's promotional evaluation, DSPTP's initial comments, and DMEPA's safety evaluation. Their initial review included tables of the names found to look and/or sound similar to Zortress. In addition, DMEPA evaluation did not identify any other factors that render the name unacceptable at this time.

12.2 *Physician Labeling*

The applicant's draft label was substantially revised by the review team. An initial revised version of certain sections of the PLR label was sent to the applicant on November 20, 2009 and on December 2, 2009. Subsequent near final complete version was attached to the Complete Response letter.

Boxed Warning, and Warnings and Precautions sections were revised as follows based on the findings from Study A2309. In addition, Boxed Warning, Warnings and Precautions were in line with the known safety profile of mTOR inhibitor class. It is noted that although the PI is near final at the time of Complete Response letter, further changes may be warranted during the next review cycle.

(b) (4)



(b) (4)



(b) (4)



12.3 Carton and Container Labels

On November 23, 2009 Novartis submitted draft examples of cartons, container labels, and blister foils for all Tablet strengths 0.25mg, 0.5mg, 0.75mg and 1.0mg, this submission is under review by OSE/DMEPA.

12.4 Medication Guide

DRISK is involved with the review of the proposed Medication Guide. This review can be finalized when the Physician Labeling is near complete.

13 Assay for Everolimus Therapeutic Drug Monitoring

The proposed regimen is an initial dose of everolimus 0.75 mg orally twice daily (i.e., 1.5 mg/day) (b) (4) The dose should be adjusted to achieve a

target whole blood trough concentration of 3 to 8 ng/mL. Therapeutic Drug Monitoring (TDM) will be crucial to the safe and effective use of the product upon approval.

(b) (4)

(b) (4)

CDRH was notified that there was no FDA approved product for (TDM) and a teleconference was held between representatives from DSPTP, CDRH (Division of In Vitro Diagnostics) and Novartis to discuss the status of the assays and Novartis's intentions on November 20, 2009. Novartis indicated that they are disappointed that there is no assay which will be cleared by the PDUFA goal date and discussed their back-up plan, which was to make available a central laboratory located in (b) (4) which utilizes a LS/MS/MS assay for processing of all patients samples with a 24-hour turnaround time for results. (b) (4)

(b) (4) Novartis states that the (b) (4) facility is a CLIA lab and the bioanalytic results and reports were submitted as part of the NDA. It is not clear that the facility is GMP compliant, which is an important requirement for CDRH. When Novartis was asked if the (b) (4) facility would be making a submission to CDRH, they replied that they did not know their plans.

In a letter dated December 2, 2009, Novartis provided authorization to representatives from the FDA Division of Special Pathogens and Transplant Products (DSPTP), and to representatives from the FDA Center of Disease and Radiologic Health (CDRH), to review and discuss those parts of the documents relevant for the monitoring of everolimus blood levels. Novartis noted in this letter that they were working separately with 4 independent external partners and provided the contact information for these (b) (4) laboratories:

(b) (4)

Subsequently, the following comments were included in the Complete Response letter regarding the assay for everolimus TDM based on the guidance received from Avis Danishefsky of CDRH via e-mail dated December 10, 2009:

1. We encourage you to work with diagnostic companies developing everolimus assays, particularly those using the same technology as the assays used in trial A2309. As we noted previously, the most straightforward comparison for any new assay would be for the new assay to measure samples from the Novartis trial (A2309) and compare their new analytical results with the analytical results

obtained during the trial. This recommendation assumes the samples are completely stable over the time period/conditions stored. If this is not the case and/or if sufficient samples from the trial are not available, we recommend that the diagnostic assay manufacturer compare clinical sample results obtained with their new assay to results obtained from the assay/laboratory used during the Novartis clinical trial A2309. We appreciate any assistance you can provide to device manufacturers regarding provision of information or materials to facilitate their studies for supporting an FDA submission.

2. Tests using different measurement technologies are often not directly comparable. Immunoassays, for example, often have significant cross-reactivities with metabolites that can bias test results. Given the narrow therapeutic range of 3-8 ng/mL which appears to be critical to use of everolimus as currently understood, we strongly encourage you to collaborate with manufacturers developing LCMSMS assays, specifically. Cross-reactivity likely to be present in immunoassays can lead, not only to bias, but also to unpredictable variability between samples due to variations in metabolite accumulation either between individual patients, or within individual patients over time.
3. The specific assay used during your clinical trial could be submitted to FDA's Center for Devices and Radiological Health as a 510(k). Please note that manufacturing of such an assay to be marketed for clinical use must follow the Quality System Regulation (21 CFR Part 820).

14 Recommendations/Risk Benefit Assessment

The efficacy results from Study A2309 showed that both everolimus treatment regimens were non-inferior to the Myfortic control regimen at 12 months with regard to the primary efficacy composite endpoint consisting of the first occurrence of treated BPAR, graft loss, death or loss to follow-up. Additionally, the incidence rate of death, graft loss and loss to follow-up was similar between both everolimus groups and Myfortic, although numerically these events were more frequent in the everolimus groups compared to the Myfortic group.

Among female patients, the primary efficacy failure rate, as well as, the rate of graft loss/death/loss to follow-up was higher in both everolimus groups compared to the Myfortic group. These differences in females were driven by higher rates of treated BPAR, death and graft loss in both everolimus groups compared to Myfortic. Specifically, graft loss occurred in 5.0%, 6.8% and 2.3% and death in 4.0%, 3.4% and 0% in the everolimus 1.5 mg, 3.0 mg and Myfortic groups respectively.

There were no notable differences in the primary efficacy failure rate among treatment groups in subgroup analyses by age and race.

In terms of GFR, there were no statistically significant differences between any of the treatment groups at month 12.

A total of 23 patients died during the first 12 months of the study, 7 in the everolimus 1.5 mg group, 10 in the 3.0 mg everolimus group, and 6 in the Myfortic control group. The most common causes of death across the study groups were related to cardiac conditions and infections. In the FDA's attributability assessment, the majority of the deaths in both of the everolimus groups were felt likely to be related to the study drug, whereas two of the deaths in the Myfortic group were felt to be unrelated (motor vehicle accidents) and another patient had been switched to sirolimus for most of the follow-up period. Of note, in the everolimus 1.5 mg group there was one patient who developed new hypercholesterolemia after starting the study drug and died of a myocardial infarction and another patient who died after the initial 12 month cut-off (and was not included in the overall numbers above) with alveolar proteinosis.

The number of graft losses in the study was 12 in the everolimus 1.5 mg group, 14 in the everolimus 3.0 mg group, and 8 in the Myfortic group. The number of graft losses due to thrombosis was six in the everolimus 1.5 mg group, four in the everolimus 3.0 mg group, and two in the Myfortic group.

Based on UNOS/USRDS data from over 84,000 renal transplants, graft thrombosis within 30 days occurs in 0.9% of transplants.⁷ The incidence of graft thrombosis in the everolimus 1.5 mg group within 30 days of transplant is 1.8% (5/274); and becomes 2.1% (6/274) if an additional patient 0515-00004 who lost his graft on day 55 is included. The incidences of graft thrombosis were 1.4% (4/278) in the everolimus 3.0 mg group and 0.7% (2/273) in the Myfortic group.

The incidence of SAEs was lower in the Myfortic group compared to both of the everolimus groups in almost in every SOC except for Infections and Infestations, Neoplasms, and Renal and Urinary Disorders.

There were more study drug discontinuations due to AEs in the everolimus 1.5 mg group compared to the Myfortic group (23.4% vs. 15.8%). The number of discontinuations in the everolimus 1.5 mg group is also higher for female patients compared to male patients.

Rates of total infections, total fungal, and total bacterial infections were similar across all treatment groups. Viral infections were higher in the Myfortic group and were driven primarily by an increased occurrence of CMV infections. There were nine SAEs of CMV infections and an additional SAE of CMV esophagitis in the Myfortic group and none in the everolimus groups. According to the patient narratives, all of these CMV infections responded promptly to treatment. The higher incidence of CMV infections in the Myfortic group did not result any cases of graft losses or death.

The higher incidence of neoplasms in the Myfortic group compared to the everolimus groups was mainly due to the higher incidence of basal and squamous cell carcinomas and there were no deaths. One patient in the everolimus 1.5 mg group died due to malignant melanoma. There was one patient with PTLD (Epstein-Barr virus-associated lymphoproliferative disorder)

⁷ Ojo AO, Hanson JA, Wolfe RA, et al. Dialysis modality and the risk of allograft thrombosis in adult renal transplant recipients. *Kidney Int.* 1999;55:1952-1960.

in the everolimus 3.0 mg group and a B-cell non-Hodgkins lymphoma in the everolimus 1.5 mg group.

Starting at six months there was a statistically significant and progressively increasing gap between the proteinuria levels, as measured by the UP/UC ratio, between the everolimus 1.5 mg group and the Myfortic group, in favor of the Myfortic group. The exposure-response analysis performed by the Pharmacometrics Reviewer found a relationship between everolimus trough concentrations and proteinuria. There were very few SAEs or discontinuations due to AEs related to proteinuria in this study.

Hyperlipidemia was reported more frequently in the everolimus group compared to the Myfortic group and lipid lowering agents were taken by more patients in these groups, as well. The exposure-response analysis performed by the Pharmacometrics Reviewer found a relationship between everolimus trough concentrations and hypercholesterolemia. There were few SAEs or discontinuations due to AEs related to hyperlipidemia.

The incidence of new onset diabetes mellitus (NODM) was 9.1% in the everolimus 1.5 mg group, 12.2% in the everolimus 3.0 mg group, and 6.6% in the Myfortic group. This trend is reflective of the known diabetogenic effects of mTOR inhibitors.

Overall rates of incisional wound complications, surgical repair or intervention were higher in both of the everolimus groups compared to the Myfortic group with the highest rates occurring in the 3.0 mg group. The total numbers of intraoperative surgical interventions required (i.e., for hernia, infection and dehiscence) were 19 in the everolimus 1.5 mg group, 22 in the everolimus group, and 9 surgical interventions in the Myfortic group. Similar to the incidence of wound-related events, fluid collections (lymphoceles and seromas) were also more common in the everolimus groups compared to the Myfortic group. The number of surgical or percutaneous interventions required for seromas and lymphoceles combined is also higher in the everolimus groups compared to the Myfortic group (24, 43, and 15 interventions, respectively).

In summary, the everolimus 1.5 mg regimen was non-inferior, with respect to the primary efficacy endpoint of treated BPAR, graft loss, death and loss-to-follow-up and demonstrated a similar GFR compared to Myfortic. Additionally, female patients receiving everolimus had a higher failure rate and more premature treatment discontinuation compared to females receiving Myfortic.

Although Study A2309 succeeded in showing the non-inferiority of the everolimus 1.5 mg regimen to the active comparator (Myfortic regimen) in terms of efficacy and also showed similar renal function at the end of 12 months; in the Clinical Reviewer's opinion the magnitude and importance of the safety problems observed in the everolimus 1.5 mg group, mainly numerically increased mortality with more deaths attributed to study medication in the everolimus group, more graft losses related to thrombosis, significantly higher levels of proteinuria and hyperlipidemia, impaired wound healing, fluid collections, and of perceived safety problems, which are explained in more detail in this review, pose serious risks for kidney transplant patients.

The CDTL and Clinical Team Leader agree that the results of Study A2309 demonstrate that everolimus has a similar safety profile to other approved immunosuppressants (i.e., risk of infection, malignancy, NODM, proteinuria, hyperlipidemia, etc.) and also appears to possess class toxicities similar to the mTOR inhibitor class due to its mechanism of action. mTOR inhibitors are known to cause endothelial dysfunction, resulting in thrombotic events, proteinuria, and gastrointestinal mucosal ulcerations. mTOR inhibitors are also known to cause an increased permeability of serosal membranes in the body to proteins and fluids resulting in fluid accumulations and alveolar proteinosis and impair wound healing. The anti-proliferative effects of mTOR inhibitors are thought to play a role in azoospermia. These class effects of m-TOR inhibitors were manifested in Study A2309 by an increased risk of graft thrombosis, proteinuria, fluid collections, and edema in the everolimus 1.5 mg group compared to the Myfortic group. However, there was no imbalance in the death rate between treatment arms or thromboembolic events such as MI. SAEs and AEs leading to discontinuation occurred more frequently in the everolimus 1.5 mg group compared to Myfortic, but the SOCs and PTs were varied and did not clearly indicate a particular toxicity or toxicities that contributed to the higher rates.

In summary, everolimus appears to possess toxicities related to its mechanism of mTOR inhibition. The Advisory Committee voted in favor of approval of this product with a REMS to mitigate these toxicities. The CDTL and Clinical Team Leader agree that the toxicities of this product can be addressed through product labeling and a REMS.

14.1 Recommendation for Postmarketing Risk Management Activities

The Division has determined that, if NDA 21-560 is approved, the Applicant will be required, pursuant to section 505(o)(3) of the FDCA, to conduct the following:

1. Submit the final report for Trial A2309 which contains the 24-month follow-up safety and efficacy data on all patients enrolled in the trial.

The specific details of this postmarketing requirement and other postmarketing studies and trials that may be required will be described more fully in the approval letter for this application, if it is approved.

14.2 Recommendation for other Postmarketing Study Commitments

None at the time Complete Response letter but these may be requested in the approval letter for this application, if approved.

14.3 Additional Comments to Applicant

In addition to the post marketing requirement described above, if approved, and the assay comments that were described under other comments for the Applicant to consider included the following:

CDTL Review

1. Please provide the results from any pre-testing of the proposed communication materials for the required REMS. This should include explanation of how the materials were modified based on the results.
2. We request that you voluntarily submit the proposed advertising and launch material that you propose to use with Zortress (everolimus).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOETTE M MEYER
12/23/2009

OZLEM A BELEN
12/23/2009

Division Director Review

Applicant: Novartis
Drug: everolimus
Trade Name: Zortress¹
Date of Submission: December 19, 2002 (approvable letter October 20, 2003)
Resubmission #1: February 27, 2004 (approvable August 27, 2004)
Resubmission #2: June 30, 2009
PDUFA Goal Date: December 30, 2009
Division Goal Date: December 23, 2009
Formulation: Tablet
Strengths: 0.25 mg, 0.5 mg, and 0.75 mg, 1 mg tablets
Indication: Prevention of rejection in kidney transplant patients
Related NDA: NDA 21-561 (dispersible tablet)
IND: IND 52,003

Material Reviewed:

Project Management: Jacquelyn Smith, Diana Willard
Safety Project Manager: Hyun Son
Clinical Review: Ergun Velidedeoglu, Joette Mever, (original submission: Arturo Hernandez, Marc Cavaille Coll)
Cross Discipline Team Leader/Safety Deputy Director: Ozlem Belen
Microbiology Review: Simone Shurland, Shukal Bala
CDRH consultation for everolimus assay: Avis Danishefsky, Courtney Harper
Clinical Pharmacology Review: Jang-Ik Lee, Dakshina Chilukuri, Kevin Krudys (pharmacometrics), Pravin Jadhav (pharmacometrics), Phil Colangelo
Statistics Review: Xiao Ding, Karen Higgins, LaRee Tracy, Mohammad Huque. John Stephen Yap, Aloka Chakravarty
Pharmacology/Toxicology Review: Stephen Kunder, William Taylor
Chemistry Manufacturing Controls Review: Mark Seggel, Stephen Miller
Division of Scientific Investigations (DSI): Susan Thompson
Office of Surveillance and Epidemiology (OSE)
OSE/Division of Medication Error and Prevention Analysis (DMEPA): Nitin Patel, Judy Park, Carol Holquist
OSE/Division of Pharmacovigilance II (DPVII): S. Christopher Jones, Melissa Truffa, Robert Boucher
OSE/Division of Drug Risk Evaluation (DRISK): Kathleen O'Connell, Suzanne Berkman Robottom
Advisors and Consultants Staff: Elaine Ferguson
Cardiovascular and Renal Drugs Advisory Committee meeting December 7, 2009: quick minutes
Safety Response Team (SRT), SWAT, and Office of Chief Counsel (OCC): review of CR letter and REMS memo

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1 RECOMMENDATIONS

Novartis will be issued a complete response (CR) letter for everolimus, requesting that the package insert be revised to reflect the findings from the clinical studies, particularly study A2309, the renal transplant study submitted June 30, 2009, reviewed by the Division and presented before the December 7, 2009 Cardiovascular and Renal Drug Advisory Committee (CRDAC) meeting. In addition, Novartis will need to submit a revised REMS, including Medication Guide, and propose other measures to manage specific risks associated with the product including: wound healing complications, hyperlipidemia, proteinuria, graft thrombosis, as well as nephrotoxicity associated with full-dose cyclosporine.

The proposed indication and dosage regimen are summarized below. The complete package insert with the Division's labeling recommendations will be attached to the action letter.

1.1 Proposed Indication

Prophylaxis of Organ Rejection in Kidney Transplantation

Zortress (everolimus) is indicated for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant [*see Clinical Studies (14.1)*]. Zortress is to be administered in combination with basiliximab and concurrently with reduced doses of cyclosporine and corticosteroids. Therapeutic drug monitoring is recommended for all patients receiving everolimus and cyclosporine [*see Dosage and Administration (2.2 and 2.3)*].

Limitations of Use

- In patients at high immunologic risk, the safety and efficacy of everolimus has not been established
- Use of everolimus for the prophylaxis of organ rejection in transplanted organs other than kidney has not been established.

- [REDACTED] (b) (4)

- [REDACTED] (b) (4)

1.2 Proposed Dosage Regimen

An initial everolimus dose of 0.75 mg orally twice daily (1.5 mg/day) is recommended for adult kidney transplant patients in combination with reduced dose cyclosporine, administered as soon as possible after transplantation [*see Therapeutic Drug Monitoring (2.2 and 2.3), Clinical Studies (14.1)*].

Routine everolimus whole blood therapeutic drug concentration monitoring is recommended for all patients using a [REDACTED] (b) (4) assay methodology. The recommended everolimus therapeutic range is 3-8 ng/mL [*see*

Clinical Pharmacology (12.5)]. Careful attention should be made to clinical signs and symptoms, tissue biopsies, and laboratory parameters.

Cyclosporine: In the clinical trial the targeted trough concentrations were 100 to 200 ng/mL (Month 1), 75 to 150 ng/mL (Month 2-3), 50 to 100 (Month 4-5), 25 to 50 (Month 6 and after). (b) (4)

1.3 Other Requests

In addition, the CR letter will ask for the 24- month study results for A2309, continued work on the everolimus assay, and voluntary submission of advertising material to see how the safety information will be presented.

2 BACKGROUND

Everolimus is known by several other names. During development it was named SDZ RAD or RAD001. It is marketed worldwide under the trade name Certican (b) (4) and now has a new US trade name, Zortress.

As summarized by Novartis, everolimus is currently approved in over 70 countries for the prophylaxis of organ rejection in adults receiving a renal or cardiac transplant, and approximately 4,000 kidney, 500 liver, and 250 heart transplant patients have been treated. The drug is approved for transplant patients in the European Union, but has not been approved in (b) (4) or the US for this use. Everolimus under the trade name Afinitor® was approved in March 2009 for use in renal cell carcinoma patients. Novartis states that everolimus has not been withdrawn from marketing for safety or efficacy reasons in any country.

The original NDA 21-560 (tablets) was submitted December 19, 2002 for the indications of heart and kidney transplantation. NDA 21-561 (dispersible tablets) was also submitted (b) (4) The heart transplantation indication was administratively assigned different NDA numbers: NDA 21-628 (tablet) and NDA 21-631 for dispersible tablet.

During development, Novartis evaluated two different starting doses of everolimus – the 1.5 mg/day (0.75 mg bid) or 3.0 mg/day (1.5 mg bid) doses. Initial studies evaluated fixed daily dose regimens (no adjustment to dose) while subsequent studies evaluated doses that were adjusted to target trough concentrations of 3-8 ng/mL and 6/12 ng/mL, respectively. The 1.5 mg/day starting dose, adjusted to 3-8 ng/mL whole blood trough concentration is proposed for approval, the higher dose was also shown to be effective but had more adverse events, including dose related adverse events of proteinuria and hyperlipidemia, and is not being sought for approval.

Two Phase 3 studies (B201 and B251) in kidney transplantation were submitted in the original NDAs in 2002 and reviewed. In these trials, the fixed dose of everolimus was 1.5

mg/day or 3 mg/day, no adjustment. Full dose cyclosporine (CsA) consisted of target trough concentrations of 150 to 400 ng/mL (Weeks 1-4), 100 to 300 ng/mL (Months 2-12), 50 to 75 ng/mL (after Month 12). Patients receive steroids, and no induction. While these trials showed efficacy, glomerular filtration rate calculated by the Nankivell method, was lower and this was judged a safety issue, therefore Novartis was asked to establish a safe and effective dosing regimen for everolimus and CsA that minimizes renal function impairment while maintaining efficacy, such as concentration-controlled regimens of everolimus and cyclosporine using therapeutic dose monitoring (TDM).

The GFR measured by Nankivell method was 6 to 8 mL lower in the everolimus 1.5 mg group and 7 to 11 mL lower in the everolimus 3.0 mg group at 12 months (in this 24 month study) compared to the control regimen containing mycophenolate mofetil (MMF) as shown below:

Table 7: Median Estimated Creatinine Clearance (mL/min) using Nankivell Method by Treatment Group (ITT Group ^a)						
	Study B201			Study B251		
	1.5 RAD (N=194)	3.0 RAD (N=198)	MMF (N=196)	1.5 RAD (N=193)	3.0 RAD (N=194)	MMF (N=196)
Baseline	18.5 (N=184)	18.7 (N=188)	18.6 (N=178)	23.7 (N=187)	24.3 (N=185)	26.8 (N=184)
RAD vs. MMF ^a	p=0.627	p=0.887	NA	p=0.039	p=0.116	NA
1.5 RAD vs. 3.0 RAD ^a	p=0.727	NA	NA	p=0.653	NA	NA
Month 3	57.3 (N=154)	54.9 (N=152)	60.0 (N=158)	61.8 (N=155)	58.1 (N=151)	64.0 (N=159)
RAD vs. MMF ^a	p=0.168	p=0.004	NA	p=0.060	p=0.001	NA
1.5 RAD vs. 3.0 RAD ^a	p=0.119	NA	NA	p=0.057	NA	NA
Month 6	56.7 (N=146)	52.9 (N=135)	61.0 (N=147)	58.4 (N=150)	54.9 (N=135)	65.6 (N=151)
RAD vs. MMF ^a	p=0.003	p<0.001	NA	p<0.001	p<0.001	NA
1.5 RAD vs. 3.0 RAD ^a	p=0.197	NA	NA	p=0.195	NA	NA
Month 12	54.3 (N=123)	53.3 (N=119)	60.3 (N=138)	58.0 (N=140)	55.2 (N=116)	66.6 (N=141)
RAD vs. MMF ^a	p=0.002	p<0.001	NA	p<0.001	p<0.001	NA
1.5 RAD vs. 3.0 RAD ^a	p=0.389	NA	NA	p=0.247	NA	NA

Following the approvable letter of October 20, 2003, the company sent in studies A2306 and A2307 on February 27, 2004 which evaluated a TDM-controlled regimen of everolimus, compared to a fixed-dose regimen, but did not include a control arm and therefore were not determined to be sufficient to overcome the safety concern. Therefore an approvable letter on August 27, 2004 was sent, and led to the design of study A2309. The Division and Novartis agreed on the design of this study, including the noninferiority design. In the current June 30, 2009 submission, the sponsor submitted data from this prospectively designed study (A2309) that compared two target concentrations for everolimus with reduced cyclosporine to mycophenolic acid (MPA) with standard dose of cyclosporine.

2.1 Other mTOR inhibitor (sirolimus, Rapamune)

Everolimus is an mTOR inhibitor, related to sirolimus (Rapamune®). Rapamune was approved as the oral solution for prevention of rejection in renal transplant patients in 1999, and the tablet formulation was approved in 2000. Initially, the 2 mg dose was used, but subsequently Wyeth conducted cyclosporine withdrawal studies, and this regimen was approved in 2004. As part of the approval it was recommended that sirolimus be

dosed to target trough concentrations of 16-24 ng/mL in the first year, and 12-20 ng/mL thereafter.

Since its approval in 1999, sirolimus has had labeling updated to include new adverse event information, as listed below:

- Boxed warning
 - Hepatic artery thrombosis in liver transplant
 - Bronchial dehiscence in lung transplant
- Warnings and Precautions
 - (b) (4)
 - Wound healing
 - Renal injury, proteinuria, low GFR
 - Hyperlipidemia
 - Interstitial pneumonitis
 - Edema, fluid collection
 - TTP/TMA/HUS
- Conversion from a CNI-based regimen – safety and efficacy of sirolimus not established

Many of these events were also seen during the review of everolimus, therefore the decision was also made to present this application before an open public advisory committee. Furthermore, depending on the course of action with the everolimus application, it is possible that similar approaches will need to be taken regarding the sirolimus application.

3 REVIEW

3.1 Chemistry Manufacturing and Controls:

Dr Seggel notes in his review of December 22, 2009 that “this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.” He adds that an "Acceptable" site recommendation from the Office of Compliance has been made. However, labeling issues are still pending as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the labeling issues are resolved.”

Dr Seggel describes everolimus as

“a semisynthetic macrolide immunosuppressant derived from sirolimus. Sirolimus, also known as rapamycin, is the active ingredient in Wyeth's approved Rapamune drug products, and is obtained by fermentation with a strain of *Streptomyces hygroscopicus*. The manufacture of sirolimus by Novartis subsidiary Biochemie G.m.b.H. (now Sandoz) is described in Drug Master File 15720. Everolimus is obtained through a short synthetic sequence in which a hydroxyethyl group is coupled to the hydroxyl group of the cyclohexyl side chain of sirolimus. Everolimus is poorly water-soluble. Like sirolimus, everolimus is susceptible to oxidation. (b) (4)

(b) (4) butylated hydroxytoluene (BHT), a commonly used antioxidant. The material (sometimes referred to as RAD n BHT) is isolated as an amorphous powder.”

3.2 Microbiology

Drs Shurland and Bala reviewed the microbiology and noted that everolimus is a macrolide, related to rapamycin, where the hydrogen of the 40-hydroxyl group in rapamycin was replaced with a 2-hydroxyethyl group, forming a stable ether bond [40-O-(2-hydroxyethyl)-rapamycin].

As proposed for labeling, everolimus is an inhibitor of intracellular signal transduction which targets mTOR (mammalian Target of Rapamycin). mTOR is a key serine/threonine kinase regulating protein synthesis and ultimately cell growth and proliferation. Everolimus shows potent immunosuppressive activity both *in vitro* and in animal models of allotransplantation. The following summary information is provided:

On a cellular level everolimus inhibits growth factor-stimulated cell proliferation irrespective of the cell lineage or growth factor involved. This inhibition is reversible, that is, everolimus is not a cytotoxic compound. On a molecular level, growth factor-stimulated phosphorylation of p70 S6 ribosomal protein kinase (p70S6K) is inhibited in the presence of everolimus. To exert its activity everolimus needs to form a complex with a cytoplasmic binding protein, FKBP-12; this everolimus/FKBP-12 complex in turn is thought to bind to and disable mTOR. p70S6K is a key translational regulator which controls protein synthesis, in particular that of pivotal proteins involved in cell growth and cell cycle regulation. p70S6K is a downstream effector of mTOR, it gets activated by mTOR-catalyzed phosphorylation. Inhibiting the activation of p70S6K by interfering with mTOR eventually results in cell cycle arrest and inhibition of cell proliferation. The immunosuppressive activity of everolimus is explained by its ability to prevent IL-2/IL-15-stimulated T cell proliferation. Antigen-induced activation of an antigen-specific T cell, reflected by the production of cytokines/interleukins (i.e. IL-2), and subsequent proliferation of the activated T cell (i.e. clonal-expansion) are the hallmark features of a T cell immune- response. Immunosuppressive treatment strategies are therefore aimed at prevention of T cell activation and/or proliferation. While cyclosporine or tacrolimus prevent the first step, the activation of T cells, everolimus inhibits the interleukin-driven clonal expansion of activated T cells by inhibiting mTOR function. The different modes of action for everolimus and cyclosporine provide an adequate rationale for the pharmacodynamic synergy which has been demonstrated *in vitro* and in animal models of allotransplantation

In animal models, including non-human primate models, everolimus effectively prevents allograft rejection resulting in prolonged graft survival (orthotopic kidney, heterotopic heart, and unilateral lung allotransplantation in the rat; orthotopic kidney and unilateral lung allotransplantation in cynomolgus monkeys). It is also able to reverse ongoing allograft rejection as shown in rat unilateral lung allotransplantation. *In vitro* experiments and rat transplantation studies indicate synergistic immunosuppressive activity of everolimus and cyclosporine. The combination of everolimus and cyclosporine has also been demonstrated to be considerably more effective in cynomolgus monkey models of unilateral lung allotransplantation than either compound alone. Everolimus has further the ability to inhibit growth factor-stimulated proliferation of vascular smooth muscle cells. Growth factor-stimulated vascular smooth muscle cell proliferation, which is triggered by injury to endothelial cells and leads to neointima formation, plays a key role in the pathogenesis of chronic rejection as defined by allograft nephropathy and cardiac allograft vasculopathy. Preclinical experiments with everolimus show inhibition of neointima formation in a rat aorta allotransplantation model. Everolimus is also found to inhibit the key events involved in

restenotic lesion formation following vascular injury in multiple species including rats, rabbits, and pigs. Finally, everolimus is a potent inhibitor of the growth and proliferation of tumor cells, endothelial cells, and fibroblasts.

In sum, everolimus acts to inhibit progression of the cell from G1 to S phase.

3.3 Toxicology

There is no new information in the current resubmission. The preclinical toxicology studies were previously reviewed by Dr Kunder and summarized in the review by Dr. Taylor and in the Cross-Discipline Team Leader (CDTL) review. A main difference between proposed labeling for Afinitor and Zortress is currently a Pregnancy Category D for Afinitor based on input from the Oncology Advisory Committee, whereas this Division and MHT recommend a Pregnancy category C, given there are no human data in pregnant women. In addition to reproductive data, information on some of the animal toxicology results (e.g., testicular atrophy, azospermia) will be included in section 13.2 of labeling. As expected with an immunosuppressant, lymphoid atrophy was seen in animals.

3.4 Clinical Pharmacology

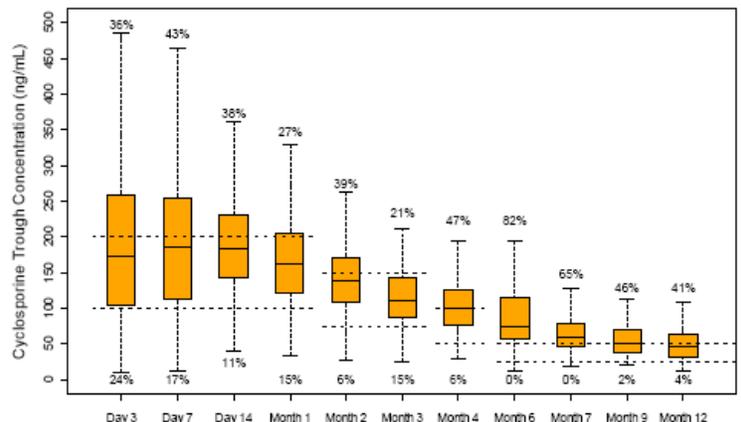
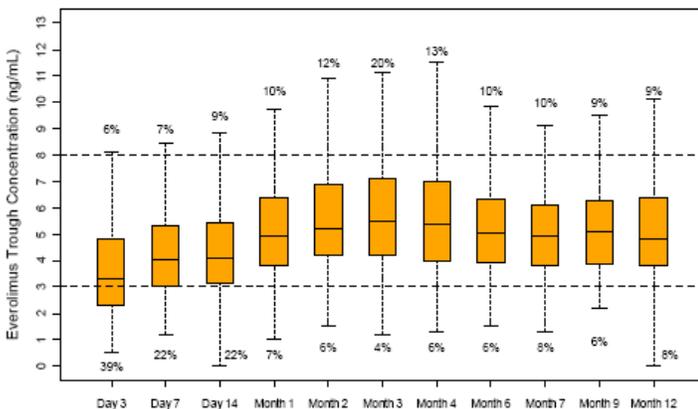
The characteristics of everolimus, including exposure response, were reviewed in detail by Drs. Lee, Chilukuri, Krudys, Pravin, and Colangelo. They determined that “80% of patients had everolimus whole blood trough concentrations within the 3 to 8 ng/mL target range (with starting dose 0.75 mg BID in Study A2309) by Month 1 and remained stable within range through Month 12,” whereas the cyclosporine concentration exceeded target troughs during months 4 to 12 between approximately 40% to 60%.

The protocol specified CsA troughs are shown below (Dr Yap’s review).

Table 2: Protocol-Specified Neoral (cyclosporine) Trough Values (mg/mL)

Groups	Month 1	Starting Month 2	Starting Month 4	Starting Month 6
Everolimus	100-200	75-150	50-100	25-50
Myfortic	200-300	-	150-250	-

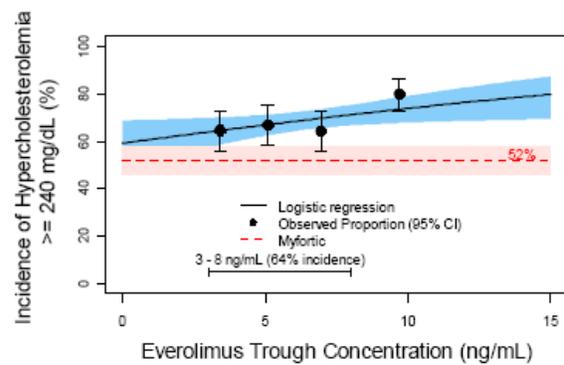
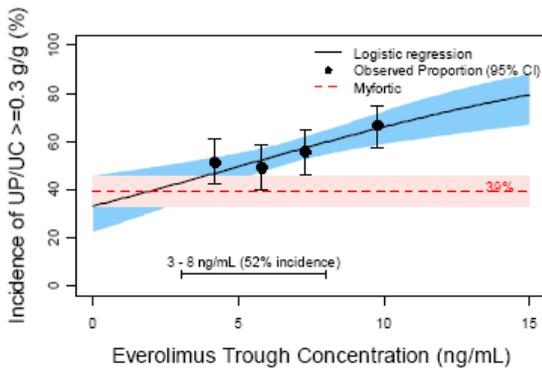
The measured everolimus concentrations are shown in the figure on the left, the cyclosporine concentrations on the right.



The data support the therapeutic target concentration of 3 to 8 ng/mL, with rates of BPAR, graft loss and death lowest when everolimus is in this target range.

Everolimus trough levels	Treated BPAR	Graft Loss	Death
< 3 ng/mL	6/33 (18.2%)	4/35 (11.4%)	1/37 (2.7%)
3 – 8 ng/mL	64/415 (15.4%)	15/410 (3.7%)	9/411 (2.2%)
> 8 ng/mL	9/99 (9.1%)	3/101 (3.0%)	5/101 (5.0%)
Myfortic	47/277 (17%)	9/277 (3.2%)	6/277 (2.2%)

Exposure-response (E-R) data showed that proteinuria (left figure) and hyperlipidemia (right figure) had a positive relationship, whereas other events such as wound healing, peripheral edema and new onset diabetes mellitus did not show an E-R relationship.



As noted in the CDTL review, based on the original clinical pharmacology reviews by Dr Lee from October 17, 2003 and August 17, 2004, everolimus is known to be a substrate for both cytochrome CYP3A4 and P-glycoprotein and such information will need to be included in labeling. Cyclosporine is a CYP3A4/P-glycoprotein inhibitor and CYP3A4 substrate; therefore, everolimus concentrations will be affected. Everolimus concentrations may decrease when doses of cyclosporine are reduced, unless the everolimus dose is increased. In a single-dose study in 12 healthy subjects, Neoral administered at a dose of 175 mg increased everolimus AUC by 168% (range, 46% to 365%) and Cmax by 82% (range, 25% to 158%) when administered with 2 mg everolimus compared with administration of everolimus alone.

3.5 Efficacy

As noted above, the original NDA contained results of studies B201 and B251, which demonstrated efficacy but safety concerns were identified. In the current submission, the statistical reviewers found that study A2309 met the predefined 10% margin for the 95%

confidence interval and was noninferior to the Myfortic (MPA) /standard dose CsA regimen for the composite endpoint of treated biopsy-proven acute rejection, graft loss, death or loss to follow-up.

Furthermore, “As compared to the Myfortic treatment regimen, both everolimus treatment regimens were demonstrated to have similar renal function measured as estimated mean glomerular filtration rate (GFR) at 12 months post-transplantation.”

Analysis by gender revealed that among female patients, rates of premature treatment discontinuation were significantly higher, but the higher number of primary efficacy failure and graft loss and death were not significant compared to the Myfortic group.

3.5.1 Study Design

A2309 was a Phase 3, randomized, open-label comparative study in 79 centers across Europe, North and South America. A total of 833 *de novo* kidney transplant male and female patients between the ages of 18 and 70 years were randomized 1:1:1 to one of the following 3 regimens:

- Everolimus 1.5 mg/day (0.75 mg bid) starting dose (target trough concentration of 3-8 ng/mL) with *reduced dose* Neoral + Simulect+corticosteroids (n=277)
- Everolimus 3.0 mg/day (1.5 mg bid) starting dose (target trough concentration of 6-12 ng/mL) with *reduced dose* Neoral + Simulect+corticosteroids (n=279)
- Myfortic 1.44 g (0.72 g bid) and standard dose Neoral + Simulect+corticosteroids (n=277)

The primary efficacy endpoint was efficacy failure at 12 months post transplantation, where efficacy failure is the composite endpoint consisting of treated biopsy-proven acute rejection (BPAR) episode (based on local laboratory assessment), graft loss, death, or loss to follow-up, based on a pre-specified 10% noninferiority (NI) margin. The study will last 24-months, the 12-months data were submitted June 30, 2009 for review.

**Table 3: Primary Efficacy Endpoint Analysis by Treatment Group
(ITT Population - 12 Month Analysis)**

	everolimus 1.5 mg (N=277)	everolimus 3.0 mg (N=279)	Myfortic 1.44 g (N=277)
Number of patients (%)			
Efficacy Failure	70 (25.3)	61 (21.9)	67 (24.2)
Treated BPAR	45 (16.3)	37 (13.3)	47 (17.0)
Graft Loss	12 (4.3)	13 (4.7)	9 (3.3)
Death	7 (2.5)	10 (3.6)*	6 (2.2)
Loss to follow-up	12 (4.3)	8 (2.9)**	9 (3.3)
95% CI (everolimus-Myfortic)	(-6.1, 8.3)	(-9.3, 4.7)	N/A
97.5% CI (everolimus-Myfortic)	(-7.1, 9.3)	(-10.3, 5.7)	N/A

* One patient who died 10 days after withdrew consent was included

** One patient who had graft loss before the randomization was considered as loss to follow-up

3.5.2 Noninferiority Margin

Dr Xiao Ding’s review includes a justification of the non-inferiority (NI) margin, submitted by Novartis to IND 52,003 on June 26, 2009. Because there are no placebo controls studies on which to base the effect of everolimus, the margin justification consisted of a review of the literature, various assumptions, and a mixed effects modeling approach. The statistical reviewers concluded that the “10% NI margin for the 12-month composite endpoint is acceptable given that the estimated lower bound around the estimated difference between the active control and the putative placebo is 18.9%. Although the lower bound is 18.9%, a margin larger than 10%; however, would be considered too large from a clinical perspective.”

3.5.3 Subset analyses

Gender, age and race subgroup analysis, respectively, did not show significant differences ($p > 0.05$) between the 1.5 mg/day and control arms in the following three tables from the statistical review.

Number of patients (%)	Males Total =556			Females Total =276		
	everolimus 1.5 mg (N=176)	everolimus 3.0 mg (N=191)	Myfortic 1.44 g (N=189)	everolimus 1.5 mg (N=100)	everolimus 3.0 mg (N=88)	Myfortic 1.44 g (N=88)
Efficacy Failure *	50 (28.4)	41 (21.5)	56 (29.6)	19 (19.0)	20 (22.7)	11 (12.5)
Treated BPAR	33 (18.8)	25 (13.1)	39 (20.6)	12 (12.0)	12 (13.6)	8 (9.1)
Graft Loss	7 (4.0)	7 (3.7)	7 (3.7)	5 (5.0)	6 (6.8)	2 (2.3)
Death	3 (1.7)	7 (3.7)**	6 (3.2)	4 (4.0)	3 (3.4)	0 (0)
Loss to follow-up	10 (5.7)	7 (3.7)	8 (4.2)	1 (1.0)	1 (1.1)	1 (1.1)
95% CI (everolimus –Myfortic)	(-10.5, 8.1)	(-16.9, 0.6)	N/A	(-3.8, 16.8)	(-0.9, 21.4)	N/A
P-value ***	p=0.82	p=0.08		p=0.24	p=0.11	

* One subject’s gender was unknown (in the everolimus 1.5 mg group) and is excluded from this analysis.

Also a statistically significant interaction between treatment and gender (Breslow-Day test p-value =0.01) was identified in the comparison of everolimus 3.0 mg to Myfortic

** One patient who died 10 days after withdrew consent was included

*** P-value for the Fisher’s exact test

Number of patients (%)	Recipient Age ≤ 50 Total =452			Recipient Age > 50 Total =380		
	everolimus 1.5mg (N=156)	everolimus 3.0mg (N=153)	Myfortic 1.44 g (N=143)	everolimus 1.5mg (N=120)	everolimus 3.0mg (N=126)	Myfortic 1.44 g (N=134)
Efficacy Failure	44 (28.2)	35 (22.9)	35 (24.5)	25 (20.8)	26 (20.6)	32 (23.9)
Treated BPAR	30 (19.2)	23 (15.0)	26 (18.2)	15 (12.5)	14 (11.1)	21 (15.7)
Graft Loss	7 (4.5)	5 (3.3)	5 (3.5)	5 (4.2)	8 (6.4)	4 (3.0)
Death	4 (2.6)	4 (2.6)	1 (0.7)	3 (2.5)	6 (4.8)**	5 (3.7)
Loss to follow-up	8 (5.1)	6 (3.9)	4 (2.8)	3 (2.5)	2 (1.6)	5 (3.7)
95% CI (everolimus – Myfortic)	(-6.3, 13.7)	(-11.3, 8.1)	N/A	(-13.3, 7.2)	(-13.4, 6.9)	N/A
P-value ***	p=0.51	p=0.79		p=0.65	p=0.55	

* One subject’s age was unknown (in the everolimus 1.5 mg group) and is excluded from this analysis

** One patient who died 10 days after withdrew consent was included

*** P-value for the Fisher’s exact test

Number of patients (%)	Black Total =113			Non-Black Total =720		
	everolimus 1.5mg (N=34)	everolimus 3.0mg (N=40)	Myfortic 1.44 g (N=39)	everolimus 1.5mg (N=243)	everolimus 3.0mg (N=239)	Myfortic 1.44 g (N=238)
Efficacy Failure	10 (29.4)	14 (35.0)	15 (38.5)	60 (24.7)	47 (19.7)	52 (21.9)
Treated BPAR	7 (20.6)	9 (22.5)	12 (30.8)	38 (15.6)	28 (11.7)	35 (14.7)
Graft Loss	3 (8.8)	4 (10.0)	2 (5.1)	9 (3.7)	9 (3.8)	7 (2.9)
Death	0 (0)	2 (5.0)	3 (7.7)	7 (2.9)	8 (3.3)**	3 (1.3)
Loss to follow-up	2 (5.9)	1 (2.5)	1 (2.6)	10 (4.1)	7 (2.9)	8 (3.4)
95% CI (everolimus – Myfortic)	(-30.7, 12.6)	(-24.7, 17.8)	N/A	(-4.7, 10.4)	(-9.5, 5.1)	N/A
P-value***	p=0.47	p=0.82		p=0.52	p=0.57	

* One subject was classified as non-black without specified actual race is included in the analysis

** One patient who died 10 days after withdrew consent was included

*** P-value for the Fisher's exact test

Subgroup analyses of the incidence of graft loss, death or loss to follow-up by recipient age and race are presented in Table 24 and Table 25, respectively. No significant differences were seen among treatments within the different age or race categories.

3.6 Safety

The safety was reviewed by the clinical and statistical reviewers, and exposure-response analysis was done by clinical pharmacology/pharmacometric group. The very comprehensive clinical reviews should be consulted for detailed information. Of note, the Medical Officer review of this application recommends that everolimus not be approved because of concerns regarding the various adverse events associated with the use of everolimus, including serious events, thrombotic episodes and a numerical difference in the number of graft losses and deaths. Key safety issues are summarized below and a discussion of the risk benefit is included in the CONCLUSIONS section.

As seen in most transplantation studies, the rates of adverse events reported in the patients was high, with over 98% of patients reporting an adverse event, as shown in the table from the submission (Table 12-5 and 12-6, pages 172-172 of submission)

Table 12-6 Incidence Rates of Most Frequent (>= 20% in any Treatment Group) Adverse events/Infections by Primary System Organ Class and Preferred Term (Safety population - 12 month analysis)

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 g N=273 n (%)
Any AE/Infection	271 (98.9)	276 (99.3)	270 (98.9)
Blood and lymphatic system disorders	99 (33.9)	112 (40.3)	111 (40.7)
Anaemia	70 (25.5)	86 (30.9)	68 (24.9)
Gastrointestinal disorders	196 (71.5)	208 (74.8)	207 (75.8)
Constipation	105 (38.3)	122 (43.9)	117 (42.9)
Nausea	79 (28.8)	80 (28.8)	85 (31.1)
Vomiting	40 (14.6)	48 (17.3)	60 (22.0)
General disorders and administration site conditions	181 (66.1)	185 (66.5)	207 (75.6)
Oedema peripheral	123 (44.9)	120 (43.2)	108 (39.6)
Infections and infestations	169 (61.7)	178 (64.0)	185 (67.6)
Urinary tract infection	60 (21.9)	57 (20.5)	63 (23.1)
Investigations	137 (50.0)	120 (43.2)	133 (48.7)
Blood creatinine increased	48 (17.5)	52 (18.7)	59 (21.6)
Metabolism and nutrition disorders	222 (81.0)	233 (83.8)	199 (72.9)
Hyperkalaemia	49 (17.9)	58 (20.9)	48 (17.6)
Hyperlipidaemia	57 (20.8)	60 (21.6)	43 (15.8)
Vascular disorders	122 (44.5)	137 (49.3)	124 (45.4)
Hypertension	81 (29.6)	76 (27.3)	82 (30.0)

Source: Table 14.3.1-1.20

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Table 12-5 Number (%) of patients experiencing adverse events/infections by system organ class and treatment group (Safety population - 12 month analysis)

System organ class	Everolimus 1.5 mg	Everolimus 3.0 mg	Myfortic 1.44 g
	N=274 n (%)	N=278 n (%)	N=273 n (%)
Any system organ class	271 (98.9)	276 (99.3)	270 (98.9)
Blood and lymphatic system disorders	93 (33.9)	112 (40.3)	111 (40.7)
Cardiac disorders	43 (15.7)	39 (14.0)	42 (15.4)
Congenital, familial and genetic disorders	7 (2.6)	4 (1.4)	2 (0.7)
Ear and labyrinth disorders	13 (4.7)	4 (1.4)	14 (5.1)
Endocrine disorders	11 (4.0)	10 (3.6)	20 (7.3)
Eye disorders	29 (10.6)	22 (7.9)	28 (10.3)
Gastrointestinal disorders	196 (71.5)	208 (74.8)	207 (75.8)
General disorders and administration site conditions	181 (66.1)	185 (66.5)	160 (58.6)
Hepatobiliary disorders	7 (2.6)	8 (2.9)	8 (2.9)
Immune system disorders	14 (5.1)	9 (3.2)	11 (4.0)
Infections and infestations	169 (61.7)	178 (64.0)	185 (67.8)
Injury, poisoning and procedural complications	163 (59.5)	174 (62.6)	163 (59.7)
Investigations	137 (50.0)	120 (43.2)	133 (48.7)
Metabolism and nutrition disorders	222 (81.0)	233 (83.8)	199 (72.9)
Musculoskeletal and connective tissue disorders	112 (40.9)	104 (37.4)	105 (38.5)
Neoplasms benign, malignant and unspecified (Incl cysts and polyps)	9 (3.3)	8 (2.9)	16 (5.9)
Nervous system disorders	92 (33.6)	96 (34.5)	109 (39.9)
Pregnancy, puerperium and perinatal conditions	1 (0.4)	0 (0.0)	0 (0.0)
Psychiatric disorders	90 (32.8)	76 (27.3)	72 (26.4)
Renal and urinary disorders	112 (40.9)	143 (51.4)	124 (45.4)
Reproductive system and breast disorders	50 (18.2)	51 (18.3)	23 (8.4)
Respiratory, thoracic and mediastinal disorders	86 (31.4)	108 (38.8)	93 (34.1)
Skin and subcutaneous tissue disorders	92 (33.6)	103 (37.1)	102 (37.4)
Social circumstances	0 (0.0)	1 (0.4)	1 (0.4)
Surgical and medical procedures	0 (0.0)	2 (0.7)	0 (0.0)
Vascular disorders	122 (44.5)	137 (49.3)	124 (45.4)

Source: [Table 14.3.1-1.1](#)

Of note, however, more everolimus patients discontinued treatment in study A2309, due to adverse events compared to Myfortic, while more MPA patients had dosage adjustment due to adverse events. Per Dr. Yap, at “Month 12, the incidence of premature treatment discontinuation in the everolimus 1.5 mg group, 3.0 mg and Myfortic groups was 30.0% (83/277), 34.1% (95/279), and 21.7% (60/277) respectively. Compared to the Myfortic group, the incidence was statistically significantly higher in the everolimus 1.5

mg group (p-value=0.03, Fisher’s exact test) and in the everolimus 3.0 mg group (p-value=0.001, Fisher’s exact test).”

Table 2: Premature Study Medication or Study Phase Discontinuation by Treatment Group (ITT Population - 12 Month Analysis)

	everolimus 1.5 mg (N=277)	everolimus 3.0 mg (N=279)	Myfortic 1.44 g (N=277)
Number of patients (%)			
Discontinued study medication	83 (30.0)	95 (34.1)	60 (21.7)
Adverse event(s)	50 (18.1)	57 (20.4)	26 (9.4)
Unsatisfactory therapeutic effect	11 (4.0)	14 (5.0)	13 (4.7)
Subject withdrew consent	11 (4.0)	4 (1.4)	5 (1.8)
Graft loss	3 (1.1)	6 (2.2)	6 (2.2)
Death	3 (1.1)	3 (1.1)	4 (1.4)
Protocol deviation	2 (0.7)	5 (1.8)	2 (0.7)
Abnormal lab value	1 (0.4)	4 (1.4)	1 (0.4)
Administrative problems	2 (0.7)	1 (0.4)	2 (0.7)
Abnormal test procedure	0 (0)	1 (0.4)	0 (0)
Unknown	0 (0)	0 (0)	1 (0.4)
Discontinued study phase	38 (13.7)	33 (11.8)	28 (10.1)
Subject withdrew consent	20 (7.2)	8 (2.9)	12 (4.3)
Graft loss	9 (3.3)	10 (3.6)	7 (2.5)
Death	7 (2.5)	9 (3.2)	6 (2.2)
Unknown	2 (0.7)	6 (2.2)	3 (1.1)

It should be noted that when premature discontinuation was factored in as “efficacy failure,” the rate was 37.2% for everolimus 1.5 mg/day and 30.3% for MPA, the 95% confidence interval was (-1.0, 14.7).

In addition Dr. LaRee Tracy presented the following table during the December 7, 2009 CRDAC meeting:

Any AE Leading to:	Everolimus 1.5 mg (n=274)	Everolimus 3.0 mg (n=278)	Myfortic 1.44 gm (n=273)
Drug Discontinuation	64 (23.4)	79 (28.4)	43 (15.8)
Dose Adjustment/Interruption	61 (22.3)	75 (27.0)	95 (34.8)
Drug Discontinuation/ Adjustment/ Interruption	100 (36.5)	131 (47.1)	119 (43.6)

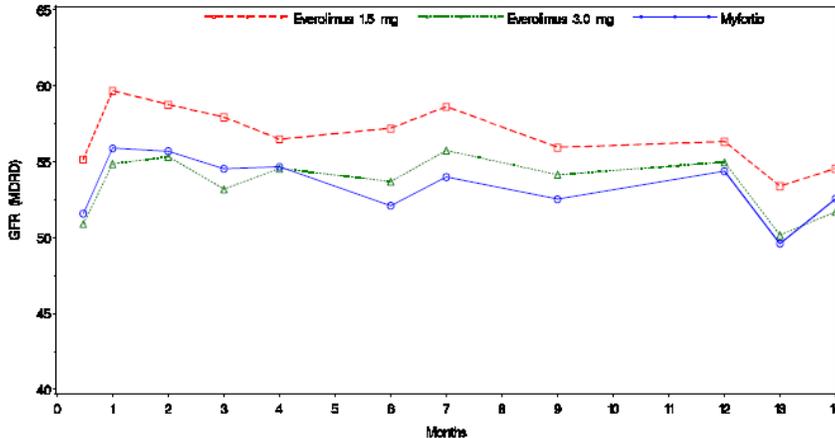
One way to interpret the above numbers is that more patients who do not tolerate everolimus versus MPA are managed with drug discontinuation (23.4% versus 15.8%) while more patients on MPA than everolimus can be managed with dose adjustment or interruption (34.8% versus 22.3%). After the initial dose, everolimus is dosed by TDM, whereas there is no assay for MPA levels, and dose adjustments are based on patients’ response and adverse events profile.

Given the results in the original studies B201 and B251, Per Dr. Yap, noted that the “main safety endpoint was renal function at Month 12 as measured by the calculated GFR using the MDRD formula. The primary safety objective of the study was to demonstrate that at least one of the everolimus treatment arms was non-inferior to the Myfortic treatment arm by an 8 mL/min/1.73 m² pre-specified non-inferiority margin within 12 months of the initial dose of study medication with respect to the main safety endpoint.” Based on the review, the GFR mean and standard deviation in mL/min/1.73 m² were 54.6 (21.7) for everolimus 1.5 mg/day, 51.1 (22.8) for everolimus 3.0 mg/day and 52.3 (26.5) for Myfortic control arm. The differences were not significant, although by the Wilcoxon test, the p-value was 0.02 for the everolimus 1.5 mg arm versus the Myfortic arm. The difference favors the everolimus arm, although in part this may be accounted for by the lower concentrations of CsA in the everolimus compared to the MPA arm.

“Various imputation methods were used to look at patients who lost grafts or discontinued treatment (LOCF), and all consistently showed that the GFR in the everolimus 1.5 mg/day are was higher (in some analyses statistically significant) compared to MPA.

Dr Yap concluded that “Study A2309 demonstrated that calculated 12-month GFR, using the modification of diet in renal disease (MDRD) formula, was similar between both everolimus groups and the Myfortic group.”

Figure 2: Mean Calculated GFR (MDRD) (ITT Population)



Note: Month 13 represents the Month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the Month 12 visit. Month 14 represents the Month 12 study endpoint consisting of the last post-baseline observation up to and including the Month 12 visit.

SAEs in the following MedDRA System Organ Classes (SOCs) were reported at a higher rate in the everolimus 1.5 mg group compared to the Myfortic group as summarized in Dr Velidedeoglu’s MO review:

- Blood and lymphatic system disorders, (4% vs. 2.9%)
- Gastrointestinal disorders (7.7% vs. 6.6%)
- General disorders and administration site conditions (5.5% vs. 4.4%)
- Injury, poisoning and procedural complications (14.2% vs. 11.7%)

- Investigations (8.4% vs. 8.1%)
- Metabolism and nutrition disorders (7.3% vs. 4.8%)
- Musculoskeletal and connective tissue disorders (1.8% vs. 0.4%)
- Nervous system disorders, psychiatric disorders (2.2% vs. 1.8%)
- Psychiatric disorders (1.1% vs. 0%)
- Reproductive system and breast disorders (1.1% vs. 0%)
- Respiratory, thoracic and mediastinal disorders (3.3% vs. 2.9%)
- Vascular disorders (9.5% vs. 7.3%)

Adverse events reported for SOC by gender at 12 months (Table 13 from Dr Yap’s review) show that many events are more common on the everolimus 1.5 mg/day arm (general, metabolic and nutrition, psychiatric, reproductive) and in some cases the outcome between women and men is discordant – one gender higher the other lower than everolimus or one no different (cardiac, endocrine, eye disorder, injury/poisoning, investigations, renal and urinary). Some events are more common in the Myfortic arm (blood and lymphatic, gastrointestinal, infection/infestations, nervous system vascular). Some events are rare, or similar between the test and control arm.

Number of patients (%)	Males Total =553			Females Total =272		
	EVR 1.5 mg (N=175)	EVR 3.0 mg (N=190)	Myfortic 1.44 g (N=188)	EVR 1.5 mg (N=99)	EVR 3.0 mg (N=88)	Myfortic 1.44 g (N=85)
Any system organ class	173 (98.9)	188 (98.9)	186 (98.9)	98 (98.9)	88 (100)	84 (98.9)
Blood and lymphatic	54 (30.9)	73 (38.4)	76 (40.4)	39 (39.4)	39 (44.3)	35 (41.2)
Cardiac disorders	22 (12.6)	33 (17.4)	29 (15.4)	21 (21.2)	6 (6.8)	14 (16.5)
Congenital/familial/genetic	5 (2.9)	4 (2.1)	2 (1.1)	2 (2.0)	0 (0.0)	0 (0.0)
Ear and labyrinth	8 (4.6)	2 (1.1)	9 (4.8)	5 (5.1)	2 (2.3)	5 (5.9)
Endocrine disorders	4 (2.3)	7 (3.7)	15 (8.0)	7 (7.1)	3 (3.4)	5 (5.9)
Eye disorders	16 (9.1)	18 (9.5)	20 (10.6)	13 (13.1)	4 (4.5)	8 (9.4)
Gastrointestinal	115 (65.7)	147 (77.4)	137 (72.9)	81 (81.8)	62 (70.5)	70 (82.4)
General disorders	110 (62.9)	133 (70.0)	110 (58.5)	72 (72.7)	54 (61.4)	51 (60.0)
Hepatobiliary	4 (2.3)	6 (3.2)	6 (3.2)	3 (3.0)	2 (2.3)	2 (2.4)
Immune system	6 (3.4)	6 (3.2)	6 (3.2)	14 (5.1)	9 (3.2)	11 (4.0)
Infections/infestations	104 (59.4)	117 (61.6)	125 (66.5)	66 (66.7)	63 (71.6)	63 (74.1)
Injury/poisoning	101 (57.7)	119 (62.6)	118 (62.8)	65 (65.7)	56 (63.6)	45 (52.9)
Investigations	84 (48.0)	85 (44.7)	101 (53.7)	53 (53.5)	35 (39.8)	33 (38.8)
Metabolism and nutrition	139 (79.4)	157 (82.6)	142 (75.5)	83 (83.8)	76 (86.4)	57 (67.1)
Musculoskeletal	72 (41.1)	76 (40.0)	71 (37.8)	40 (40.4)	31 (35.2)	34 (40.0)
Neoplasms	7 (4.0)	7 (3.7)	14 (7.4)	2 (2.0)	1 (1.1)	2 (2.4)
Nervous system	57 (32.6)	66 (34.7)	71 (37.8)	35 (35.4)	30 (34.1)	38 (44.7)
Pregnancy/puerperium	0 (0)	0 (0)	0 (0)	1 (1.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	53 (30.3)	54 (28.4)	46 (24.5)	37 (37.4)	22 (25.0)	26 (30.6)
Renal and urinary	68 (38.9)	99 (52.1)	92 (48.9)	45 (45.5)	45 (51.1)	33 (38.8)
Reproductive system/breast	27 (15.4)	34 (17.9)	16 (8.5)	23 (23.2)	18 (20.5)	7 (8.2)
Respiratory/thoracic	54 (30.9)	78 (41.1)	65 (34.6)	33 (33.3)	31 (35.2)	28 (32.9)
Skin	65 (37.1)	70 (36.8)	70 (37.2)	27 (27.3)	33 (37.5)	32 (37.6)
Social circumstances	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (1.1)	0 (0.0)
Surgical	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Vascular disorders	74 (42.3)	92 (48.4)	93 (49.5)	49 (49.5)	45 (51.1)	31 (36.5)

In summary, the following adverse events of special interest were more often seen in the everolimus arm:

- Hyperlipidemia is significantly higher and dose dependent
- Proteinuria is significantly higher and dose dependent.
- Wound healing is comparable in the 1.5 mg/day arm, but significantly higher in the 3.0 mg/day arm.
- Edema including peripheral edema was significantly higher on everolimus (Page 36 of Dr Yap's review shows that female 1.5 mg/day have a rate of 65% while 3.0 mg/day have 52% and MPA 44%, suggesting something else may be contributing to the difference, given that it does not seem plausible that the higher everolimus dose would be protective).
- New onset diabetes mellitus
- Graft losses are numerically higher, and more graft thromboses of renal vein were seen
- Noninfectious pneumonitis/ alveolar proteinosis
- TMA/TTP/HUS
- Gonadal function

By comparison, these events more common in the control arm:

- Infections, especially CMV
- Hirsutism and gingival hyperplasia
- Leukopenia
- Gastrointestinal adverse events

Comment:

There are more treatment discontinuations in the everolimus arms, and more adverse events involving multiple organ systems, including wound healing, proteinuria, hyperlipidemia, graft thromboses, nephrotoxicity with full dose cyclosporine, new onset diabetes mellitus, peripheral edema and fluid collection, mouth ulcerations, hormonal adverse findings. By comparison, the control MPA arm with full dose cyclosporine had more viral infections including CMV and BK, more neoplasms, more hirsutism, gingival hyperplasia and dose interruptions/adjustments to manage adverse events.

Notably, GFR, the adverse event that led to two previous approvable actions while Novartis evaluated alternative TDM-controlled dosage regimen, was shown to be better in all analyses of study A2309. Other renal toxicity, namely proteinuria, was higher in the everolimus arm. Interestingly, these findings may be contributed to by the action of cyclosporine, which constricts the efferent arteriole, resulting in reduced GFR and also reduced protein in the urine. Therefore, by seeing lower doses/concentrations of CsA, patients on everolimus have both better GFR and more proteinuria.

The relationship between cyclosporine and GFR values is elegantly illustrated in the table below from Dr Krudys's review, showing that GFR < 30 ml/min/1.73m² goes up as cyclosporine troughs go up, but is not affected by everolimus trough concentrations below or above 8 ng/mL.

Everolimus trough levels	Cyclosporine trough 0-100 ng/mL	Cyclosporine trough 100-200 ng/mL	Cyclosporine trough >200 ng/mL
3 – 8 ng/mL	10/171 (5.8%)	35/183 (19.0%)	10/19 (52.6%)
> 8 ng/mL	1/34 (2.9%)	6/43 (14%)	7/15 (48.7%)

As noted above the Medical Officer writes a comprehensive review of safety and recommends nonapproval because of the adverse events. A discussion of the risk/benefit and input from the Advisory Committee is included in the CONCLUSIONS section of this review.

4 CONSULTATIVE REVIEWS

4.1 Compliance

Inspections of manufacturing sites were found acceptable, as summarized in Dr. Seggel's review.

4.2 Division of Scientific Investigations (DSI)

Everolimus studies submitted in the original NDA were reviewed. Afinitor (NDA 22-334) was approved for renal cell carcinoma in March 2009. Dr. Thompson of DSI indicated the further inspections were not needed for the application to be approved.

4.3 OSE/Division of Medication Error and Prevention Analysis (DMEPA)

(b) (4)

The subsequent proposed name of "Zortress" is considered acceptable by DMEPA. It was noted in discussion that the name does sound similar to the word "fortress" which is defined as "A fortified place, especially a large, permanent military stronghold that often includes a town."

The carton and container labeling initially submitted did not include any statement about Medication Guide, but the version sent November 23, 2009 (Global Submit submission 0038) includes the statement "Dispense with Medguide." A consult for the labeling was sent to DMEPA November 17, 2009 to Global Submit submission 0010.

4.4 OSE/Division of Pharmacovigilance II (DPVII)

Dr Jones reviewed the postmarketing safety of everolimus and in his review of November 4, 2009 including adverse events of interest such as proteinuria, interstitial lung disease, thromboembolic events, thrombocytopenia, fluid collection or edema, and infections leading to death, hospitalization or prolongation of hospitalization. There were 650

domestic AERS reports; “with reports originating from a total of 42 countries.” Because the indications covered included transplantation and cancer (Afinitor approved for renal cell carcinoma treated with 10 mg everolimus), the review notes that patients may have co-morbidities and causation of death or hospitalization is challenging. Proteinuria is not a labeled event in the Afinitor labeling. Other reported AERS events are interstitial lung disease, thromboembolic events, thrombocytopenias, fluid collection and serious infections that occurred concurrent with everolimus therapy.

4.5 OSE/Division of Drug Risk Evaluation (DRISK)

Preliminary review of the voluntarily submitted REMS was discussed with DRISK. Based on the recommendation of the CRDAC, further work is needed on this topic and will be requested as part of the CR letter.

A voluntary REMS proposal was submitted in the June 30, 2009 submission, and a revised REMS and revised supporting REMS documents were sent on November 9, 2009, in response to October 28, 2009 Division request, while revised carton and container labeling was sent November 23, 2009 in response to FDA letter October 28, 2009

Novartis wrote November 9, 2009 that the “objectives of the Medication Guide specific to the REMS are to educate and inform patients about:

- The potential for proteinuria, hypercholesterolemia and hypertriglyceridemia
- The signs and symptoms of delayed wound healing and proteinuria
- The importance of notifying their health care providers (HCP) immediately if they experience signs or symptoms of delayed wound healing and telling their health care provider about changes in urine or appearance of edema
- The need to comply with therapeutic drug monitoring for everolimus levels to lower the risk of transplant rejection and kidney damage”

As part of its communication plans, Novartis proposes to communicate with the following:

Association Outreach

Novartis will leverage existing relationships and forge new partnerships with numerous

medical associations including:

- American Society of Nephrology (ASN)
- American Society of Transplantation (AST)
- American Society of Transplant Surgeons (ASTS)
- American Association of Kidney Patients (AAKP)
- National Foundation for Transplants
- American Nephrology Nurses Association (ANNA)
- National Kidney Foundation (NKF)
- European Society of Organ Transplantation (ESOT)
- International Transplant Nurses Society
- The Transplantation Society

- North American Transplant Coordinators Organization (NATCO)
- American Society of Health System Pharmacists
- American College of Clinical Pharmacy
- American Pharmacists Association

4.6 Center for Devices and Radiological Health (CDRH)

The Division has been in contact with CDRH regarding the everolimus assay, given that therapeutic drug monitoring (TDM) to target trough concentrations of 3 to 8 ng/mL is part of the management of patients. Although there is an expectation that there will be at least one or two manufacturers for the device, these have not submitted applications to CDRH at this time, and therefore may not be available at this time. During a teleconference with Novartis, the company indicated they would make available the assay that was used during A2309 by making available a central laboratory located in (b) (4) (b) (4) which utilizes a LS/MS/MS assay for processing of all patients samples with a 24-hour turnaround time for results. (b) (4)

Other groups that Novartis has approached include (b) (4), according to their November 4, 2009 letter.

The bioanalytical report on everolimus assay conduct was examined, and further information requested from the company on December 4, 2009 and submitted December 11, 2009.

Several comments from CDRH encouraging the development of the assay will be included in the CR letter.

4.7 Pediatric and Maternal Health Staff

(b) (4)

Dr Belen and Cavaille Coll summarized the history of everolimus pediatric development:

The PWR was issued April 25, 2000. Novartis submitted a report of clinical studies conducted under the PWR on December 19, 2002, (b) (4)

(b) (4)
The PWR has since expired.

(b) (4)

Once the decision is made regarding labeling and REMS for the kidney indication, the pediatric development plan will be discussed with the Pediatric and Maternal Health Staff.

4.8 Cardiovascular and Renal Drugs Advisory Committee meeting December 7, 2009

After presentations by FDA and Novartis, the CRDAC discussed and addressed the questions posed by FDA; twelve members voted. The vote was 11 yes and 1 no that sirolimus showed efficacy for the indication of prophylaxis of acute rejection in *de novo* renal transplant recipients. The committee then voted that the application could be approved with a REMS (9 yes, 3 no), but none of the members considered that safety was demonstrated in the absence of a REMS (0 yes). Regarding safety, committee members were interested in long term follow up information, access to TDM, and information directed at health care professionals, and evaluation of whether the safety provisions are working. The final vote for approval was 11 yes and 1 no. The member who voted no thought the 10% noninferiority margin should have been even more conservative.

5. CONCLUSIONS

The Zortress (everolimus) Tablet application has been reviewed and cannot be approved until labeling and REMS are resolved. DMEPA has reviewed the trade name, and the carton and container labeling.

The Compliance inspections are “acceptable” and DSI inspections of this study are not needed, given previous inspection results (per Dr Thompson).

There is no device to measure everolimus concentrations for TDM approved at this time, and Novartis will be encouraged to identify a manufacturer. Given there is no written Agency policy that a TDM device needs to be available at the time of approval, this will be a request but not a deficiency at this time. The Division has been in contact with CDRH regarding discussions about options for the everolimus assay, given that TDM is important to keep patients concentrations within the target range.

Although many reviewers considered the information submitted for study A2309 as providing evidence that the product is effective and can be used in patients as long as a REMS program is in place, some reviewers and some committee members had concerns about the safety profile of everolimus. There are a number of adverse events that are now recognized as being mTOR-related events, due to the recognized anti-proliferative activity of everolimus as well as sirolimus, activity which is also responsible for the immunosuppressive effect by blocking progression of T-cells from G1 to S phase. A number of these adverse events, such as proteinuria and hyperlipidemia show an exposure-response relationship. Some patients tolerate everolimus, while others develop adverse events, including serious events that lead to discontinuation of everolimus. Other events such as wound healing, fluid collection, edema, and graft thrombosis did not show an exposure-response pattern but were more frequent in everolimus patients, although not

statistically significant. As noted above, adjustment of doses to target trough concentrations, or discontinuation of everolimus were two of the measures used to manage patients. In A2309, a higher dose of everolimus (3.0 mg/day, target trough 6-12 ng/mL) was also evaluated and shown to have higher adverse event rates, including serious events. Therefore, the higher dose was not selected for labeling, and suggests toxicity may be related to exposure, even though such a relationship was only shown for proteinuria and hyperlipidemia. By comparison, there were more adjustments in doses in the Myfortic arm for leucopenia and for viral infections, particularly CMV infection. Gastrointestinal adverse events were higher only in female patients, but not male patients.

Although the adverse events and rates associated with everolimus should not be underestimated, they should also be taken in context. All immunosuppressant agents used in solid organ transplantation have associated toxicities, and thus other agents continue to be developed. Corticosteroids and azathioprine were used initially but were insufficiently effective and had safety findings. In A2309, the overall rate of adverse events exceeded 98% in each study arm.

Cyclosporine was the first calcineurin inhibitor approved, and has a range of toxicities, most notably renal toxicity, which is paradoxical considering that it is used for prevention of rejection in kidney transplant, yet causes nephrotoxicity especially with chronic use. In A2309, the measure of renal function as GFR was comparable in the everolimus and Myfortic arms, while proteinuria was higher in the everolimus arm. This could be explained by the mechanisms of action of cyclosporine, constricting afferent arterioles, reducing GFR and reducing the amount of protein that can pass into the nephron and urine. Other CsA toxicities include hypertension, and less frequently hyperlipidemia. Cosmetic changes include gingival hyperplasia and hirsutism which are not serious but apparently cause great concern especially to female patients.

Tacrolimus when approved was associated with various neurotoxicities and new onset diabetes mellitus was a noteworthy toxicity. Examination of the Prograf package insert shows that a fair number of adverse events occur in greater frequency than the CsA control regimen.

Mycophenolate mofetil and mycophenolic acid are associated with leucopenias, often more gastrointestinal toxicity and viral infections, particularly CMV. Induction agents, such as the monoclonals and polyclonal have hypersensitivity reactions or immunotoxicity and may require pretreatment.

Other products have abandoned development for failing to demonstrate efficacy or immediately life threatening toxicity (bradycardia, asystole, and potential sudden death).

Everolimus, similarly to sirolimus, can be used effectively in a reduced cyclosporine regimen. While most transplant patients do develop adverse reactions on treatment (over 98% for all three arms of A2309), many are mild, and the severe or serious events need to be monitored and decisions can be made whether to continue treatment or switch to alternative therapy. It is noted that sirolimus use is lower than the use of tacrolimus or

cyclosporine. Therefore, a REMS program will be requested of Novartis, to include a Medication Guide and a Communication plan, and will be reviewed in collaboration with colleagues from OSE. Once the adult indication is finalized, Pediatric development will be revisited.

6. SUMMARY

A Complete Response letter will be issued, asking for updated labeling and REMS. Other issues mentioned will include a request for the 24-month data, continued efforts to bring an everolimus assay to market, and voluntary submission of advertising material to see how the various safety issues are presented in advertising.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

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/s/

RENATA ALBRECHT
12/23/2009

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21-560
Priority or Standard	Resubmission
Submit Date(s)	June 30, 2009
Received Date(s)	July 2, 2009
PDUFA Goal Date	December 30, 2009
Division / Office	DSPTP/OAP/OND/CDER
Reviewer Name(s)	Ergun Velidedeoglu
Review Completion Date	December 18, 2009
Established Name	Everolimus
(Proposed) Trade Name	Zortress*
Therapeutic Class	Immunosuppressant (M-TOR inhibitor)
Applicant	Novartis
Formulation(s)	Tablet
Dosing Regimen	Initial dose of 0.75 mg bid; then adjusted to a trough concentration of 3 to 8 ng/mL
Indication(s)	Prevention of allograft rejection
Intended Population(s)	Kidney transplant recipients

* [REDACTED] (b) (4)
(b) (4) The Applicant submitted the name Zortress on October 19, 2009,
which DMEPA found to be acceptable.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Everolimus is being developed for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant. Everolimus is to be administered in combination with basiliximab and concurrently with reduced doses of cyclosporine and corticosteroids.

Mammalian target of rapamycin (M-TOR) is a protein kinase that controls cell growth, proliferation, and survival. M-TOR signaling is often upregulated in cancer. To exert its activity everolimus (and other M-TOR inhibitors) needs to form a complex with a cytoplasmic binding protein, FKBP-12; this everolimus/FKBP-12 complex in turn is thought to bind to and disable M-TOR. On a cellular level everolimus inhibits growth factor-stimulated cell proliferation irrespective of the cell lineage or growth factor involved. The immunosuppressive activity of everolimus is explained by its ability to prevent IL-2/IL-15-stimulated T cell proliferation.

Sirolimus (Rapamune®) is another M-TOR inhibitor that was approved in 1999, also for the indication of prevention of kidney transplant rejection. Several M-TOR inhibitors, using a different dose and regimen than in kidney transplant, are also approved for use in renal cell carcinoma, including everolimus (Afinitor®).

The initial New Drug Application (NDA 21-560) for everolimus for the prophylaxis of organ rejection was submitted to the FDA on December 19, 2002 by the applicant, Novartis. The submission contained the results from two Phase 3 trials (Studies B201 and B251) in *de novo* renal transplant recipients and one study in *de novo* heart transplant recipients (Study B253). The regimen that was studied was fixed-dose everolimus (1.5 mg and 3.0 mg per day given in two divided doses) with standard dose CsA, which was compared to mycophenolate mofetil (MMF; CellCept®) also with standard dose CsA

Efficacy of everolimus was demonstrated in Studies B201 and B251; however, interpretation of the results was complicated by the premature treatment discontinuations due to reduced graft function and higher serum creatinine concentrations seen in the everolimus groups compared to the MMF control groups. The 12 month analysis of GFR showed increased rate of renal impairment in both of the everolimus groups compared to the MMF control group in both studies.

Due to these observed renal toxicities, the applicant was given an Approvable letter on October 20, 2003. The applicant was asked to establish a safe and effective dosing regimen for everolimus and CsA that minimized renal function impairment while

maintaining efficacy, such as concentration-controlled regimens of everolimus and cyclosporine using therapeutic dose monitoring (TDM).

Data from two additional open-label, non-comparative kidney transplant trials (A2306 and A2307), along with some exposure-response analyses, were submitted to the NDA as a Complete Response by the applicant on February 27, 2004. Studies A2306 (without basiliximab) and A2307 (with basiliximab) were conducted, using concentration-controlled everolimus dosing (initial doses of 1.5 mg and 3.0 mg per day adjusted to trough concentrations above 3 ng/mL) and reduced-dose CsA. As these studies were designed to compare the 1.5 mg and 3.0 mg doses of everolimus and did not include an active control group, the analyses in the submission were based primarily on cross-study comparisons between A2306 and A2307 and studies in the original submission. FDA noted these and other limitations in the studies' design, therefore the applicant was issued a second Approvable letter on August 27, 2004 and asked to provide additional information to establish a safe and effective dosing regimen for everolimus and CsA.

Subsequently Novartis designed a new study of concentration-controlled everolimus with low dose CsA both adjusted using TDM in *de novo* kidney transplant recipients, and the protocol was discussed with FDA. Study A2309, which is the basis for this NDA resubmission, is a 24-month, multicenter, multinational, randomized, open-label, three-group trial that enrolled 833 *de novo* adult renal transplant recipients. The current submission contains data from the first 12-months of the study.

Patients were randomized to one of three groups: everolimus starting at either 1.5 or 3.0 mg per day combined with reduced dose CsA, or mycophenolic acid (MPA; Myfortic®) 1.44 gm per day with standard dose CsA. The starting dose of everolimus in this study was the same as used in the initial studies B201 and B251. However, in this study everolimus doses were adjusted to achieve blood trough concentrations of 3 to 8 ng/mL (low dose group, starting at 1.5 mg/day) and 6 to 12 ng/mL (high dose group, starting at 3.0 mg/day) combined with reduced exposure to CsA, which was tapered over time. Both drug concentrations were guided by TDM. Dosing regimens and target trough concentrations for everolimus and CsA in Studies B201, B251, and the current A2309 are compared in the table below

Table 1. Dose and Target Concentrations for Everolimus and CsA across Studies

Study Treatment Group	Drug	Study B201	Study B251	Study A2309
Everolimus 1.5 mg/day group	Everolimus	0.75 mg bid	0.75 mg bid	Target trough 3-8 ng/mL
	CsA	Full Dose: 150 to 400 ng/mL (Weeks 1-4), 100 to 300 ng/mL (Months 2-12), 50 to 75 ng/mL (after Month 12)	Full Dose: 200 to 350 ng/mL (Weeks 1-4), 100 to 300 ng/mL (Months 2-12), 50 to 75 ng/mL (after Month 12)	Reduced Dose:* 100 to 200 ng/mL (until Month 2), 75 to 150 ng/mL (Months 2-4), 50 to 100 ng/mL (Months 4-6) and 25 to 50 ng/mL (after Month 6)
Everolimus 3.0 mg/day group	Everolimus	1.5 mg bid	1.5 mg bid	Target trough 6-12 ng/mL
	CsA	Full Dose – same as above	Full Dose – same as above	Reduced Dose:* same as above
Control group	MMF or MPA	MMF 1gm bid	MMF 1 mg	MPA 720 mg bid per day
	CsA	Full Dose – same as above	Full Dose – same as above	Standard:* 200 to 300 ng/mL (Month 1), 100 to 250 ng/mL (Month 2-12)

* pages 113 and 5772 of 14,328 from Study Report RAD001A2309, submitted June 30, 2009.

The control regimen in studies B201 and B251 contained MMF (Mycophenolate Mofetil), while in this study it was MPA (Mycophenolic Acid) in conjunction with CsA. The dose of MPA was selected to provide the same molar dose as 1 gm of MMF (720 mg Myfortic is the molar equivalent of 1 gm MMF) and is the approved dose for use in combination with cyclosporine. All patients were given basiliximab as induction therapy and maintained on concomitant corticosteroids, which were dosed based on local practice.

In this NDA resubmission, the applicant is seeking approval only of the everolimus 1.5 mg regimen which is adjusted to target trough concentrations of 3 to 8 ng/mL. The everolimus 3.0 mg regimen was used primarily in the safety analysis to determine a dose-response for adverse events.

The efficacy results from Study A2309 showed that both everolimus treatment regimens were non-inferior to the Myfortic control regimen at 12 months with regard to the primary efficacy composite endpoint consisting of the first occurrence of treated BPAR, graft loss, death or loss to follow-up. In terms of GFR, there were no statistically significant differences between any of the treatment groups at month 12.

The efficacy results from Study A2309 adequately address the deficiencies noted in the October 20, 2003 and August 27, 2004 everolimus Approvable letters.

The results of the safety analysis in Study A2309 showed that compared to the Myfortic control group, the everolimus 1.5 mg group had:

- Numerically more deaths with a causality association, as assessed by the Reviewer, to everolimus
- Numerically more graft losses
- Three times as many graft thromboses which all resulted in graft losses
- Higher rates of study drug discontinuations with more being due to adverse events
- More patients with abnormally high lipid levels with a diminished response to statins
- Higher levels of proteinuria mainly driven by male patients
- Higher incidence of NODAT (New Onset Diabetes After Transplantation)
- More patients with wound problems with a higher proportion of these requiring surgical and non-surgical intervention for treatment
- More patients with peripheral edema and localized fluid collections
- More patients with mouth ulcerations
- More male patients with sex hormone associated adverse events

The Myfortic control group had:

- More patients with Cytomegalovirus (CMV) and BK virus infections
- More patients with benign and malignant neoplasms (however, the only tumor-related death is in the everolimus 1.5 mg group)
- More study drug dose adjustments and interruptions
- More tremor, hirsutism and gingival hyperplasia.

These safety differences are explained in more detail in Section 1.2 and other relevant sections of this review.

It is evident from the 12 month data from Study A2309 that there are imbalances between the safety profiles of the two regimens in favor of the Myfortic control. The Clinical Reviewer believes that these everolimus-related adverse effects will become more pronounced over time, as supported by the published literature on the use of other M-TOR inhibitors in transplant patients.

It is not unreasonable to expect that these adverse effects, especially those related to cardiovascular risk (hyperlipidemia, NODAT, proteinuria and thrombogenicity) will result in higher rates of mortality and other complications over the course of years. Cardiovascular events are the number one cause of long term mortality in kidney transplant patients and everolimus therapy is further de-optimizing the cardiovascular risk factors in this patient group.

Other adverse events like peripheral edema, mouth ulcerations and gonadal effects will further lower the quality of life in these patients who are already struggling with various issues related to chronic immunosuppression.

M-TOR inhibitors are known to be associated with proteinuria and hyperlipidemia, which are also seen with other immunosuppressants, but which occur to a greater degree and more frequently with M-TOR inhibitors. In addition, M-TOR inhibitors cause other adverse effects related to their mechanism of action, like thromboembolic complications, wound healing problems, non-infectious pneumonitis, localized fluid collections, mouth ulcerations and gonadal dysfunction.

In the Clinical Reviewer's opinion, although Study A2309 succeeded in demonstrating the efficacy of the everolimus 1.5 mg regimen in terms of non-inferiority to the active comparator (Myfortic regimen), as measured by the composite end point, and also showed similar renal function at the end of 12 months, the magnitude and importance of the safety problems above pose serious risks for kidney transplant patients.

In addition, the Clinical Reviewer believes that the applicant has not demonstrated the role of everolimus in the treatment of kidney transplant patients. Calcineurin inhibitors (CsA and tacrolimus) remain the backbone of immunosuppressive regimens despite attempts to reduce or eliminate them from the regimen, in an effort to prevent CNI-related toxicities, primarily nephrotoxicity. The current everolimus treatment regimen utilizes reduced doses of CsA, however, M-TOR class toxicities outweigh any advantages that may be gained from reducing exposure to CsA. Finally, everolimus may be considered an alternative to CNIs in the population of patients who fails or are intolerant of CNIs. However, the Reviewer believes this population is very small and there are other alternative therapies available (such as Myfortic).

Therefore, the Clinical Reviewer's recommendation is non-approval of the everolimus 1.5 mg regimen (adjusted to a target trough concentration of 3 to 8 ng/mL) in combination with reduced dose CsA for the indication of prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant.

<p>Of Note: The Division's intended action for this product is a Complete Response. As noted above, the efficacy results from Study A2309 adequately address the deficiencies noted in the October 20, 2003 and August 27, 2004 everolimus Approvable letters for</p>

kidney transplant. However, the Division is requiring the submission of a Risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide and Communication Plan, in order to ensure that the benefits of the drug outweigh the risks. The following risks are believed to be able to be mitigated by the REMS: graft thrombosis, wound healing complications, hyperlipidemia, proteinuria, and nephrotoxicity when co-administered with standard doses of cyclosporine.

1.2 Risk Benefit Assessment

In this risk/benefit analysis only the everolimus 1.5 mg group (targeted trough concentrations: 3-8 ng/mL) will be compared to the control (Myfortic) group since this is the everolimus regimen which the indication is sought for by the Applicant. The everolimus 3.0 mg group (targeted trough concentrations of 6 to 12 ng/mL) will be mentioned where it is thought to be relevant such as pointing to an exposure-response association. It is important to remember that the targeted trough levels in both of the everolimus groups overlap so for safety purposes it may not be always possible and appropriate to completely differentiate them.

The efficacy results from Study A2309 showed that both everolimus treatment regimens were non-inferior to the Myfortic control regimen at 12 months with regard to the primary efficacy composite endpoint consisting of the first occurrence of treated BPAR, graft loss, death or loss to follow-up. The incidence rate of efficacy failure was 25.3% (70/277) in the everolimus 1.5 mg group and 24.2% (67/277) in the Myfortic group [95% CI of the difference (-6.1%, 8.3%)]. Based on the protocol defined and justified non-inferiority margin of 10%, and using the Hochberg's procedure to adjust for multiple comparisons, non-inferiority of everolimus 1.5 mg to Myfortic was demonstrated by the fact that the upper limits of the 95% confidence interval of the difference was less than the 10% non-inferiority margin

Both everolimus regimens were also demonstrated to be similar to the Myfortic regimen in the incidence of graft loss, death or loss to follow-up at 12 months (main secondary efficacy endpoint). Similar results were shown for the other secondary efficacy endpoints, including treated biopsy proven acute rejection (BPAR) at 12 months.

The calculated 12-month GFR, using the modification of diet in renal disease (MDRD) formula, was similar between both everolimus groups and the Myfortic group: 54.6 mL/min in the everolimus 1.5 mg group and 52.3 mL/min in the Myfortic group, using the using a Last Observation Carried Forward (LOCF) approach for missing data. Various sensitivity analyses, modeling and imputation methods for missing values resulted in similar results in 12-month GFR across treatment groups.

The difference in GFR of approximately 2 mL at 12 months, in favor of the everolimus 1.5 mg group which was not statistically significant, can be compared to a difference of 6 mL/min and 8 mL/min in Studies B201 and B251, respectively, with fixed dose

everolimus 1.5 mg and standard dose CsA at 12 months, in favor of the MMF (control) groups.

There was a disproportionate rate of premature treatment discontinuation within the initial 12 months of Study A2309, driven by higher rates of adverse events in both everolimus groups compared to Myfortic which may bias the interpretation of the study safety and efficacy results. Premature treatment discontinuations occurred in 30% of patients in the everolimus 1.5 mg group compared to 21.7% in the Myfortic group.

The following is a discussion of the safety profile of everolimus from Study A2309.

1.2.1 Deaths:

A total of 23 patients died during the first 12 months of the study, 7 (2.5%) in the everolimus 1.5 mg group, 10 (3.6%) in the 3.0 mg everolimus group, and 6 (2.2%) in the Myfortic control group. The most common causes of death across the study groups were related to cardiac conditions and infections. The Reviewer evaluated the narratives and Case Report Forms (CRFs) for the patients who died in this study and, after excluding five deaths because of lack of any discernable association between the cause of death and the study medication, concluded a probable association between the other 18 deaths and the study medication as follows:

- 7 deaths in the 1.5 mg everolimus group
- 8 deaths in the 3.0 mg everolimus group
- 3 deaths in the Myfortic (control) group

According to this final assessment of study drug attributability of patient deaths there are more than twice as many deaths in both of the everolimus groups compared to the Myfortic group that shows a probable association with the study medication.

Although a direct comparison is not possible because of the differences in the study designs and treatment regimens, it may be relevant to mention that in both of the previous studies of fixed dose everolimus with standard dose CsA (Studies B201 and B251) there were numerically more deaths in both of the everolimus groups compared to the MMF control group.

1.2.2 Serious Adverse Events (SAEs):

SAEs in the following MedDRA System Organ Classes (SOCs) were reported at a higher rate in the everolimus 1.5 mg group compared to the Myfortic group:

- Blood and lymphatic system disorders, (4% vs. 2.9%)
- Gastrointestinal disorders (7.7% vs. 6.6%)
- General disorders and administration site conditions (5.5% vs. 4.4%)

- Injury, poisoning and procedural complications (14.2% vs. 11.7%)
- Investigations (8.4% vs. 8.1%)
- Metabolism and nutrition disorders (7.3% vs. 4.8%)
- Musculoskeletal and connective tissue disorders (1.8% vs. 0.4%)
- Nervous system disorders, psychiatric disorders (2.2% vs. 1.8%)
- Psychiatric disorders (1.1% vs. 0%)
- Reproductive system and breast disorders (1.1% vs. 0%)
- Respiratory, thoracic and mediastinal disorders (3.3% vs. 2.9%)
- Vascular disorders (9.5% vs. 7.3%)

SAEs in the following SOCs were higher in the Myfortic group compared to the everolimus 1.5 mg group:

- Infections and infestations (25.3% vs. 19.7%)
- Neoplasms (1.8% vs. 1.5%)
- Renal and urinary disorders (13.2% vs. 10.2%)

The higher incidence of renal and urinary disorders in the Myfortic group is mainly due to the higher number of cases with hydronephrosis and ureteric obstruction which are usually due to poor surgical technique. Also 5 patients who were reported to have toxic nephropathy or blood creatinine increase in the Myfortic group were concomitantly receiving sirolimus in addition to the Myfortic study regimen.

Graft Losses and Graft Thromboses

Another M-TOR inhibitor, sirolimus, has a Boxed Warning regarding the increased incidence of hepatic artery thromboses in liver transplant patients, so this is a recognized class effect. The number of graft losses was 12 (4.3%) in the everolimus 1.5 mg group, 14 (5.0%) in the everolimus 3.0 mg group and 8 (2.9%) in the Myfortic group over the 12 month study period. One of the patients with renal vein thrombosis in the everolimus 1.5 mg group died later as a result of the events started by this complication (patient 0114-0001).

The Reviewer and the applicant agreed on the assessment of the number of patients who developed graft thrombosis (artery and vein) and consequently lost their grafts:

- 6 graft thromboses (4 renal artery and 2 renal vein) in the everolimus 1.5 mg group
- 4 graft thromboses (4 renal artery) with another probable 5th patient again with renal artery thrombosis according to the narrative in the everolimus 3.0 mg group
- 2 graft thromboses (2 renal artery) in the Myfortic group.

In the everolimus 1.5 mg group the incidence of early graft thromboses (within 30 days of transplant) is 1.8% and we see the same trend in the everolimus 3.0 mg group with

an incidence of 1.4% which are both above the national average of 0.9% and in line with the well known thrombogenic effect of M-TOR inhibitors.

1.2.3 Discontinuations due to Adverse Events

Significantly more patients prematurely discontinued study medication due to adverse events in the everolimus group (18.1%) compared to the Myfortic group (9.4%) (p-value=0.004). This difference was primarily driven by significant differences between treatment groups among female patients.

1.2.4 Significant Adverse Events

Infections

Infections reported as AEs had a lower incidence in the everolimus 1.5 mg group compared to the Myfortic group (62% vs. 68%) which is mainly due to the more frequent CMV, BK virus and other herpes virus infections in the Myfortic group. When we look at the infections reported as SAEs the only notable differences between the two groups are 9 CMV infections and 4 herpes zoster infections in the Myfortic group vs. no CMV infection and 1 herpes zoster infection in the everolimus 1.5 mg group. All the CMV and herpes zoster infections reported as SAEs were successfully treated without any patient or graft losses.

There are no deaths due to infections in the Myfortic group whereas 2 deaths in the everolimus 1.5 mg group and 5 deaths in the everolimus 3.0 mg group are due to infections. Although numerically there were more infections in the Myfortic group the infections in the everolimus group were more serious and resulted in at least two deaths.

Proteinuria

The median UP/UC ratios over the 12 months of the study in the safety on-treatment population, which was defined as the population of safety patients whose assessments were obtained on and after day 1 but no later than two days after the discontinuation of randomized study medication. The median ratios in the everolimus 1.5 mg group were consistently higher than those of Myfortic throughout the study including the Month 12 TEP¹, as shown as Month 13. The differences between the groups became significant starting at Month 6 onwards.

There is a difference of 210 mg/g between the everolimus 1.5 mg group and the Myfortic group in favor of the Myfortic group using the Month 12 TEP values and this difference is even higher for the male patients since higher levels of proteinuria in the everolimus 1.5 mg group is driven by the male patients. The biological mechanism for higher levels of

¹ TEP=treatment endpoint (imputation by LOCF)

proteinuria in males is not known. Therefore, the Reviewer believes there is an augmented risk for the male patients over female patients. The fact that the differences between the two treatment groups became significant starting Month 6 raises concerns that the gap may continue to widen in favor of the Myfortic group with longer follow-up and may be more severe for the male patients. Proteinuria is a known risk factor for cardiovascular disease, diabetes and may contribute to hyperlipidemia at high levels. It has also been shown to decrease patient and graft survival in kidney transplantation.

Hypertriglyceridemia, diabetes and proteinuria (at the microalbuminuria level) are all components of the metabolic syndrome, which is linked to adverse patient and graft outcomes^{2,3} and they occur with higher incidence and severity in both of the everolimus treatment groups compared to the Myfortic group. It is not unreasonable to assume that this coexistence of hyperlipidemia, NODAT and proteinuria with higher severity or higher incidence compared to the control group will result in higher cardiovascular morbidity and mortality in this high cardiac risk population in the long term if not during shorter periods of follow-up like one year.

Hyperlipidemia

Hyperlipidemia was reported as an AE in 57 (20.8%) patients in the everolimus 1.5 mg group, 60 (21.6%) patients in the everolimus 3.0 mg group, and 43 (15.8%) patients in the Myfortic group.

All through the 12 month study period mean total cholesterol and triglyceride values were significantly higher in both of the everolimus groups compared to the Myfortic group. Generally, after the 9 month time point, the mean values of both total cholesterol and triglycerides came down to the normal range in the Myfortic group, whereas the mean values in both of the everolimus groups stayed above the upper limit of normal ranges. LDL values in the everolimus groups were also significantly higher in the everolimus groups compared to the Myfortic group.

In the everolimus 1.5 mg group almost three times as many patients (16% vs. 6%) have total cholesterol levels above 350 mg/dL and almost twice as many patients (4.4% vs. 2.6%) have triglyceride values above 500 mg/dL compared to the Myfortic group.

Lipid lowering agents were taken by a higher percentage of patients in the everolimus treatment groups (64.6%, 72.3% and 57.5% of patients in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm treatment groups, respectively).

Among patients with high baseline cholesterol values before the statin treatment was initiated, 27.4% (17/62) in the everolimus 1.5 mg group compared to 13.9% (5/36) in the Myfortic group did not move down to the normal range despite the statin treatment. A

2 de Vries et al. Metabolic Syndrome Is Associated with Impaired Long-term Renal Allograft Function; Not All Component criteria Contribute Equally. American Journal of Transplantation 2004; 4: 1675–1683
3 Sharif. Metabolic Syndrome and Solid-Organ Transplantation. American Journal of Transplantation 2009; 9: 1–6

similar trend was also observed for triglycerides in a similar analysis. Among patients with high baseline triglyceride values before the statin treatment was initiated, 49% (22/45) in the everolimus 1.5 mg group compared to 26% (5/19) in the Myfortic group did not move down to the normal range despite the statin treatment.

Usage of statins in the everolimus groups also resulted in significantly higher levels of CK (Creatine kinase) levels which may indicate excessive muscle tissue breakdown despite the mean levels stayed within the normal range.

A 39 year old male patient (0124-00076), whose death was attributed to acute myocardial infarction, developed severe dyslipidemia (hypercholesterolemia) after the transplant which gradually worsened until his death on Day 85. His total cholesterol increased from 147 mg/dL to 432 mg/dL and his LDL cholesterol increased from 81 mg/dL to 212 mg/dL (normal levels: up to 129 mg/dL) during the course of the study. Although this patient had a history of hypertensive heart disease the rapid rise of all lipid levels from normal range to very high values in a short period of time might have contributed to his death.

Hyperlipidemia is common in chronic kidney disease patients and the incidence increases after kidney transplantation. Various immunosuppressants, including CsA, corticosteroids, and M-TOR inhibitors, have been recognized as a major contributor to dyslipidemias seen after transplant. According to published research¹⁴ even mild elevations in cholesterol levels may double the risk of developing ischemic heart disease in kidney transplant recipients unlike the milder increase of risk in the general population and the associated increase in mortality affects the younger recipients more than the older recipients.

Wound Healing and Wound Fluid Collections

Incisional wound complications were more frequent in the two everolimus groups compared to the Myfortic group with the highest number occurring in the 3.0 mg group. In each of the Dehiscence, Hernia and Infection categories, more patients required surgical intervention (i.e., intraoperative repair or debridement/ drainage) in the everolimus groups compared to the Myfortic group. The total number of surgical interventions was 19 in the everolimus 1.5 mg group, 22 in the everolimus 3.0 mg group, and 9 in the Myfortic group.

Similar to the incidence of wound-related events, fluid collections (lymphoceles and seromas) were also more commonly reported in the everolimus groups compared to the Myfortic group

Fluid Accumulation, Including Peripheral Edema, Ascites, and Pleural Effusions

At Month 12 the incidence of edema related events was statistically significantly higher in both everolimus groups than in the Myfortic group (55.5% and 54.7% versus 45.1%). Peripheral edema possibly contributed to the death of 1 patient in study 2309 who was

in the everolimus 1.5 mg group. This patient (0516-00002) was treated with furosemide because of edema on day 102 and died on day 156 due to congestive heart failure.

MACE (Major Cardiac Adverse Events)

Although the overall incidence of MACE events are much higher in the everolimus 3.0 mg group compared to the other two groups in the study, everolimus 1.5 mg group and the Myfortic group look similar to each other except for the numerical increase in myocardial infarctions in the Myfortic group (2 vs 4). When those cases with myocardial infarctions are analyzed in the reviewer's assessment only one case, 39 year old male patient (0124-00076) in the everolimus 1.5 mg treatment group can be associated with the study medication (everolimus).

Hematologic Adverse Events including Thrombocytopenia

The overall incidence of hematologic AEs was 33.9% in the 1.5 mg group, 40.3% in the 3.0 mg group, and 40.7% in the Myfortic group. The higher incidence in the Myfortic group was mainly driven by the higher incidence of leucopenia. Leucopenia associated with mycophenolic-acid (MPA) is very common in clinical practice and is usually responsive to dose reductions or interruptions. Hematologic events reported as SAEs were reported in eleven patients in the everolimus 1.5 mg group, ten in the everolimus 3.0 mg group, and eight patients in the Myfortic group.

Thrombocytopenia contributed to one patient's death in the everolimus 3.0 mg group (patient 0549-0001).

TMA/TTP/HUS

Thrombotic microangiopathies [TMA (Thrombotic Microangiopathy), TTP (Thrombotic Thrombocytopenic Purpura) and HUS (Hemolytic Uremic Syndrome)] are rare events traditionally associated with calcineurin inhibitors (CNIs), like CsA, until the recent discovery that they are also associated with M-TOR immunosuppression and the combined usage of M-TOR inhibitors and CNIs may increase the incidence. In Study A2309 a total of 4 TMA cases (1 TMA, 1 TTP and 2 cases of HUS) were reported all in the everolimus 1.5 mg group. TTP reported in the everolimus 1.5 mg group also contributed to one graft loss (patient 0192-00002).

Non Infectious Pneumonitis, Including Alveolar Proteinosis

Non infectious pneumonitis, including alveolar proteinosis, is a class effect of M-TOR inhibitors. It is relatively rare but may have a fatal outcome, especially if it is not recognized or treated appropriately. The diagnosis must be considered in every patient who develops dyspnea especially if they are on an M-TOR inhibitor. Infectious pneumonia is also commonly superimposed. Treatment includes discontinuation of the M-TOR inhibitor and steroids.

A total of six patients were reported to have interstitial lung disease identified by the applicant. Two cases were in the everolimus 1.5 mg group, three in the everolimus 3.0

mg group, and one is in the Myfortic group. The patient in the Myfortic group had no record of lung related pathology in narrative.

One patient developed alveolar proteinosis (0304-00016) in the everolimus 1.5 mg group following the initial 12 months of the study and died due to pneumonia and septic shock 60 days after the diagnosis.

Neoplasms

Neoplasms, benign and malignant, were reported at a lower incidence in the everolimus 1.5 mg group compared to the Myfortic group (9 patients compared to 16 patients, respectively) but the only malignancy death in the study (malignant melanoma) was also reported in the everolimus 1.5 mg group and the only lymphoma (PTLD) was observed in the everolimus 3.0 mg group.

New Onset Diabetes after Transplantation (NODAT)

Fasting plasma glucose \geq 126 mg/dL (7.0 mmol/L), which is part of the standard definition for NODAT by the ADA (American Diabetes Association) was not included as part of the other screening criteria for NODAT in this study. Therefore, the Reviewer believes the resulting estimation of NODAT in all three study groups is lower than anticipated. The incidence of NODAT was 9.1% in the everolimus 1.5 mg group, 12.2% in the everolimus 3.0 mg group, and 6.6% in the Myfortic group.

The reported incidence of NODAT among kidney transplant recipients with standard immunosuppression in the literature is around 30% though it may be higher depending on the type of CNJ inhibitor utilized and in some publications it is reported to be as high as 50%. The numbers reported in Study A2309 are not compatible with the published literature. If the screening criteria had been more stringent (ADA recommended criteria) the incidences would be higher in all treatment groups with a possible increase of the difference between the everolimus group and the Myfortic group in favor of the Myfortic group.

Gastrointestinal Adverse Events

Gastrointestinal adverse events like nausea vomiting and diarrhea are commonly observed with MPA treatment. However, in the study gastrointestinal adverse events overall had a similar incidence in the everolimus 1.5 mg and the Myfortic groups (72% compared to 76%, respectively).

Gastrointestinal events reported as SAEs were more frequent and tended to be more severe, as described below, in the everolimus 1.5 mg group. The everolimus 3.0 mg group had the highest incidence of SAEs in the SOC of Gastrointestinal Disorders (28 patients) followed by the 1.5 mg group (21 patients) and the Myfortic group (18 patients), respectively.

Two cases of hemorrhagic esophagitis in the everolimus 1.5 mg group and one case of mesenteric vessel thrombosis in the everolimus 3.0 mg group were reported as SAEs, which may be associated with the ulcerative and thrombogenic class effects of M-TOR inhibitors.

Male Endocrine Effects

At 9 months patients in the everolimus 1.5 mg group displayed a lower mean testosterone level and higher mean LH and FSH levels when compared to the Myfortic group. The mean values for all three hormones were still within the normal ranges with FSH level in the everolimus 1.5 mg group being at the upper level of normal. The difference between the testosterone levels across the two treatment groups at 9 months appeared to be caused by a decrease of testosterone levels in the everolimus 1.5 mg group throughout the 9 month period during which the testosterone levels in the Myfortic group stayed the same. Month 9 mean testosterone levels are still within the normal range in both groups despite the significant decrease in the everolimus 1.5 mg group.

The mean FSH levels in the everolimus 1.5 mg group increased and rose up to the upper limit of the normal range (11.1 ± 9 U/L) at 9 months which may be indicative of decreased sperm production. Sperm counts were not performed as part of the protocol in Study A2309. However, oligospermia or azospermia, which is usually reversible, is reported in the literature for other M-TOR inhibitors and documented in the non-clinical studies for everolimus. The effect is partly due to the anti-proliferative effects of M-TOR inhibitors.

1.2.5 Other Concerns: Drug-Drug Interactions

Both everolimus and CsA are metabolized through the CYP3A4 enzyme system in the liver. On the other hand, MPA is mainly metabolized through glucuronidation.

For both everolimus and CsA, concurrent treatment with strong 3A4 inhibitors, such as azole antifungals (ketoconazole, itraconazole, voriconazole) and macrolide antibiotics (clarithromycin, telithromycin) gives rise to significant increases in the concentrations of these drugs and concurrent use is not recommended. In addition, CsA also has a significant drug interaction with some of the HMG-CoA reductase inhibitors and use with lovastatin and simvastatin is also not recommended.

In addition, co-administration of CsA with everolimus significantly increases the concentrations of everolimus. Therefore, if the dose of CsA is increased, everolimus toxicity is possible if everolimus concentrations are not carefully monitored and the dose of everolimus adjusted. Another difficulty with the TDM regulation of the everolimus is the relatively long plasma half life which is around 30 hours in kidney transplant recipients. At least 5 days need to elapse before a meaningful trough concentration can be obtained every time either the everolimus or the CsA dose is changed

On the other hand, there is no CYP3A4 interaction between MPA and CsA. In fact, there is a small effect of CsA on the enterohepatic circulation of MPA such that an increase in CsA exposure decreases MPA exposure and reduces the possibility of increased toxicity due to this interaction.

1.2.6 Non-Clinical Findings and Possible Risk of Cataracts

Eye examinations were not included in the study protocol so it is not known if there is an increased incidence with everolimus treatment but in non-clinical studies (in rats) everolimus at clinically relevant doses caused fibrillar degeneration in the lens (see section 4.3).

1.2.7 Conclusion

The efficacy results from Study A2309 showed that both everolimus treatment regimens were non-inferior to the Myfortic control regimen at 12 months with regard to the primary efficacy composite endpoint consisting of the first occurrence of treated BPAR, graft loss, death or loss to follow-up. Although the incidence rate of death, graft loss and loss to follow-up was similar between both everolimus groups and Myfortic group, numerically these events were more frequent in the everolimus groups and displayed a clear association with everolimus treatment.

In terms of GFR, there were no statistically significant differences between any of the treatment groups at month 12.

However, there were significant safety findings in the everolimus 1.5 mg group compared to the Myfortic control specifically:

- Numerically increased mortality with more causality associations,
- Numerically increased graft losses with an increased incidence of graft thromboses one of which resulted in death.
- More hyperlipidemia
- More NODAT
- More proteinuria
- More wound healing problems with more patients requiring surgical or non-surgical interventions for treatment
- Interstitial lung disease which contributed to the death of one patient
- TMA/TTP/HUS one of which contributed to the graft loss in one patient
- Severe thrombocytopenia which contributed to the death of one patient in the everolimus 3.0 mg group. It is not known if this adverse effect is exposure dependent. Thrombocytopenia has been frequently associated with M-TOR inhibition in the literature, although it may also be encountered with MPA treatment it is usually milder in nature.

- Adverse effects on the male gonadal function.
- More study drug discontinuations due to adverse events which may partly be due to the difficulty of managing the regimen.

Therefore, it is the Reviewer's opinion that the safety findings with the everolimus 1.5 mg regimen far outweigh the benefits of the regimen and probably will result in increased mortality both in the short term and the long term when compared to the comparator Myfortic regimen or other similar immunosuppressive regimens currently being used. The higher morbidity and mortality associated with everolimus may become more noticeable in the long term since some of the associated risks like hyperlipidemia, NODAT and proteinuria continue to exert their effects over the course of the years and immunosuppression is a life long treatment unlike many other treatments.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Division is requiring the submission of a Risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide and Communication Plan, in order to ensure that the benefits of the drug outweigh the risks. The following risks are believed to be able to be mitigated by the REMS: graft thrombosis, wound healing complications, hyperlipidemia, proteinuria, and nephrotoxicity when co-administered with standard doses of cyclosporine.

1.4 Recommendations for Postmarket Requirements and Commitments

If approved, in the Clinical Reviewer's opinion, possible effects on short and long term cardiovascular morbidity and mortality, effects on the lens and effects on gonads should be studied; and the 24 month results of Study A2309 should be submitted for review.

2.0 Introduction and Regulatory Background

An NDA supporting the use of everolimus in combination with cyclosporine (Neoral®; cyclosporine, USP MODIFIED) for the prophylaxis of organ rejection in allogeneic kidney and heart transplant patients was submitted on December 19, 2002 (NDA 21-560). In the original submission the Applicant presented two Phase III *de novo* renal allograft trial (B201 and B251) for the kidney indication and one key *de novo* heart study (B253) for the heart indication. Although efficacy was demonstrated, an unacceptable safety profile was observed with the original everolimus fixed dose regimen and use of full dose CsA. An approvable letter dated October 20, 2003 was issued with the following deficiencies from letter:

1. Provide information supporting a safe and effective dosing regimen for everolimus and cyclosporine that would minimize renal function impairment while maintaining adequate protection against graft rejection, graft loss, or death in *de novo* renal transplantation. In order to do this, we believe that it will be necessary for you to provide data from an adequate and well-controlled study or studies prospectively evaluating concentration-controlled regimens of everolimus in combination with concentration-controlled cyclosporine in *de novo* renal transplant recipients, which would support therapeutic drug monitoring (TDM) schemes for everolimus and cyclosporine.

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On November 16, 2005 the Cardiovascular and Renal Drugs Advisory Committee met to discuss the use of everolimus for prophylaxis of rejection in heart transplantation.⁴ While the committee agreed that a fixed-dose regimen of everolimus with standard-dose CsA should not be used in heart transplant due to short-term and long-term loss of renal function, they also commented that additional data were needed to characterize the safety and efficacy of everolimus using TDM regimens to maintain everolimus concentrations while rapidly tapering CsA to minimize renal toxicity.

Study A2309 was designed as a 24-month study, but FDA agreed to accept 12-month results from the study and the NDA was resubmitted with this data on June 30, 2009.

Although the following study A2310 is for another indication, prevention of rejection in heart transplant recipients it may be helpful to mention here since the study design and the treatment regimens are the same as in the kidney transplant study A2309.

On December 21, 2007, the Applicant resubmitted NDA 21-628 for the heart indication. After reviewing the resubmission DSPTP decided that the submitted information did not provide provided a complete response to FDA's August 27, 2004 approvable letter for this NDA. This was communicated to Novartis during the February 4, 2008 meeting and the following letter dated 4/9/2008:

The deficiencies were communicated to Novartis in the response letter dated 4/9/2008:

1. Provide information supporting a safe and effective dosing regimen for everolimus and cyclosporine that would minimize renal function impairment while maintaining adequate protection against graft rejection, graft loss, or death in *de novo* renal transplantation. In order to do this, we believe that it will be necessary for you to provide data from an adequate and well-controlled study or studies prospectively evaluating concentration-controlled regimens of everolimus in combination with concentration-controlled cyclosporine

⁴ <http://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4183M1.pdf>

in *de novo* renal transplant recipients, which would support therapeutic drug monitoring (TDM) schemes for everolimus and cyclosporine.



A communication from Novartis dated April 1, 2008 to FDA stated that in the heart transplant study 2310, which employed the same treatment regimens as in the currently reviewed kidney transplant study A2309, further patient enrollment into the higher dose group (everolimus 3.0 mg per day or 1.5 mg BID) was stopped per the Data Monitoring Committee (DMC) recommendations. The DMC recommendations were based on the statistically significant difference in mortality between patients in the everolimus 1.5 mg BID group of study (9.9%) and patients in the control group (2.8%).

Based on this submission DSPT issued a partial hold letter for everolimus IND 52,003 on May 29, 2008 which stated:

Based on the above, you may not enroll any *de novo* heart transplant recipient in the everolimus 1.5 mg BID (6-12 ng/mL) arm of study CRAD001A2310, as recommended by the DMC. We note that you state that you complied with this request on March 27, 2008.

Furthermore, in the March 28, 2008 letter to the investigators, which was included in your April 1, 2008 submission, you state that "All patients already enrolled into the everolimus 1.5 mg BID (6-12 ng/mL) arm who are within 90 days post-randomization, must be converted to the standard of care at your center with 7 days of this notification." This is consistent with the DMC recommendation.

The lower dose group (everolimus 1.5 mg per day or 0.75 mg BID) in the heart transplant study is still continuing.

Although the indications are different, in study A2310 there was a statistically significant increased mortality in the everolimus 3.0 mg group compared to the Myfortic control group. The baseline characteristics in both groups are presumed to be similar since this is a randomized study and the fact that the everolimus regimen is causing a higher mortality effect compared to the control regimen in a patient population with similar baseline characteristics to the control group may be pointing to the higher toxicity associated with the everolimus treatment.

2.1 Product Information

Everolimus combined with CsA, first received marketing authorization in *de novo* renal and *de novo* heart transplantation, in Mexico, on July 8, 2003. Everolimus, marketed as Certican®, is currently approved in 70 countries for the prophylaxis of organ rejection in

adults receiving a renal or cardiac transplant and has not been withdrawn from marketing for safety or efficacy reasons in any country. Everolimus, for these indications, has not been approved in (b) (4), but new or amended applications are planned.

On March 30, 2009, everolimus (Afinitor®), as monotherapy, received US marketing authorization for patients with advanced renal cell carcinoma after treatment failure with sunitinib or sorafenib.

As of March 31, 2009, the Applicant's estimated cumulative exposure to everolimus was:

- for *commercialized* everolimus (transplant indications): approximately 44,000 treatment-years
- for exposure in *clinical trials* (trials with at least 1 month planned exposure)
 - kidney transplantation: 4,807 patients
 - heart transplantation: 1,358 patients
 - liver transplantation: 455 patients
 - other transplant: 507 patients
 - autoimmune diseases, other indications: 378 patients
- for *clinical development* in oncology: approx. 4,915 advanced cancer patients.

2.2 Currently Available Treatments for Proposed Indications

The following products for use in kidney transplant recipients as induction, prevention, or treatment of acute rejection have been approved. The wording from the **Indications and Usage** sections of the package insert is provided below.

Induction

Basiliximab (Simulect®)

Simulect® is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplantation when used as part of an immunosuppressive regimen that includes cyclosporine, USP (MODIFIED) and corticosteroids.

The efficacy of Simulect® for the prophylaxis of acute rejection in recipients of other solid organ allografts has not been demonstrated.

Daclizumab (Zenapax®)

ZENAPAX is indicated for the prophylaxis of acute organ rejection in patients receiving renal transplants. It is used as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids.

The efficacy of ZENAPAX for the prophylaxis of acute rejection in recipients of other solid organ allografts has not been demonstrated.

Thymoglobulin® (rabbit-derived antithymocyte globulin), Campath® (alemtuzumab), Atgam® (anti-thymocyte globulin, Orthoclone OKT3® (muromomab-CD3)

Off-label use only for prophylaxis of rejection; all are indicated for the treatment of rejection (see below), except Campath® which is approved only for treatment of B-cell chronic lymphocytic leukemia (B-CLL).

Prevention of Rejection

Tacrolimus (Prograf® and generics)

Prograf is indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver, kidney, or heart transplants. It is recommended that Prograf be used concomitantly with adrenal corticosteroids. Because of the risk of anaphylaxis, Prograf injection should be reserved for patients unable to take Prograf capsules orally. In heart and kidney transplant recipients, it is recommended that Prograf be used in conjunction with azathioprine or mycophenolate mofetil (MMF). The safety and efficacy of the use of Prograf with sirolimus has not been established

Cyclosporine A (Neoral® and generics)

Kidney, Liver, and Heart Transplantation

Neoral® is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. Neoral® has been used in combination with azathioprine and corticosteroids.

Mycophenolic acid (Myfortic®)

Myfortic® (mycophenolic acid) delayed-release tablets are indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids.

Mycophenolate mofetil (CellCept® and generics)

Renal, Cardiac, and Hepatic Transplant

CellCept is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. CellCept should be used concomitantly with cyclosporine and corticosteroids. CellCept Intravenous is an alternative dosage form to CellCept capsules, tablets and oral suspension. CellCept Intravenous should be administered within 24 hours following transplantation. CellCept Intravenous can be administered for up to 14 days; patients should be switched to oral CellCept as soon as they can tolerate oral medication.

Sirolimus (Rapamune®)

Prophylaxis of Organ Rejection in Renal Transplantation

Rapamune (sirolimus) is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants. Therapeutic drug monitoring is recommended for all patients receiving Rapamune.

In patients at low- to moderate-immunologic risk, it is recommended that Rapamune be used initially in a regimen with cyclosporine and corticosteroids; cyclosporine should be withdrawn 2 to 4 months after transplantation.

In patients at high-immunologic risk (defined as Black recipients and/or repeat renal transplant recipients who lost a previous allograft for immunologic reason and/or patients with high panel-reactive

antibodies [PRA; peak PRA level > 80%]), it is recommended that Rapamune be used in combination with cyclosporine and corticosteroids for the first year following transplantation.

Azathioprine (Imuran® and generics)

IMURAN is indicated as an adjunct for the prevention of rejection in renal homotransplantation. It is also indicated for the management of active rheumatoid arthritis to reduce signs and symptoms. **Renal Homotransplantation:** IMURAN is indicated as an adjunct for the prevention of rejection in renal homotransplantation. Experience with over 16,000 transplants shows a 5-year patient survival of 35% to 55%, but this is dependent on donor, match for HLA antigens, anti-donor or anti-B-cell alloantigen antibody, and other variables. The effect of IMURAN on these variables has not been tested in controlled trials.

Corticosteroids

No specific labeling regarding use in transplantation

Treatment of Rejection

Lymphocyte immune globulin, anti-thymocyte globulin [equine] sterile solution (Atgam®)

Renal Transplantation

ATGAM Sterile Solution is indicated for the management of allograft rejection in renal transplant patients. When administered with conventional therapy at the time of rejection, it increases the frequency of resolution of the acute rejection episode. The drug has also been administered as an adjunct to other immunosuppressive therapy to delay the onset of the first rejection episode. Data accumulated to date have not consistently demonstrated improvement in functional graft survival associated with therapy to delay the onset of the first rejection episode.

Muromonab-CD3 (Orthoclone OKT®3) Sterile Solution – murine monoclonal antibody

ORTHOCLONE OKT3 is indicated for the treatment of acute allograft rejection in renal transplant patients.

ORTHOCLONE OKT3 is indicated for the treatment of steroid-resistant acute allograft rejection in cardiac and hepatic transplant patients.

The dosage of other immunosuppressive agents used in conjunction with ORTHOCLONE OKT3 should be reduced to the lowest level compatible with an effective therapeutic response.

Anti-Thymocyte Globulin (Rabbit) (Thymoglobulin®)

Thymoglobulin is indicated for the treatment of renal transplant acute rejection in conjunction with concomitant immunosuppression.

2.3 Availability of Proposed Active Ingredient in the United States

Afinitor® (everolimus) NDA 22-334 (stamp date: June 30, 2008) was recently approved by the FDA on March 30, 2009 for the treatment of patients with advanced renal cell carcinoma.

2.4 Important Safety Issues with Consideration to Related Drugs

The first drug to be approved in the M-TOR inhibitor class of immunosuppressants for the indication of prevention of rejection in renal transplant patients was sirolimus (Rapamune®, NDA 21-083), oral solution, in September, 1999. Later, a 1 mg tablet (in August 2001) and a 2 mg tablet (August 2002) were approved under NDA 21-110.

The initial safety profile of sirolimus in the original NDA was characterized by reductions in platelet, white blood cell, and hemoglobin counts; and in elevation of fasting triglycerides, cholesterol and lactate dehydrogenase (LDH) concentrations. Therapeutic drug concentration monitoring (TDM) was not used in the clinical trials leading to approval and no specific recommendations were made about the TDM at the time. New-onset hypercholesterolemia required treatment in a significant proportion of patients treated with sirolimus. No excess in cardiovascular adverse events were reported in the initial 12 months follow-up of patients treated in the phase 3 studies, but it was thought there was insufficient follow-up to evaluate the long term consequences of toxicity. In pivotal trials seventeen patients (all in the sirolimus treatment groups) had non-fatal life threatening adverse events during the first 12 months post-transplant: severe pneumonia (due to opportunistic infections such as *Pneumocystis jiroveci*, tuberculosis, and coccidioidomycosis), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS).

Hyperlipidemia

In the Phase 3 trials of renal transplant patients, increased serum cholesterol and triglycerides were significantly more frequent in patients on Rapamune (sirolimus) than azathioprine (AZA) or placebo control, and significantly more patients on Rapamune required lipid-lowering agents (42-52%) than patients on AZA (22%) or placebo (16%).

(b) (4)

Renal Effects

In the Phase 3 trials of renal transplant patients in the original NDA submission, elevated serum creatinine and decreased glomerular filtration rate (GRF) was more frequent in the Rapamune group than the AZA or placebo groups, (b) (4)

These studies compared two dose levels of Rapamune oral solution (2 mg and 5 mg, once daily) with AZA (Study 1) or placebo (Study 2) when administered in combination with CsA and corticosteroids (Table).

Table 2. Overall Calculated GFR (Mean±SEM, cc/min) Post-Transplant

Parameter	Rapamune® 2 mg/day (n=233)	Rapamune® 5 mg/day (n=226)	Azathioprine 2-3 mg/kg/day (n=127)	Placebo (n=101)
Study 1				
Mean (SE)	57.4 (1.28)	55.1 (1.28)	65.9 (1.69)	
Study 2	(n=190)	(n=175)		(n=101)
Mean (SE)	54.9 (1.26)	52.9 (1.46)		61.7 (1.81)

*Adapted from the Rapamune package insert, September 1999, GRF calculated using Nankivell Equation

Hepatic Artery Thrombosis in Liver Transplantation

In two multicenter, randomized controlled studies in *de novo* liver transplant recipients, the use of sirolimus in combination with cyclosporine or tacrolimus was associated with an increase in hepatic artery thrombosis. Enrollment was suspended in a Phase 2 clinical study comparing sirolimus in combination with tacrolimus/corticosteroids to tacrolimus/corticosteroids alone in *de novo* liver transplant patients. This action was prompted by an imbalance in the observed rates of hepatic artery thrombosis with a rate of 5.5% (6/110) in the sirolimus-tacrolimus treatment group, all of which occurred within 16 days post-liver transplantation, compared to 0.9% (1/112) in the tacrolimus-treated control group.

(b) (4)

(b) (4)

Interstitial Lung Disease

(b) (4)

Some of the cases

were fatal. Also in some of the cases, interstitial lung disease resolved upon discontinuation or dose reduction of sirolimus. The risk is thought to be increased with higher sirolimus trough concentrations.

Abnormal Healing

In addition, the reports of abnormal healing following transplant surgery have been added, including fascial dehiscence and anastomotic disruption (e.g. wound, vascular, airway, ureteral, biliary).

(b) (4)

Reports of bronchial anastomotic dehiscence, including fatal cases, in patients treated with sirolimus were reported in a publication in *Transplantation* in 2003. This report was the result of consecutive case study of lung transplant recipients treated with regimen including sirolimus.⁵ Out of the 15 total subjects who were enrolled in the study, significant airway complication occurred in four of the subjects, three of whom died. The cause of death was directly related to an anastomotic dehiscence in three of the four study-group patients that died; the fourth patient died of fungal sepsis and multi-organ failure without anastomotic failure. One death in the comparator group was attributed to anastomotic complications.

The following wording was added to the Boxed Warning:

(b) (4)

⁵ Airway Anastomotic Dehiscence Associated with Use of Sirolimus Immediately after Lung Transplantation. King-Biggs M, Dunitz JM, Park SJ, et al. *Transplantation*. 2003 (75): 1437-1443.

(b) (4)

[Redacted]

[Redacted]

[Redacted]

(b) (4)

The new information was obtained from a conversion study in which stable patients were randomized to conversion from a calcineurin inhibitor (CNI)-based regimen to a sirolimus-based regimen or continuation of the CNI. The data showed an increased urinary protein excretion observed from 6 months through 24 months in the group converted to sirolimus. Patients with the greatest amount of urinary protein excretion prior to sirolimus conversion were also those whose protein excretion increased the most after conversion. New onset nephrotic syndrome was also reported as a treatment emergent adverse event in 2.2% of the sirolimus conversion group in comparison to 0.4% in the CNI continuation group of patients. Nephrotic range proteinuria, defined as urinary protein to creatinine ratio > 3.5 was reported in 9.2% in the sirolimus conversion group of patients in comparison to 3.7% in the CNI continuation group of patients. In some patients, reduction in the degree of urinary protein excretion was observed following the discontinuation of sirolimus. In this study, enrollment in patients with baseline calculated GFR less than 40 mL/min was discontinued due to higher rate of serious adverse events, including pneumonia, acute rejection, graft loss and death.

Angioedema

(b) (4)

This new subsection was created to provide information on the association of sirolimus with the development of angioedema and that the concomitant use of sirolimus with other drugs known to cause angioedema, such as ACE-inhibitors, may increase this risk.

(b) (4)

Male Hypogonadism and azospermia:

(b) (4)

There are also published articles about the adverse effects of M-TOR inhibitors on male gonads.

According to the 2007 data reported by OPTN (Organ Procurement and Transplant Network), 4.8% of the kidney transplant recipients are on a immunosuppressant regimen containing at the time of discharge from the hospital after the transplantation.⁶

This number might have further decreased since 2007 (this data is not published yet) since the percentage of kidney transplant patients who have been discharged from the hospital on a sirolimus containing regimen have constantly declined since 2001, which was the peak level of usage (17.2%) achieved after FDA approval in 1999.

In summary, information on the adverse reactions associated with the use of sirolimus, the first approved drug in the M-TOR class, has been evolving since its approval, based on the data obtained from additional studies in renal, hepatic, lung transplantation and from post-marketing reports.

⁶ http://optn.transplant.hrsa.gov/ar2008/data_tables.htm

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The protocol for Study A2309 was discussed with the applicant and comments were sent regarding the study design (IND 52-003; FDA comments on A2309 concept sheet, December 3, 2004 and FDA comments on A2309 protocol design, April 14, 2005).

In designing the protocol for Study A2309, the Applicant also followed the EMEA guidance on the use of combination therapy in transplantation [CHMP, EMEA Guideline on Clinical Investigation of Immunosuppressants for Solid Organ Transplantation 24-July-2008].

In addition to the 12 month results from Study A2309, the Applicant agreed to submit the following additional data in the NDA resubmission:

- a safety update that provides a side-by-side presentation of the new data and the data submitted in the original NDA (i.e., Studies B201 and B251)
- a PK/PD analysis of exposure–response relationships from Study A2309
- an update of foreign marketing history and labeling

The Applicant also agreed to cross-reference documents already reviewed in the everolimus renal and heart transplantation NDAs (21-560 and 21-628).

2.6 Other Relevant Background Information

None.

3.0 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

DSI Inspections were not performed, since this is not an NME (approved recently as Affinitor).

3.2 Compliance with Good Clinical Practices

The study and any amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each center. The study was conducted according to the ethical principles of the Declaration of Helsinki and US Code of Federal Regulations 21 CFR part 50 and 51. Informed consent was obtained from each subject in writing before randomization although some of the risks associated with the M-TOR inhibitors like male hypogonadism are not adequately communicated in the informed consent form to the

patients enrolled in this study. The study was described by the investigator, who answered any questions, and written information was also provided.

3.3 Financial Disclosures

OMB Form 0910-0396 was submitted and reviewed. The applicant obtained certification from each investigator and sub-investigator who enrolled subjects in Study A2309. No investigator had any disclosable information to reveal.

4.0 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please refer to CMC Review by Mark R. Seggel, PhD (final December 22, 2009)

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. However, labeling issues are still pending as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the labeling issues are resolved.

4.2 Clinical Microbiology/Immunology

Please refer to Microbiology/Immunology Review by Simone M. Shurland, PhD (11/24/2009)

Everolimus is a chemical derivative of the macrolide, rapamycin (a macrolide produced by *Streptomyces hygroscopicus*). The main structural difference between everolimus and rapamycin is that the hydrogen of the 40-hydroxyl group in rapamycin was replaced with a 2-hydroxyethyl group, thus forming an ether bond [40-O-(2-hydroxyethyl)-rapamycin]. The ether bond is metabolically stable, that is everolimus is not converted to rapamycin.

Mechanism of Action

On a cellular level everolimus inhibits growth factor-stimulated cell proliferation irrespective of the cell lineage or growth factor involved. This inhibition is reversible, that is, everolimus is not a cytotoxic compound. On a molecular level, growth factor-stimulated phosphorylation of p70 S6 ribosomal protein kinase (p70S6K) is inhibited in the presence of everolimus. To exert its activity everolimus needs to form a complex with a cytoplasmic binding protein, FKBP-12; this everolimus/FKBP-12 complex in turn

is thought to bind to and disable mTOR. p70S6K is a key translational regulator which controls protein synthesis, in particular that of pivotal proteins involved in cell growth and cell cycle regulation. p70S6K is a downstream effector of mTOR, it gets activated by mTOR-catalyzed phosphorylation. Inhibiting the activation of p70S6K by interfering with mTOR eventually results in cell cycle arrest and inhibition of cell proliferation.

The immunosuppressive activity of everolimus is explained by its ability to prevent IL-2/IL-15-stimulated T cell proliferation. Antigen-induced activation of an antigen-specific T cell, reflected by the production of cytokines/interleukins (i.e. IL-2), and subsequent proliferation of the activated T cell (i.e. clonal-expansion) are the hallmark features of a T cell immune- response. Immunosuppressive treatment strategies are therefore aimed at prevention of T cell activation and/or proliferation. While cyclosporine or tacrolimus prevent the first step, the activation of T cells, everolimus inhibits the interleukin-driven clonal expansion of activated T cells by inhibiting mTOR function. The different modes of action for everolimus and cyclosporine provide an adequate rationale for the pharmacodynamic synergy which has been demonstrated in vitro and in animal models of allotransplantation.

Some of the Comments from the Review:

The applicant stated that everolimus prolongs lung allograft survival in rats and nonhuman primates, as well as heterotopic heart transplants in rats. Studies in rats and primates showed that everolimus did not appear to have a significant effect at prolonging lung transplants; severe rejection by day 14 and 21 post-lung allograft was reported which was similar to that of vehicle control animals.

Only one experiment was conducted to measure the activity of everolimus in the heterotopic heart transplant model; the range of survival in everolimus treated animals was higher (12 to 33 days) than vehicle treated animals (6 to 8 days). However, testing is limited to one experiment and efficacy in clinical trials was not demonstrated. It is recommended that no reference to the effect of everolimus on heart and lung survival should be included in section 12.1 of the labeling.

The applicant claims that everolimus is able to reverse ongoing allograft rejection as was shown in the rat unilateral lung allotransplantation. The study referenced showed that everolimus followed by the administration of CsA 6 hours later were effective in improving lung graft survival. Treatment with everolimus and Neoral was initiated at the time of surgery. However, there were no studies in rats that showed that everolimus was able to reverse ongoing allograft rejection after unilateral lung allotransplantation. (b) (4)

4.3 Preclinical Pharmacology/Toxicology

See Pharmacology Toxicology Review by Steve Kunder, PhD (10/20/03; original NDA submission):

Animal reproductive toxicology studies showed effects in rats and rabbits. In a 13-week fertility study in male rats, testicular morphology was altered at a dose of 0.5 mg/kg/day (providing a systemic exposure approximately 0.2x that of the maximum clinical dose). Marked effects on male fertility occurred at 5.0 mg/kg (providing a systemic exposure approximately 1.0x that of the maximum clinical dose) including inability to impregnate females as well as testicular atrophy, oligospermia, aspermia and vacuolation of duct epithelium of the epididymides. Sperm motility, testicular sperm head count and plasma testosterone levels were reduced.

Pregnancy Category C

In the reproductive toxicity studies in female rats, everolimus crossed the placenta. At all doses, toxicity to fetus was observed. Increased pre- and postimplantation losses and an increased incidence in skeletal retardations occurred at all doses. An increase in the incidence of spontaneously occurring malformations was seen at doses of 0.3 and 0.9 mg/kg (providing an exposure approximately 0.9 x that of the maximum clinical dose based exposure comparisons).

Toxicities affected by immunosuppression included myocardial degeneration/myocarditis in monkeys and rats at 1.5 mg/kg (approximately 1.7-4.5x human exposure); this is likely related to viral infection emerging under immunosuppression. Other toxicities included reproductive organ toxicity in all species tested including testicular atrophy in monkeys at 0.3 mg/kg (0.9x human exposure)

Lung toxicity in mice at 1.5 mg/kg (15x human exposure) and rats at 0.5 mg/kg (0.1x human exposure); and toxicity to the eye as swelling and disruption of cortical fibers of the lens at a dose of 0.9 mg/kg in rats (0.4 x human exposure).

Some of the nonclinical safety issues relevant to clinical use from the review:

- Eye toxicity seen in rats (disruption of fibers in lens) may cause vision problems.
- Decreased male fertility may prevent males from impregnating partners after transplantation.

The preclinical safety profile of everolimus was assessed in mice, minipigs, monkeys and rabbits. The major target organs were male and female reproductive systems (testicular tubular degeneration, reduced sperm content in epididymides, and uterine atrophy) in several species: lungs (increased alveolar macrophages) in rats and mice; and eyes (lenticular anterior suture line opacities) in rats only. Minor kidney changes were seen in the rat (exacerbation of age-related lipofuscin in tubular epithelium, increases in hydronephrosis) and mouse (exacerbation of background lesions).

There was no indication of kidney toxicity in monkey or minipigs. Spontaneously occurring background disease (chronic myocarditis in rats, Coxsackie virus infection of plasma and heart in monkeys, coccidian infestation of the gastrointestinal tract in minipigs, skin lesions in mice and monkeys) appeared to be exacerbated by the treatment with everolimus. These findings were generally observed at systemic exposure levels within the range of therapeutic exposure or above, with the exception of the findings in rats, which occurred below the therapeutic exposure-due to a high tissue distribution.

Cyclosporine in combination with everolimus caused higher systemic exposure to everolimus and increased toxicity. There were no new target organs in the rat. Monkeys showed hemorrhage and arteritis in several organs.

Nonclinical safety issues relevant to clinical use

(as stated by Steve Kunder PhD.):

- **-Renal toxicity** is of prime importance, especially for renal transplantation. It is well characterized for calcineurin inhibitors.
- **-Pancreatic toxicity**, also well characterized for calcineurin inhibitors, potentially leading to post-transplantation diabetes mellitus.
- **-Reproductive toxicity/male fertility**, counter indicates Certican (review written in 2003) for pregnant women; however, organ transplantation is typically not conducted in pregnant women. Decreased male fertility may prevent males from impregnating partners after transplantation.
- **-Eye toxicity** seen in rats (disruption of fibers in lens) may cause vision problems.
- **-Hypercholesterolemia and hypertriglyceridemia**, seen in rats and monkeys, and typical of other immunosuppressant drugs used for organ transplantation, may be treated with current antihyperlipodemic therapies following transplantation.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Everolimus (40-O-(2-hydroxyethyl)-rapamycin) is a macrolide immunosuppressant and has a stable 2-hydroxyethyl chain substitution at position 40 on the sirolimus

(rapamycin) as apparent from the chemical formula. It was developed to increase the oral bioavailability of sirolimus.

The mechanism of action of everolimus is similar to sirolimus. Everolimus, like sirolimus, binds to FKBP12 (FK506-binding protein), forming a complex that binds to mammalian target of rapamycin (M-TOR), a key regulatory kinase. The M-TOR protein is a serine-threonine kinase that is pivotal for a number of important processes such as cell growth and proliferation, cellular metabolism, autophagy, and angiogenesis. The FKBP12-everolimus-M-TOR complex dephosphorylates and inhibits p70S6 kinase which, when activated, stimulates the ribosomes for protein synthesis and cell-cycle progression. This blockade by everolimus inhibits:

- T cell activation and proliferation that occurs in response to antigenic and cytokine (IL-2 and IL-15) stimulation;
- IL-6 stimulated B cell activation, proliferation, and antibody production;
- Proliferation of non-immune cells like smooth muscle cells.

4.4.2 Pharmacodynamics

Not applicable

4.4.3 Pharmacokinetics

Please refer to Clinical Pharmacology Review conducted with the original NDA submission by Ike Lee, PhD. The following version is from the final label:

Everolimus pharmacokinetics have been characterized after oral administration of single and multiple doses to adult kidney transplant patients, hepatic-impaired patients, and healthy subjects.

Absorption

After oral dosing, peak everolimus concentrations occur 1 to 2 h post dose. Over the dose range of 0.5 mg to 2 mg twice daily, everolimus C_{max} and AUC are dose proportional in transplant patients at steady-state.

Food Effect

In 24 healthy subjects, a high-fat breakfast (44.5 g fat) reduced everolimus C_{max} by 60%, delayed t_{max} by a median 1.3 hours, and reduced AUC by 16% compared with a fasting administration. To minimize variability, everolimus should be taken consistently with or without food [see *Dosage and Administration (2.4)*].

Distribution

The blood-to-plasma ratio of everolimus is concentration dependent ranging from 17% to 73% over the range of 5 ng/mL to 5000 ng/mL. Plasma protein binding is

approximately 74% in healthy subjects and in patients with moderate hepatic impairment. The apparent distribution volume associated with the terminal phase (V_z/F) from a single-dose pharmacokinetic study in maintenance kidney transplant patients is $342 + 107$ L (range 128 to 589 L).

Metabolism

Everolimus is a substrate of CYP3A4 and P-glycoprotein. The main metabolic pathways identified in man were monohydroxylations and O-dealkylations. Two main metabolites were formed by hydrolysis of the cyclic lactone. Everolimus was the main circulating component in blood. None of the main metabolites contribute significantly to the immunosuppressive activity of everolimus.

Excretion

After a single dose of radiolabeled everolimus was given to transplant patients receiving cyclosporine, the majority (80%) of radioactivity was recovered from the feces and only a minor amount (5%) was excreted in urine. Parent drug was not detected in urine or feces.

Specific Populations

Hepatic Impairment

Everolimus AUC was increased an average 2-fold in 8 patients with moderate hepatic impairment (Child-Pugh Class B) compared with 8 healthy subjects. AUC was positively correlated with serum bilirubin concentration and with prolongation in prothrombin time and negatively correlated with serum albumin concentration. The AUC of everolimus tended to be greater than that of healthy subjects if bilirubin was >34 $\mu\text{mol/L}$, prothrombin time was >1.3 INR > 4 sec prolongation, and/or albumin concentration was <35 g/L. The impact of severe hepatic impairment (Child-Pugh Class C) on everolimus pharmacokinetics has not been assessed but the effect on everolimus AUC is likely to be as large or larger compared with moderate impairment. There is no information on the effects of severe hepatic impairment (Child-Pugh Class C) on everolimus pharmacokinetics. [see *Dosage and Administration* (2.5)]

Renal Impairment

No pharmacokinetic studies in renally-impaired patients were conducted. Post-transplant renal function (creatinine clearance range 11-107 mL/min) did not affect the pharmacokinetics of everolimus; therefore, no dosage adjustments are needed in renally-impaired patients.

Pediatrics

The safety and efficacy of everolimus has not been established in pediatric patients.

Geriatrics

A limited reduction in everolimus oral CL of 0.33% per year was estimated in adults (age range studied was 16-70 years). There is no evidence to suggest that elderly patients will require a different dosage recommendation from younger adult patients.

Race

Based on analysis of population pharmacokinetics, oral clearance (CL/F) is, on average, 20% higher in Black transplant patients.

4.4.4 Pharmacokinetics/Pharmacodynamics

Please refer to Pharmacometrics Review by Kevin M. Krudys PhD (12/17/2009).

Potential relationships between blood trough levels of everolimus and various efficacy events were explored by the Applicant using the pooled data from both everolimus dose groups and are summarized in Table 3.

4.4.4.1 *Exposure-Response for Efficacy*

A whole blood trough concentration of 3 ng/mL was previously identified as the minimum target concentration to preserve efficacy in renal and heart transplantation from the exposure-response (ER) analyses from the renal transplantation studies B201 and B251, and heart transplantation study B253.

Both everolimus groups were pooled together (everolimus 1.5 mg group had target of 3-8 ng/mL and the everolimus 3.0 mg group had a target level of 6-12 ng/mL). The efficacy results from Study A2309 were used to evaluate the robustness of this trough concentration of 3 ng/mL, as shown in Table 3. Consistent with the defined everolimus target ranges, a low number of patients had exposure lower than 3 ng/mL or higher than 12 ng/mL. The frequency of treated BPAR becomes progressively lower as everolimus trough concentrations increase. The risk of graft loss was higher at everolimus trough concentrations less than 3 ng/mL (11.4%) than between 3 and 8 ng/mL (3.7%). Above a minimum everolimus level of 3 ng/mL rates of treated BPAR are all numerically reduced compared to that with Myfortic. However, the risk of death was the highest (5.0%) at everolimus trough concentrations above 8 ng/mL, the upper limit of the sponsor proposed target therapeutic range. These results therefore support the 3 to 8 ng/mL target range for everolimus trough concentrations with regard to efficacy. Within these ranges BPAR, graft loss and death rates are comparable to those occurring with Myfortic.

Table 3. Association between Everolimus Target Trough levels and Efficacy
 (Source: Pharmacometrics Review by Kevin Krudys Ph.D)

Everolimus trough levels	Treated BPAR	Graft Loss	Death
< 3 ng/mL	6/33 (18.2%)	4/35 (11.4%)	1/37 (2.7%)
3 – 8 ng/mL	64/415 (15.4%)	15/410 (3.7%)	9/411 (2.2%)
> 8 ng/mL	9/99 (9.1%)	3/101 (3.0%)	5/101 (5.0%)
Myfortic	47/277 (17%)	9/277 (3.2%)	6/277 (2.2%)

4.4.4.2 Exposure-Response for Safety

The relationship between whole blood everolimus trough concentrations and selected safety events up to 12 months post transplant in Study A3209 was established for the following:

- Proteinuria, defined as the urinary protein / urinary creatinine (UP/UC) ratio ≥ 0.3 g/g after Month 1

Clinical Reviewer’s Comment: According to NKF(National Kidney Foundation) the cut-off value is (UP/UC) ratio ≥ 0.2 which is a lower cut-off value than as stated by the Applicant. Having a higher cut-off value may decrease the incidence of proteinuria in all of the treatment groups simultaneously but also the differences in-between the groups also become smaller losing their significance.

- Wound healing complications/events based on the applicant’s analysis of all the relevant preferred terms
- Peripheral edema adverse events
- Hypercholesterolemia, defined as total cholesterol ≥ 6.2 mmol/L, or ≥ 240 mg/dL
- Hypertriglyceridemia, defined as triglycerides ≥ 5.6 mmol/L, or 500 mg/dL

Clinical Reviewer’s Comment: These events were selected because they are associated with the M-TOR inhibitor class of drugs (i.e., sirolimus), were identified as clinically relevant, and were observed at higher rates in the everolimus treatment groups compared to the Myfortic control treatment group in Study A2309.

Figure 1. Everolimus Trough Concentrations and Proteinuria
 (Source: Pharmacometrics Review by Kevin Krudys Ph.D)

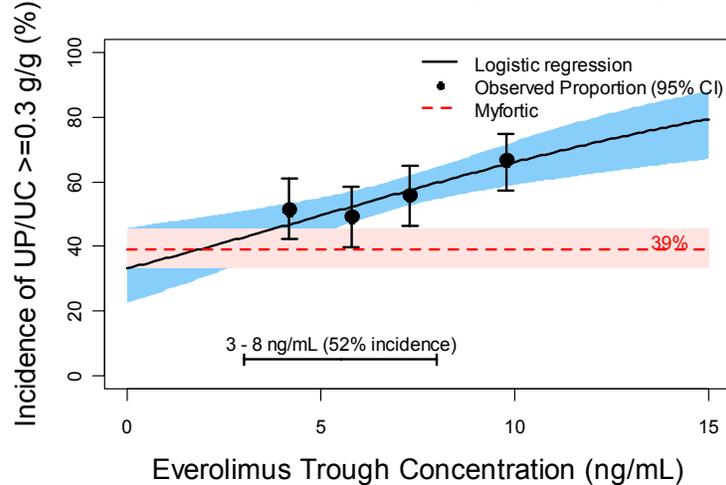
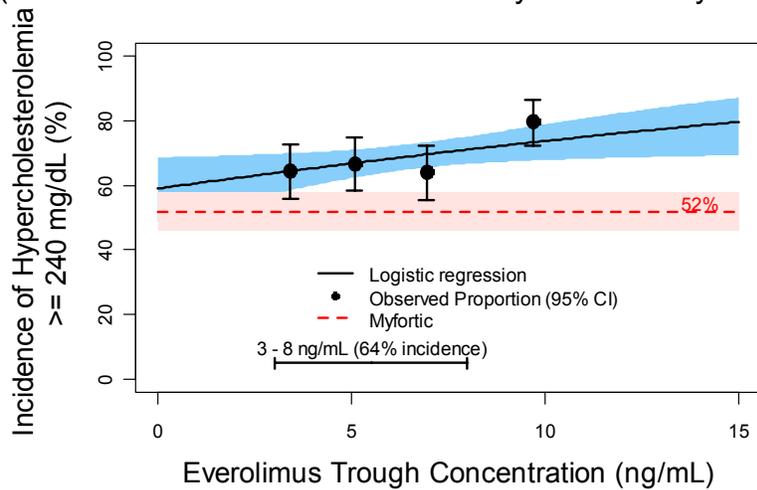


Figure 2. Everolimus Trough Concentrations and Hypercholesterolemia.
 (Source: Pharmacometrics Review by Kevin Krudys Ph.D)



There was not a strong relationship between higher everolimus concentrations and the incidence of the following events:

- Peripheral edema adverse events
- Wound healing complications
- Hypertriglyceridemia (triglycerides >490 mg/dL)
- New onset diabetes mellitus

However, the incidence of these events was higher in everolimus treatment groups

The increased incidence rate of these safety events observed in the everolimus treatment groups suggests these events more closely correspond to everolimus exposure than CsA exposure because CsA whole blood trough concentrations were lower in the everolimus + CsA treatment groups than in the Myfortic + CsA. Time normalized everolimus concentrations calculated up to Month 12 post transplant or the occurrence of the event were used in the analysis.

Table 4. Everolimus Trough Concentrations are not Associated with Renal Function Impairment

Relationship between everolimus and cyclosporine trough concentrations and GFR < 30 mL/min/1.73m ²			
Everolimus trough levels	Cyclosporine trough 0-100 ng/mL	Cyclosporine trough 100-200 ng/mL	Cyclosporine trough >200 ng/mL
3 – 8 ng/mL	10/171 (5.8%)	35/183 (19.0%)	10/19 (52.6%)
> 8 ng/mL	1/34 (2.9%)	6/43 (14%)	7/15 (48.7%)

5.0 Sources of Clinical Data

ECTD submission: <\\Cdsesub1\evsprod\NDA021560\0010>
 Current submission contained Study A2309 which will be the subject of this review. The sponsor submitted electronic datasets located at <\\Cdsesub1\evsprod\NDA021560\0010>.

Previously the sponsor conducted other studies B201 and B251 which will be utilized in the safety analysis. The sponsor also resubmitted the listing and analysis datasets for these studies as well.

5.1 Tables of Studies/Clinical Trials

Study A2309 and the previous studies B251 and B201, which used fixed dose everolimus and full dose CsA, are summarized in Table XX.

Table 5. Summary of main Phase III studies
 (Source: Clinical Overview section of CSR)

Study	Objective, Population	No.	Time	Treatments	Efficacy Endpoint
Key, new study A2309 (blood level control of everolimus, <i>reduced dose</i> CsA, steroids)					
[A2309]	efficacy / safety (renal, overall) of titrated everolimus with titrated reduced dose CsA versus Myfortic with titrated standard dose CsA (both with steroids and basiliximab induction) in <i>de novo</i> kidney recipients	833	12 mo + 12 mo	1.5 mg/d everolimus 3.0 mg/d everolimus (with reduced CsA) versus 1.44 g/d Myfortic (with standard CsA)	BPAR, GL, death, LtFU (6mo) BPAR, GL, death, LtFU (12 mo)
Studies in the NDA amendment (blood level control of everolimus, <i>reduced dose</i> CsA, steroids)					
A2306	efficacy / safety / tolerability of titrated everolimus with titrated reduced dose CsA (with steroids but no induction) in <i>de novo</i> kidney recipients	237	12 mo	1.5 mg/d everolimus 3.0 mg/d everolimus (with reduced CsA)	Renal function (6mo) BPAR, GL, death, LtFU (6mo) BPAR, GL, death, LtFU (12 mo)
A2307	efficacy / safety / tolerability of titrated everolimus with titrated reduced dose CsA (with steroids and basiliximab induction) in <i>de novo</i> kidney recipients	256	12 mo	1.5 mg/d everolimus 3.0 mg/d everolimus (with reduced CsA)	Renal function (6mo) BPAR, GL, death, LtFU (6mo) BPAR, GL, death, LtFU (12 mo)
Pivotal studies in the original NDA (fixed dose everolimus, <i>standard dose</i> CsA, steroids)					
B201	efficacy / safety of fixed dose everolimus with titrated standard dose CsA versus MMF with titrated standard dose CsA (both with steroids but no induction) in <i>de novo</i> kidney recipients	588	12 mo (double blind) + 24 mo	1.5 mg/d everolimus 3.0 mg/d everolimus (with standard CsA) versus 2 g/d MMF (with standard CsA)	BPAR, GL, death, LtFU (6mo) GL, death, LtFU (12 mo)
B251	efficacy / safety of fixed dose everolimus with titrated standard dose CsA versus MMF with titrated standard dose CsA (both with steroids but no induction) in <i>de novo</i> kidney recipients	583	12 mo (double blind) + 24 mo	1.5 mg/d everolimus 3.0 mg/d everolimus (with standard CsA) versus 2 g/d MMF (with standard CsA)	BPAR, GL, death, LtFU (6mo) GL, death, LtFU (12 mo)

MMF = mycophenolate mofetil, Myfortic® = enteric-coated mycophenolate sodium, CsA = cyclosporine A; basiliximab = interleukin-2 receptor antagonist, BPAR = biopsy-proven acute rejection, LtFU = loss to follow up, GL=graft loss

5.2 Review Strategy

The focus of this review is Study A2309 but safety information will be compared across the three studies (i.e., A2309, B201, and B251).

5.3 Discussion of Individual Studies/Clinical Trials

The original NDA submission contained the results from Studies B201 and B251 in *de novo* renal transplant recipients.

Both studies compared two fixed-dose regimens of everolimus, 1.5 mg per day and 3 mg per day given in two divided doses twice daily, to the approved dose of MMF 1g twice daily and standard CsA plus corticosteroid regimens. Induction therapy was not given in these trials. A total of 193 and 194 subjects were randomly assigned to the 1.5 mg total dose of everolimus, while an additional 194 and 198 subjects were assigned to the 3.0 mg total dose of everolimus, in studies B201 and B251, respectively. For a detailed discussion of these studies and the results, see the Statistical Review by Ruthanna Davi, MS filed with the original NDA.

Both studies were double-blind for the first 12 months following transplantation and were extended as open-label studies for an additional two years. The 12 month analysis of GFR showed increased rate of renal impairment in the everolimus groups compared to the MMF control group in both studies.

Efficacy of everolimus was demonstrated in Studies B201 and B251; however, interpretation of the results was complicated by the premature treatment discontinuations due to reduced graft function and higher serum creatinine concentrations seen in the everolimus groups compared to the MMF control groups. Due to these observed renal toxicities, the NDA was not approved and the applicant was asked to establish a safe and effective dosing regimen for everolimus and CsA that minimizes renal function impairment while maintaining efficacy, such as concentration-controlled regimens of everolimus and cyclosporine using therapeutic dose monitoring (TDM).

GFR is considered to be an endpoint for safety because of its association with chronic allograft injury but GFR may also reversibly change due to acute factors like CsA induced afferent arteriole vasoconstriction.

The reason there was interest in this endpoint is because in the previous renal transplant studies, B201 and B251, which evaluated fixed doses of everolimus and full-dose CsA, renal function was worse in the everolimus groups compared to the MMF control group, as estimated by the Nankivell method. Therefore, the question was whether a regimen consisting of concentration-controlled everolimus and reduced-dose CsA would yield renal function similar to a regimen of Myfortic and CsA. The results of the statistical analysis to test if there was a difference in mean GFR between treatment groups in Study A2309 are shown in Table 20. The difference in GFR was approximately 2 mL at 12 months, in favor of everolimus, compared to a difference of 6 mL (B201) and 8 mL (B251) at 12 months, in favor of MMF. In the comparison of the 3.0

mg everolimus group compared to the MMF control group, the differences were 7 mL (B201) and 11 mL (B251) at 12 months, also in favor of MMF.

Data from two additional open-label, non-comparative kidney transplant trials (A2306 and A2307), along with some exposure-response analyses, were submitted to the NDA as a Complete Response by the applicant on February 27, 2004. Studies A2306 (without basiliximab) and A2307 (with basiliximab) were conducted, using concentration-controlled everolimus dosing (initial doses of 1.5 mg and 3.0 mg per day adjusted to trough concentrations above 3 ng/mL) and reduced-dose CsA. As these studies were designed to compare the 1.5 mg and 3.0 mg doses of everolimus and did not include an active control group, the analyses in the submission were based primarily on cross-study comparisons between A2306 and A2307 and studies in the original submission. FDA noted these and other limitations in the studies' design, therefore the applicant was asked to provide additional information to establish a safe and effective dosing regimen for everolimus and CsA.

Subsequently Novartis designed a new study of concentration-controlled everolimus with low dose CsA both adjusted using TDM in *de novo* kidney transplant recipients, and the protocol was discussed with FDA. Study A2309, which is the basis for this NDA resubmission, is a 24-month, multicenter, randomized, open-label, three-arm trial that enrolled 833 *de novo* adult renal transplant recipients in Africa, Asia, Australia, Europe, North and South America. Patients were randomized to one of three groups: everolimus starting at either 1.5 or 3.0 mg per day combined with reduced dose CsA, or mycophenolic acid (MPA; Myfortic®) 1.44 gm per day with standard dose CsA. The starting dose of everolimus in this study was the same as used in the initial studies B201 and B251. However, in this study everolimus doses were adjusted to achieve blood trough concentrations of 3 to 8 ng/mL (low dose group, starting at 1.5 mg/day) and 6 to 12 ng/mL (high dose group starting at 3.0 mg/day) combined with reduced exposure to CsA, which was tapered over time. Both drug concentrations were guided by TDM. The upper limit of the CsA target range for everolimus groups at Day 3 was 200 ng/mL compared to 300 ng/mL in the control group. At Month 2, CsA target concentrations were a maximum of 150 ng/mL in the everolimus groups, while in the control group, the target CsA maximum was 250 ng/mL. The target trough concentrations for CsA were lower in the everolimus groups compared to the everolimus groups in studies B201 and B251, while exposure to CsA in the control groups was similar in all 3 studies and higher than in the everolimus groups in this study. The control regimen in studies B201 and B251 was MMF, while in this study it was MPA. The dose of MPA was selected to provide the same molar dose as 1 gm of MMF (720 mg Myfortic is the molar equivalent of 1 gm MMF) and is the approved dose for use in combination with cyclosporine. All patients were given basiliximab as induction therapy and maintained on concomitant corticosteroids, which were dosed based on local practice. The current submission contains data from the first 12-months of the study.

Table 6. Dose and Target Concentrations for Everolimus and CsA across Studies

Study Treatment Group	Drug	Study B201	Study B251	Study A2309
Everolimus 1.5 mg/day group	Everolimus	0.75 mg bid	0.75 mg bid	Target trough 3-8 ng/mL
	CsA	Full Dose: 150 to 400 ng/mL (Weeks 1-4), 100 to 300 ng/mL (Months 2-12), 50 to 75 ng/mL (after Month 12)	Full Dose: 200 to 350 ng/mL (Weeks 1-4), 100 to 300 ng/mL (Months 2-12), 50 to 75 ng/mL (after Month 12)	Reduced Dose:* 100 to 200 ng/mL (until Month 2), 75 to 150 ng/mL (Months 2-4), 50 to 100 ng/mL (Months 4-6) and 25 to 50 ng/mL (after Month 6)
Everolimus 3.0 mg/day group	Everolimus	1.5 mg bid	1.5 mg bid	Target trough 6-12 ng/mL
	CsA	Full Dose – same as above	Full Dose – same as above	Reduced Dose:* same as above
Control group	MMF or MPA	MMF 1gm bid	MMF 1 mg	MPA 720 mg bid per day
	CsA	Full Dose – same as above	Full Dose – same as above	Standard:* 200 to 300 ng/mL (Month 1), 100 to 250 ng/mL (Month 2-12)

* pages 113 and 5772 of 14,328 from Study Report RAD001A2309, submitted June 30, 2009.

6.0 Review of Efficacy

Note: Tables in this section were obtained from the Applicant's Clinical Study Report (CSR) of Study A2309, as noted. Tables created by the reviewer, or obtained elsewhere are also noted.

6.1 Indication

Zortress (everolimus) is indicated for the prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant [see *Clinical Studies*

(14.1)]. Zortress is to be administered in combination with basiliximab and concurrently with reduced doses of cyclosporine and corticosteroids.

In the current study low-moderate immunologic risk patient is defined as ABO blood type compatible first time organ or tissue transplant recipient with anti-HLA Class I panel reactive antibodies < 20% by a Complement Dependent Cytotoxicity (CDC)-based assay or < 50% by a flow cytometry or Enzyme Linked Immunosorbent Assay (ELISA)-based assay and with a negative T-cell crossmatch.

6.1.1 Methods

6.1.1.1 Objectives

The primary objective of the study was to demonstrate that at least one of the everolimus treatment regimens was not inferior to the Myfortic treatment regimen within 12 months of the initial dose of study medication with respect to primary efficacy failure, namely, the composite efficacy endpoint of treated BPAR episodes, graft loss, death, or loss to follow-up.

The main secondary efficacy objective was to compare the composite incidence of graft loss, death, or loss to follow-up between everolimus and Myfortic treatment groups at 12 months post-transplantation.

The main safety objective was to demonstrate that non-inferior renal function was achieved in the everolimus treatment groups compared to the Myfortic treatment group at 12 months post-transplantation. Renal function was measured with calculated glomerular filtration rate (GFR) using the MDRD formula (Coresh et al 2003).

6.1.1.2 Study Design

Study A2309 is a 24-month, multi-national, open-label, randomized (1:1:1) trial comparing two concentration-controlled everolimus regimens of 1.5 mg per day starting dose (targeting 3 to 8 ng/mL) and 3.0 mg per day starting dose (targeting 6 to 12 ng/mL) with reduced doses of cyclosporine (CsA) and corticosteroids, to 1.44 gm per day of mycophenolic acid (Myfortic) with standard doses of CsA and corticosteroids. All patients received basiliximab induction therapy.

It was anticipated that 100 centers would be needed to enroll approximately 825 patients in Africa, Asia, Australia, Europe, North and South America. Enrollment was to be stopped after randomization of 825 patients.

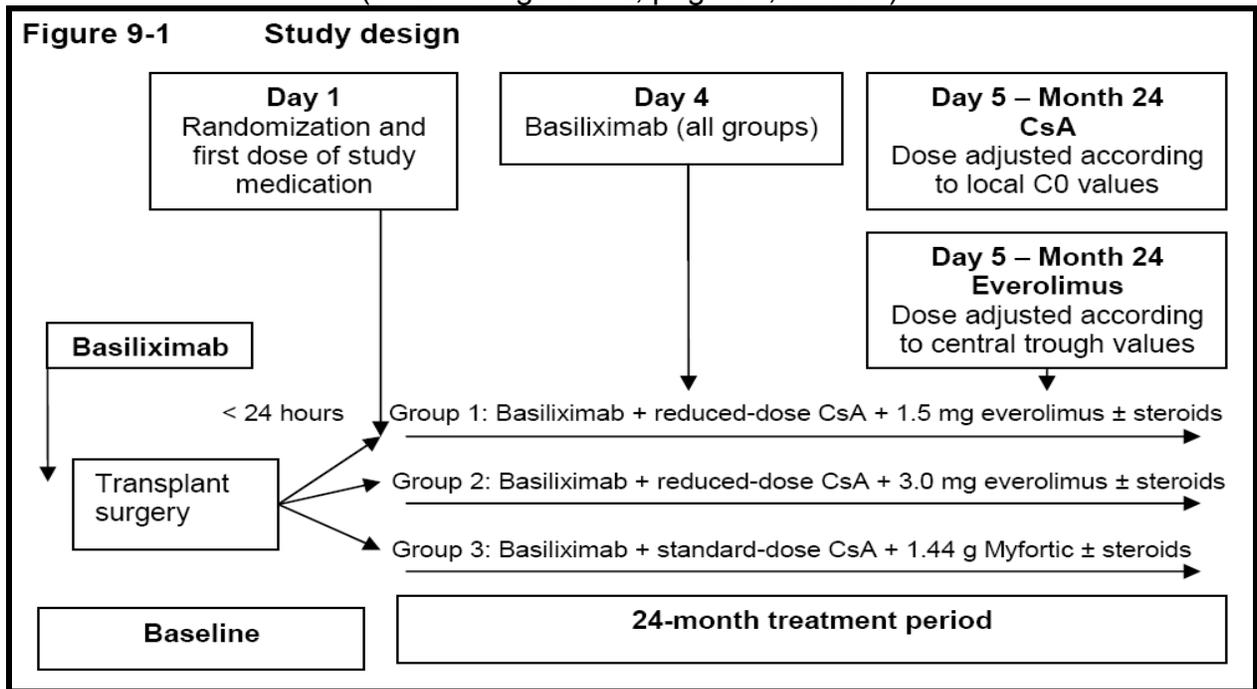
The trial is open-label. However, the Applicant’s staff supporting the conduct of the study were blinded with regard to treatment assignments, doses and blood levels of study medication and CsA for the entire 12 month treatment period.

The investigator, pharmacist, and patient were aware of which treatment was administered to the patient. The investigator should have, however, withheld the treatment assignment from the local pathologist interpreting the biopsies. The local pathologist provided the investigator their interpretation for clinical management of the patient.

The planned duration of treatment is 24 months. The data in this review represent the 12 month analysis.

Within 24 hours after transplantation, after having met all eligibility criteria, patients were randomized to one of the three treatment groups in a 1:1:1 ratio. Patients were not randomized until they were able to take oral medication.

Figure 3. Study A2309 Design
 (Source: Figure 9-1, page 96, of CSR)



6.1.1.3 *Discussion of Endpoints*

Primary Endpoint

The primary efficacy endpoint was efficacy failure at 12 months post transplantation, where efficacy failure was defined as the composite endpoint of treated biopsy-proven acute rejection (BPAR), graft loss, death, or loss to follow-up. Each of these components is further defined below.

Treated Biopsy-Proven Acute Rejection (BPAR)

Biopsies were read by the local pathologist according to the 1997 updated Banff criteria. Determination of the need for treatment was made according to the local pathologist's findings and the overall clinical presentation of rejection. The local pathologist was blinded to patient treatment. A BPAR episode was defined as a biopsy graded IA, IB, IIA, IIB, or III that was treated with anti-rejection therapy.

Death

Death was recorded at either study completion, follow-up, or as the outcome of an adverse event, if it occurred.

Graft loss

Graft loss was defined as any of the following:

- Loss of the graft. The allograft was presumed to be lost on the day the patient started dialysis and was not able to be subsequently removed from dialysis.
- Re-transplant

Loss to Follow-up

A patient who did not experience treated BPAR, graft loss or death and whose last day of contact was prior to study Day 316, which is the protocol defined lower limit of Month 12 visit window, was considered lost to follow-up.

Note: Loss to follow-up in the analysis of death, graft loss and loss to follow-up was defined as any patient who did not experience a graft loss or death and whose last day of contact was prior to Day 316.

Secondary Endpoints

The main secondary endpoint was the incidence rate of the composite endpoint of graft loss, death or loss to follow up at 12 months. Other secondary endpoints included efficacy failure (as defined for the primary endpoint) at 6 months, treated BPAR at 6 and 12 months, graft loss at 6 and 12 months, death at 6 and 12 months, biopsy proven chronic allograft nephropathy (CAN) at 12 months, graft loss or death at 6 and 12 months, graft loss, death or loss to follow up at 6 months, and antibody treated BPAR at 12 months.

Primary Safety Endpoint

The main safety endpoint of Study A2309 was serum creatinine at month 12 by calculated glomerular filtration rate (GFR) using the MDRD (Modification of Diet in Renal Disease) formula. The main safety objective was to show that the mean GFR of either everolimus 1.5 mg or 3.0 mg group was no worse than (non-inferior to) the Myfortic group by 8 mL/min/1.73m² at month 12 using t-test based, two-sided 95% and 97.5% confidence intervals.

Clinical Reviewer's Comment: *There is no justified non-inferiority margin for GFR in de novo kidney transplantation. Results of this endpoint will be assessed for clinical importance.*

6.1.1.4 Inclusion/Exclusion Criteria

Male and female renal transplant patients aged 18 to 70 years receiving a primary cadaveric, living unrelated or non-human leukocyte antigen (HLA) identical living related, donor kidney were eligible for study participation if they met all of the inclusion/exclusion criteria defined below.

Inclusion Criteria

Eligible patients were required to meet all of the following inclusion criteria:

- Male or female renal recipients 18-70 years of age undergoing primary kidney transplantation
- Provided written informed consent to participate in the study
- Females must have had a negative pregnancy test prior to randomization

Exclusion criteria

Patients were excluded from the study if they met any of the following exclusion criteria:

- No evidence of graft function within 24 hours of transplantation
- Receipt of kidneys from HLA-identical living related donors
- Donor organ with a cold ischemia time > 40 hours
- Received kidney from a non-heart beating donor
- Donor age > 65 years
- Platelet count < 100,000/mm³ at the evaluation before randomization
- Absolute neutrophil count (ANC) < 1,500/mm³ at baseline before surgery or white blood cell (WBC) count < 4,500/mm³
- Receipt of dual kidney transplants
- Recipients of multiple solid organ or tissue transplants or recipients of a previous organ or tissue transplant
- Severe hypercholesterolemia (> 350 mg/dL; > 9 mmol/L) or hypertriglyceridemia (> 500 mg/dL; > 8.5 mmol/L); controlled hyperlipidemia was acceptable
- Abnormal liver profile such as alanine aminotransferase (ALT), aspartate

- aminotransferase (AST), alkaline phosphatase, or total bilirubin > 3 times the upper limit of normal (ULN)
- Known hypersensitivity to either of the study drugs or their class, or to any of the excipients
- Treatment with drugs that are strong inducers or inhibitors of cytochrome P450
- Treatment with terfenadine, astemizole, or cisapride
- Inability to take oral medication at the time of randomization
- Receipt of an investigational drug or treatment with a non-protocol immunosuppressive drug or treatment within 30 days or five half-lives prior to randomization
- History of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there was evidence of local recurrence or metastases, with the exception of localized excised non-melanomatous skin lesions
- Most recent anti-HLA Class I panel reactive antibodies > 20% by a Complement Dependent Cytotoxicity (CDC)-based assay or > 50% by a flow cytometry or Enzyme Linked Immunosorbent Assay (ELISA)-based assay
- Receipt of ABO incompatible transplants or T-cell crossmatch positive transplant
- Patients who have tested positive for HIV, hepatitis C, or hepatitis B surface antigen.
- Laboratory results obtained within 6 months prior to randomization were acceptable, otherwise these tests were performed within 1 week of randomization
- Receipt of organs from donors who tested positive for hepatitis B surface antigen, hepatitis C, or HIV
- Clinically significant systemic infection at the time of transplant or within 2 weeks of transplant
- Severe diarrhea, active peptic ulcer disease, or uncontrolled diabetes mellitus
- Cardiac failure at the time of screening (resting dyspnea with grade ≥ 3 according to old New York Heart Association classification or any severe cardiac disease as determined by the investigator)
- Any surgical or medical condition, which, in the opinion of the investigator, might have significantly altered the absorption, distribution, metabolism, and excretion of study medication
- • Abnormal physical or laboratory findings of clinical significance within 2 weeks of randomization which could have interfered with the objectives of the study
- Any history of coagulopathy or medical condition requiring long-term anticoagulation that would preclude renal biopsy after transplantation (low dose aspirin treatment or interruption of chronic anticoagulant was allowed)
- Women of childbearing potential who were pregnant and/or lactating, planning to become pregnant, or who were unwilling to use effective means of contraception

6.1.1.5 *Treatments administered*

Everolimus

Therapeutic drug monitoring of everolimus trough concentrations was mandatory throughout the study. From Day 5 onwards, the following dose adjustments applied:

Everolimus 1.5 mg group: the 0.75 mg bid dose was increased if the everolimus trough level was < 3 ng/mL and reduced if the trough level was > 8 ng/mL to maintain the everolimus trough levels within the 3-8 ng/mL target range.

Everolimus 3.0 mg group: the 1.5 mg bid dose was increased if the trough level was <6 ng/mL, and reduced if the trough level was > 12 ng/mL to maintain the everolimus trough levels within the 6-12 ng/mL target range.

Follow-up everolimus trough levels were measured 5 days after any dose adjustment to everolimus to ensure that the recommended troughs were achieved. An everolimus trough was also measured 5 days after the 6-month CsA dose adjustment.

Cyclosporine

Neoral capsules were administered orally bid unless Neoral oral solution or intravenous administration of CsA could not be avoided. The lowest permitted dosing of Neoral in this study was 25 mg bid. If CsA was discontinued for more than 21 days, study drug was to be discontinued.

If CsA was administered via NG tube, it was to be administered immediately after everolimus or MMF. The drugs were not to be mixed. Two different syringes were to be used for the two drugs. After each administration, the NG tube was to be clamped for a minimum of 30 minutes.

CsA dosing was managed by monitoring local CsA trough levels as described below. In the event of CsA intolerance (e.g. nephrotoxicity, neurotoxicity), dose reduction of CsA may have been necessary.

CsA dose adjustments were based on CsA trough levels (C0). Although a central laboratory was utilized to collect trough levels for data analysis, patient clinical management was determined by the local laboratory results for the trough levels. C0 levels were determined from whole blood samples taken 12 ± 1 hour after the last evening dose at the time points indicated in the assessment schedule table (Table 8). The patients were instructed to adjust the medication schedule on the day prior to the blood draw to achieve proper timing and to bring the morning study medication dose to the visit so the next dose of study medication could be administered after the blood sampling was completed.

C0 values in both everolimus groups and in the Myfortic group were used to adjust the CsA dose to achieve CsA trough concentrations within the specified target ranges as shown in Table 9-3. Follow-up CsA trough levels were measured 5 days after any dose adjustment to CsA to ensure that the recommended troughs were achieved.

Table 7. Targeted CsA Trough Levels in Study 2309
 (Source Page 113 of CSR)

Table 9-3 C0 value ranges for CsA		
Day/month	Everolimus treatment groups	Myfortic treatment group
Starting Day 5	100-200 ng/mL	200-300 ng/mL
Starting Month 2 visit	75-150 ng/mL	100-250 ng/mL
Starting Month 4 visit	50-100 ng/mL	100-250 ng/mL
Starting Month 6 visit	25-50 ng/mL	100-250 ng/mL

The upper limit of the CsA target range for everolimus groups at Day 3 was 200 ng/mL compared to 300 ng/mL in the Myfortic group. At Month 2, CsA target levels were a maximum of 150 ng/mL in the everolimus treatment groups, while in the Myfortic group, the target maximum was 250 ng/mL.

Myfortic

1.44 g Myfortic qd (two 360-mg tablets bid) was administered to patients in the control group. If Myfortic MMF suspension was administered NG tube, it was to be administered according to the package insert. After each administration, the NG tube was to be clamped for a minimum of 30 minutes.

Basiliximab Induction:

All patients received two 20 mg doses of basiliximab administered intravenously. The first dose was to be given within 2 hours prior to transplant surgery and the second dose was to be administered on Day 4, or each dose could have been administered according to local practice.

Corticosteroids:

Oral corticosteroids were administered according to local practice during the trial. At the same center, all patients were to follow the same steroid administration protocol.

Clinical Reviewer's Comment: *The results showed that the mean and median doses of prednisone equivalent corticosteroids were highest on Day 1 (means of 3.73, 3.69 and 3.64 mg/kg/day for everolimus 1.5 mg, everolimus 3.0 mg and Myfortic 1.44 gm, respectively),. Doses of glucocorticoids decreased in all*

treatment groups over the course of the study with mean values at Month 12 of 0.10, 0.10 and 0.09 mg/kg/day for everolimus 1.5 mg, everolimus 3.0 mg and Myfortic 1.44 gm, respectively.

6.1.1.6 Study Drug Supply

Everolimus and the specific proprietary products of mycophenolic acid (MPA; Myfortic), cyclosporine (Neoral), and basiliximab (Simulect) used in the study are manufactured by Novartis.

Everolimus and Myfortic were also supplied by Novartis. Neoral and basiliximab were obtained by the sites using a commercial supply, or per local practice based on local health authority regulations.

6.1.1.7 Dose Adjustments Based on Adverse Events or Laboratory Findings

For patients unable to tolerate the protocol-specified dosing schedule, dose adjustments were permitted in order to keep the patient on study drug. Reasons for study drug dose reductions included a decrease in WBC count or platelet count, an increase in cholesterol or triglyceride level, or other AEs. Severe and unremitting changes may have resulted in study drug discontinuation. If study medication was interrupted for safety reasons for longer than 21 consecutive days or more than two episodes of 7 days or longer, discontinuation of study medication was discussed between the investigator and the Applicant. Study drug was permitted to be interrupted during antibody treatment of rejection episodes. A twice daily schedule was to be followed at all times.

The following guidelines for dose reductions due to safety reasons were provided to investigators:

- Everolimus 1.5 mg group: reduce everolimus dose from 0.75 mg bid to 0.5 mg bid. For further flexibility, 0.25 mg tablets were provided.
- Everolimus 3.0 mg group: reduce everolimus dose from 1.5 mg bid to 1.0 mg bid. For further flexibility 0.25 and 0.5 mg tablets were provided.
- Myfortic 1.44 gm group: reduce Myfortic dose from 720 mg bid to 360 mg bid.

Complete guidelines for everolimus and Myfortic dose reduction based on laboratory findings were provided in the CSR (Appendix 16.1.1-Protocol-Appendix 6).

6.1.1.8 Treatment Interruptions

If a patient developed a short-term intolerance of oral medication after the initial dose of study medication, study drug may have been temporarily interrupted. Alternatively, everolimus or MMF suspension may have been administered via a nasogastric (NG) tube. Such administration of study drug was considered study drug interruption. If this

period was more than 21 consecutive days or more than two episodes of 7 days or longer, study drug discontinuation was discussed between the investigator and the Applicant. Patients were to return to oral medication as soon as possible after an interruption of oral administration of study medication.

6.1.1.9 Treatment Discontinuations

In addition to the standard criteria for patient discontinuation (i.e., adverse event, withdrawal of consent, protocol violation) Patients were discontinued from study treatment in the case of pregnancy or administration of prohibited immunosuppressive medication (excluding immunosuppressive medications used to treat acute rejection).

All patients discontinuing study treatment prior to the 12 month treatment period were contacted at scheduled Months 3, 6, 9, and 12 visits to obtain follow-up information and were not considered withdrawn from the study. Information was collected on vital signs, hospitalizations, rejection episodes, central laboratory samples (proteinuria and serum creatinine), graft loss/re-transplant, SAEs, malignancies, opportunistic infections, patient survival, cytomegalovirus (CMV) infections, and immunosuppressive therapy. In addition, major adverse cardiac events (MACE) were reported during the follow-up period.

If patients refused to return for these visits or were unable to do so, every effort was to be made to contact them or a knowledgeable informant by telephone to determine the information on survival status, graft loss/re-transplant, rejection episodes, malignancies, opportunistic infections, and immunosuppressive therapies. Because patients were followed even after discontinuation of study medication, the Study Completion electronic Case Report Form (eCRF) page was only to be completed at Month 12 or earlier if the patient could no longer be followed (e.g. death, lost to follow-up, withdrawal of consent). No study drug was provided for patients who discontinued study treatment prior to Month 12.

6.1.1.10 Concomitant Therapy

Nephrotoxic Drugs

Co-administration of nephrotoxic drugs and drugs known to interfere with CsA metabolism were to be avoided if possible. If these drugs were required, the investigator was to carefully monitor renal function and adjust the CsA dose if needed. A for a list of drugs with the potential to interact with CsA can be found in the CSR (Appendix 16.1.1-Protocol-Appendix 5).

Cytomegalovirus (CMV) Prophylaxis

CMV prophylaxis for a minimum of 30 days was mandatory for all cases in which the donor tested positive and the recipient tested negative for CMV. Treatment with ganciclovir, cytomegalovirus hyperimmune globulin, acyclovir, or valacyclovir was permitted and was administered according to local practice. All cases other than CMV-positive donors to CMV-negative recipients were treated according to local practice.

***Pneumocystis jiroveci* Pneumonia Prophylaxis**

All patients were started on trimethoprim-sulfamethoxazole when oral medication could be tolerated and continuing for the first year of study medication per local practice. The same regimen was to be administered to all patients at a given study center. Aerosolized pentamidine or dapsone could have been administered to patients unable to tolerate trimethoprim-sulfamethoxazole.

Treatment of Oral Candida

For oral thrush (Candida), nystatin may have been used in a swish and swallow regimen. Alternatively, clotrimazole lozenges/troches could have been used. Routine use of systemic antifungal agents (i.e. itraconazole, voriconazole, and fluconazole) was not allowed unless patients were systemically infected. Because administration of azoles can increase blood concentrations of both CsA and everolimus, their use was to be minimized and particular attention to side effects was required.

Lipid Lowering Medications

HMG CoA reductase inhibitors (e.g. fluvastatin (Lescol®)) were to be administered according to local practice for the management of hyperlipidemia. Patients requiring treatment with this class of medication (especially lovastatin)* were to be monitored closely for signs of rhabdomyolysis. Lipid-lowering therapy was to be optimized before dose reduction of study medication was considered.

Reviewer's Comment: *Although lovastatin and simvastatin were not allowed according to the study protocol the Applicant still placed guidelines for watching signs of rhabdomyolysis in case they are used.*

6.1.1.11 Study Assessments

Baseline assessments occurred in the time period starting 24 hours pre-transplantation and ended at the time of randomization. No deviation in the evaluation schedule was allowed during Days 1 through 3. After Day 3, a visit window of 2 days up to Day 28, 1 week from Day 28 to Month 6, and 2 weeks after Month 6 was acceptable.

Table 8. Assessment Schedule
(Source: Table 9-2 Assessment schedule, page 108, CSR)

Examination	Pre-op ¹	Base-line ²	Day							Month								
	-2	-1 ³	1	3	4 ¹⁶	5 ¹⁶	7	14	28	2	3	4	6	7	9	12	18	24 ¹⁷
Randomization			X															
Background information	X																	
Inclusion/exclusion	X	X																
Medical history	X	X																
Transplant information		X																
Viral serology ⁴	X																	
Pregnancy test ⁵	X																	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam.		X														X		
Laboratory test ⁶		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Endocrine tests ⁷		X										X		X		X		
Pharmacogenetic sample ⁸	X																	
Study medication ⁹			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Basiliximab dosage ¹⁰	X				X													
CsA dosage										Per protocol								
RAD trough level ¹¹			X			X	X	X	X	X	X	X	X	X	X	X	X	X
CsA trough level (C0) ¹¹			X			X	X	X	X	X	X	X	X	X	X	X	X	X
CsA C ₂ level (optional)			X			X	X	X	X	X	X	X	X	X	X	X	X	X
Immunosuppressive therapy			As needed															
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events ¹²			As needed															
Hospitalizations ¹³							X	X	X	X	X	X	X	X	X	X	X	X
MACE events			As needed															
CMV infections			As needed															
Renal biopsy ¹⁴		X								As needed						X	As needed	
Allograft rejection			As needed															
Graft loss record			As needed															
Dialysis log			As needed															
Infection log			As needed															
End of treatment			As needed															
Comments			As needed															
Follow-up record ¹⁵			Completed at 3, 6, 9, 12, 18, and 24 months after the first dose of study medication for patients who prematurely discontinued study medication prior to Month 24. Renal biopsies performed at 12 months ¹⁴ (patients with proteinuria or where 1 year post-transplantation biopsies were performed as part of standard institutional protocol).															

¹Informed consent was obtained at the pre-op visit (Visit 1), prior to any study-related procedures. The pre-op visit was normally Day -2 but may have extended up to 4 weeks prior to transplant (e.g. for scheduled living donor transplants).

²Baseline covered the period from 24 hours prior to surgery until randomization. The post-surgery baseline assessments (e.g. functioning graft, ability to take oral medication) occurred within 24 hours prior to randomization.

³Study days -2 and -1 may have been the same date depending on the time of transplant.

⁴Viral serology included hepatitis C, HIV, and hepatitis B surface antigen. Measurements made within the last 6 months were accepted, otherwise these tests were to be performed within 1 week of randomization. Patients testing positive for any such viral serology test were discontinued from study medication and entered the follow-up period.

⁵Only for females, a pregnancy test may have been carried out according to local practice. Local results must have been available and negative within 48 hours prior to randomization. A pregnancy test was also obtained at end of study.

⁶Safety laboratory included: biochemistry (sodium, potassium, chloride, calcium, magnesium, inorganic phosphate, urea, creatinine, glucose, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, creatine phosphokinase (CPK), lipase, amylase (LDL and HDL only at baseline, Week 4, Month 6, 12; 18, and 24); urinalysis (protein, glucose); hematology, platelets, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) and differential count), spot urine for a quantitative protein/creatinine ratio (central labs) at every visit.

⁷Testosterone, follicle stimulating hormone (FSH), lutenizing hormone (LH) (males only).

⁸Pharmacogenetic sample may have been obtained at a later timepoint if the patient was unable to provide a baseline sample.

⁹First dose of study medication was given (together with CsA) immediately following randomization, which occurred within 24 hours of transplantation.

¹⁰The first dose of basiliximab was given within 2 hours prior to transplant or according to local practice. The second dose was given on Day 4 or according to local practice.

¹¹Blood draw for everolimus and CsA trough concentrations 5 days \pm 2 days following each clinic visit in which everolimus or CsA doses were changed. Patient clinical management for CsA was based on local C₀ levels.

¹²Serious adverse events, infections, and pregnancies were reported for up to 30 days after the last dose of study medication.

¹³Hospitalization data: data to be collected at each visit for economic analyses.

¹⁴Baseline renal biopsies were performed on all patients. Renal biopsies were performed in cases of suspected acute rejections and at Month 12 in all patients with significant proteinuria (defined as > 0.5 g/day (on or off ACE inhibitors or ARBs) or suboptimal renal function (estimated GFR by MDRD < 50 mL/min/1.72m²)). In a subset of centers, renal biopsies were performed on all patients at Month 12.

¹⁵Follow-up evaluations included vital signs, hospitalizations, rejection episodes, central lab samples (proteinuria and serum creatinine), graft loss/re-transplant, SAEs, malignancies, opportunistic infections, patient survival, CMV infections, immunosuppressive therapy, and MACEs.

¹⁶Day 4 and Day 5 procedures and assessments could have been performed earlier if the patient was discharged from the hospital in accordance with local practice.

¹⁷All Month 24 evaluations were performed at end of study or at the time of premature discontinuation of study medication. Study completion form was only to be completed after patients completed 24 months in study (whether on or off study medication).

Timing of Kidney Biopsies

Baseline biopsies were obtained on all patients. At selected centers, 12-month biopsies were obtained for all patients at the site. In addition, biopsies were also collected for any patient with significant proteinuria (defined as > 0.5 g/day, on or off ACE inhibitors or

ARB) or suboptimal renal function (defined as estimated GFR by MDRD < 50 mL/min/1.72m²) at Month 12 in all centers.

Renal biopsies were also collected for all cases of suspected acute rejection. For all suspected rejection episodes, regardless of initiation of anti-rejection treatment, a graft core biopsy must have been performed within 48 hours.

Determination of Acute Rejection

In all suspected rejection episodes, regardless of initiation of anti-rejection treatment, a graft core biopsy was to be performed within 48 hours. Biopsies were read by the local pathologist according to the 1997 updated Banff criteria (full criteria provided in CSR; Appendix 16.1.1-Protocol-Appendix 7). Determination of the need for treatment was made according to the local pathologist's findings and the overall clinical presentation of rejection. The local pathologist remained blinded to the patient treatment.

The results of the biopsy read by the local pathologist were listed on the Kidney Allograft Biopsy eCRF and were used for patient management of acute rejection. A treated BPAR was defined as a biopsy graded IA, IB, IIA, IIB, or III and which was treated with anti-rejection therapy. Biopsy specimen slides from all biopsies were submitted to a independent central pathologist(s) for blinded review.

If the investigator chose to permanently stop CsA or to switch to another primary immunosuppressive agent, study medication was discontinued. However, the patient was to be followed until completion of the trial.

Acute rejections were considered protocol-exempted Serious Adverse Events (SAEs). They were not to be reported simply because they resulted in hospitalization and thus met the criteria for SAEs. However, acute rejections were to be reported as SAEs if they were unusual in appearance or clinical course or were graft threatening.

Definition and Timing of Graft Loss

An allograft was presumed to be lost on the day a patient started dialysis and was not able to subsequently be removed from dialysis. If the patient underwent a graft nephrectomy, then the day of nephrectomy was the day of graft loss.

Graft loss was considered a SAE.

6.1.1.12 Analysis Populations

The Intent-To-Treat (ITT) population consisted of all patients randomized after transplantation. Following the intent-to-treat principle, patients were analyzed according to the treatment they were assigned to at randomization.

The Safety population consisted of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. Patients were analyzed according to treatment received.

The Per-protocol (PP) population consisted of all randomized patients who took study treatment according to the protocol without any major deviations from the protocol procedures.

The following deviations were considered as major deviations and led to exclusion of the corresponding patients from the PP population:

- The patient had received multiple transplants or had previous transplants;
- Renal cold ischemia time was > 40 hours;
- The transplant donor's age was > 65 years.

Non-protocol deviation criteria which must have been satisfied for inclusion in the PP population were:

- At least 6 months treatment with study medication;
- At least one post-baseline safety evaluation;
- Had received 2 doses of Simulect (around Day -1 and Day 4) administered intravenously.

All Per-Protocol analyses were on-treatment analyses, using data observed while on treatment. An on-treatment observation was assessment obtained on and after Day 1 but no later than two days after the discontinuation of randomized study medication.

Safety data was analyzed on the Safety population as defined above except for the analysis of renal function which was performed on the ITT and PP populations. Efficacy analyses were performed on the ITT and PP population.

Table 9 Analysis Populations

(Source: Table 11-1, page 142, CSR)

Table 11-1 Analysis populations – n (%) of patients by treatment group (12 month analysis)			
	Everolimus 1.5 mg (N=277) n (%)	Everolimus 3.0 mg (N=279) n (%)	Myfortic 1.44 g (N=277) n (%)
Population category			
Intent-to treat (ITT) population	277 (100.0)	279 (100.0)	277 (100.0)
Safety population	274 (98.9)	278 (99.6)	273 (98.6)
Per protocol (PP) population	215 (77.6)	205 (73.5)	230 (83.0)
Source: Table 14.1-2.1			

6.1.1.12 *Statistical Analysis*

Analysis was performed on the ITT and PP populations. Patients who discontinued study drug were included in the 12 month analyses and evaluated according to their study drug assignment. Patients who discontinued study before the 12 month endpoint but otherwise had no efficacy failures were treated as efficacy failures and included in the efficacy analyses as lost to follow-up. Sensitivity analyses were performed to confirm the appropriateness of this approach.

The primary objective of the study was tested for each of the 2 treatment comparisons of everolimus to Myfortic, with regard to the following null hypothesis:

H0: the proportion of patients experiencing efficacy failure at 12 months on the everolimus group is higher than that of the Myfortic group by 10% or more, where 10% represents the non-inferiority margin chosen.

The non-inferiority tests were based on confidence intervals (CI) constructed using the Z-test statistic, performed on the ITT population. The trial was to be claimed as successful if the incidence rate of the primary composite efficacy failure from either of the two everolimus groups was non-inferior to the Myfortic group. Hence, to control for multiple comparisons (i.e., everolimus 1.5 mg vs. Myfortic and everolimus 3.0 mg vs. Myfortic) the Hochberg procedure was used to maintain the overall Type I error rate at 0.05.

Following the Hochberg procedure, two-sided 95% and 97.5% CIs for the difference in primary efficacy failure rates at 12 months between the everolimus and Myfortic groups were computed. An everolimus group was claimed to have non-inferior efficacy failure rate at 12 months to Myfortic if the upper limit of the appropriate CI was less than 10%. As a supportive analysis and robustness check, the primary analysis was repeated using the PP population.

The main safety objective of the trial was to demonstrate that non-inferior renal function (calculated GFR using the MDRD formula) was achieved between an everolimus treatment group and the Myfortic treatment group at 12 months post-transplantation. The main safety endpoint was calculated GFR using the MDRD formula. Central laboratory serum creatinine values were used for all renal function data analysis. If the serum creatinine value from central laboratory was missing within a visit window, the serum creatinine value from local laboratory was used for that visit window. Again the multiple comparison method outlined for the primary endpoint was applied. T-test based, two-sided 95% and 97.5% confidence intervals (CI) for the difference in mean GFR at 12 months between the everolimus and Myfortic groups were computed. An everolimus group was claimed to have non-inferior renal function at 12 months to the Myfortic group if the lower limit of the appropriate CI was greater than -8 mL/min.

Reviewer's Comment: *There is no NI margin agreed upon for calculated GFR. The results of GFR analysis are evaluated according to the clinical significance of the findings.*

6.1.1.13 Justification of the Non-Inferiority (NI) Margin

Please refer to Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D. for a detailed discussion of the justification of the NI margin

For confirmatory non-inferiority trials, the Applicant is required to provide a detailed justification of the proposed NI margin using information from historical trials. For Study A2309, the Applicant submitted a justification for the primary efficacy endpoint (i.e. efficacy failure: a composite of treated BPAR, death, graft loss or loss to follow-up at 12 months), which is acceptable. Additionally, a margin for the endpoint of death, graft loss or loss to follow-up was not able to be justified due to a lack of sufficient information on these endpoints from historical information. It should be noted that while the primary endpoint includes components of death, graft loss, and loss to follow-up; proof of efficacy is mainly driven by the treated BPAR component of the composite endpoint in trials of *de novo* kidney transplantation.

Study A2309 was designed as a non-inferiority trial comparing everolimus to the current standard of care (Myfortic) for assessing efficacy failure using this composite endpoint (treated BPAR, graft loss, death or loss to follow-up) with a 10% non-inferiority margin.

To justify the selected non-inferiority margin a meta-analysis of historical trials was performed by the Applicant to estimate the efficacy failure rates of the Myfortic group (control group) and basiliximab + standard-dose CsA ± corticosteroids (putative placebo). A detailed description of literature search, statistical methodology to estimate control effect, and the results for the justification was submitted separately to the everolimus IND (52,003).

The control effect was estimated to be 24.6% [95% CI: 18.9%, 30.2%]. Based on the conservative 95_{NI}-95_H confidence interval approach, a non-inferiority margin of 18.9% would have been statistically justified to demonstrate indirectly the efficacy of everolimus+ basiliximab + reduced-dose CsA ± corticosteroids over putative placebo. The 10% noninferiority margin selected for the new study represents approximately 50% preservation of the estimated control effect.

The applicant's methods and the three additional methods, performed by the FDA, provide estimates that are supportive of the proposed 10% margin. Given the lack of historical RCTs, the approach used to derive these estimates is acceptable.

6.1.2 Demographics

Transplant recipients had a mean age of 46.1 years and were predominantly Caucasian males (Table 10). All patients were aged between 18 and 70 as per the protocol, and there was little difference between treatment groups with regard to any recipient demographics.

Recipient Demographics:

Table 10. Baseline Demographics by Treatment Group (ITT population)
(Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 g (N=277)
Recipient Age (years) Mean (\pm SD) Range	45.7 (12.7) 18 – 70	45.3 (13.4) 18 – 70	47.2 (12.7) 18 – 70
Donor Age (years) Mean (\pm SD) Range	41.4 (13.9) 5 – 67	41.1 (13.0) 5 – 69	41.8 (13.6) 5 – 67
Recipient age group < 50 years \geq 50 years Unknown	156 (56.3%) 120 (43.3%) 1 (0.4%)	153 (54.8%) 126 (45.2%) 0 (0%)	143 (51.6%) 134 (48.4%) 0 (0%)
Donor age group < 50 years \geq 50 years Unknown	181 (65.3%) 95 (34.3%) 1 (0.4%)	203 (72.8%) 76 (27.2%) 0 (0%)	182 (65.7%) 94 (33.9%) 1 (0.4%)
Recipient gender Male Female Unknown	176 (63.5%) 100 (36.1%) 1 (0.4%)	191 (68.5%) 88 (31.5%) 0 (0%)	189 (68.2%) 88 (31.8%) 0 (0%)
Donor gender Male Female Unknown	154 (55.6%) 122 (44.0%) 1 (0.4%)	139 (49.8%) 140 (50.2%) 0 (0%)	136 (49.1%) 140 (50.5%) 1 (0.4%)
Recipient race Caucasian Black Asian Other Unknown	193 (69.7%) 34 (12.3%) 32 (11.6%) 17 (6.1%) 1 (0.4%)	180 (64.5%) 40 (14.3%) 38 (13.6%) 21 (7.5%) 0 (0%)	190 (68.6%) 38 (14.1%) 36 (13.0%) 12 (4.3%) 0 (0%)

	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 g (N=277)
Donor race			
Caucasian	193 (69.7%)	191 (68.5%)	197 (71.1%)
Black	20 (7.2%)	22 (7.9%)	25 (9.0%)
Asian	32 (11.6%)	35 (12.5%)	31 (11.2%)
Other	27 (9.8%)	26 (9.3%)	19 (6.9%)
Unknown	5 (1.8%)	5 (1.8%)	5 (1.8%)

Table 11. Height, Weight and BMI of the Recipients
(Source: Table 14.1-3.1a, Page 334 of CSR)

Table 14.1-3.1a (Page 2 of 2) Patient Demographics - Recipient (ITT Population - 12 Month Analysis)				
Demographic Variable	RAD 1.5mg N=277	RAD 3.0mg N=279	Myfortic 1.44g N=277	Total N=833
Height (cm)				
n	270	272	270	812
Mean	170.0	170.0	170.7	170.2
SD	10.78	11.20	10.45	10.81
Minimum	143	145	142	142
Median	170.0	169.0	172.0	170.0
Maximum	197	221	198	221
Weight (kg)				
n	271	268	269	808
Mean	75.06	75.35	75.67	75.36
SD	18.278	19.040	16.554	17.966
Minimum	36.7	35.5	43.0	35.5
Median	72.90	72.65	74.50	73.45
Maximum	140.0	138.5	127.0	140.0
Body Mass Index (kg/m**2)				
n	265	264	264	793
Mean	25.79	25.84	25.86	25.83
SD	5.140	5.010	4.709	4.950
Minimum	15.7	15.2	17.2	15.2
Median	24.97	25.18	25.31	25.15
Maximum	43.6	39.5	42.3	43.6

The primary disease leading to end stage renal disease in recipients was similar across the treatment groups (Table 12); the most frequent diseases being hypertension/nephrosclerosis, glomerulonephritis/glomerular disease and diabetes mellitus. The majority of patients were receiving hemodialysis at the time of transplantation, and approximately one-half had not had a previous blood transfusion. Over one-half of patients had at least one HLA mismatch at the A, B and DR loci, and over 70% of patients had more than 3 mismatches. A higher proportion of patients in the everolimus 1.5 mg group had 3 or more HLA mismatches than the everolimus 3.0 mg group. The mean percentage of panel reactive antibodies (most recent evaluation) was 2.0%, 1.4% and 0.9% for the everolimus 1.5 mg, everolimus 3.0 mg and Myfortic 1.44

gm groups, respectively, with all groups having a median of 0%. There were no major differences between treatment groups with regards to recipient disease characteristics.

Table 12. Recipient background characteristics summary by treatment group
(ITT population - 12 month analysis, Source: page 144 CSR)

	Everolimus 1.5mg N=277 n (%)	Everolimus 3.0mg N=279 n (%)	Myfortic 1.44g N=277 n (%)
Primary disease leading to transplantation			
Glomerulonephritis/glomerular disease	43 (15.5)	55 (19.7)	40 (14.4)
Pyelonephritis	8 (2.9)	3 (1.1)	7 (2.5)
Polycystic disease	36 (13.0)	29 (10.4)	33 (11.9)
Hypertension/nephrosclerosis	50 (18.1)	56 (20.1)	45 (16.2)
Drug induced toxicity	1 (0.4)	4 (1.4)	0 (0.0)
Diabetes mellitus	39 (14.1)	29 (10.4)	45 (16.2)
Interstitial nephritis	3 (1.1)	4 (1.4)	5 (1.8)
Vasculitis	2 (0.7)	3 (1.1)	0 (0.0)
Obstructive disorder/reflux	15 (5.4)	7 (2.5)	10 (3.6)
Renal hyperplasia/dysplasia	0 (0.0)	1 (0.4)	0 (0.0)
IgA nephropathy	18 (6.5)	17 (6.1)	29 (10.5)
Unknown	34 (12.3)	37 (13.3)	39 (14.1)
Other	27 (9.7)	34 (12.2)	23 (8.3)
Missing	1 (0.4)	0 (0.0)	1 (0.4)
Current dialysis			
None	46 (16.6)	37 (13.3)	46 (16.6)
Hemodialysis	182 (65.7)	197 (70.6)	188 (67.9)
Peritoneal dialysis	48 (17.3)	45 (16.1)	42 (15.2)
Missing	1 (0.4)	0 (0.0)	1 (0.4)
Number of previous blood Transfusions			
None	143 (51.6)	157 (56.3)	132 (47.7)
< 5	71 (25.6)	61 (21.9)	80 (28.9)
5 - 10	12 (4.3)	7 (2.5)	9 (3.2)
> 10	1 (0.4)	3 (1.1)	3 (1.1)
Unknown	48 (17.3)	51 (18.3)	52 (18.8)
Missing	2 (0.7)	0 (0.0)	1 (0.4)
HLA mismatches			
0	10 (3.6)	15 (5.4)	15 (5.4)
1	19 (6.9)	18 (6.5)	19 (6.9)
2	37 (13.4)	51 (18.3)	40 (14.4)
3	85 (30.7)	78 (28.0)	85 (30.7)
4	46 (16.6)	49 (17.6)	45 (16.2)
5	50 (18.1)	37 (13.3)	45 (16.2)
6	29 (10.5)	30 (10.8)	27 (9.7)
< 3	66 (23.8)	84 (30.1)	74 (26.7)
≥ 3	210 (75.8)	194 (69.5)	202 (72.9)
Missing	1 (0.4)	1 (0.4)	1 (0.4)
Panel reactive antibodies			
Most recent evaluation ≥ 20%	7 (2.6)	5 (1.8)	4 (1.5)
Peak evaluation ≥ 20%	17 (6.3)	13 (4.8)	11 (4.1)

Donor Demographics

Organ donors were more equally distributed amongst the sexes than recipients (Table 13). Donor mean ages were similar to recipients but with a slightly lower age range. Donors were predominantly Caucasian. The majority of organs came predominantly from living donors, and groups were balanced with respect to the number of patients who received a graft from living donors (53.0%, 54.1%, 53.5%). There were no differences between treatment groups with regard to donor characteristics.

Table 13. Donor Characteristics
 (Source: Table 11-4, Page 145, CSR)

Table 11-4 Donor characteristics summary by treatment group (ITT population - 12 month analysis)		Everolimus 1.5 mg N=277	Everolimus 3.0 mg N=279	Myfortic 1.44g N=277
Age (years)	Mean ± SD	41.4 ± 13.87	41.1 ± 12.97	41.8 ± 13.59
	Median (range)	43.0 (5.0-67.0)	43.0 (5.0-69.0)	45.0 (5.0-67.0)
Gender - n (%)	Male	154 (55.6)	139 (49.8)	136 (49.1)
	Female	122 (44.0)	140 (50.2)	140 (50.5)
	Missing	1 (0.4)	0 (0.0)	1 (0.4)
Race - n (%)	Caucasian	193 (69.7)	191 (68.5)	197 (71.1)
	Black	20 (7.2)	22 (7.9)	25 (9.0)
	Asian	32 (11.6)	35 (12.5)	31 (11.2)
	Native American	0 (0.0)	1 (0.4)	1 (0.4)
	Other	27 (9.7)	25 (9.0)	18 (6.5)
	Missing	5 (1.8)	5 (1.8)	5 (1.8)
Characteristics - n (%)	Cadaveric heart beating	128 (46.2)	126 (45.2)	127 (45.8)
	Cadaveric non-heart beating	1 (0.4)	2 (0.7)	1 (0.4)
	Living related	99 (35.7)	111 (39.8)	101 (36.5)
	Living unrelated	48 (17.3)	40 (14.3)	47 (17.0)
	Missing	1 (0.4)	0 (0.0)	1 (0.4)
Hypotension prior to procurement - n (%)	Yes	21 (7.6)	28 (10.0)	28 (10.1)
	No	196 (70.8)	195 (69.9)	196 (70.8)
	Unknown	59 (21.3)	56 (20.1)	52 (18.8)
	Missing	1 (0.4)	0 (0.0)	1 (0.4)

Source: [Table 14.1-3.1b](#) and [14.1-3.4](#)

Relevant medical histories and current medical conditions showed no major differences

between treatment groups (Table 12). Preferred terms where more than 10% of the ITT population were affected were; hypertension (89.3%), anaemia (37.3%), hyperlipidemia (20.4%), arteriovenous fistula operation (18.4%), chronic renal failure (15.8%), drug hypersensitivity (14.8%), gout (12.1%), incision site pain (12.0%), hyperparathyroidism (11.3%), gastroesophageal reflux disease (10.6%), hyperphosphatemia (10.4%) and depression (10.4%). Medical history preferred terms which had a difference in incidence of 5% or more of patients between treatment groups were diabetes mellitus (5.1%, 6.8% and 10.8% for the everolimus 1.5 mg, everolimus 3.0 mg and Myfortic 1.44 gm groups, respectively) and hypercholesterolemia (6.1%, 6.5%, 11.6%, for the everolimus 1.5 mg, everolimus 3.0 mg and myfortic 1.44 gm groups, respectively).

Over 60% of both recipients and donors were positive for CMV, and 99% were negative for hepatitis C. Six recipient patients were positive for HBsAg (two in each treatment group), and one recipient patient in the myfortic treatment group was positive for HIV.

6.1.3 Subject Disposition

Baseline demographics and characteristics for recipients and donors were similar among the three treatment groups. All randomized patients were between the ages of 18 and 70 years; more than 43% were 50 years of age or older. More than 63% of all recipients were male and more than 64% were Caucasian. Among donors, more than 49% were male and more than 68% were Caucasian. The primary disease leading to end stage renal disease in recipients was similar across the treatment groups. The most frequent diseases leading to transplantation were hypertension/nephrosclerosis, glomerulonephritis/glomerular disease and diabetes mellitus. There were no major differences among treatment groups with regards to recipient disease characteristics.

Among the 833 randomized patients in the ITT population, approximately 29% prematurely discontinued study medication by Day 450, which was the protocol defined cutoff date for 12 month analyses. As presented in Table 14, the incidence of premature treatment discontinuation was imbalanced across the three treatment groups. At Month 12, the incidence of premature treatment discontinuation in the everolimus 1.5 mg group, 3.0 mg and Myfortic groups were 30.0% (83/277), 34.1% (95/279), and 21.7% (60/277). Compared to the Myfortic group, the incidence was statistically significantly higher in the everolimus 1.5 mg group (p -value=0.03, Fisher's exact test) and in the everolimus 3.0 mg group (p -value=0.001, Fisher's exact test).

The most common reason for premature discontinuation of study treatment was adverse events, which accounted for 18%, 20%, and 9% in the everolimus 1.5 mg, 3.0 mg and Myfortic groups respectively. In the everolimus 1.5 mg group, 18.1% of the patients prematurely discontinued treatment due to adverse events, which was statistically significantly higher than the incidence in the Myfortic group (9.4%) with p -value=0.004 (Fisher's exact test). The incidence of treatment discontinuation due to adverse events

was also statistically significantly higher in the everolimus 3.0 mg group than in the Myfortic group (20.4% versus 9.4%, with p-value<0.0001, Fisher's exact test).

Approximately 12% of the randomized patients prematurely discontinued study. Study discontinuations were more frequent in both of the everolimus groups than in the Myfortic group (13.7% and 11.8% versus 10.1%), but the differences were not statistically significant (p-value= 0.24 and 0.59 respectively, Fisher's exact test).

Table 14. Premature Study Medication or Study Phase Discontinuation by Treatment Group (ITT Population- 12 Month Analysis)

(Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 g (N=277)
Discontinued study medication	83 (30.0%)	95 (34.1%)	60 (21.7%)
Adverse event(s)	50 (18.1%)	57 (20.4%)	26 (9.4%)
Unsatisfactory therapeutic effect	11 (4.0%)	14 (5.0%)	13 (4.7%)
Subject withdrew consent	11 (4.0%)	4 (1.4%)	5 (1.8%)
Graft loss	3 (1.1%)	6 (2.2%)	6 (2.2%)
Death	3 (1.1%)	3 (1.1%)	4 (1.4%)
Protocol deviation	2 (0.7%)	5 (1.8%)	2 (0.7%)
Abnormal lab value	1 (0.4%)	4 (1.4%)	1 (0.4%)
Administrative problems	2 (0.7%)	1 (0.4%)	2 (0.7%)
Abnormal test procedure	0 (0%)	1 (0.4%)	0 (0%)
Unknown	0 (0%)	0 (0%)	1 (0.4%)
Discontinued study phase	38 (13.7%)	33 (11.8%)	28 (10.1%)
Subject withdrew consent	20 (7.2%)	8 (2.9%)	12 (4.3%)
Graft loss	9 (3.3%)	10 (3.6%)	7 (2.5%)
Death	7 (2.5%)	9 (3.2%)	6 (2.2%)
Unknown	2 (0.7%)	6 (2.2%)	3 (1.1%)

6.1.4 Analysis of Primary Endpoint(s)

The efficacy portion of the review was conducted by Xiao Ding, Ph.D. and LaRee Tracy, Ph.D, Biostatistics. See complete review filed with the NDA resubmission.

The primary endpoint of the study was primary efficacy failure, defined as the composite endpoint (treated BPAR episodes, graft loss, death, or loss to follow-up at 12 months). Each of these components are defined below.

Treated BPAR

A treated BPAR episode was defined as a biopsy graded IA, IB, IIA, IIB, or III that was treated with anti-rejection therapy. The identification of treated BPAR was based on local laboratory biopsy results.

Death

Death was recorded at either study completion, follow-up, or as the outcome of an AE or infection, if it occurred.

Graft loss

Graft loss was defined as any of the following:

- Graft loss (the allograft was presumed to be lost on the day the patient started dialysis and was not able to subsequently be removed from dialysis)
- Re-transplant

Loss to follow-up

A loss to follow-up patient was a patient who did not experience treated BPAR, graft loss, or death and whose last day of contact is prior to study Day 316, which is the lower limit of Month 12 visit window. For 6 Month analysis, study Day 151, the lower limit of Month 6 visit window, was used.

The percentage of patients experiencing the composite endpoint and each individual variable is shown in Table 15. Treated BPAR was the most frequently reported of all the endpoints, affecting 65.5% of all patients who met the definition of the composite efficacy endpoint.

**Table 15. Primary Efficacy Endpoint Analysis by Treatment Group
 (ITT Population - 12 Month Analysis)
 (Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)**

	everolimus 1.5 mg (N=277)	everolimus 3.0 mg (N=279)	Myfortic 1.44 g (N=277)
Efficacy Failure	70 (25.3%)	61 (21.9%)	67 (24.2%)
Treated BPAR	45 (16.3%)	37 (13.3%)	47 (17.0%)
Graft Loss	12 (4.3%)	13 (4.7%)	9 (3.3%)
Death*	7 (2.5%)	10 (3.6%)	6 (2.2%)
Loss to follow-up**	12 (4.3%)	8 (2.9%)	9 (3.3%)
95% CI (everolimus-Myfortic)	(-6.1%, 8.3%)	(-9.3%, 4.7%)	N/A
97.5% CI (everolimus-Myfortic)	(-7.1%, 9.3%)	(-10.3%, 5.7%)	N/A

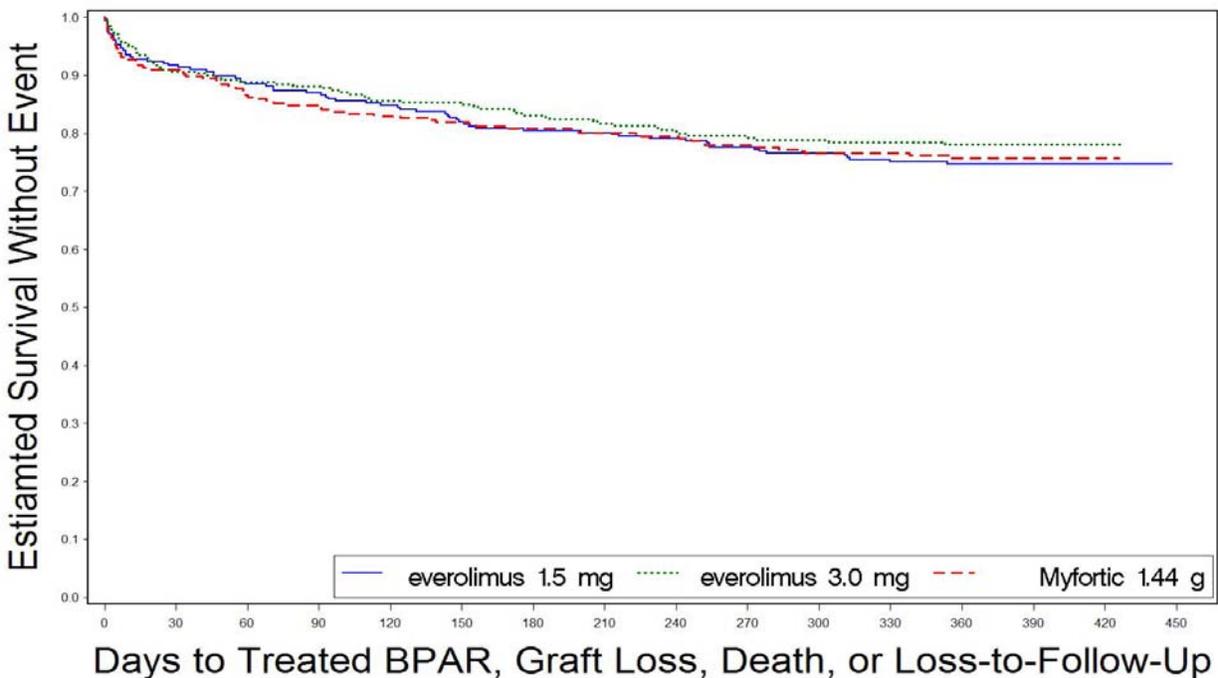
* One patient who died 10 days after withdrew consent was included

** One patient who had graft loss before the randomization was considered as loss to follow-up

Based on the protocol defined and justified non-inferiority margin of 10% and using the Hochberg's procedure to adjust for multiple comparisons, non-inferiority of both everolimus groups to Myfortic with respect to the primary efficacy endpoint was achieved. This was demonstrated by the fact that the upper limits of both 95% confidence interval were less than the 10% non-inferiority margin.

The Kaplan Meier plot for the primary efficacy endpoint within 12 months was provided in Figure 4. Based on the log-rank test, median time to event was not statistically significantly different between everolimus 1.5 mg (p-value=0.83) and everolimus 3.0 mg (p-value=0.49) and Myfortic. No statistically significantly difference of time to event was shown between the two everolimus groups (p-value=0.37). If loss to follow-up patients were treated as censored rather than efficacy failure, similar results were reported by using time-to-event analyses. The p-value of log-rank test was 0.97 for everolimus 1.5 mg group versus Myfortic 1.44 g group, and was 0.53 for everolimus 3.0 mg group versus 1.44 g group, demonstrating that no significant differences between each of the everolimus groups and the Myfortic group.

Figure 4. Kaplan-Meier Estimates for the Primary Efficacy Endpoint by Treatment Group (ITT population- 12 Month Analysis)
(Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)



As a sensitivity analysis, the primary efficacy analysis was repeated using the central pathologist's assessment. The rate of composite efficacy failure was 17.3%, 15.4% and 15.9% for the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm treatment groups. These

results are lower for all treatment groups than those obtained when using the local pathologist's evaluation, due to a number of missing central biopsy readings for patients who had an acute rejection confirmed by local readings.

To assess the impact of the disproportionate rates of premature treatment discontinuation on the primary efficacy endpoint, treatment discontinuation was treated as failure along with the primary efficacy composite endpoint. *In this sensitivity analysis, both everolimus groups failed to demonstrate non-inferiority to Myfortic, given that the upper limits of both 95% confidence interval exceed 10% (Table 16).* The Kaplan Meier plot for this sensitivity analysis was provided in Figure 4. The survival curve of the Myfortic group was always above either of the everolimus group, while median time to event was not statistically significantly different based on log-rank test (p=0.12 for everolimus 1.5 mg versus Myfortic, and p=0.08 for everolimus 3.0 mg versus Myfortic).

Table 16. Primary Efficacy Endpoint with Premature Treatment Discontinuation as Failure by Treatment Group (ITT Population- 12 Month Analysis)
 (Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

	everolimus 1.5 mg (N=277)	everolimus 3.0 mg (N=279)	Myfortic 1.44 g (N=277)
Efficacy Failure or Premature Treatment Discontinuation	103 (37.2%)	106 (38.0%)	84 (30.3%)
95% CI (everolimus - Myfortic)	(-1.0%, 14.7%)	(-0.2%, 15.5%)	N/A
97.5% CI (everolimus - Myfortic)	(-2.1%, 15.8%)	(-1.3%, 16.7%)	N/A

6.1.5 Analysis of Secondary Endpoints(s)

The main secondary efficacy objective was to compare the incidence rate of the composite endpoint of death, graft loss, or loss to follow-up between the everolimus and Myfortic treatment groups at 12 months post-transplantation.

As presented in Table 17 the incidence of death, graft loss or loss to follow up was similar between the two everolimus groups (11.6% and 11.1% respectively), and was 9.4% in the Myfortic group. Note that a non-inferiority margin for the endpoint of death, graft loss or loss to follow-up was not able to be justified due to a lack of sufficient data from historical information (see Appendix 2). However, the applicant stated that a 10% margin would be used. As shown in bold in Table , both 95% confidence intervals for the everolimus groups compared to Myfortic excluded this margin based on the upper bound.

**Table 17. Main Secondary Efficacy Endpoint Analysis by Treatment Group
 (ITT Population -12 Month Analysis)**

(Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 gm (N=277)
Graft loss, death or loss to follow up	32 (11.6%)	31 (11.1%)	26 (9.4%)
Graft Loss	12 (4.3%)	13 (4.7%)	9 (3.3%)
Death	7 (2.5%)	9 (3.2%)	6 (2.2%)
Loss to follow-up *	14 (5.1%)	10 (3.6%)	11 (4.0%)
95% CI (Everolimus-Myfortic)	(-2.9%, 7.3%)	(-3.3%, 6.8%)	N/A
97.5% CI (Everolimus-Myfortic)	(-3.7%, 8.0%)	(-4.0%, 7.5%)	N/A

A loss to follow-up patient is a patient who did not experience graft loss or death and whose last day of contact is prior to study Day 316

Treated BPAR at 12 months was also a secondary endpoint of the study. As presented in Table 18, the grade and the number of treated BPAR episodes were similar between the two everolimus groups and the Myfortic group. In all three treatment groups, more than 85% of patients who experienced treated BPAR had only one treated BPAR event during the first 12 months of the study (Table 19).

**Table 18. Grade of Treated BPAR by Treatment Group
 (ITT Population -12 Month Analysis)**

(Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

N (%) of patient with any grade of treated BPAR	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 gm (N=277)
Total episodes	45 (16.3%)	37 (13.3%)	47 (17.0%)
Banff Type IA	21 (7.6%)	16 (5.7%)	22 (7.9%)
Banff Type IB	7 (2.5%)	9 (3.2%)	6 (2.2%)
Banff Type IIA	7 (2.5%)	9 (3.2%)	15 (5.4%)
Banff Type IIB	1 (0.4%)	3 (1.1%)	2 (0.7%)
Banff Type III	1 (0.4%)	0 (0%)	1 (0.4%)
Missing grade	6 (2.2%)	4 (1.4%)	3 (1.1%)

**Table 19. Number of Treated BPAR Episodes by Treatment Group
 (ITT Population -12 Month Analysis)**

(Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

N (%) of patient with treated BPAR by number of BPAR	Everolimus 1.5 mg (N=277)	Everolimus 3.0 mg (N=279)	Myfortic 1.44 gm (N=277)
0 treated BPAR	232 (83.8%)	242 (86.7%)	230 (83.0%)
1 treated BPAR	39 (14.1%)	32 (11.5%)	41 (14.8%)
2 treated BPAR	5 (1.8%)	5 (1.8%)	5 (1.8%)
3 treated BPAR	0 (0%)	0 (0%)	0 (0%)
4 treated BPAR	1 (0.4%)	0 (0%)	0 (0%)

6.1.6 Other Endpoints

Primary Safety Endpoint – Renal Function

See Statistical Review of Safety by John Stephen Yap Ph.D.

The main safety endpoint of Study A2309 was serum creatinine at month 12 by calculated glomerular filtration rate (GFR) using the MDRD (Modification of Diet in Renal Disease) formula. The main safety objective was to show that the mean GFR of either everolimus 1.5 mg or 3.0 mg group was no worse than (non-inferior to) the Myfortic group by 8 mL/min/1.73m² at month 12 using t-test based, two-sided 95% and 97.5% confidence intervals.

Reviewer’s Comment: *There is no justified non-inferiority margin for GFR in de novo kidney transplantation. Results of this endpoint will be assessed for clinical importance.*

As shown in Table 20, Study A2309 demonstrated that calculated 12-month GFR, using the modification of diet in renal disease (MDRD) formula, was similar between both everolimus groups and the Myfortic group (Table 1). Various sensitivity analyses, modeling and imputation methods for missing values resulted in similar results in 12-month GFR across treatment groups. Analyses of GFR trends found that the median GFR levels in the everolimus 1.5 mg group were numerically higher than those of Myfortic across most study visit windows but the treatment groups were not statistically significantly different at all time points.

Table 20. Renal Function (MDRD calculated GFR) at 12 Months
 (Source: Statistical Review of Safety by John Stephen Yap Ph.D.)

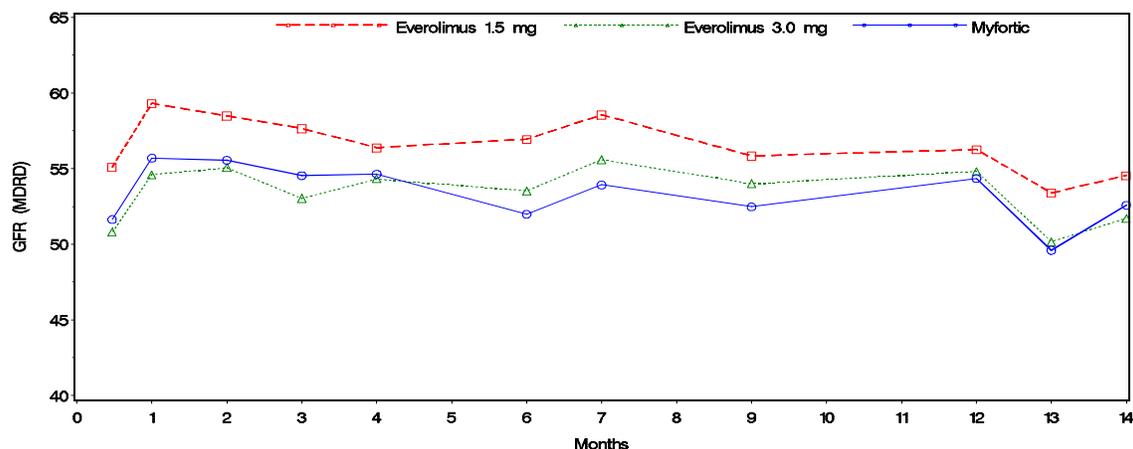
Method	Everolimus 1.5 mg	Everolimus 3.0 mg	Myfortic 1.44 gm
Method 1: LOCF*	n=275	n=278	n=277
Mean (SD)	54.6 (21.7)	51.3 (22.7)	52.2 (26.7)
Median (Range)	55.0 (0-140.9)	51.6 (0-124.0)	49.7 (0-366.40)
Difference in Mean*	2.4	-0.9	
t-test based 95% CI	(-1.7,6.4)	(-5.0,3.2)	
t-test based 97.5% CI	(-2.3,7.0)	(-5.6,3.8)	
p-value, t-test (no difference)	0.3**	0.7**	
Method 2: No imputation at 12 months	n=245	n=244	n=248
Mean (SD)	56.2 (20.1)	54.8 (19.6)	54.4 (26.4)
Median (Range)	55.3 (4.6-140.9)	53.8 (8.7-124.0)	50.8 (6.8-366.4)
Difference in Mean*	1.9	0.5	
t-test based 95% CI	(-2.3,6.0)	(-3.7,4.6)	
t-test based 97.5% CI	(-2.9,6.6)	(-4.3,5.2)	
p-value, t-test (no difference)	0.4**	0.8**	
* Everolimus-Myfortic; **Satterthwaite approximation for unequal variances			

LOCF=last observation carried forward approach for missing

* The actual numbers of patients with non-missing GFR values were 275, 278 and 277 in the everolimus 1.5 mg, 3.0 mg and Myfortic groups respectively.

Using the protocol defined last observation carried forward (LOCF) imputation approach (primary imputation approach) and with no imputation, mean GFR values were similar across treatment groups. In the LOCF analysis, patients with a graft loss were considered as having a GFR of 0, while those who died had their last value used. Additional methods for imputation were also used and similar results were obtained. Figure shows the mean GFR over time of the complete data (no imputation).

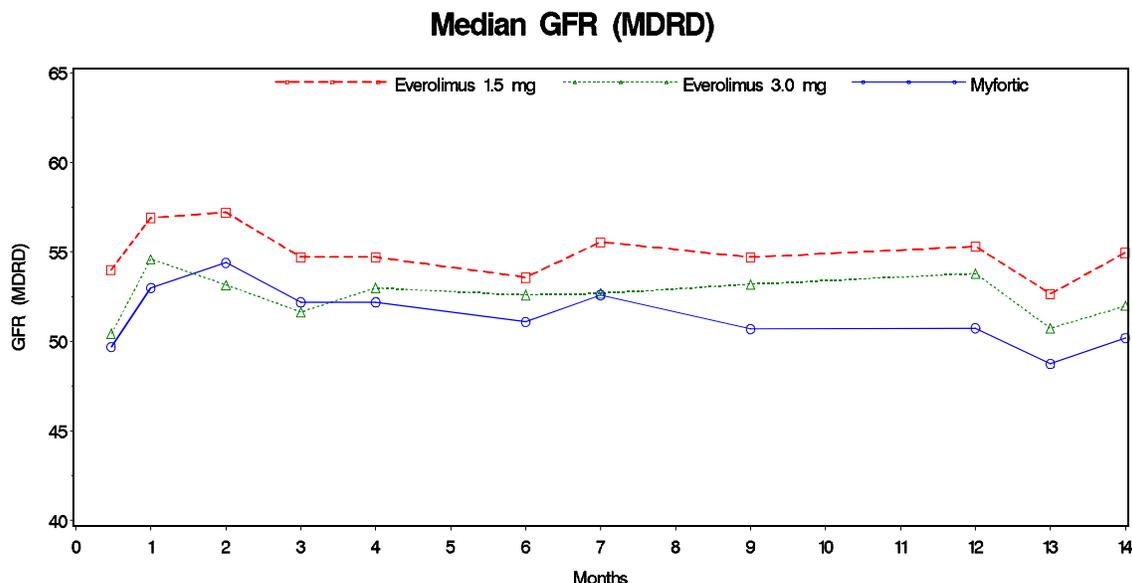
Figure 5. Mean GFR (MDRD) Over Time
(Statistical Review of Safety by John Stephen Yap Ph.D.)
Mean GFR (MDRD)



Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit. Month 14 represents the month 12 study endpoint consisting of the last post-baseline observation up to and including the month 12 visit.

Figure 6 shows the median GFR plots for the 12-months of study. The medians at each visit window for the everolimus 1.5 mg group were consistently higher than those of the Myfortic group and of the everolimus 3.0 mg group. The treatment groups were statistically significantly different (based on the Wilcoxon rank-sum test) at months 1 (p-value 0.0371), 6 (p-value 0.0135), 7 (p-value 0.0153), 9 (p-value 0.0228), 12 TEP (p-value 0.0412) and 12 SEP (p-value 0.0324). Note: The month 12 TEP (defined as the last post-baseline on-treatment observation up to and including month 12 visit) and month 12 SEP (defined as the last post-baseline observation up to and including month 12 visit) are shown in Figure 6 as months 13 and 14, respectively. There were no statistically significant differences between the everolimus 3.0 group and the Myfortic group at any visit windows. *Note: These multiple comparisons are unadjusted.*

Figure 6. Median GFR (MDRD) Over Time
(Statistical Review of Safety by John Stephen Yap Ph.D.)



Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit. Month 14 represents the month 12 study endpoint consisting of the last post-baseline observation up to and including the month 12 visit.

Reviewer's Comment: At the end of 12 month study period the difference between the mean calculated GFR values of the everolimus 1.5 mg and the Myfortic groups is 1.9 mL without LOCF (Last Observation Carried Forward) method and 2.4 mL with the LOCF method which are both statistically non-significant. Since there is higher CsA exposure in the Myfortic group compared to the everolimus groups a relative decrease in GFR is expected due to the CsA induced afferent glomerular arteriole vasoconstriction even if the both groups have the same degree of chronic allograft injury.

6.1.7 Subpopulations

Gender

Subgroup analysis of the primary efficacy endpoint by gender is presented in Table 21. Among male patients, the efficacy failure rate at 12 months post-transplantation was 28.4%, 21.5%, and 29.6%, in the everolimus 1.5 mg, 3.0 mg and Myfortic groups respectively. Compared to the Myfortic group, the everolimus 1.5 mg group had a slightly lower incidence of efficacy failure with risk difference of -1.2% (95% CI: -10.5, 8.1). The incidence was marginally significantly lower in the everolimus 3.0 mg group compared to the Myfortic group (RD= -8.1% (-16.9, 0.6), p-value=0.08).

In contrast, the primary efficacy failure among female patients was more frequent in both everolimus groups than in the Myfortic groups. The incidence rate in the everolimus 1.5 mg, 3.0 mg and Myfortic groups was 19.0%, 22.7%, and 12.5% respectively. The difference between everolimus 1.5 mg and Myfortic was 6.5% (95% CI: -3.8, 16.8, p=0.24), and difference between everolimus 3.0 and Myfortic was 10.2% (95% CI: -0.9, 21.4, p=0.11). Additionally, a statistically significant interaction between treatment and gender (Breslow-Day test p-value=0.01) was indentified in the comparison of everolimus 3.0 mg to Myfortic. No statistically significant interaction between treatment and gender was found in the comparison between everolimus 1.5 mg to Myfortic (Breslow-Day test p-value=0.24). When interpreting these subgroup analysis results, one must take into account that multiple comparisons according to various subgroups were not adjusted.

Table 21: Primary Efficacy Endpoint Analysis by Gender and Treatment Group (ITT Population - 12 Month Analysis)*

(Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

	Males Total =556			Females Total =276		
	Everolimus 1.5 mg (N=176)	Everolimus 3.0 mg (N=191)	Myfortic 1.44 g (N=189)	Everolimus 1.5 mg (N=100)	Everolimus 3.0 mg (N=88)	Myfortic 1.44 g (N=88)
Efficacy Failure*	50 (28.4%)	41 (21.5%)	56	19 (19.0%)	20 (22.7%)	11
Treated BPAR	33 (18.8%)	25 (13.1%)	(29.6%)	12 (12.0%)	12 (13.6%)	(12.5%)
Graft Loss	7 (4.0%)	7 (3.7%)	39	5 (5.0%)	6 (6.8%)	8 (9.1%)
Death**	3 (1.7%)	7 (3.7%)	(20.6%)	4 (4.0%)	3 (3.4%)	2 (2.3%)
Loss to follow-up	10 (5.7%)	7 (3.7%)	7 (3.7%)	1 (1.0%)	1 (1.1%)	0 (0%)
			6 (3.2%)			1 (1.1%)
			8 (4.2%)			
95% CI (everolimus – Myfortic)	(-10.5%, 8.1%)	(-16.9%, 0.6%)	N/A	(-3.8%, 16.8%)	(-0.9 %, 21.4%)	N/A
P-value***	p=0.82	p=0.08		p=0.24	p=0.11	

* One subject's gender was unknown and is excluded from this analysis

** One patient who died 10 days after withdrew consent was included

** P-value for the Fisher's exact test

Subgroup analysis of the main secondary endpoint (graft loss, death, or loss to follow-up) by gender is presented in Table 22. The observed incidence of graft loss, death, or loss to follow-up was similar across all three treatment groups (12.5% and 10.5% in the everolimus groups versus 12.7% in the Myfortic group) in male patients. Among female patients, the rate of graft loss, death, or loss to follow-up was 11.0%, 12.5%, 5.7% in the everolimus 1.5 mg, 3.0 mg and Myfortic groups respectively (p=0.09, everolimus1.5 mg v. Myfortic; p=0.05 everolimus 3.0 mg v. Myfortic, Fisher's exact test). Additionally, a statistically significant interaction between treatment and gender (Breslow-Day test p-

value=0.03) was identified in the comparison of everolimus 3.0 mg to Myfortic. No statistically significant interaction between treatment and gender was found in the comparison between everolimus 1.5 mg to Myfortic (Breslow-Day test p-value=0.11).

Table 22. Graft Loss, Death, or Loss to Follow-up by Gender and Treatment Group (ITT Population - 12 Month Analysis)*

(Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

	Males Total =556			Females Total =276		
	Everolimus 1.5 mg (N=176)	Everolimus 3.0 mg (N=191)	Myfortic 1.44 g (N=189)	Everolimus 1.5 mg (N=100)	Everolimus 3.0 mg (N=88)	Myfortic 1.44 g (N=88)
Graft Loss, Death or Loss to follow-up	21 (11.9%)	20 (10.5%)	23 (12.2%)	10 (10.0%)	11 (12.5%)	3 (3.4%)
Graft Loss	7 (4.0%)	7 (3.7%)	7 (3.7%)	5 (5.0%)	6 (6.8%)	2 (2.3%)
Death **	3 (1.7%)	7 (3.7%)	7 (3.7%)	4 (4.0%)	3 (3.4%)	0 (0%)
Loss to follow-up	11 (6.3%)	8 (4.2%)	6 (3.2%)	2 (2.0%)	2 (2.3%)	1 (1.1%)
95% CI (everolimus – Myfortic) P-value***	(-6.9%, 6.5%) p=1.0	(-8.1%, 4.7%) p=0.63	N/A	(-0.4%, 13.6%) p=0.09	(1.2 %, 17.0%) p=0.05	N/A

* One subject's gender was unknown and is excluded from this analysis

** One patient who died 10 days after withdrew consent was included

*** P-value for the Fisher's exact test

Analysis results for premature discontinuation by gender are presented in Table 23. In female patients, the incidence of premature treatment discontinuation in the everolimus 1.5 mg , 3.0 mg and Myfortic groups was 32.0% (32/100), 38.6% (34/88), and 15.9% (14/88) respectively, resulting in a p-value of 0.01 (everolimus 1.5 mg – Myfortic) and a p-value of 0.001 (everolimus 3.0 mg – Myfortic). Furthermore, in the everolimus 1.5 mg group, approximately 22% of the female patients prematurely discontinued treatment due to adverse events, which was statistically significantly higher (p-value= 0.004) than the Myfortic group (6.8%). Similarly, the incidence of premature treatment discontinuation due to adverse events in female patients in the everolimus 3.0 mg group was statistically significantly higher compared to the Myfortic group (21.6% versus 6.8%, with p-value=0.009). Additionally, female patients prematurely discontinued the study phase more frequently in the everolimus groups than the Myfortic group (14% and 11.8% versus 4.6%, p-value=0.04 and 0.16 respectively).

Difference in rates of premature treatment discontinuation was not observed among male patients in the study. Specially, the incidence of premature treatment discontinuation among male patients in the everolimus 1.5 mg , 3.0 mg and Myfortic groups was 29.0% (51/176), 31.9% (61/191), and 24.3% (46/189) respectively (p-

value=0.34 for everolimus 1.5 mg versus Myfortic and p-value=0.11 for everolimus 3.0 mg versus Myfortic). Study discontinuation, among male patients, was similar across all three groups (13.6% and 12.0% versus 12.7%).

Table 23. Premature Study Medication or Study Phase Discontinuation by Gender and Treatment Group (ITT Population - 12 Month Analysis) *
 (Source: Efficacy Review by Xiao Ding Ph.D. and LaRee Tracy Ph.D)

	Males Total =556			Females Total =276		
	Everolimus 1.5 mg (N=176)	Everolimus 3.0 mg (N=191)	Myfortic 1.44 g (N=189)	Everolimus 1.5 mg (N=100)	Everolimus 3.0 mg (N=88)	Myfortic 1.44 g (N=88)
Discontinued study medication	51 (29.0%)	61 (31.9%)	46 (24.3%)	32 (32.0%)[#]	34 (38.6%)[#]	14 (15.9%)
Adverse event(s)	28 (15.9%)	38 (19.9%)	20 (10.6%)	22 (22.0%) [#]	19 (21.6%) [#]	6 (6.8%)
Unsatisfactory therapeutic effect	8 (4.6%)	9 (4.7%)	9 (4.8%)	3 (3.0%)	5 (5.7%)	4 (4.6%)
Others	15 (8.5%)	14 (7.3%)	17 (9.0%)	7 (7.0%)	10 (11.4%)	4 (4.5%)
Discontinued study phase	24 (13.6%)	23 (12.0%)	24 (12.7%)	14 (14.0%)[#]	10 (11.4%)	4 (4.6%)
Subject withdrew consent	14 (8.0%)	8 (4.2%)	11 (5.8%)	6 (6.0%)	0 (0%)	1 (1.1%)
Death	3 (1.7%)	6 (3.1%)	6 (3.2%)	4 (4.0%)	3 (3.4%)	0 (0%)
Graft loss	6 (1.7%)	5 (2.6%)	6 (3.2%)	3 (3.0%)	5 (5.7%)	0 (0%)
Unknown	1 (0.6%)	4 (2.1%)	6 (3.2%)	1 (1.0%)	2 (2.3%)	1 (1.1%)
			1 (0.5%)			2 (2.3%)

* One subject's gender was unknown and is excluded from this analysis

[#] p<0.05 compared to Myfortic for Fisher's exact test

Age and Race

No significant differences were seen among treatments between older and younger patients (categorized as ≤50 and >50 years of age). Among Black patients, the observed incidence of efficacy failure was lower in both everolimus groups than in the Myfortic group (29.4% and 35.0% versus 38.5%); however, no statistically significant differences were found (p=0.47 and 0.82 respectively). Note that Black patients represent only 13.5% of the total study population, therefore, caution should be used when interpreting findings in this small subgroup

Other Special/Subgroup Populations

Subgroup analysis of the primary efficacy endpoint (composite consisting of treated BPAR, graft loss, death, or loss to follow-up) by diabetic status and delayed graft function were also performed. The incidence of efficacy failure was similar between the everolimus groups and the Myfortic group in all the subgroups, and no statistically significant difference was identified.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The clinical development of everolimus in *de novo* renal transplantation has evolved from using fixed doses of everolimus (0.75 or 1.5 mg bid) with conventional doses of cyclosporine (CsA) to using blood trough level monitoring to adjust initial doses of everolimus (0.75 or 1.5 mg bid) to target trough levels (3-8 or 6-12 ng/mL, respectively) with reduced dose CsA.

The initial pivotal phase 3 studies B251 and B201, which used fixed dose everolimus and full dose CsA showed that an everolimus based regimen was effective in preventing acute rejection. However, the results showed that fixed dose everolimus when used in combination with standard dose CsA could lead to impaired renal function.

Pharmacokinetic/Pharmacodynamic modeling indicated that CsA was the primary factor lowering renal function, and that everolimus levels greater than 3 ng/mL were required to retain efficacy. Based upon these results two prospective studies A2306 (without basiliximab) and A2307 (with basiliximab) were conducted, using everolimus therapeutic drug monitoring (TDM) and reduced-dose CsA. Both studies showed improved renal function compared to the B251 and B201 studies and preserved efficacy, but did not include a non-everolimus control group.

This submission is based on a large new study, A2309, in *de novo* renal transplantation (n=833) that prospectively tested the efficacy and safety of 2 everolimus based regimens against an active comparator (standard treatment regimen combining MPA and standard dose of CsA). The same initial everolimus doses as in the previous pivotal studies B201 and B251 were used. Everolimus doses were then adjusted to reach blood trough level targets of 3-8 ng/mL and 6-12 ng/mL and combined with reduced exposure to Neoral guided by trough monitoring. The target trough levels for CsA in Study A2309 were lower in the everolimus arms compared to the everolimus arms in studies B201 and B251, while exposure to CsA in the MPA control groups was similar in all 3 studies and higher than in the everolimus groups in study A2309.

This new study (A2309) extends the data already submitted in *de novo* renal transplantation of the 2 prior pivotal studies with fixed doses of everolimus (B201 and B251) and the 2 large supportive studies (A2306 and A2307) using trough monitoring of

everolimus (>3 ng/mL) with reduced CsA exposure guided by monitoring blood levels 2 hours after dosing (C2).

The dose of Myfortic, the active comparator, was selected to provide the same molar dose as 1 g of mycophenolate mofetil (MMF) (720 mg Myfortic is equivalent to 1 g MMF) and is an approved dose of Myfortic for use in combination with cyclosporine (Neoral®). The dose selection rationale for everolimus was based on statistical PK/PD modeling of data obtained from earlier studies to determine the exposure of everolimus in combination with CsA that would preserve efficacy while optimizing renal function.

In summary, the 2 previous pivotal de novo renal transplant studies (B201, B251), showed comparable efficacy between everolimus 1.5 or 3.0 mg/day and the MMF comparator, but lower renal function. The PK/PD analyses showed clear relationships between high CsA blood levels and impairment of renal function, and low everolimus blood levels (<3 ng/mL) and higher rates of acute rejection.

Based on these results, 2 open-label studies were performed (A2306, A2307) to re-examine everolimus 1.5 and 3 mg/day, while adapting doses to keep trough levels of everolimus above 3 ng/mL and cyclosporine below those targeted previously. The studies showed improved renal function and efficacy comparable to that of MMF in earlier studies (B201, B251).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Both according to the published literature and according to the results of the Study A2309, a decrease in efficacy over time or development of tolerance has not been a problem with everolimus.

6.1.10 Additional Efficacy Issues/Analyses

It has been shown by Novartis, and confirmed by the Clinical Pharmacology reviewer, that there is an unacceptably high risk of acute rejection below trough levels of 3 ng/mL and the incidence of adverse events increase to unacceptable levels beyond trough levels of 12 ng/mL.

Table 24. Association Between Everolimus Trough Levels and Efficacy
 (Source: Pharmacometrics Review by Kevin Krudys, PhD)

Everolimus trough concentrations > 3 ng/mL demonstrate efficacy			
Everolimus trough levels	Treated BPAR	Graft Loss	Death
< 3 ng/mL	6/33 (18.2%)	4/35 (11.4%)	1/37 (2.7%)
3 – 8 ng/mL	64/415 (15.4%)	15/410 (3.7%)	9/411 (2.2%)
> 8 ng/mL	9/99 (9.1%)	3/101 (3.0%)	5/101 (5.0%)
Myfortic	47/277 (17%)	9/277 (3.2%)	6/277 (2.2%)

6.1.11 Efficacy Summary

Based on protocol specified and justified 10% non-inferiority margin, results from Study A2309 showed that both everolimus treatment regimens were non-inferior to the Myfortic treatment regimen at 12 months with regard to the primary efficacy composite endpoint consisting of the treated BPAR, graft loss, death or loss to follow-up. Additionally, the incidence rate of death, graft loss and loss to follow-up was similar between both everolimus groups and the Myfortic group.

A disproportionate rate of premature treatment discontinuation, driven by higher rates of adverse events, must be taken into consideration in the interpretation of both safety and efficacy outcomes in this study. More patients in both of the everolimus groups prematurely discontinued study treatment and were subsequently switched to alternate therapy than in the Myfortic group, which may bias the interpretation of the study results. A sensitivity analysis including premature treatment discontinuation as failure in the primary efficacy endpoint concluded that neither of the everolimus treatment regimens achieved non-inferiority to the Myfortic treatment regimen.

Analysis by gender revealed that among female patients, rates of premature treatment discontinuation, efficacy failure and the graft loss/death endpoint were considerably higher in both everolimus groups compared to the Myfortic group. Further analyses of these findings are ongoing. No differences were seen in the analysis of age (< 50 years and ≥ 50 years) or in the analysis by race, although about 14% of patients were Black, the others were Caucasian, Asian and other races.

Clinical Reviewer's Comment: Higher rates of graft loss and death in the everolimus subjects compared to Myfortic is concerning. Study A2309 may not provide adequate information to determine a safe and efficacious everolimus regimen for females patients

The primary safety endpoint of Study A2309 was estimated GFR using the MDRD formula at 12 months following the kidney transplantation. No statistically significant differences in estimated GFR at month 12 were shown between each of the everolimus regimens and the Myfortic regimen.

The majority of patients were maintained within the targeted everolimus and CsA blood levels with the exception of higher than targeted CsA levels between 6 and 9 months in the everolimus groups.

7.0 Review of Safety

Note: Tables in this section were obtained from the Applicant's Clinical Study Report (CSR) of Study A2309, as noted. Tables created by the reviewer, or obtained elsewhere are also noted.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Individual patient data from Study A2309 was used to evaluate safety. Previous fixed everolimus dose studies B201 and B251 are not included in the evaluation of safety since the drug exposures are different compared to the TDM Study A2309.

7.1.2 Categorization of Adverse Events

According to the study protocol adverse events (AEs) are reported up to 8 days after the discontinuation of the study medication and serious adverse events (SAEs) are reported up to 30 days after the discontinuation of the study medication. There was no cut-off time for reporting the graft losses and deaths.

Reviewer's Comment: As will be discussed, there was a higher rate of treatment discontinuation in the everolimus groups compared to the Myfortic group. These

early cut-off dates for reporting the AEs and SAEs possibly favored the everolimus groups.

During the study, information on study drug discontinuations due to AEs was collected on two different CRFs. According to the information from the first form (Treatment and Study Completion CRF) the overall incidence of study drug discontinuations due to AEs according to this first data collection form were 18.1% in the everolimus 1.5 mg group, 20.4% in the everolimus 3.0 mg group, and 9.4% in the Myfortic group.

The information collected on the second form (AE/infections CRF) was more specific and contained information about the type of AE leading to study drug discontinuation. According to the second form, the rates of discontinuation were 23.4% in the everolimus 1.5 mg group, 28.4% in the everolimus 3.0 mg group and 15.8% in the Myfortic group. It was assumed that the information obtained from the second form would be more accurate and detailed; therefore this information is utilized for the analysis of AEs leading to drug discontinuation.

Infections Reported as AEs

Infection data was coded with SNOMED for micro-organism and type of infection (viral, bacterial, fungal and others). In addition to being analyzed similarly as AEs and SAEs, as described above, the incidence rate of infection by type and micro-organism was tabulated for each treatment group.

AEs Related to Wound Healing

The applicant identified AEs related to wound healing events through a retrospective search of the AE and infectious events databases. Identified terms were reviewed by their clinical team to determine relevance and then paper CRFs were dispatched to the sites for further information regarding the events prior to database lock.

AEs Related to Interstitial Lung Disease

The study database was searched for adverse event terms entering into the MedDRA special search query (SMQ) for interstitial lung disease (ILD, narrow) which included the adverse event preferred terms: *acute interstitial pneumonitis, allergic granulomatous angiitis, alveolar proteinosis, alveolitis, alveolitis allergic, alveolitis fibrosing, alveolitis, necrotizing bronchiolitis, diffuse alveolar damage, eosinophilia myalgia syndrome, eosinophilic pneumonia, eosinophilic pneumonia acute, eosinophilic pneumonia chronic, interstitial lung disease, lung infiltration, necrosis of bronchioli, obliterative bronchiolitis, pneumonitis, progressive massive fibrosis, pulmonary fibrosis, pulmonary necrosis, pulmonary radiation injury, pulmonary toxicity, pulmonary vasculitis, radiation alveolitis, radiation fibrosis – lung, radiation pneumonitis, transfusion-related acute lung injury.* The reports identified by this search are included in the analysis.

AEs Related to Major Cardiac Events

A specific case report form was designed in order to capture information on the occurrence of major cardiac events (MACE) in the study. The applicant collected information on the following AEs:

- acute myocardial infarction
- congestive heart failure
- percutaneous coronary intervention
- coronary artery bypass graft
- automatic internal cardiac defibrillator
- cerebrovascular accident
- peripheral vascular disease

Vital signs variables included measurements of systolic and diastolic blood pressures, pulse, and body weight. Vital signs were examined for abnormal values and change from baseline according to pre-specified clinically notable criteria.

Systolic BP

- 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).

Diastolic BP

- 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).

AEs and SAEs were categorized both according to the MedDRA System Organ Class (SOC) and to Preferred Term (PT) in the 12 month analysis of the safety population.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Results from Study A2309 will not be pooled with previous studies, for several reasons: Only Study A2309 uses TDM of everolimus and reduced doses of CsA; Studies B201 and B251 used fixed doses of everolimus and standard doses of CsA.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

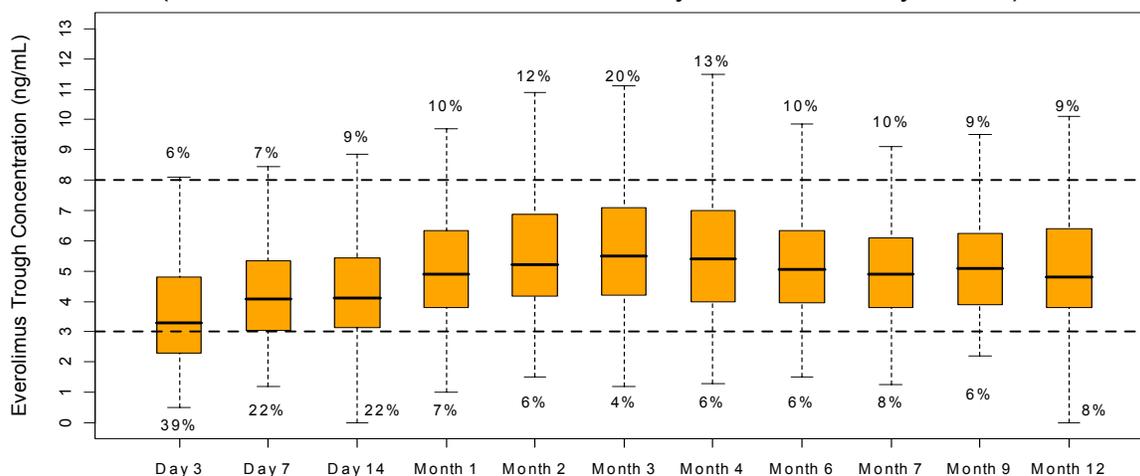
7.2.1.1 Trough Concentrations

Everolimus

The majority of patients in the everolimus 1.5 mg treatment group from Month 1 onwards, had everolimus trough blood levels within the target ranges. As seen in Figure 7 approximately 80% of trough everolimus concentrations were within target (3-8 ng/mL) from Month 1 onwards in the everolimus 1.5 mg group. Up to Month 1, patients were more likely to have had trough levels below the target range rather than above. Over the course of the study the percentage of patients achieving the target range increased. A higher percentage of patients in the everolimus 3.0 mg dose group had trough levels below the target range than in the everolimus 1.5 mg dose group.

Figure 7. Everolimus Cmin throughout the 12 Month Study Period in Everolimus 1.5 mg Group

(Source: Pharmacometrics Review by Kevin M. Krudys Ph.D)



Cyclosporine A

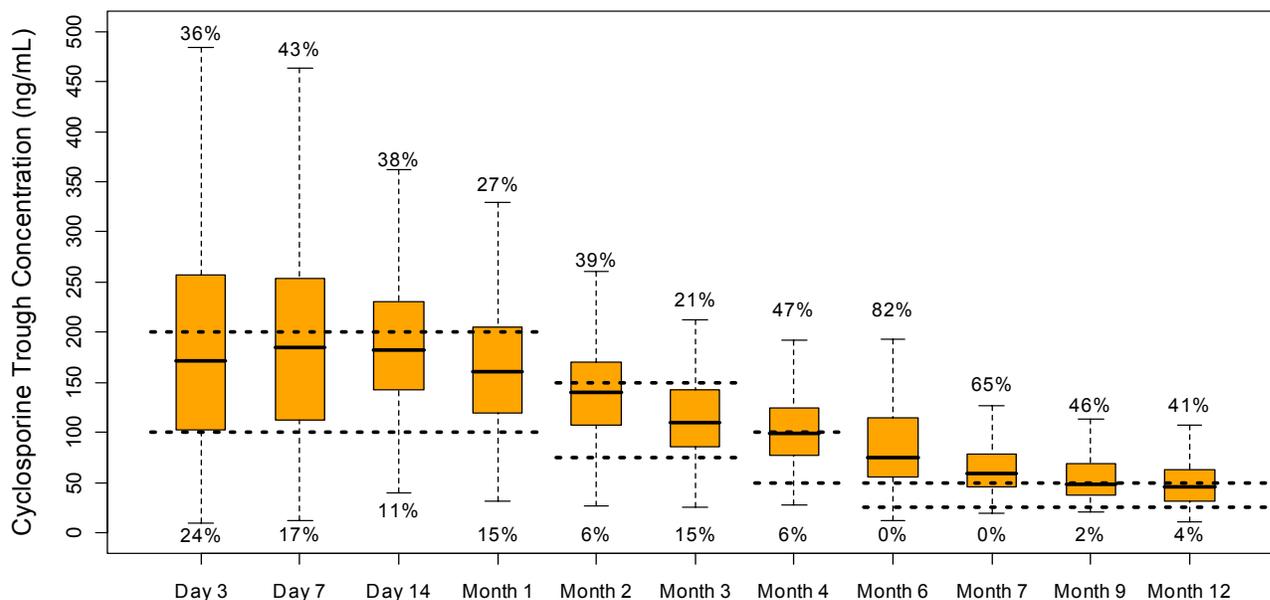
The CsA targets for the investigational groups were different from the control group beginning in the first week post-transplant. The targets were lower and the width of the target CsA windows progressively narrowed for the everolimus groups in contrast to the higher and progression to a wider window for the control group. In addition, the protocol driven CsA reduction was more regimented for the everolimus groups requiring four different windows compared to two different windows for the control group.

Mean CsA trough levels were lower in the everolimus treatment groups than the Myfortic group at all time points, as specified in the study protocol. CsA levels decreased over time for all treatment groups, with levels in the everolimus groups lower than the Myfortic group. At 12 months post-transplant the mean CsA trough levels were approximately three fold lower in the everolimus groups as compared to the Myfortic group. The upper limit of the CsA target range for everolimus groups at Day 3 was 200 ng/mL compared to 300 ng/mL in the Myfortic group. At Month 2, CsA target levels were a maximum of 150 ng/mL in the everolimus treatment groups (with over 50% of patients below this level), whilst in the Myfortic group, the target maximum was 250 ng/mL.

As shown in Figure 8, Cyclosporine concentrations tended to exceed target in everolimus 1.5 mg. group. The percentage of patients with CsA trough levels within the target range was greater than 50% from Day 14 onwards for the everolimus treatment groups, with the exception of Months 6 and 7 for the 1.5 mg group, and Months 4, 6 and 7 for the 3.0 mg group (at these points the target level decreased, and a higher percentage of patients had trough levels above the target range; data not shown).

Figure 8. Cyclosporine Cmin throughout the 12 Month Study Period (Everolimus 1.5 mg Group)

(Source: Pharmacometrics Review by Kevin M. Krudys Ph.D)



Clinical Reviewer's Comment: As seen in Figure X Cyclosporine Cmin was above the upper limit of targeted trough (50 ng/mL) at Month 6 and 7 and came down to 50 ng/mL starting Month 9 which may be indicative of the difficulty of managing this regimen with 2 TDMs with a DDI in-between.

7.2.1.2 *Dose Adjustment*

Dose variation was permitted in all treatment groups for safety reasons, and from Day 5 onwards doses could be adjusted in order to maintain trough levels within the target window. For everolimus and Myfortic dose changes (including temporary dose interruption), the majority (greater than 97%) were as permitted by the protocol. In the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm dose groups 52.6%, 64.7% 24.5% of patients had more than two dose changes. In the everolimus treatment groups, the main reason for any dose change was to achieve the target level (67.5% for the 1.5 mg group and 70.6% for the 3.0 mg group).

An adverse event was the main reason for dose change in the Myfortic 1.44 gm group, and the second most frequent reason in the everolimus treatment groups (24.7%, 31.0% and 52.4% of dose-adjusted patients in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm treatment groups, respectively).

A dosing error was the reason for change in approximately 10% of any dose changes in any treatment group. Over 96% of any CsA dose changes (including interruptions) were as per the protocol (Table 14.3-1.2b). The majority of patients had more than two dose changes (96.0%, 95.3% and 95.6% in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm treatment groups, respectively).

In all treatment groups more than 80% of changes were to achieve the target level (83.2%, 86.2% and 81.9% of any changes in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm treatment groups, respectively). Adverse events were a reason for any dose change in fewer than 20% of patients in any treatment group.

7.2.1.3 *Average Daily Doses*

The average daily doses of everolimus and Myfortic are shown in Table 25 below. Mean values showed some variation for the everolimus groups, however median values remained constant.

Table 25. Average Daily Dose of Everolimus
 (Source: Table 12-1, page 168, CSR):

Visit	Statistics	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 g N=273
Total	n	274	278	273
	Mean (SD)	2.64 (9.615)	5.81 (46.501)	1.344 (0.2104)
	Median (Range)	1.54 (0.3 – 149.6)	2.86 (1.1 – 776.5)	1.438 (0.70 – 2.23)
Day 1	n	274	278	273
	Mean (SD)	3.23 (22.600)	2.68 (0.452)	1.313 (0.1836)
	Median (Range)	1.50 (0.8 – 361.1)	3.00 (1.1 – 3.8)	1.440 (0.72 – 1.44)
Day 7	n	270	272	267
	Mean (SD)	2.72 (12.816)	2.90 (0.419)	1.419 (0.1216)
	Median (Range)	1.50 (0.4 – 150.0)	3.00 (1.1 – 4.5)	1.440 (0.67 – 2.16)
Month 1	n	257	257	257
	Mean (SD)	2.94 (13.065)	3.02 (1.133)	1.402 (0.1484)
	Median (Range)	1.50 (0.0 – 150.0)	3.00 (1.2 – 15.0)	1.440 (0.59 – 1.93)
Month 3	n	234	232	242
	Mean (SD)	3.06 (13.688)	9.02 (94.361)	1.361 (0.2190)
	Median (Range)	1.50 (0.4 – 150.0)	3.00 (0.5 – 1440.0)	1.440 (0.43 – 2.16)
Month 6	n	215	209	235
	Mean (SD)	2.50 (10.136)	2.69 (0.972)	1.334 (0.3064)
	Median (Range)	1.50 (0.5 – 150.0)	3.00 (1.0 – 7.3)	1.440 (0.00 – 2.88)
Month 9	n	206	198	225
	Mean (SD)	2.58 (10.354)	2.71 (0.967)	1.309 (0.2902)
	Median (Range)	1.50 (0.5 – 150.0)	3.00 (0.6 – 6.4)	1.440 (0.40 – 2.16)
Month 12	n	195	185	215
	Mean (SD)	2.64 (10.643)	3.38 (9.774)	1.314 (0.2880)
	Median (Range)	1.50 (0.5 – 150.0)	3.00 (0.8 – 135.0)	1.440 (0.54 – 2.16)

In calculating average daily doses, zero doses are used for periods of temporary interruption of study medication, regardless of whether this is due to safety reasons or non-compliance.
 Source: [Table 14.3-1.3a](#)

The maximum values for everolimus groups in some cases were implausibly high and these were noted by the Applicant as likely erroneous (such as a maximum of 1.44 gm, which suggested the patient was switched to Myfortic). The analysis was repeated by the Applicant, and those doses of everolimus greater than 100 mg were replaced with a value of 0 based on the likelihood of a switch to Myfortic. Recorded doses of between 10 and 100 mg were divided by 10 to obtain a substitute value in Table 26 below.

Table 26. Average Daily Doses of Everolimus and Myfortic by Visit
(Source: Table 12-2, page 168, CSR):

Visit	Statistics	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 g N=273
Total	n	274	278	273
	Mean (SD)	1.83 (1.060)	2.28 (0.844)	1.344 (0.2104)
	Median (Range)	1.54 (0.3 – 15.0)	2.85 (1.1 – 7.4)	1.438 (0.70 – 2.23)
Day 1	n	274	278	273
	Mean (SD)	1.42 (0.586)	2.68 (0.452)	1.313 (0.1836)
	Median (Range)	1.50 (0.8 – 7.0)	3.00 (1.1 – 3.8)	1.440 (0.72 – 1.44)
Day 7	n	270	272	267
	Mean (SD)	1.65 (1.190)	2.90 (0.419)	1.419 (0.1216)
	Median (Range)	1.50 (0.4 – 15.0)	3.00 (1.1 – 4.5)	1.440 (0.67 – 2.16)
Month 1	n	257	257	257
	Mean (SD)	1.89 (1.322)	3.02 (1.133)	1.402 (0.1484)
	Median (Range)	1.50 (0.0 – 15.0)	3.00 (1.2 – 15.0)	1.440 (0.59 – 1.93)
Month 3	n	234	232	242
	Mean (SD)	1.91 (1.388)	2.81 (1.080)	1.361 (0.2190)
	Median (Range)	1.50 (0.4 – 15.0)	3.00 (0.0 – 8.0)	1.440 (0.43 – 2.16)
Month 6	n	215	209	235
	Mean (SD)	1.87 (1.183)	2.69 (0.972)	1.334 (0.3064)
	Median (Range)	1.50 (0.5 – 15.0)	3.00 (1.0 – 7.3)	1.440 (0.00 – 2.88)
Month 9	n	206	198	225
	Mean (SD)	1.92 (1.230)	2.71 (0.967)	1.309 (0.2902)
	Median (Range)	1.50 (0.5 – 15.0)	3.00 (0.6 – 6.4)	1.440 (0.40 – 2.16)
Month 12	n	195	185	215
	Mean (SD)	1.95 (1.278)	2.71 (1.238)	1.314 (0.2880)
	Median (Range)	1.50 (0.5 – 15.0)	2.99 (0.8 – 13.8)	1.440 (0.54 – 2.16)

In calculating average daily doses, zero doses are used for periods of temporary interruption of study medication, regardless of whether this is due to safety reasons or non-compliance.
Overall = from Day 1 to Month 12.
Those records with Morning dose or Evening dose higher than 10 mg for RAD groups (everolimus 1.5 mg and everolimus 3.0 mg groups) are modified for this analysis; if dose >100 mg, then replaced by 0; if 0 < dose ≤ 100, then divided by 10.
Source: [Table 14.3-1.3a1](#)

Mean and median doses decreased over the course of the study for all treatment groups, and were consistently lower in the everolimus treatment groups than the Myfortic group, as would be expected from the study design, with median Month 12 values of 1.36 mg/kg/day in the everolimus 1.5 mg group, and 2.93 mg/kg/day in the Myfortic 1.44 gm group.

7.2.1.3 *Duration of Exposure*

Median duration of treatment with everolimus or Myfortic was similar in all treatment groups, whilst mean duration of exposure was slightly longer in the Myfortic treatment group. Median exposure was at least 360 days, as shown in Table 27 below.

Table 27. Overall Exposure and Summary Statistics by Treatment Group (Safety population - 12 month analysis)
 (Source: Table 12-4, page 171, CSR)

Table 12-4 Overall exposure and summary statistics by treatment group (Safety population - 12 month analysis)			
	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 g N=273
Exposure (days)			
Mean ± SD	288.7 ± 129.9	276.4 ± 134.6	310.3 ± 115.2
Median (range)	362.0 (2.0 – 408.0)	360.0 (1.0 – 391.0)	363.0 (2.0 – 426.0)
Categorical exposure duration (days) – n (%)			
≥ 1 day	274 (100.0)	278 (100.0)	273 (100.0)
≥ 5 days	270 (98.5)	272 (97.8)	267 (97.8)
≥ 12 days	261 (95.3)	263 (94.6)	261 (95.6)
≥ 22 days	257 (93.8)	257 (92.4)	257 (94.1)
≥ 45 days	243 (88.7)	248 (89.2)	250 (91.6)
≥ 76 days	234 (85.4)	231 (83.1)	242 (88.6)
≥ 106 days	225 (82.1)	221 (79.5)	238 (87.2)
≥ 151 days	216 (78.8)	209 (75.2)	234 (85.7)
≥ 196 days	211 (77.0)	201 (72.3)	231 (84.6)
≥ 241 days	207 (75.5)	198 (71.2)	225 (82.4)
≥ 316 days	196 (71.5)	186 (66.9)	215 (78.8)
Average daily dose during the study			
Mean ± SD	2.64 ± 9.615	5.81 ± 46.501	1.344 ± 0.2104

Source: [Table 14.3-1.1](#) and [14.3-1.3a](#)

7.2.2 Explorations for Dose Response

7.2.2.1 Exposure-Response for Efficacy

A whole blood trough concentration of 3 ng/mL was previously identified as the minimum target concentration to preserve efficacy in renal and heart transplantation from the exposure-response (ER) analyses from the renal transplantation studies B201 and B251, and heart transplantation study B253.

Both everolimus groups were pooled (one had target 3-8 and the other 6-12) for exposure-response analyses.

The efficacy results from Study A2309 were used to evaluate the robustness of this trough concentration of 3 ng/mL, as shown in Table 28. Consistent with the defined everolimus target ranges, a low number of patients had exposure lower than 3 ng/mL or higher than 12 ng/mL. The frequency of treated BPAR becomes progressively lower as everolimus trough concentrations increase. The risk of graft loss was higher at everolimus trough concentrations less than 3 ng/mL (11.4%) than between 3 and 8 ng/mL (3.7%). Above a minimum everolimus level of 3 ng/mL rates of treated BPAR are all numerically reduced compared to that with Myfortic. However, the risk of death was the highest (5.0%) at everolimus trough concentrations above 8 ng/mL, the upper limit of the sponsor proposed target therapeutic range. These results therefore support the 3 to 8 ng/mL target range for everolimus trough concentrations with regard to efficacy. Within these ranges BPAR, graft loss and death rates are comparable to those occurring with Myfortic.

Table 28. Association between Everolimus Target Trough levels and Efficacy

(Source: Review By Kevin Krudys, Ph.D.)

Everolimus trough levels	Treated BPAR	Graft Loss	Death
< 3 ng/mL	6/33 (18.2%)	4/35 (11.4%)	1/37 (2.7%)
3 – 8 ng/mL	64/415 (15.4%)	15/410 (3.7%)	9/411 (2.2%)
> 8 ng/mL	9/99 (9.1%)	3/101 (3.0%)	5/101 (5.0%)
Myfortic	47/277 (17%)	9/277 (3.2%)	6/277 (2.2%)

7.2.2.2 *Exposure-Response for Safety*

The relationship between whole blood everolimus trough concentrations and selected safety events up to 12 months post transplant in Study A3209 was established for the following:

- Proteinuria, defined as the urinary protein / urinary creatinine (UP/UC) ratio ≥ 0.3 g/g after Month 1

Clinical Reviewer's Comment: According to NKF (National Kidney Foundation) the cut-off value is (UP/UC) ratio ≥ 0.2 .

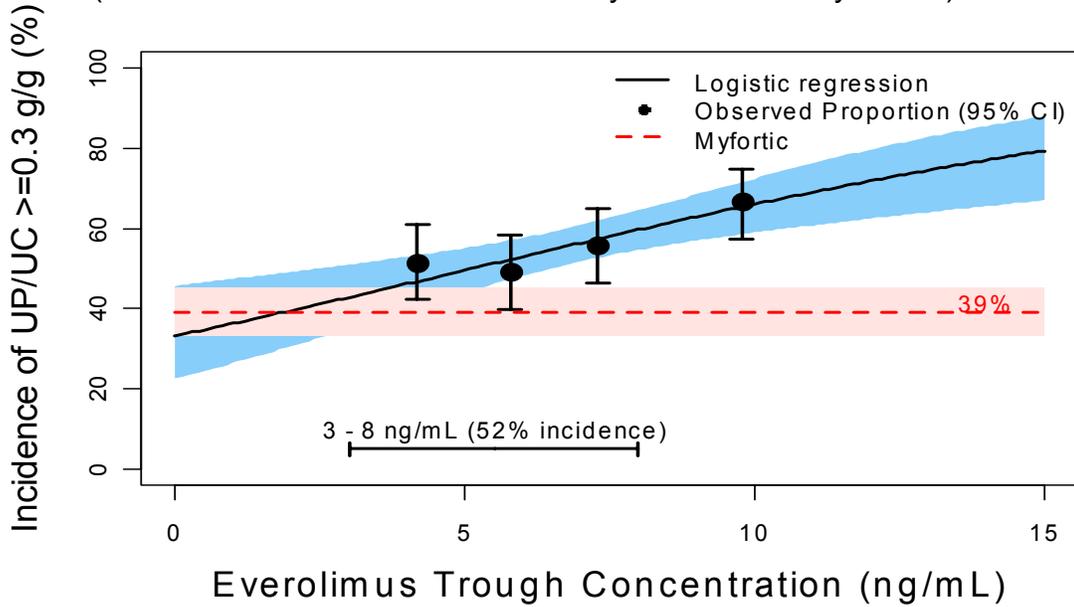
- Wound healing complications/events based on the applicant's analysis of all the relevant preferred terms
- Peripheral edema adverse events
- Hypercholesterolemia, defined as total cholesterol ≥ 6.2 mmol/L, or ≥ 240 mg/dL
- Hypertriglyceridemia, defined as triglycerides ≥ 5.6 mmol/L, or 500 mg/dL

Clinical Reviewer's Comment: These events were selected because they are associated with the M-TOR inhibitor class of drugs (i.e., sirolimus), were identified as clinically relevant, and were observed at higher rates in the everolimus treatment groups compared to the Myfortic control treatment group in Study A2309.

Proteinuria

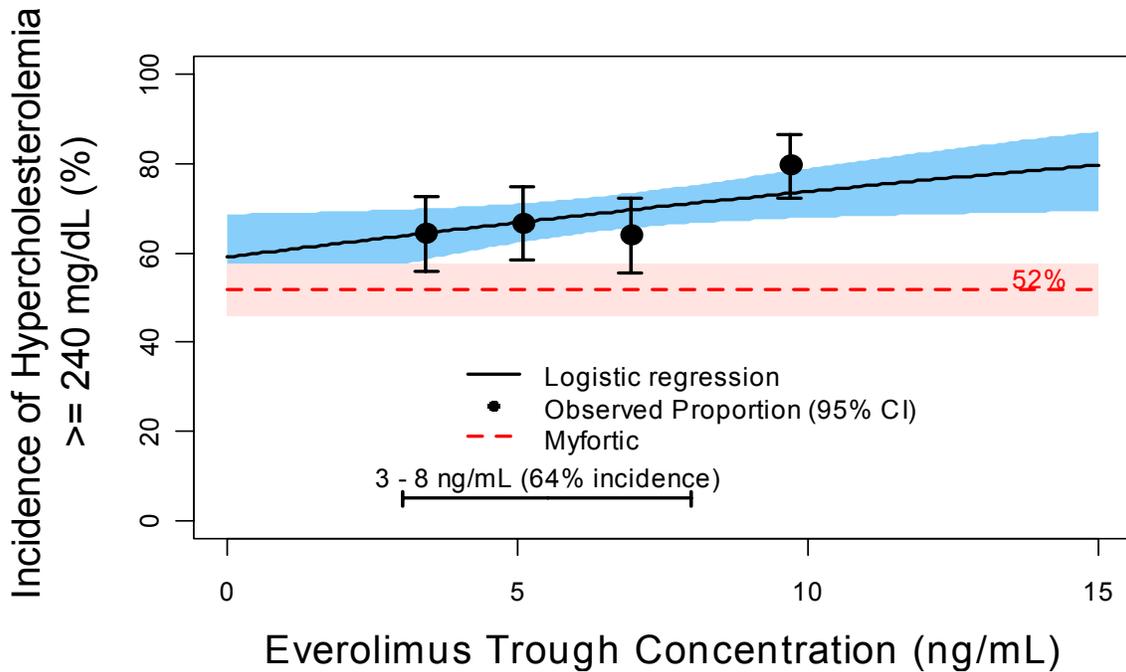
Incidence of proteinuria increases with higher everolimus concentrations (Figure 9).

Figure 9. Everolimus Trough Concentrations and Proteinuria.*
(Source: Pharmacometrics Review by Kevin M. Krudys Ph.D)



Hypercholesterolemia

Figure 10. Everolimus Trough Concentrations and Hypercholesterolemia.
(Source: Pharmacometrics Review by Kevin M. Krudys Ph.D)



Other Events

There was not a strong relationship between higher everolimus concentrations and the incidence of the following events:

- Peripheral edema adverse events
- Wound healing complications
- Hypertriglyceridemia (triglycerides >490 mg/dL)
- New onset diabetes mellitus

However, the incidence of these events was higher in the everolimus treatment groups.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to Section 4.3

7.2.4 Routine Clinical Testing

7.2.5 Metabolic, Clearance, and Interaction Workup

Everolimus pharmacokinetics has been characterized after oral administration of single and multiple doses to adult kidney transplant patients, hepatically-impaired patients, and healthy subjects.

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7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The known M-TOR inhibitor class effects are:

- Hepatic artery thrombosis in liver transplantation and other Thromboembolic events
- Hyperlipidemia
- Proteinuria

- Wound healing problems like dehiscence, Incisional hernia, anastomotic separation (bronchial anastomotic dehiscence in lung transplantation)
- Peripheral edema
- Localized fluid collections like lymphocele, pericardial and pleural effusions, Ascites
- NODAT (New Onset Diabetes After Transplantation)
- Interstitial lung disease
- TMA/TTP/HUS
- Thrombocytopenia
- Angioedema
- Mouth ulcerations

7.3 Major Safety Results

7.3.1 Deaths

A total of 23 patients died during the first 12 months of the study, 7 (2.5%) in the everolimus 1.5 mg group, 10 (3.6%) in the 3.0 mg everolimus group, and 6 (2.2%) in the Myfortic control group. The most common causes of death across the study groups were related to cardiac conditions and infections. Table 26 through Table 28 for the everolimus and Myfortic groups, respectively; include relevant information regarding the patient's clinical course, along with the principal cause of death as assessed by the applicant and by FDA.

Four of the deaths occurred more than 30 days after discontinuation of study medication (one in the 1.5 mg everolimus group, two in the 3.0 mg everolimus group, and one in the Myfortic group).

One of the deaths in the everolimus 3.0 mg group (A2309-0168-00017) occurred in a patient who experienced multi-organ failure and died on Day 34. This patient not included in the applicant's clinical database because the patient discontinued treatment and withdrew consent on Day 24.

Reviewer's Comment: *Although this patient (0168-00017) withdrew consent on Day 24 and died on Day 34, the chain of events that led to the demise of the patient (MI and pulmonary edema) started on Day 14 while he was still on treatment and there is only 10 days in between stopping the treatment medication and the death of the patient. This patient was included by FDA in their analysis of both the efficacy and safety populations.*

**Table 26. All Deaths Reported During the 12-month Study Period
 Everolimus 1.5 mg Group**
 (Source: Adapted by the Reviewer from Section 12.3 page 180 of the CSR)

Everolimus 1.5 mg (Investigator: 2 (3?) infectious, 3 cardiac, 1 PE, 1 malignancy = 7 deaths) (FDA: 2 (3?) infectious, 3 cardiac, 1 PE, 1 malignancy = 7 deaths)					
Patient	Day of Death	Day of D/C Study Medication	Relevant History	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
- 1 - 0125-00002 (F, 47, C)	31	30 (septic shock)	D16: lymphocele, UTI (rehospitalized) D22: cardiogenic shock and septic shock	Septic Shock	Septic Shock
- 2 - 0115-00020 (F, 43, C)	28	9 (Renal vein thrombosis)	D16: Transplant nephrectomy (renal vein thrombosis,) D23: re-laparotomy for evacuation of hematoma, abdominal sepsis D25: massive hemorrhage,	Abdominal sepsis	Abdominal sepsis
- 3 - 0100-00008 (F, 49, C)	148	76 (ureteral necrosis, urinoma nephrostomy)	D74: ureteral necrosis, urinoma, wound infection, cellulitis D77: nephrostomy, D87: psychosis	Poss ble pulmonary embolism	Pulmonary embolism? Multiple infections
- 4 - 0124-00076 (M, 39, C)	85 (sudden chest pain)	85 (death)	HTN Hypercholesterolemia after transplant Hypertensive cardiomyopathy	Myocardial infarction?	Myocardial infarction?
- 5 - 0516-00002 (M, 61, C)	156	156 (death)	D48: incisional hernia D 55: Hernia repair D102: edema, Lasix treatment CHF	Congestive heart failure (CHF)	Congestive heart failure (CHF)
- 6 - 0514-0003 (F, 51, O)	278	277 (sudden cardiac arrest at home)	On-study: intermittent reports of anemia, hypokalemia D277: cardiac arrest of unknown cause	Cardiac arrest (cause unknown)	Cardiac arrest (cause unknown)
- 7 - 0118-00012 (M, 52, C)	122	121 (melanoma)	D15: Lymphocele drainage D112: diagnosed with malignant melanoma D122: liver and brainstem metastases,	Metastatic melanoma	Metastatic melanoma

**Table 27. All Deaths Reported During the 12-month Study Period
Everolimus 3.0 mg Group**
(Source: Adapted by the Reviewer from Section 12.3 of the CSR)

Everolimus 3.0 mg [Investigator: 3 infectious (2 pneumonia), 5 cardiac, 1 renal failure, 1 multiorgan failure = 10 deaths] [FDA: 5 infectious (6?) (3 pneumonia), 3 MI, 1 thrombocytopenia, 1 renal failure = 10 deaths]					
Patient	Day of Death	Day of D/C study Medication	Relevant History	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
- 1 - 0100-00002 (M, 56, C)	269	263 (pneumonia) <u>Everolimus dose reduced to 1.5 mg qd on D17 and to 1.25 mg on D34</u>	D16: perinephric collection-urinary fistula D30: recurrence urinary fistula D50 : recurrence urinary fistula D100: urolithiasis D263:pneumonia,	Septic Shock (Pneumonia)	Septic Shock (Pneumonia)
- 2 - 0114-0001 (M, 34, C)	243	45 (wound infection)	D2: coronary occlusion, angioplasty D30: wound infection D106: Bx. Rejection (methylprednisone, switch to tacrolimus) D140: graft loss, hemodialysis D243:X-Ray, pneumonia	Cardiac arrest (Pneumonia)	Pneumonia
- 3 - 0166-00025 (M, 30, C)	16	15 (cardio-pulmonary failure)	History: congestive cardiomyopathy, bronchopneumonia, pulmonary edema, f brotisans alveolitis Autopsy: Pneumonia	Cardiopulmonary failure (Autopsy: pneumonia)	Pneumonia
- 4 - 0507-0019 (M, 69, C)	234	230 (cardiac arrest)	History: coronary bypass, pulmonary HTN D56: Pneumonia D222: Myocardial infarction and staphylococcal pneumonitis D230: congestive heart failure, pulmonary edema,	Myocardial infarction	Pneumonia, Myocardial infarction
- 5 - 0532-0008 (F, 40, NA)	175	174 (death)	D175: severe renal abscess, pyelonephritis (autopsy: confirmed cardiomegaly – no further information)	Sudden death, Cardiomegaly	<u>Renal abscess, sepsis?</u> Congestive heart failure.
- 6 - 0553-0009 (F, 43, B)	322	316 (colitis)	D52: diarrhea (moderate) D 190-192: diarrhea (SAE, moderate) D265: culture of <i>Clostridium difficile</i> D308: <i>C.difficile</i> pancolitis. Fatal despite therapy, anemia	Colitis (<i>C. difficile</i>)	Colitis (<i>C. difficile</i>)
- 7 - 0168-00017	34	24 (withdrew consent)	D13: rejection, graft loss D14: pulmonary edema, non Q-wave MI-anticoagulation	Multi-organ failure	Myocardial infarction

Everolimus 3.0 mg					
[Investigator: 3 infectious (2 pneumonia), 5 cardiac, 1 renal failure, 1 multiorgan failure = 10 deaths]					
[FDA: 5 infectious (6?) (3 pneumonia), 3 MI, 1 thrombocytopenia, 1 renal failure = 10 deaths]					
Patient	Day of Death	Day of D/C study Medication	Relevant History	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
(M, 59, C)			D23: Surgery for retroperitoneal hematoma, hemorrhagic shock D24: Transplant nephrectomy		Hemorrhagic shock
- 8 - 0520-0009 (M, 65, C)	7	7 (death)	D6: MI, coronary occlusion by angiogram, stent placement D7: bradycardia with fatal cardiac arrest	Myocardial infarction	Myocardial infarction
- 9 - 0173-00003 (F, 52, B)	185	2 (TTP)	D3: thrombocytopenic purpura, hemolytic anemia D17: urine leak, infection D26: nephrotic syndrome, D89: purulent discharge in the wound D141:UTI, nephrotic syndrome	Renal failure, Fluid overload (No access to dialysis)	Renal failure, Fluid overload (No access to dialysis) Infection
- 10 - 0549-0001 (M, 55, C)	24	17 (Thrombocytopenia , sepsis)	History: aortic aneurism D16: Laparotomy: retroperitoneal hematoma, (No intestinal obstruction), D17 Platelets: 16,000 (Baseline: 165,000) Sepsis, Atrial fibrillation	Sepsis (Bowel obstruction)	Retroperitoneal bleeding, Thrombocytopenia, Sepsis

**Table 28. All Deaths Reported During the 12-month Study Period
 Myfortic Group**

(Source: Adapted by the Reviewer from Section 12.3 of the CSR)

Myfortic					
(Investigator: 2 cardiac, 1 stroke, 1 traffic accident, 1 natural = 6 deaths) (FDA: 2 MI, 1 stroke, 2 traffic accidents, 1 unknown = 6 deaths)					
Patient	Day of Death	Day of D/C Study Medication	Relevant History	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
- 1 - 0502-00016 (M, 58, B)	253	6 (rejection)	D4: Acute rejection D21: bacteremia Staph aureus D253: cardiac arrest at home. Also reported as acute myocardial infarction Switched to SIROLIMUS on D4	Cardiac Arrest (at home)	Myocardial infarction?
- 2 - 0544-00012 (M, 61, C)	34	33 (death)	Coronary bypass, asthma, diabetes hyperbilirubinemia D17: hypoglycemia (73 mg/dL)	Myocardial infarction	Myocardial infarction
- 3 - 0513-00010 (M, 64, C)	15	14 (stroke)	Bilateral femoral stent insertion D15: epistaxis, hyperglycemia (892), malignant HTN (226/100), hemorrhagic stroke D16: no cerebral activity EEG	Hemorrhagic stroke	Hemorrhagic stroke
- 4 - 0521-00007 (M, 57, B)	356	356 (death)	D356: traffic accident, died instantaneously	Motor vehicle accident	Motor vehicle accident
- 5 - 0122-00003 (M, 62, C)	250	243 (sepsis)	D237: Motor vehicle accident, Multiple fractures, fever, hypotension D240: sepsis (<i>E. coli</i>)	Pulmonary embolism	Motor vehicle accident,
- 6 - 0553-00014 (M, 47, B)	55	55 (death)	History: heart murmur, obesity	"Natural cause" (no further information)	Unknown

Applicant's Assessment of Deaths

A difference was noted between the groups as regards to fatal infections (everolimus 1.5 mg: 2 cases, everolimus 3.0 mg: 4 cases, Myfortic 1.44 g: none). There were also a greater number of deaths ascribed to MI in the everolimus 3.0 mg group than in either of the other two treatment groups (everolimus 1.5 mg: 1 case; everolimus 3.0 mg: 3 cases; Myfortic 1.44 g: 1 case).

In the Applicant's review of deaths, 20 out of 22 were thought to be unrelated to study drug (not counting patient 0168-00017 who withdrew consent). The 2 deaths thought study drug-related were one case of late stage, metastatic melanoma in the 1.5 mg everolimus group and one case of cardiopulmonary failure with known congestive cardiomyopathy and hypertension in the 3.0 mg everolimus group.

In the everolimus 3 mg group, cardiac disorders and infections led to most deaths, none of which were considered drug-related except the case of cardiopulmonary failure mentioned above. The other deaths were randomly distributed across system organ classes and events.

Reviewer's Assessment of Deaths: A discussion of the deaths in each of the treatment groups follows along with an overall conclusion regarding the attributability of the deaths to the study medication.

Everolimus 1.5 mg Group:

Among the seven deaths in the everolimus 1.5 mg/d group, 3 are due to cardiac and 2 are due to infectious reasons and there is one case with possible pulmonary emboli in addition to co-existent infection and one malignancy associated death. The reviewer believes that there is an association between all the seven deaths reported in this group and the study medication (everolimus) including patient 0100-00008 who died more than 30 days after the discontinuation of the study medication.

Patients of special interest:

Patient 125-00002: This 47 year old female patient was rehospitalized on Day 13 after the transplant with the diagnosis of lymphocele and urinary tract infection (UTI). On Day 20 deep wound dehiscence with wound infection is also reported in the CRF. On Day 22 she had abdominal pain, anuria, nausea and was diagnosed with severe septic shock and severe cardiogenic shock secondary to propranolol intoxication. Her blood culture grew Acinetobacter species. Anasarca (generalized edema), is also described in the CRF during this period which lasted until the patient's death.

The events that started the decline of this patient are UTI, wound dehiscence, wound infection and lymphocele. UTI and wound infection which may be associated with the study drug gave rise to septic shock. Wound healing problems and lymphocele are well described M-TOR class toxicities and probably also contributed to the death of this patient.

Patient 0115-00020: Graft thrombosis possibly related to the thrombogenic effects of everolimus (M-TOR inhibitors in general) led to intraabdominal infection which caused the death of this 43 year old female patient.

Patient 0100-00008: Although this patient died on Day 148, 70 days after stopping the study medication (everolimus) there is a highly possible association between the death of this patient and the study medication. This 49 year old female patient developed urethral necrosis followed by urinoma and nephrostomy placement for the treatment of this complication. At the same time this patient developed wound infection with cellulitis which altogether led to prolonged hospitalization and immobilization and also developed psychosis during this period. Wound related problems like delayed healing, dehiscence and infections are among the well characterized adverse effects of M-TOR inhibitors. It is very likely that the pulmonary emboli which is presented as the cause of death was caused by the preceding prolonged hospitalization and immobilization.

Patient 0124-00076: This 39 year old male patient whose death was attributed to acute myocardial infarction developed severe dyslipidemia (hypercholesterolemia) after the transplant which gradually worsened until his death on Day 85. His total cholesterol increased from 147 mg/dL to 432 mg/dL and his LDL cholesterol increased from 81 mg/dL to 212 mg/dL (normal levels: up to 129 mg/dL) during the course of the study. This 39 year old patient had a documented prior history of hypertensive cardiac disease (myocarditis).

Hypercholesterolemia is a well known class toxicity of M-TOR inhibitors and might have contributed to the death of this patient who had normal lipid levels before the start of the study treatment. Thrombogenicity of everolimus might have additionally contributed to this outcome by enhancing the coronary artery occlusion. It is also known from the non-clinical studies that everolimus has a potential to cause myocarditis which might have exacerbated the already existing hypertensive myocarditis.

Patient 0516-00002: This 61 year old male patient developed an incisional hernia after the transplant and had surgical hernia repair. He also had perinephric fluid collection. On Day 102, he was diagnosed to have edema and was put on furosemide treatment. On Day 156, he was diagnosed with severe congestive heart failure. The study medication was permanently discontinued due to the event. He died on the same day due to congestive cardiac failure.

This patient developed edema and other types of fluid collection like perinephric fluid followed by congestive heart failure which resulted in his death. Edema and other type of fluid collections in various compartments of the body are among the

class toxicities of M-TOR inhibitors and hypervolemia may cause or enhance congestive heart failure.

Patient 0118-00012: A 52 year old male who had a biopsy of the bladder on Day 112 which revealed malignant melanoma. On Day 119, the patient experienced severe hematuria and on Day 121 a liver ultrasound revealed findings which were consistent with hepatic and brain stem metastases. The patient died subsequently due to metastatic malignant melanoma.

This is the only patient who died of cancer in the study. There may be an association with the study drug since it is known that systemic immunosuppression in general increases the incidence of malignancies.

Everolimus 3.0 mg Group:

The reviewer does not intend to give a detailed discussion of the deaths in this group since the applicant accepts the high incidence of adverse events in this treatment group and is not seeking approval of this dose. Details of the patients in this group will be given if there is an implication for the everolimus 1.5 mg group.

Among the 10 deaths in the everolimus 3.0 mg/day group, 5 are due to infectious reasons, 3 are due to myocardial infarction, one due to retroperitoneal bleeding associated with thrombocytopenia, and one is due to renal failure in a patient who did not have access to hemodialysis. It is important to note that of the five deaths caused by infections three were due to pneumonia.*

Patient 0100-00002: This 56 year old male patient was switched to 1.5 mg qd dosing on day 17 and the dose was further reduced down to 1.25 mg qd although he was in the everolimus 3.0 mg group. He stayed on the 1.25 mg qd dosing until his death on Day 263 due to pneumonia. Therefore the reviewer believes that this patient should be considered among the deaths in the everolimus 1.5 mg group for the evaluation of safety.

Patient 0549-0001: This 55 year old male patient died due to retroperitoneal bleeding which apparently started in association with severe thrombocytopenia which probably was drug induced. M-TOR inhibitors are known to cause thrombocytopenia. This patient had a laparotomy on Day 16 for suspected intestinal obstruction was found to have retroperitoneal hematoma. His baseline platelet count was 165,000. On Day 3 platelet count was down to 128,000, and on Day 14 it was down to 38,000. Between Day 7 and Day 14 his hemoglobin level also dropped from 15.4 g/dL down to 11.4 g/dL. On Day 16 he had the laparotomy which disclosed the hematoma. On Day 18 his platelet count was 16,000 and everolimus was discontinued because of thrombocytopenia. The

reviewer found this patient to be of special interest because of the association between the thrombocytopenia and this patient's death. It is not very common to see kidney transplant patients die due to hemorrhage which is associated with thrombocytopenia. Although other immunosuppressants like MPA derivatives may also cause thrombocytopenia it is very uncommon to see deaths and the thrombocytopenia due to MPA derivatives usually respond to dose reduction or discontinuation before resulting in a fatal outcome.

Myfortic Group

Among the 6 deaths in the control (Myfortic) group 3 are due to cardiovascular events. Two patients had myocardial infarctions and one patient had a hemorrhagic stroke. Of the remaining three two are due to motor vehicle accidents and one case of death on Day 55 in a 47 year old male patient reported as natural cause with no further information.

Patient 0502-00016: This 58 year old male patient died on Day 253 due to myocardial infarction. This patient was placed on Sirolimus (another M-TOR inhibitor) starting Day 4 and the study medication was discontinued starting Day 6 because of an acute rejection episode. Although this patient was in the control (Myfortic) group, he had been on Sirolimus treatment for 249 days when he died and he received the study medication only for 4 days after the transplant.

Although this patient (0502-00016) was randomized to the control group he received the study medication only for four days and he was on a different immunosuppressive regimen for the last 249 days that preceded his death. The reviewer believes that this incidence of death should not be counted among the deaths in the control group.

Patient 0122-00003: This 62 year old male patient died as a result of pulmonary emboli following a major motor vehicle accident on Day 237 of the study and sustained multiple fractures during the accident. He later developed E. coli sepsis and died on Day 250, 13 days after the accident. The cause of death for this patient is listed as pulmonary emboli by the sponsor.

Although the final event causing the death for this patient (0122-00003) might have been pulmonary emboli (no record of autopsy) this happened 13 days after a severe motor vehicle accident during which the patient sustained multiple fractures. It is very clear that this accident started the chain of events (sepsis and possible pulmonary emboli) that led to the death of this patient so the reviewer believes that the real cause of death in this otherwise stable patient is the motor vehicle accident.

Patient 0521-00007: This patient also died due to a motor vehicle accident and expired instantly on the scene of the accident.

Reviewer's conclusion on the study medication attributability of mortality:

The total number of deaths reported during the study period is 23 including patient 0168-00017 (explained in more detail above) who withdrew consent on Day 24 and died on Day 34. After reviewing the narratives and CRFs, as an overall evaluation of mortality in Study A2309 the reviewer believes that the actual number of deaths which may have a causality association with the study drugs is 18. As stated above the reasons for excluding the possibility of any association between the study medication and the death event in 5 patients are:

In the Myfortic group, two patients (0122-00003 and 0521-00007) died as a result of motor vehicle accidents and the third patient (0502-00016) has been on a different immunosuppressive regimen (Sirolimus) almost for the whole duration of the study period until his death (249 days out of the total of 253 days).

In the everolimus 3.0 mg group, Patient 0173-00003 died 183 days after discontinuing the study medication. Patient 0114-0001 died on Day 243, 198 days after discontinuing the study medication.

After excluding these five cases of deaths because of lack of association between the death and the study medication the distribution of the number deaths with a probable association with the study medication across the study groups are as follows:

- 7 deaths in the 1.5 mg everolimus group*
- 8 deaths in the 3.0 mg everolimus group*
- 3 deaths in the Myfortic (control) group*

There is one patient (0100-00002) in the everolimus 3.0 mg group whose dose of everolimus was reduced down to 1.5 mg qd starting Day 17 and down to 1.25 mg qd starting Day 34 and stayed at this level until his death on Day 269. The reviewer believes that although this patient was assigned to the 3.0 mg group he has been on 1.25 mg everolimus qd for almost the whole duration of the study period (252 days) he should be included in the 1.5 mg qd group for purposes of safety evaluation. After the transfer of this patient to 1.5 mg everolimus group the final distribution of patient deaths with a probable attributability to the study medication:

- 8 deaths in the 1.5 mg everolimus group*
- 7 deaths in the 3.0 mg everolimus group*
- 3 deaths in the Myfortic (control) group*

According to this final assessment of study drug attributability of patient deaths there are more than twice as many deaths in both of the everolimus groups compared to the Myfortic group that shows a probable association with the study medication.

This assessment is in line with mortality rates reported from another concentration controlled everolimus heart transplant study. In this heart transplant study (Study 2310), which utilized the same immunosuppressant regimens with same study design as in Study A2309, and utilized concentration controlled everolimus administration, the everolimus 3.0 mg group was terminated by the DMC due to excessive mortality in this group

In a study in de novo liver transplant patients, the use of Rapamune in combination with tacrolimus was associated with excess mortality and graft loss (22% in combination versus 9% on tacrolimus alone). Many of these patients had evidence of infection at or near the time of death.

In a clinical study in stable liver transplant patients 6-144 months post-liver transplantation and receiving a CNI-based regimen, an increased number of deaths was observed in the group converted to a sirolimus-based regimen compared to the group who was continued on a CNI-based regimen, although the difference was not statistically significant (3.8% versus 1.4%). This study was terminated by the Sponsor.

Although heart and liver transplants are different than de novo kidney transplant patients, the signal of increased mortality with everolimus 3.0 mg and sirolimus in combination with CsA or tacrolimus, observed in these other studies is consistent with Study A2309 and the known effects of the M-TOR inhibitors.

Another interesting observation in the assessment of the deaths was the high occurrence of wound complications among the patients who died in both of the everolimus groups. Although it is difficult to explain the association between this high occurrence of wound complications among the patients who died in both of the everolimus groups it is almost certain that there is a trend. In the everolimus 1.5 mg group 5 of the 7 patients who died, in the everolimus 3.0 mg group 4 of the 10 patients who died developed wound related complications sometime after the transplant surgery compared to 1 out of 6 patients who died in the Myfortic group. Wound complications observed in the everolimus groups may be a surrogate for the patient's intolerance to the study drug. This association is explained in more detail in the section of the review regarding wound complications.

** In another study of Sirolimus (M-TOR inhibitor) conversion in stable liver transplant patients, study 314 the applicant (Wyeth) found an association between the Cmin of Sirolimus and the occurrence of pneumonia. This study was terminated early due to excessive number of deaths in the Sirolimus conversion group.*

Death Reported Beyond the Initial 12 Month Analysis Period

The data in the NDA resubmission covers the period of April 24 through June 30, 2009 (12-month data analysis). However, the study is still ongoing and 5 additional deaths occurred beyond the 12 month analysis period. These deaths were included in the NDA resubmission, but not included as part of the 12-month analysis (patients 0304-00016, 0361-00002, 0517-00004, 0305-00004, and 553-00002). In addition after the NDA resubmission, there was one death (0181-00011) reported separately to FDA as a part of the applicant's commitment to provide periodic safety updates in this continuing study. These six additional deaths are summarized in Table 19.

Among these deaths of particular importance is the 47 year old male patient (0304-00016) in the everolimus 1.5 mg group who eventually died of pneumonia and septic shock on Day 436 after a series of events. This patient developed dyspnea starting day 316 and was diagnosed to have alveolar proteinosis by lung biopsy on Day 370. His condition gradually deteriorated until his death on Day 436. Alveolar proteinosis is a rare but potentially serious event associated with M-TOR inhibitors and is probably the primary cause of death in this patient. These deaths are summarized in Table 29 below:

**Table 29. Deaths Reported After the Initial 12 Month Study Period
 All Treatment Groups**
 (Source: Adapted by the Reviewer from Section 12.3 of the CSR)

Patient	Day of Death	Day of D/C Study Medication	Relevant History	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
Everolimus 1.5 mg					
0304-00016 (M, 47, A)	436	435 (septic shock)	D316: dyspnea D370: Lung biopsy, alveolar proteinosis D434: pneumonia, septic shock	Septic shock	Alveolar proteinosis, pneumonia, septic shock
0181-00011 (M, 47, C)	602	496 (Presumptive acute rejection)	D434: Ao. valve incompetence: valve replacement. Warfarin D486: coronary by pass D494: Acute Rejection D499: Resp. failure, intubation, dialysis D505: mitral insufficiency. Valve replacement D600: endocarditis	Endocarditis Sepsis Circulatory Failure Mitral valve Failure	Endocarditis Sepsis Circulatory Failure Mitral valve Failure
Everolimus 3.0 mg					
0361-00002 (F, 39, C)	528	528 (death)	D366: hematuria after biopsy done for proteinuria (UP/UC: 79 mg/mmol) D528: malaise, death.	Presumed AMI	Presumed AMI
Myfortic					
0517-00004 (M, 67, B)	755 (After 24 month study period)	732 (completed study)	D570: suspected acute rejection D733: chest pain, nausea vomiting (feculent matter), cardiac arrest. ECG: A. fib., possible inferior and anterolateral subendocardial injury.	Cardiac arrest	Myocardial infarction?
0305-00004 (F, 32, A)	594	490 (Switched to Tacrolimus)	D420: Increased serum creatinine, acute rejection, treated with corticosteroids and Tacrolimus. According to the narrative tacrolimus was started without discontinuing CsA D 560: cough, chills pyrexia, hospitalized, diagnosed with Pneumocystis Jiroveci pneumonia	Pneumocystis Jiroveci pneumonia	Pneumocystis Jiroveci pneumonia
0553-00002 (M, 48, C)	535	522	D 503: peripheral neuropathy, acute renal failure D508: diarrhea, fever, dehydration, Myfortic dose increased, diarrhea worsened D522: double vision, nystagmus, encephalitis	West Nile virus infection	West Nile virus infection

Patient	Day of Death	Day of D/C Study Medication	Relevant History	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
			D525: positive for West Nile virus thought to contribute to kidney injury		

Reviewer's Comment:

Although these deaths occurred beyond the 12 month study period and it is not possible to make a numerical comparison across the treatment groups with regard to these deaths still they are discussed to point to the causality association between everolimus and the death of especially patient 0304-00016 in the everolimus 1.5 mg group.

In the everolimus 1.5 mg group:

Patient 0304-00016: This 47 year old male patient died due to pneumonia and septic shock 60 days after a biopsy confirmed diagnosis of alveolar proteinosis which in the Reviewer's opinion caused the pneumonia and is the real cause of death. Alveolar proteinosis is a class effect of M-TOR inhibitors.

In the everolimus 3.0 mg group:

Patient 0181-00011 who had multiple cardiac problems also developed pancreatitis on Day 209 which was attributed to hyperparathyroidism but could also be related to everolimus since M-TOR inhibitors are known to cause pancreatitis. Novartis has reported an incidence of pancreatitis over 1% in their database.

Pancreatitis which developed on Day 209 in this patient (0181-0001) probably has little association with the death event if any, on Day 602 but may have contributed to the overall decline of the patient.

In the Myfortic group:

A total of 3 additional deaths were reported after the 12 month study period:

Patient 0517-00004 died on Day 755 after he has completed the 2 year study period and 23 days after the last dose of the study medication.

Patient 0305-00004 was switched to another CNI inhibitor, a generic formulation of tacrolimus 100 days before her death and there was a period of overlap approximately 1 month or longer in duration while the patient was receiving two different CNIs (CsA and tacrolimus) at the same time. The 100 day period

between the discontinuation of the study medication and the death event and the fact that this patient two different CNIs at the same time for a considerable period makes it very difficult to find any causality or attributability association between the study medication and the death event.

Patient 0553-00002 who died of West Nile virus infection on D 535 started to have symptoms of this infection including peripheral neuropathy starting D 503 but the correct diagnosis was made on D 525, 22 days after the start of significant symptoms. During the delayed diagnosis period the dose of Myfortic was increased probably thinking that the symptoms were due to rejection which further deteriorated the condition of the patient. In this case although the study medication may have contributed to the patient's death the element of misdiagnosis and the consequent increase in immunosuppression must be taken into account. It is also important to note that the West Nile virus infection is not an opportunistic infection though it may have a more severe course in immunosuppressed patients and possibly transmitted by mosquitoes.

The overall conclusion for the deaths reported after the 12 month study period again in the Myfortic group we see less association between the deaths and the study medication and the reviewer believes that it may not be justified to include patient 0517-00004 in the Myfortic group in this discussion since the death occurred after the 2 year study period was over.

7.3.2 Serious Adverse Events

Across the three groups, the highest incidence of SAEs, including fatal and non-fatal, are in the everolimus 3.0 mg group (60%) followed by the everolimus 1.5 mg group (57%) and the Myfortic group (54%). Most common SAEs are in the infections and infestations group in all three groups.

SAEs which had an incidence of $\geq 1.5\%$ and clinically important SAEs are included in Table 30 and discussed following the table. Adverse events which are known to be related to the M-TOR class of drugs are also included in the table and in the discussion, although they may not reach an incidence of 1.5% in any treatment group. These adverse events which are known to be related to the M-TOR class of drugs include:

- Thrombocytopenia, Thrombotic Thrombocytopenic Purpura (TTP), Thrombotic Microangiopathy (TMA), Hemolytic Uremic Syndrome (HUS)
- Ulcerative esophagitis
- All thrombotic events
- Edema and fluid collections/lymphocele
- Wound related events

- Hyperlipidemia
- Diabetes and related terms
- Focal glomerulosclerosis (FGS), focal segmental glomerulosclerosis (FSGS) and rapidly progressive glomerulonephritis (RPGN)
- Alveolar proteinosis and related terms (interstitial lung disease, lung infiltration)

In addition, equivalent and similar preferred terms for the same SAE are also included (i.e., acute myocardial infarction, myocardial infarction, acute coronary syndrome, coronary artery occlusion). General terms like “infection” which is not informative of the type and localization of the infection are not included. SAEs like appendicitis, tonsillitis, chronic sinusitis which occurred only in one patient have a very low probability of being drug related are not included.

In the infections and infestations section which has the highest occurrence of SAEs in all three groups all the sepsis and equivalent terms are included due to their clinical significance.

Within each System Organ Class (SOC) the related preferred terms (PTs) are grouped together for easy comparison and SAEs with less than 1.5% occurrence are in *italics*.

Table 30. Number (%) of Patients with SAEs ≥ 1.5% per Treatment Group and Clinically Important SAEs *

Source: Table 12-14 on page 189 of the Clinical Study Report

**(A patient with multiple occurrences of an event is counted only once in the SAE category. A patient with multiple events within a primary system organ class is counted only once in the total row)*

Within each System Organ Class (SOC) the related preferred terms are grouped together for easy comparison and SAEs with less than 1.5% occurrence are in italics.

Primary System Organ Class Preferred Term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
Any SAE	155 (56.6)	168 (60.4)	147 (53.8)
Blood and lymphatic system disorders (total)	11 (4.0)	10 (3.6)	8 (2.9)
Anemia	2 (0.7)	5 (1.8)	2 (0.7)
<i>Hemolysis</i>	<i>1 (0.4)</i>	<i>0 (0.0)</i>	<i>0 (0.0)</i>
<i>Hemolytic anemia</i>	<i>1 (0.4)</i>	<i>0 (0.0)</i>	<i>0 (0.0)</i>
<i>Hemolytic uremic syndrome</i>	<i>1 (0.4)</i>	<i>0 (0.0)</i>	<i>0 (0.0)</i>
<i>Thrombocytopenia</i>	<i>2 (0.7)</i>	<i>3 (1.1)</i>	<i>2 (0.7)</i>
<i>Thrombocytopenic purpura</i>	<i>0 (0.0)</i>	<i>1 (0.4)</i>	<i>0 (0.0)</i>
<i>TTP and TMA^s</i>	<i>2 (0.7)</i>	<i>1 (0.4)</i>	<i>0 (0.0)</i>
Cardiac disorders (total)	11 (4.0)	15 (5.4)	11 (4.0)
<i>Acute coronary syndrome</i>	<i>0 (0.0)</i>	<i>1 (0.4)</i>	<i>0 (0.0)</i>
<i>Acute myocardial infarction</i>	<i>0 (0.0)</i>	<i>2 (0.7)</i>	<i>0 (0.0)</i>
Myocardial infarction	0 (0.0)	5 (1.8)	2 (0.7)

Primary System Organ Class Preferred Term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
<i>Angina Pectoris</i>	2 (0.7)	0 (0.0)	0 (0.0)
<i>Coronary artery occlusion</i>	0 (0.0)	3 (1.1)	0 (0.0)
Gastrointestinal disorders (total)	21 (7.7)	28 (10.1)	18 (6.6)
Diarrhea	1 (0.4)	6 (2.2)	1 (0.4)
Vomiting	2 (0.7)	7 (2.5)	4 (1.5)
<i>Esophagitis ulcerative</i>	1 (0.4)	0 (0.0)	0 (0.0)
<i>Esophagitis hemorrhagic</i>	1 (0.4)	0 (0.0)	0 (0.0)
<i>Upper gastrointestinal hemorrhage</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Mesenteric vessel thrombosis</i>	0 (0.0)	1 (0.4)	0 (0.0)
General disorders and administration site conditions (total)	15 (5.5)	25 (9.0)	12 (4.4)
<i>Implant site effusion</i>	1 (0.4)	1 (0.4)	0 (0.0)
<i>Edema</i>	0 (0.0)	1 (0.4)	0 (0.0)
Edema peripheral	1 (0.4)	6 (2.2)	0 (0.0)
Pyrexia	7 (2.6)	12 (4.3)	10 (3.7)
Immune system disorders (total)	4 (1.5)	2 (0.7)	6 (2.2)
Kidney transplant rejection	3 (1.1)	2 (0.7)	4 (1.5)
Infections and infestations (total)	54 (19.7)	74 (26.6)	69 (25.3)
<i>Abdominal sepsis</i>	1 (0.4)	0 (0.0)	0 (0.0)
Sepsis	3 (1.1)	5 (1.8)	5 (1.8)
<i>Bacteremia</i>	3 (1.1)	3 (1.1)	1 (0.4)
<i>Septic shock</i>	1 (0.4)	1 (0.4)	0 (0.0)
Pyelonephritis	4 (1.5)	5 (1.8)	2 (0.7)
Urinary tract infection	18 (6.6)	16 (5.8)	19 (7.0)
Pneumonia	5 (1.8)	10 (3.6)	8 (2.9)
CMV infection	0 (0.0)	0 (0.0)	9 (3.3)
Herpes zoster	1 (0.4)	5 (1.8)	4 (1.5)
Upper resp. tract infection	2 (0.7)	2 (0.7)	6 (2.2)
Gastroenteritis	6 (2.2)	3 (1.1)	6 (2.2)
Injury, poisoning and procedural complications (total)	39 (14.2)	47 (16.9)	32 (11.7)
<i>Abdominal wound dehiscence</i>	0 (0.0)	1 (0.4)	1 (0.4)
<i>Wound complication</i>	1 (0.4)	1 (0.4)	0 (0.0)
<i>Wound dehiscence</i>	2 (0.7)	3 (1.1)	1 (0.4)
<i>Wound secretion</i>	1 (0.4)	1 (0.4)	0 (0.0)
<i>Incisional hernia</i>	2 (0.7)	1 (0.4)	0 (0.0)
<i>Incisional hernia, obstructive</i>	0 (0.0)	0 (0.0)	1 (0.4)
<i>Perinephric collection</i>	1 (0.4)	4 (1.4)	1 (0.4)
<i>Renal lymphocele</i>	0 (0.0)	1 (0.4)	1 (0.4)
<i>Seroma</i>	0 (0.0)	2 (0.7)	0 (0.0)

Primary System Organ Class Preferred Term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
Perirenal hematoma	2 (0.7)	2 (0.7)	4 (1.5)
Post procedural hemorrhage	3 (1.1)	0 (0.0)	1 (0.4)
Post procedural hematoma	0 (0.0)	1 (0.4)	0 (0.0)
Renal hematoma	0 (0.0)	1 (0.4)	0 (0.0)
Post procedural urine leak	2 (0.7)	4 (1.4)	2 (0.7)
Complications of transplanted kidney	8 (2.9)	4 (1.4)	5 (1.8)
Renal graft loss*	2 (0.7)	2 (0.7)	3 (1.1)
Graft loss*	5 (1.8)	8 (2.9)	3 (1.1)
Investigations (total)	23 (8.4)	21 (7.6)	22 (8.1)
Blood creatinine increased	19 (6.9)	18 (6.5)	18 (6.6)
Metabolism and nutrition disorders (total)	20 (7.3)	23 (8.3)	13 (4.8)
Dehydration	6 (2.2)	5 (1.8)	4 (1.5)
Diabetes mellitus	3 (1.1)	3 (1.1)	1 (0.4)
Diabetic foot	1 (0.4)	0 (0.0)	0 (0.0)
Diabetic ketoacidosis	0 (0.0)	0 (0.0)	1 (0.4)
Hyperglycemia	1 (0.4)	7 (2.5)	1 (0.4)
Hypoglycemia	0 (0.0)	1 (0.4)	1 (0.4)
Hyperlipidemia	1 (0.4)	0 (0.0)	0 (0.0)
Malnutrition	2 (0.7)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue Disorders (total)	5 (1.8)	3 (1.1)	1 (0.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps) (total)	4 (1.5)	3 (1.1)	5 (1.8)
Nervous system disorders (total)	6 (2.2)	7 (2.5)	5 (1.8)
Psychiatric disorders (total)	3 (1.1)	1 (0.4)	0 (0.0)
Renal and urinary disorders (total)	28 (10.2)	37 (13.7)	36 (13.2)
Hematuria	5 (1.8)	4 (1.4)	4 (1.5)
Hydronephrosis	2 (0.7)	2 (0.7)	6 (2.2)
Renal failure acute	6 (2.2)	4 (1.4)	5 (1.8)
Renal impairment	6 (2.2)	2 (0.7)	1 (0.4)
Ureteric obstruction	1 (0.4)	0 (0.0)	6 (2.2)
Focal glomerulosclerosis	0 (0.0)	1 (0.4)	0 (0.0)
Focal segmental glomerulosclerosis	0 (0.0)	1 (0.4)	1 (0.4)
Glomerulonephritis rapidly progressive	0 (0.0)	1 (0.4)	0 (0.0)

Primary System Organ Class Preferred Term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
<i>Proteinuria</i>	2 (0.7)	4 (1.4)	0 (0.0)
<i>Nephrotic syndrome</i>	0 (0.0)	1 (0.4)	0 (0.0)
Reproductive system and breast disorders	3 (1.1)	1 (0.4)	0 (0.0)
Respiratory, thoracic and mediastinal disorders (total)	9 (3.3)	18 (6.5)	8 (2.9)
<i>Alveolar proteinosis</i>	1 (0.4)	0 (0.0)	0 (0.0)
<i>Interstitial lung disease</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Lung infiltration</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Dyspnea</i>	2 (0.7)	9 (3.2)	3 (1.1)
<i>Respiratory arrest</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Respiratory distress</i>	0 (0.0)	0 (0.0)	2 (0.7)
<i>Respiratory failure</i>	1 (0.4)	0 (0.0)	0 (0.0)
<i>Acute respiratory failure</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Pleural effusion</i>	2 (0.7)	1 (0.4)	0 (0.0)
<i>Pulmonary edema</i>	1 (0.4)	2 (0.7)	0 (0.0)
<i>Acute Pulmonary edema</i>	0 (0.0)	1 (0.4)	0 (0.0)
Vascular disorders (total)	26 (9.5)	28 (10.1)	20 (7.3)
<i>Deep vein thrombosis</i>	6 (2.2)	3 (1.1)	4 (1.5)
<i>Thrombosis</i>	1 (0.4)	0 (0.0)	0 (0.0)
<i>Venous thrombosis limb</i>	1 (0.4)	0 (0.0)	0 (0.0)
<i>Subclavian vein thrombosis</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Lymphocele</i>	14 (5.1)	15 (5.4)	7 (2.6)
<i>Lymphorrhea</i>	2 (0.7)	0 (0.0)	0 (0.0)

* Not all of the graft losses are reported as SAEs. In the safety analysis of the ITT population there are 12 graft losses in the everolimus 1.5 mg group, 14 graft losses in the everolimus 3.0 mg group and 8 graft losses in the Myfortic group but only 7, 10 and 6 respectively are reported as SAEs.

SAEs in the following SOCs were reported at a higher rate in the everolimus 1.5 mg group compared to the Myfortic group:

- Blood and lymphatic system disorders, (4% vs. 2.9%)
- Gastrointestinal disorders (7.7% vs. 6.6%)
- General disorders and administration site conditions (5.5% vs. 4.4%)
- Injury, poisoning and procedural complications (14.2% vs. 11.7%)
- Investigations (8.4% vs. 8.1%)
- Metabolism and nutrition disorders (7.3% vs. 4.8%)
- Musculoskeletal and connective tissue disorders (1.8% vs. 0.4%)
- Nervous system disorders, psychiatric disorders (2.2% vs. 1.8%)

- Psychiatric disorders (1.1% vs. 0%)
- Reproductive system and breast disorders (1.1% vs. 0%)
- Respiratory, thoracic and mediastinal disorders (3.3% vs. 2.9%)
- Vascular disorders (9.5% vs. 7.3%)

The incidence of SAEs in the everolimus 3.0 mg group was higher than in the Myfortic group in all of the SOC, except for Investigations and Neoplasms.

SAEs in the following SOC were higher in the Myfortic group compared to the everolimus 1.5 mg group:

- Infections and infestations (25.3% vs. 19.7%)
- Neoplasms (1.8% vs. 1.5%)
- Renal and urinary disorders (13.2% vs. 10.2%)

The higher incidence of SAEs in the renal and urinary disorders SOC in the Myfortic group is driven by the high incidence of hydronephrosis and ureteric obstruction (both 2.2%) in the Myfortic group, which may be related to surgical technique.

7.3.2.1 *Graft Losses*

According to the study protocol, graft loss was reported as a SAE.

The number of graft losses was 12 (4.3%) in the everolimus 1.5 mg group, 14 (5.0%) in the everolimus 3.0 mg group and 8 (2.9%) in the Myfortic group over the 12 month study period as shown in Table 31 through Table 33. One patient (0543-00007) with a graft loss in the Myfortic group never received the study drug and is not included in the safety population, but is included in the ITT population. As a consequence, there were nine graft losses in the Myfortic group in the efficacy analysis but only eight graft losses in the safety analysis. The most frequent cause of graft loss was renal artery thrombosis in the everolimus groups whereas the causes are more evenly distributed in the Myfortic group. Three patients died after they lost their grafts: one in the everolimus 1.5 mg group (0114-00001) and the other two in the everolimus 3.0 mg group (0115-00020 and 0168-00017).

Applicant's Analysis of Graft Losses

According to the applicant's analysis, using verbatim terms reported by the investigators, the number of graft losses due to renal artery thrombosis was four in the everolimus 1.5 mg group, one in the everolimus 3.0 mg group and one in the Myfortic group. Also one graft in the everolimus 1.5 mg group was lost due to renal vein thrombosis. The distribution of other causes like infarcted kidney, acute rejection and chronic rejection are listed in Table 31 through Table 33 for each of the treatment groups

Reviewer's Assessment of Graft Losses

According to FDA's analysis, one patient (0102-00005) in the everolimus 1.5 mg group whose cause of graft failure is listed as "other" by the investigator was presumed to have lost his graft due to renal vein thrombosis. Also three patients in the everolimus 3.0 mg group whose cause of graft loss was listed as infarcted kidney (0115-00006, and 0520-00019) or acute rejection (0166-00020) and one patient in the Myfortic group (0166-00008) were assessed to have lost their grafts due to renal artery thrombosis, according to the FDA's interpretation of the patient narratives. Another patient (0118-00009) in the Myfortic group who was listed with a diagnosis of infarcted kidney as the cause of graft loss as per the investigator was determined to have lost her graft due to renal artery rupture and consequent hematoma.

Despite these differences in use of terms, the Applicant and the FDA are in agreement regarding the number of graft losses in the study, as shown in Tables 31 through 33: 12 in the everolimus 1.5 mg group, 14 in the everolimus 3.0 mg group, and 8 in the Myfortic group.

Table 31. Graft Loss by 12 Month Analysis Everolimus 1.5 mg Group
 (Source: Table 12-18, page 197 of CSR)

Everolimus 1.5 mg, 12 graft losses				
(Applicant: 4 renal artery thrombosis, 1 renal vein thrombosis, 1 other)				
(FDA: 4 renal artery thrombosis, 2 renal vein thrombosis)				
Patient No. (Age, sex)	Day of graft loss (Day of death)	Day of last dose of medication	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
0124-00048 (46, M)	4	4	Renal artery thrombosis	Renal artery thrombosis
0501-00020 (54, F)	11	11	Renal artery thrombosis	Renal artery thrombosis
0515-00004 (58, M)	55	55	Renal artery thrombosis	Renal artery thrombosis
0543-00014 (24, F)	8	9	Renal artery thrombosis	Renal artery thrombosis
0102-00005 (59, M)	4	4	Other (Renal vein thrombosis)	Renal vein thrombosis
0115-00020 (43, F)	7 (28)	9	Renal vein thrombosis	Renal vein thrombosis
0192-00002 (32, M)	116	116	Acute Rejection	Thrombotic thrombocytopenic purpura (TTP)
0511-00019 (67, M)	185	135	Other	Proliferative glomerulonephritis
0200-00008 (64, F)	54	54	Other	Acute rejection
0122-00004 42, M	215	12	Chronic rejection	Chronic rejection
0553-00016 (25, F)	366	206	Chronic rejection	Chronic rejection
0510-00001 (48, M)	31	31	Primary non-function	Primary non-function

Table 32. Graft Loss by 12 Month Analysis Everolimus 3.0 mg Group
 (Source: Table 12-18, page 197 of CSR)

Everolimus 3.0 mg, 14 graft losses				
(Applicant: 1 Renal artery thrombosis, 2 infarcted kidneys, 1 PNF)				
(FDA: 4 Renal artery thrombosis, 1 PNF/Renal artery thrombosis?)				
Patient No. (Age, sex)	Day of graft loss (Day of death)	Day of last dose of medication	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
0192-00003 (22, M)	7	8	Renal artery thrombosis	Renal artery thrombosis
0115-00006 (58, F)	7	7	Infarcted kidney	Renal artery thrombosis
0166-00020 (57, F)	14	19	Acute rejection	Renal artery thrombosis
0520-00019 (45, M)	5	25	Infarcted kidney	Renal artery thrombosis
0544-00005 (68, F)	4	4	Primary non-function	Renal artery thrombosis?
0168-00017 (59, M)	13 (34)	24	Acute rejection	Acute rejection
0114-00001 (34, M)	91 (243)	45	Acute rejection	Acute rejection
0161-00001 (52, M)	153	38	Chronic rejection	Chronic rejection
0519-00001 (55, F)	354		Non-compliance	Chronic rejection, UTI
0501-00019 (37, F)	161	161	Chronic rejection	Chronic rejection, pyelonephritis
0168-00015 (43, F)	34	34	Other	urine leak, septic shock,
0528-00008 (66, M)	213	213	Other	<i>E. coli</i> infection and cardiac arrest
0511-00017 (66, M)	50	50	Primary non-function	Primary non-function
0529-00002 (66, M)	108	108	Primary non-function	Primary non-function?

Table 33. Graft Loss by 12 Month Analysis Myfortic Group
 (Source: Table 12-18, page 197 of CSR)

Myfortic, 8 graft losses (Applicant: 1 Renal artery thrombosis, 1 infarcted kidney) (FDA: 2 Renal artery thrombosis)				
Patient No. (Age, sex)	Day of graft loss (Day of death)	Day of last dose of medication	Investigator's Assessment of Attributability	FDA's Assessment of Attributability
0100-00011 (19, M)	1	4	Renal artery thrombosis	Renal artery thrombosis
0166-00008 (55, M)	14	14	Infarcted kidney	Renal artery thrombosis
0118-00009 (44, F)	4	4	Infarcted kidney (Renal artery rupture)	Renal artery rupture
0361-00003 (27, M)	34	34	Urological complications	Urological complications
0501-00008 (62, M)	217	217	Chronic rejection	Chronic rejection
0529-00006 (59, M)	25	28	Acute rejection	Primary non-function
0100-00004 (27, M)	132	132	Primary non-function	Primary non-function
0553-00012 (60, M)	164	153	Non-compliance	Non-compliance

Graft Losses Followed by Death of the Patient

One of the patients with renal vein thrombosis in the everolimus 1.5 mg group died later as a result of the events started by this complication (patient 0114-0001). Please refer to Section on mortality for details.

Renal Artery Thrombosis and Overall Assessment of Graft Losses

FDA and the applicant agreed on the assessment of the number of patients who developed graft thrombosis (artery and vein) and consequently lost their grafts:

- 6 graft thromboses (4 renal artery and 2 renal vein) in the everolimus 1.5 mg group,
- 4 graft thromboses (4 renal artery) with another probable 5th patient again with renal artery thrombosis according to the narrative in the everolimus 3.0 mg group
- 2 graft thromboses (2 renal artery) in the Myfortic group.

Reviewer's Comment: *In the reviewer's assessment one of the patients with renal vein thrombosis in the everolimus 1.5 mg group died later as a result of the events started by this complication. Thrombogenicity is a well known class effect of M-TOR inhibitors.*

Based on a comprehensive analysis taken from United Network for Organ Sharing/United States Renal Disease Study (UNOS/USRDS) data that includes over 84,000 renal transplants, graft thrombosis within 30 days occurs in 0.9% of transplants.⁷ The incidence of graft thrombosis in the everolimus 1.5 mg group within 30 days of transplantation is 1.8% (5/274), and becomes 2.1% (6/274) if patient 0515-00004 who lost his graft on day 55 is included. The same incidences are 1.4% (4/278) in the everolimus 3.0 mg group and 0.7% (2/273) in the Myfortic group.

One patient in the everolimus 1.5 mg group and two patients, who later died, in the everolimus 3.0 mg group lost their grafts due to acute rejection compared to none in the Myfortic group. Two patients in the everolimus 1.5 mg group, three patients in the everolimus 3.0 mg group, and one patient in the Myfortic group lost their grafts due to chronic rejection.

One patient in the everolimus 1.5 mg group (0192-00002) lost his graft due to TTP, a known toxicity of M-TOR inhibitors.

Reviewer's assessment of graft losses:

In the everolimus 1.5 mg group the incidence of early graft thromboses (within 30 days of transplant) is 1.8% and we see the same trend in the everolimus 3.0 mg group with an incidence of 1.4% which are both above the national average and in line with the well known thrombogenic effect of M-TOR inhibitors. Sirolimus, another M-TOR inhibitor which is approved, contains a Boxed Warning for hepatic artery thrombosis (HAT).

This thrombogenic effect of M-TOR inhibitors may be partly due to their adverse effect on the endothelial regeneration which may be affecting the graft vasculature most because of the surgical and the immunologic trauma due to the transplant procedure. From non-clinical studies everolimus is also known to increase fibrinogen levels. This high incidence of graft thrombosis in the everolimus groups is very concerning since it not only resulted in loss of the graft in all instances but also contributed to the death of one patient in the everolimus 1.5 mg group (patient 0115-00020).

Additionally more patients lost their grafts due to acute and chronic rejection in each of the everolimus groups compared to the Myfortic group which raises questions about efficacy although no significant differences between the treatment groups with regard to the incidence of BPAR was found in the efficacy analysis. Although there was no statistically significant difference between the treatment groups numerically more kidney grafts were lost in each of the everolimus groups compared to the Myfortic group.

⁷ Ojo AO, Hanson JA, Wolfe RA, et al. Dialysis modality and the risk of allograft thrombosis in adult renal transplant recipients. *Kidney Int.* 1999;55:1952-1960

7.3.3 Dropouts and/or Discontinuations

During the study, information on study drug discontinuations due to AEs was collected on two different CRFs. The information from the first form (Treatment and Study Completion CRF) is summarized in Table 34. As noted in the table, the overall incidence of study drug discontinuations due to AEs according to this first data collection form were 18.1% in the everolimus 1.5 mg group, 20.4% in the everolimus 3.0 mg group, and 9.4% in the Myfortic group.

**Table 34 Patient disposition – n (%) of patients by treatment group*
(ITT population - 12 month analysis)**

(Source: Adapted from Table 10-, page 138, CSR)

(Discontinuations which are especially higher in the everolimus 1.5 mg group shown in light green)

	Everolimus 1.5 mg, n (%)	Everolimus 3.0 mg, n (%)	Myfortic 1.44 gm, n (%)
Total no. of patients	277 (100)	279 (100)	277 (100)
Completed study medication	194 (70.0)	184 (65.9)	217 (78.3)
Completed study phase	239 (86.3)	246 (88.2)	249 (89.9)
Discontinued study medication	83 (30.0)	95 (34.1)	60 (21.7)
Adverse events	50 (18.1)	57 (20.4)	26 (9.4)
Abnormal lab values	1 (0.4)	4 (1.4)	1 (0.4)
Abnormal test procedure	0 (0.0)	1 (0.4)	0 (0.0)
Unsatisfactory Therapeutic effect	11 (4.0)	14 (5.0)	13 (4.7)
Protocol deviation	2 (0.7)	5 (1.8)	2 (0.7)
Subject withdrew consent	11 (4.0)	4 (1.4)	5 (1.8)
Administrative problems	2 (0.7)	1 (0.4)	2 (0.7)
Death	3 (1.1)	3 (1.1)	4 (1.4)
Graft loss	3 (1.1)	6 (2.2)	6 (2.2)
Did not receive study drug	0 (0.0)	0 (0.0)	1 (0.4)
Discontinued study	38 (13.7)	33 (11.8)	28(10.1)
Subject withdrew consent	20 (7.2)	8 (2.9)	12 (4.3)
Death	7 (2.5)	9 (3.2)	6 (2.2)
Graft loss	9 (3.2)	10 (3.6)	7 (2.5)
Other	2 (0.7)	6 (2.2)	3 (1.1)

The information collected on the second form (AE/infections CRF) was more specific and contained information about the type of AE leading to study drug discontinuation.

According to the second form, the rates of discontinuation were 23.4% in the everolimus 1.5 mg group, 28.4% in the everolimus 3.0 mg group and 15.8% in the Myfortic group. It was assumed that the information obtained from the second form would be more accurate and detailed; therefore this information is utilized for the analysis of AEs leading to drug discontinuation in Table 35. In the table, discontinuations $\geq 1\%$ per treatment group and clinically relevant SAEs related to class toxicities of M-TOR inhibitors and MPA are included.

Adverse events leading to study drug discontinuation in the following SOCs were more frequently reported in the everolimus 1.5 mg group than the Myfortic group:

- Blood and lymphatic system disorders
- Investigations (including the preferred term of increased blood creatinine and others);
- Injury, poisoning and procedural complications (including the preferred term of therapeutic agent toxicity, etc.);
- Renal and urinary disorders (proteinuria etc.); and
- Vascular disorders

Infections and infestations, and gastrointestinal disorders were the only SOCs where there were more discontinuations in the Myfortic group compared to the everolimus 1.5 mg group. However, the rate of discontinuation in both of these SOCs was higher in the everolimus 3.0 mg group than the Myfortic group.

Table 35. Number (%) of Patients with Adverse Events (AEs) Leading to Study Drug Discontinuation *

(Source: Table 12-5 on page 173 of CSR)

**(A patient with multiple occurrences of an AE/infection is counted only once in the AE category. A patient with multiple AEs/infections within a primary system organ class is counted only once in the total row.)*

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 gm N=273
	n (%)	n (%)	n (%)
Any AE leading to study drug discontinuation	64 (23.4)	79 (28.4)	43 (15.8)
Blood and lymphatic system disorders	7 (2.6)	2 (0.7)	3 (1.1)
Anemia	1 (0.4)	0 (0.0)	0 (0.0)
Leucopenia	1 (0.4)	0 (0.0)	2 (0.7)
Thrombocytopenia	0 (0.0)	1 (0.4)	1 (0.4)
TTP and TMA	2 (0.7)	2 (0.7)	0 (0.0)
Cardiac disorders	2 (0.7)	4 (1.4)	1 (0.4)
Gastrointestinal disorders	3 (1.1)	7 (2.5)	6 (2.2)
Hemorrhagic esophagitis	1 (0.4)	0 (0.0)	0 (0.0)
Ulcerative esophagitis	1 (0.4)	0 (0.0)	0 (0.0)

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 gm N=273
	n (%)	n (%)	n (%)
General disorders and administration site conditions	4 (1.5)	1 (0.4)	1 (0.4)
Death	0 (0.0)	0 (0.0)	1 (0.4)
Edema peripheral	3 (1.1)	1 (0.4)	0 (0.0)
Immune system disorders	3 (1.1)	0 (0.0)	3 (1.1)
Kidney transplant rejection	2 (0.7)	0 (0.0)	3 (1.1)
Infections and infestations	4 (1.5)	17 (6.1)	8 (2.9)
Pyelonephritis & renal abscess	0 (0.0)	3 (1.0)	0 (0.0)
Wound infection & abscess	0 (0.0)	6 (2.2)	0 (0.0)
Wound secretion	0 (0.0)	1 (0.4)	0 (0.0)
Injury, poisoning and procedural complications	14 (5.1)	20 (7.2)	6 (2.2)
Graft loss	2 (0.7)	6 (2.2)	3 (1.1)
Therapeutic agent toxicity	5 (1.8)	2 (0.7)	0 (0.0)
Wound dehiscence & impaired healing	1 (0.4)	6 (2.2)	0 (0.0)
Investigations	9 (3.3)	10 (3.6)	6 (2.2)
Blood creatinine increased	8 (2.9)	9 (3.2)	2 (0.7)
Metabolism and nutrition disorders	4 (1.5)	1 (0.4)	1 (0.4)
Musculoskeletal and connective tissue disorders	2 (0.7)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.4)	1 (0.4)	0 (0.0)
Nervous system disorders	0 (0.0)	2 (0.7)	1 (0.4)
Renal and urinary disorders	11 (4.0)	18 (6.5)	10 (3.7)
Focal segmental glomerulosclerosis	0 (0.0)	3 (1.1)	0 (0.0)
Nephropathy toxic	1 (0.4)	3 (1.1)	3 (1.1)
Proteinuria	2 (0.7)	4 (1.4)	0 (0.0)
Reproductive system and breast disorders	1 (0.4)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	2 (0.7)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	2 (0.7)	1 (0.4)
Vascular disorders	3 (1.1)	4 (1.4)	2 (0.7)
Lymphocele	3 (1.1)	4 (1.4)	0 (0.0)

** *Thrombotic thrombocytopenic purpura (TTP), Thrombotic microangiopathy (TMA)*

Since this is an open label study it is important to evaluate and compare rates of SAEs and study drug discontinuation due to those SAEs, as an indirect measure of whether there was any investigator bias for or against the investigational everolimus regimen compared to the approved control regimen, which may have resulted in differential discontinuations for the same type of event. To assess for this possible bias, FDA compared the drug discontinuation rates to SAE rates, since SAEs would be expected to result in drug discontinuations in many cases.

As seen in Table 36 below, while the incidence of SAEs by SOC for the everolimus 1.5 mg group or Myfortic group ranged from 2.9% to 25.3%, the rate of drug discontinuations for these events is noticeably lower, ranging from 0.4% to 5.1%. Thus, although there was a range of SAEs reported, some were managed with discontinuation of drug, while others were presumably managed by other measures, potentially including dose reduction. One can also compare that for some SAEs, close to half the patients reporting SAEs had drug discontinued (e.g., Blood and Lymphatic System Disorders), while for others SOCs about 1/10th of the patients with SAE had drug discontinued (e.g., Infections and Infestations). And finally, consistent with Table 24 and 26, for many of the SOC categories, proportionally more everolimus patients with SAE discontinued drug than Myfortic patients (e.g., Investigations/blood creatinine increased, Renal Urinary Disorders).

Table 36. Comparative Study Drug Discontinuation Rates Due to AEs in Relation to the Incidence of SAEs in the Same Category

System Organ Class Preferred Term resulting in Study Drug Discontinuation	Everolimus 1.5 mg		Myfortic	
	Drug Discontinuation (%)	Incidence of SAE (%)	Drug Discontinuation (%)	Incidence of SAE (%)
Blood and Lymphatic System Disorders	2.6	4.0	1.1	2.9
Cardiac Disorders	0.7	4.0	0.4	4.0
Gastrointestinal Disorders	1.1	7.7	2.2	6.6
General disorders and administration site conditions (total)	1.5	5.5	0.4	4.4
<i>Edema peripheral</i>	1.1	0.4	0.0	0.0
Infections and Infestations	1.5	19.7	2.9	25.3
Injury, Poisoning and Procedural Complications	5.1	14.2	2.2	11.7
Investigations	3.3	8.4	2.2	8.1
<i>Blood creatinine increased</i>	2.9	6.9	0.7	6.6
Metabolism and Nutrition Disorders	1.5	7.3	0.4	4.8
Renal and Urinary Disorders	4.0	10.2	3.7	13.2
Vascular Disorders	1.1	9.5	0.7	7.3

Reviewer's Comments: According to the analysis of patients with adverse events leading to study drug discontinuation again more patients in the everolimus 1.5 mg group discontinued the study medication because of adverse events compared to the Myfortic group (23.4% vs. 15.8%). Discontinuations were even higher in the everolimus 3.0 mg group (28.4).

Injury, poisoning and procedural complications which includes wound healing problems and investigations for blood creatinine increases were more common in both of the everolimus groups compared to the Myfortic group. The incidence of infections as a cause for drug discontinuation in the 3.0 mg everolimus group was twice as high as in the Myfortic group while this incidence in the 1.5 mg group was lower compared to the Myfortic group. 6 patients in the everolimus 3.0 mg

discontinued the study drug due to wound abscess and wound infections while this number was "0" in the other two groups.

Graft loss, focal segmental glomerulosclerosis, toxic nephropathy and proteinuria were more frequently reported as a reason for discontinuation in the 3.0 mg group than the 1.5 mg group. Blood and lymphatic system disorders, increased blood creatinine, therapeutic agent toxicity, proteinuria peripheral edema, and lymphocele were more frequently reported as AEs leading to study drug discontinuation in the 1.5 mg everolimus treatment group than the Myfortic 1.44 gm group. Therapeutic agent toxicity was always related to CsA according to the investigators' recording of adverse events. Infections and infestations, leukopenia and gastrointestinal disorders were the only causes that resulted in more discontinuations in the Myfortic group compared to any of the everolimus groups.

In contrast, as stated in the following paragraphs and also as shown in Table 37. AEs requiring an adjustment or interruption to treatment were reported in 22.3% of patients in the everolimus 1.5 mg group, 27.0% of patients in the everolimus 3.0 mg group, and 34.8% of patients in the Myfortic group. This higher incidence of dose adjustment/interruption in the Myfortic group was mainly due to the higher incidence of adjustment or interruption in blood and lymphatic system disorders (11.4% in the Myfortic group vs. 3.6% in the everolimus 1.5 mg group and 4.3% in the everolimus 3.0 mg group), gastrointestinal disorders (11.0% in the Myfortic group vs. 2.6% in the everolimus 1.5 mg group and 2.9% in the everolimus 3.0 mg group) and infections and infestations (13.6% in the Myfortic group vs. 4.4% in the everolimus 1.5 mg group and 7.2% in the everolimus 3.0 mg group). This may partly be explained by the high incidence of gastrointestinal adverse effects and leukopenia associated with MPA which usually requires frequent dose adjustments and interruptions in clinical practice. Modification of study medication dose due to renal and urinary disorders and metabolism and nutrition disorders was more frequent in everolimus groups compared to Myfortic, with a dose response effect indicated.

Table 37. Number (%) of Patients with Adverse Events Leading to Study Drug Dose Adjustment/Interruption ($\geq 1\%$ per treatment group) (Safety population - 12 month analysis)

**(A patient with multiple occurrences of an AE/infection is counted only once in the AE category. A patient with multiple AEs/infections within a primary system organ class is counted only once in the total row)*

Reproduced from Table 12-6 on page 194 of the applicant's Clinical Study Report for Study A2309 in the NDA resubmission

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 gm N=273
	n (%)	n (%)	n (%)
Any AE leading to dose adjustment/interruption	61 (22.3)	75 (27.0)	95 (34.8)
Blood and lymphatic system disorders	10 (3.6)	12 (4.3)	31 (11.4)
Anemia	1 (0.4)	3 (1.1)	4 (1.5)
Leucopenia	4 (1.5)	4 (1.4)	23 (8.4)
Thrombocytopenia	3 (1.1)	5 (1.8)	3 (1.1)
Cardiac disorders	0 (0.0)	1 (0.4)	1 (0.4)
Ear and labyrinth disorders	1 (0.4)	0 (0.0)	0 (0.0)
Eye disorders	0 (0.0)	0 (0.0)	1 (0.4)
Gastrointestinal disorders	7 (2.6)	8 (2.9)	30 (11.0)
Abdominal pain	0 (0.0)	1 (0.4)	3 (1.1)
Diarrhea	1 (0.4)	1 (0.4)	14 (5.1)
Nausea	1 (0.4)	0 (0.0)	4 (1.5)
Vomiting	1 (0.4)	2 (0.7)	4 (1.5)
General disorders and administration site conditions	3 (1.1)	6 (2.2)	3 (1.1)
Impaired healing	0 (0.0)	3 (1.1)	0 (0.0)
Edema peripheral	3 (1.1)	0 (0.0)	0 (0.0)
Pyrexia	0 (0.0)	1 (0.4)	3 (1.1)
Hepatobiliary disorders	1 (0.4)	0 (0.0)	0 (0.0)
Immune system disorders	3 (1.1)	1 (0.4)	1 (0.4)
Infections and infestations	12 (4.4)	20 (7.2)	37 (13.6)
BK virus infection	0 (0.0)	1 (0.4)	3 (1.1)
Cytomegalovirus infection	0 (0.0)	0 (0.0)	7 (2.6)
Cytomegalovirus viremia	0 (0.0)	0 (0.0)	3 (1.1)
Herpes zoster	1 (0.4)	2 (0.7)	5 (1.8)
Sepsis	0 (0.0)	0 (0.0)	4 (1.5)
Upper respiratory tract infection	1 (0.4)	1 (0.4)	3 (1.1)
Urinary tract infection	5 (1.8)	4 (1.4)	3 (1.1)
Injury, poisoning and procedural complications	3 (1.1)	8 (2.9)	8 (2.9)
Therapeutic agent toxicity	0 (0.0)	2 (0.7)	4 (1.5)
Investigations	12 (4.4)	13 (4.7)	12 (4.4)

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 gm N=273
	n (%)	n (%)	n (%)
Blood creatinine increased	8 (2.9)	8 (2.9)	5 (1.8)
White blood cell count decreased	0 (0.0)	1 (0.4)	3 (1.1)
Metabolism and nutrition disorders	5 (1.8)	6 (2.2)	0 (0.0)
Dyslipidemia	2 (0.7)	4 (1.4)	0 (0.0)
Nervous system disorders	2 (0.7)	2 (0.7)	1 (0.4)
Renal and urinary disorders	6 (2.2)	13 (4.7)	4 (1.5)
Nephropathy toxic	0 (0.0)	4 (1.4)	1 (0.4)
Renal tubular necrosis	1 (0.4)	3 (1.1)	0 (0.0)
Reproductive system and breast disorders	1 (0.4)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	4 (1.4)	1 (0.4)
Skin and subcutaneous tissue disorders	2 (0.7)	3 (1.1)	0 (0.0)
Vascular disorders	5 (1.8)	4 (1.4)	2 (0.7)
Lymphocele	4 (1.5)	1 (0.4)	0 (0.0)

Reviewer's Comment:

As explained in detail above there have been more study drug discontinuations in both of the everolimus groups compared to the Myfortic group due to adverse events. On the contrary study drug dose adjustments and interruptions due to adverse events are more frequent in the Myfortic group compared to the everolimus groups. The applicant is trying to put forward an argument based on this two different set of events which apparently go in the opposite direction.

The argument of the applicant is both the everolimus groups and the Myfortic group have their own weaknesses with regard to tolerability of the study regimen such that everolimus groups have a higher rate of study drug discontinuations but Myfortic group has a higher rate of dose adjustments and interruptions due to adverse events. The reviewer sees the higher rate of dose adjustments and interruptions due to AEs as strength of the Myfortic regimen not as a weakness, it proves the manageability of the Myfortic immunosuppressive regimen. The reviewer, as a physician who has taken care of transplant patients knows that it is very common in clinical practice to adjust the dose or temporarily stop MPA derivatives because of decreases in leukocyte counts or gastrointestinal symptoms like diarrhea, nausea or vomiting which usually are not severe in nature and quickly respond to dose reduction partly due to the shorter half life of MPA (18 hrs). These symptoms almost serve as a surrogate for MPA trough levels and obviate the need for measuring trough levels of MPA derivatives and

allow the physician to easily tailor the immunosuppressive regimen for each patient without checking the trough levels of MPA.

Since the AEs of leukopenia, nausea, vomiting and diarrhea are almost like surrogates for trough levels of MPA it may be justified to compare all of the dose adjustments and study drug discontinuations across the three study groups:

In the Table 38 below another perspective about study drug adjustments or discontinuations is presented.

Table 38 Overall Dose Adjustments & Drug Discontinuations
 (Analysis performed by Clinical Pharmacology Reviewer Kevin M. Krudys Ph.D)

	Everolimus 1.5 mg, n (%)	Everolimus 3.0 mg, n (%)	Myfortic 1.44 gm, n (%)
More than 2 Dose Adjustments	52.6%,	64.7%	24.5%
All Discontinuations	103 (37.2%)	106 (38.0%)	84 (30.3%)

Reviewer's Comment: *In the table above we see that when look at all dose adjustments regardless of the cause (for TDM or due to AEs) the number of everolimus dose adjustments far exceed the number of dose adjustments for Myfortic.*

- In the reviewer's opinion the main reason that resulted in a higher rate of study drug discontinuations in the everolimus groups is the difficulty of managing the everolimus- low dose CsA immunosuppressive regimen. The reasons for difficulty are:*
- The half-life of everolimus is around 31 hours (Cyclosporine has a half-life of 8 hours and MPA has a half life of 18 hours) and any trough level obtained sooner than 5 days after the dose change will not give an accurate estimate.*
- CsA exposure affects the everolimus exposure so everytime CsA dosage is changed everolimus trough levels also need to be checked in addition to checking the CsA levels but this cannot be done earlier than 5 days after the change.*
- As a consequence of the above during times when a dose change is needed due to an adverse event like infection or wound healing problem the physician will not be able to see the result before a minimum of 5 days or sometimes longer with the everolimus regimen and if further adjustments are needed this will cause additional delays while the observed AE is still in progress.*

- *In the Myfortic regimen there is no need for TDM for MPA and the trough levels come down quicker in case of dose reduction because of the shorter half life. Also the effect of CsA exposure on the MPA exposure is minimal (by affecting the enterohepatic circulation) and unlike the additive effect between the CsA exposure and the everolimus exposure the interaction between the CsA and MPA act in a negative way such that CsA dose increases result in decreased exposure to MPA which in a way acts as a buffer mechanism.*

Because of the explained reasons investigators were probably more inclined to discontinue the everolimus treatment regimen rather than trying to adjust it.

7.3.4 Significant Adverse Events

In this section infections observed in Study A2309, class related effects of M-TOR inhibitors and MPA related adverse events will be discussed.

7.3.4.1 Infections

Rates of total infections, total fungal, and total bacterial infections were similar across all treatment groups. The lowest total rates were seen in the everolimus 1.5 mg group, which was due primarily to the low rates of viral infections [Cytomegalovirus (CMV) and BK virus] in this group.

As stated above in Sections 7.3.1 (Deaths) and 7.3.2.1 (Graft Loss), as per the FDA's assessment of attributability, infectious were the second most common primary cause of death in the study overall and appeared to be responsible for two deaths in the everolimus 1.5 mg group, five deaths in the everolimus 3.0 mg group (and appeared to contribute to the death in an additional patient), and appeared to contribute to four of the 14 graft losses in the everolimus 3.0 mg group.

The overall incidence of SAEs related to infectious causes are approximately 20% in the everolimus 1.5 mg group, 26% in the everolimus 3.0 mg group and 25% in the Myfortic group, as shown in Table 39, which includes all bacterial and viral infections are included to be able to make an accurate comparison across the study groups.

In Table 39, below, clinically relevant preferred terms for infections are grouped together, in order to make comparisons easier. Infection rates reported as SAEs in the following resulting groupings were compared:

- sepsis, bacteremia and septic shock
- musculoskeletal and extremity infections
- wound-related infections

- urinary system infections
- lung infections
- viral infections in general

The incidence of infections reported as SAEs is higher in the everolimus 1.5 mg group compared to the Myfortic group in the first four clinically relevant groupings, whereas the incidences are higher in the Myfortic group in the last three groupings. In the table below different colors are used for consecutive groupings for ease of following.

There were nine SAEs of CMV infections (including one case of CMV esophagitis) in the Myfortic group and none in the everolimus groups. According to the patient narratives, all of these CMV infections in the Myfortic group promptly responded to treatment with gancyclovir or valgancyclovir and resolved within a few days. In one patient Guillain-Barre syndrome secondary to CMV infection developed after the CMV infection had resolved. The patient also recovered from Guillan-Barre syndrome with treatment. CMV or any other type of viral infection did not cause any deaths or graft losses in any of the treatment groups.

There was one BK virus infection reported as SAE in the everolimus 1.5 mg group, no cases in the everolimus 3.0 mg group, and two cases in the Myfortic group.

Table 39. Number (%) of Patients with Infections Reported as SAEs *
(Source: Table 12-8 on page 177 of CSR)

**(A patient with multiple occurrences of an event is counted only once in the SAE category. A patient with multiple events within a primary system organ class is counted only once in the total row.)*

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
Infections and infestations (total)	54 (19.7)	74 (26.6)	69 (25.3)
<i>Abdominal sepsis</i>	1 (0.4)	0 (0.0)	0 (0.0)
Sepsis	3 (1.1)	5 (1.8)	5 (1.8)
<i>Bacteremia</i>	3 (1.1)	3 (1.1)	1 (0.4)
<i>Septic shock</i>	1 (0.4)	1 (0.4)	0 (0.0)
<i>Abscess limb</i>	1 (0.4)	0 (0.0)	0 (0.0)
<i>A/V graft site infection</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Catheter site infection</i>	0 (0.0)	0 (0.0)	1 (0.4)
<i>Arthritis bacterial</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Osteomyelitis</i>	3 (1.1)	0 (0.0)	0 (0.0)
<i>Incision site infection</i>	0 (0.0)	4 (1.4)	1 (0.4)
<i>Postoperative wound infection</i>	1 (0.4)	3 (1.1)	2 (0.7)
<i>Wound abscess</i>	0 (0.0)	1 (0.4)	0 (0.0)
<i>Wound infection</i>	1 (0.4)	2 (0.7)	1 (0.4)
<i>Wound infection</i>	1 (0.4)	0 (0.0)	0 (0.0)

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
<i>staphylococcal</i>			
Cellulitis	3 (1.1)	2 (0.7)	1 (0.4)
Abdominal wall abscess	1 (0.4)	0 (0.0)	0 (0.0)
Subcutaneous abscess	1 (0.4)	0 (0.0)	0 (0.0)
Infected lymphocele	0 (0.0)	1 (0.4)	0 (0.0)
Perinephric abscess	1 (0.4)	1 (0.4)	0 (0.0)
Pyelonephritis	4 (1.5)	5 (1.8)	2 (0.7)
Pyelonephritis acute	0 (0.0)	4 (1.4)	1 (0.4)
Renal abscess	0 (0.0)	1 (0.4)	0 (0.0)
Stent related infection	1 (0.4)	0 (0.0)	0 (0.0)
Urosepsis	2 (0.7)	2 (0.7)	2 (0.7)
Urinary tract infection	18 (6.6)	16 (5.8)	19 (7.0)
Bronchopneumonia	2 (0.7)	1 (0.4)	0 (0.0)
Lobar pneumonia	0 (0.0)	1 (0.4)	1 (0.4)
Pneumonia	5 (1.8)	10 (3.6)	8 (2.9)
Pneumonia klebsiella	1 (0.4)	0 (0.0)	0 (0.0)
BK virus infection	1 (0.4)	0 (0.0)	2 (0.7)
CMV infection	0 (0.0)	0 (0.0)	9 (3.3)
CMV viremia	0 (0.0)	1 (0.4)	0 (0.0)
CMV esophagitis	0 (0.0)	0 (0.0)	1 (0.4)
Herpes simplex	1 (0.4)	0 (0.0)	2 (0.7)
Herpes virus infection	0 (0.0)	0 (0.0)	1 (0.4)
Herpes zoster	1 (0.4)	5 (1.8)	4 (1.5)
Herpes zoster disseminated	0 (0.0)	0 (0.0)	1 (0.4)
Upper resp. tract infection	2 (0.7)	2 (0.7)	6 (2.2)
Gastroenteritis	6 (2.2)	3 (1.1)	6 (2.2)
Fungal Infections	0 (0.0)	3 (1.1)	0 (0.0)
Tuberculosis	0 (0.0)	1 (0.4)	1 (0.4)

Infection data was coded with SNOMED for micro-organism and type of infection (viral, bacterial, fungal and others). In addition to being analyzed similarly as AEs and SAEs, as described above, the incidence rate of infection by type and micro-organism was tabulated for each treatment group.

The incidences of all infections (bacterial, fungal, and viral) reported as AEs was 61.7% in the everolimus 1.5 mg group, 64% in the everolimus 3.0 mg group and 67.8% in the Myfortic group, as shown in Table 40. The causative organisms for viral infections with an incidence of $\geq 1\%$ are included. Organisms causing bacterial fungal infections were not included, as they were similar across the study groups.

Table 40. Number of Patients (%) with Infections by Type of Organism
 Source: Table 14.3.1-1.7 on page 1467 of CSR

Type of Infection	Everolimus 1.5 mg N=274, n (%)	Everolimus 3.0 mg N=278, n (%)	Myfortic 1.44 gm N=273, n (%)
All infections	169 (61.7)	178 (64.0)	185 (67.8)
Bacterial - Total	71 (25.9)	69 (24.8)	69 (25.3)
Fungal - Total	12 (4.4)	14 (5.0)	14 (5.1)
Viral - Total	27 (9.9)	20 (7.2)	57 (20.9)
<i>BK virus</i>	2 (0.7)	3 (1.1)	11 (4.0)
<i>Cytomegalovirus, nos</i>	3 (1.1)	1 (0.4)	23 (8.4)
<i>Human herpes simplex virus, nos</i>	7 (2.6)	11 (4.0)	14 (5.1)
<i>Human herpes virus 3</i>	4 (1.5)	2 (0.7)	7 (2.6)
<i>Polyomavirus, nos</i>	5 (1.8)	0 (0.0)	3 (1.1)
<i>Virus, nos</i>	4 (1.5)	3 (1.1)	0 (0.0)
Other - Total	135 (49.3)	135 (48.6)	129 (47.3)

nos = not otherwise specified

The incidence of CMV, herpes simplex and BK virus infections was higher in the Myfortic group compared to both of the everolimus groups and is the main cause of the difference in the overall rates of infections across the three groups. The incidence of CMV infections was 5.9% (16 patients) in the Myfortic group vs. 0.7% (2 patients) in the everolimus 1.5 mg group. Also, there were five cases of CMV viremia reported in the Myfortic group compared to one case in the everolimus 1.5 mg group, which brings the total number of CMV infections to 23 patients (8.4%) in the Myfortic group and 3 patients (1.1%) in the everolimus 1.5 mg group, as shown in Table 40.

In an analysis of CMV-related events according to the donor/recipient CMV status, the advantage in the everolimus groups over the Myfortic group in terms of the incidence of CMV related events disappears if the donor is seropositive and the recipient is seronegative for CMV. The incidences of CMV events in the donor (+)/recipient (-) combination are 10% in the everolimus 1.5 mg group, 21.4% in the everolimus 3.0 mg group, and 14.3% in the Myfortic group. According to the protocol, CMV prophylaxis was mandatory for all cases in which the donor tested positive and the recipient tested negative for CMV. All other cases were treated according to local practice.

CMV syndrome, defined as fever for two days, neutropenia, leukopenia viral syndrome, was more frequently reported in the Myfortic group (4.4%) compared to 1.5% or 1.4% in the everolimus 1.5 mg and 3.0 mg treatment groups but none of the CMV syndromes were reported as SAEs.

The incidence of infections reported as SAEs are higher in the Myfortic group compared to the everolimus 1.5 mg group (25.3% vs. 19.7%) whereas the incidence is highest of all in the everolimus 3.0 mg group (26.6%). The difference between the everolimus 1.5

mg group and the Myfortic group is mainly due to the higher incidence of viral infections (CMV, BK virus and Herpes virus) in the Myfortic group. The incidence of bacterial and fungal infections between these two groups are similar. A total of 9 CMV infections were reported as SAEs in the Myfortic group compared to none in the everolimus 1.5 mg group and 2 BK virus infections were reported as SAEs in the Myfortic group compared to 1 case in the everolimus 1.5 mg group. Also a total of 4 Herpes Zoster infections were reported as SAEs in the Myfortic group compared to 1 case in the everolimus 1.5 mg group.

All of the CMV infections reported as SAEs in the Myfortic group responded to treatment and all the patients recovered. Guillain-Barré syndrome was reported in one of these patients after the patient has recovered from the CMV infection and was attributed to the CMV infection but this also resolved without any sequel.

BK virus infections also did not result in any graft losses and apparently responded to treatment according to the narratives. One patient in the Myfortic group who according to the narrative developed herpes encephalitis and the event was continuing at the time of reporting, no further information was available but this patient was not reported among the deaths or graft losses after the 12 month study period.

Reviewer's Comment:

In the Reviewer's opinion having less viral infections mainly less CMV infections is an advantage of the everolimus treatment but having more CMV infections or other types of viral infections did not result in any deaths or graft losses in the Myfortic group, there were 2 deaths in the everolimus 1.5 mg group and 5 deaths in the everolimus 3.0 mg group as a consequence of infections during the 12 month study period. No deaths due to infection were reported in the Myfortic group during the 12 month study period.

The Reviewers conclusion is although everolimus-low dose CsA regimen results in lower numbers of CMV and other types of viral infections; bacterial infections tend to be more severe and appear as one of the main causes of death with this regimen.

7.3.4.2 Proteinuria

Proteinuria was assessed by the Applicant by evaluating the ratio of spot urine protein (measured in milligrams) to creatinine (measured in grams) (UP/UC ratio) based on an estimate of an average 24 hour excretion. According to the study protocol the UP/UC ratio was defined as:

- Normal (<30 mg/g);
- Mild proteinuria (30 – <300 mg/g);
- Sub-Nephrotic proteinuria (300 - <3000 mg/g);

- Nephrotic proteinuria (≥ 3000 mg/g).

According to the National Kidney Foundation (NKF) definition of proteinuria, as shown in Table XX, the normal range is defined as a UP/UC ≤ 200 mg/g and clinical proteinuria occurs at values > 200 mg/g.

In the FDA analysis of proteinuria, the UP/PC results are expressed in units of gm/gm or a unitless ration. The NKF definition and grading system was also utilized and various ranges of UP/UC were explored (≤ 0.2 , > 0.2 to < 0.5 , 0.5 to < 1 , 1 to < 2 , 2 to < 3 and ≥ 3) to have a better understanding of the distribution of patients at various ranges of proteinuria.

Table 41 NKF Definition of Proteinuria and Albuminuria
 (http://www.kidney.org/professionals/kdoqi/guidelines_bp/background.htm)

Table 28. Definitions of Proteinuria and Albuminuria				
	Urine Collection Method	Normal	Micro-albuminuria	Albuminuria or Clinical Proteinuria
Total Protein	24-Hour Excretion (varies with method)	<300 mg/d	NA	>300 mg/d
	Spot Urine Dipstick	<30 mg/dL	NA	>30 mg/dL
	Spot Urine Protein-to-Creatinine Ratio (varies with method)	<200 mg/g	NA	>200 mg/g
Albumin	24-Hour Excretion	<30 mg/d	30–300 mg/d	>300 mg/d
	Spot Urine Albumin-Specific Dipstick	<3 mg/dL	>3 mg/dL	NA
	Spot Urine Albumin-to-Creatinine Ratio	<30 mg/g	30–300 mg/g	>300 mg/g
	Spot Urine Albumin-to-Creatinine Ratio (gender-specific definition) ^a	<17 mg/g (men) <25 mg/g (women)	17–250 mg/g (men) 25–355 mg/g (women)	>250 mg/g (men) >355 mg/g (women)

^aUse of the same cut-off value for men and women leads to higher values of prevalence for women than men.¹ Gender-specific cut-off values are from two studies.^{18, 19}
 Note: There is no uniformly accepted conversion between urine albumin and total protein. In general, a spot urine total protein-to-creatinine ratio >200 mg/g corresponds approximately to a spot urine albumin-to-creatinine ratio of >120 mg/g.

Proteinuria was reported as a SAE in two (0.7%) patients in the everolimus 1.5 mg group, four (1.4%) patients in the everolimus 3.0 mg group and one (0.4%) patient in the Myfortic group. Also, two patients in the everolimus 1.5 mg group, 4 patients in the everolimus 3.0 mg group discontinued treatment due to proteinuria. No patient discontinued treatment due to proteinuria in the Myfortic group. Proteinuria was reported as an AE in 9.1% of the patients in the everolimus 1.5 mg group, 12.9% of the patients in the everolimus 3.0 mg group and 7.3% of the patients in the Myfortic group.

The following analyses were performed by Biostatistics Reviewer John S. Yap Ph.D. In the following tables “on treatment”** analyses of proteinuria are presented from three different perspectives:

- 1- Comparison of the average Proteinuria / Creatinuria ratio in the everolimus 1.5 mg group vs. Myfortic group at different time points over the 12 month study period.

- 2- Comparison of the percentage of patients in different severity ranges of proteinuria in the everolimus 1.5 mg group vs. Myfortic group at different time points over the 12 month study period.
- 3- Proteinuria levels of patients in different groups at the end of the study period in relation to their proteinuria level at month 1.

*****On treatment analysis:*** Any assessment obtained no later than 2 days after discontinuation of study medication was considered an on-treatment value; the baseline value is represented by the last non-missing observation during the baseline period; for others, multiple assessments within a given visit-window for one patient were averaged.

Analyses of the data indicate that the UP/UC ratios distributions are skewed due to extreme outlying values such that the means were greater than the medians. To account for the lack of symmetry in the data, these data were analyzed by comparing medians at each visit window between treatment groups and using the nonparametric Wilcoxon rank-sum test to test for treatment differences.

Table 41 shows the mean and median UP/UC ratios in the everolimus 1.5 mg and Myfortic treatment groups in the safety on-treatment population, which was defined as the population of safety patients whose assessments were obtained on and after day 1 but no later than two days after the discontinuation of randomized study medication. Of note, ratios in the everolimus 3.0 mg group are not presented in the tables related to proteinuria for the ease of reviewing. However, the everolimus 3.0 mg group performed worse than everolimus 1.5 mg when compared to Myfortic. These data are also plotted in Figure XX illustrating that the medians ratios in everolimus 1.5 mg group were consistently higher than those of Myfortic throughout the study including the Month 12 TEP (shown as Month 13).

**Table 42. UP/UC Ratios for Safety On-Treatment Population
 (in gm/gm; no unit)**

(Source: Safety Review by John S. Yap Ph.D)

Visit Window	Treatment Group	n (%) [*]	Mean (SD)	Median (Range)	p-value ^{**}
Day 14	Everolimus 1.5 mg	241(89)	0.60 (1.29)	0.33 (0.06-17.05)	0.1881
	Myfortic	244 (90)	0.62 (1.28)	0.29 (0.08-13.04)	
Month 1	Everolimus 1.5 mg	246 (91)	0.43 (0.76)	0.26 (0.06-8.51)	0.0025
	Myfortic	244 (90)	0.40 (0.85)	0.20 (0.06-9.51)	
Month 3	Everolimus 1.5 mg	219 (81)	0.28 (0.42)	0.17 (0.02-3.90)	0.0338
	Myfortic	224 (83)	0.27 (0.50)	0.13 (0.05-4.19)	
Month 6	Everolimus 1.5 mg	188 (69)	0.25 (0.43)	0.15 (0.00-4.96)	0.0292
	Myfortic	207 (77)	0.25 (0.50)	0.12 (0.00-4.65)	
Month 9	Everolimus 1.5 mg	188 (69)	0.25 (0.30)	0.15 (0.00-2.24)	<0.0001
	Myfortic	198 (73)	0.22 (0.42)	0.11 (0.03-3.88)	
Month 12	Everolimus 1.5 mg	183 (68)	0.31 (0.59)	0.15 (0.03-6.15)	<0.0001
	Myfortic	192 (71)	0.27 (0.61)	0.11 (0.00-5.12)	
Month 12 TEP ^{***}	Everolimus 1.5 mg	271	0.70 (3.64)	0.21 (0.03-58.00)	<0.0001
	Myfortic	270	0.49 (1.23)	0.12 (0.00-10.39)	

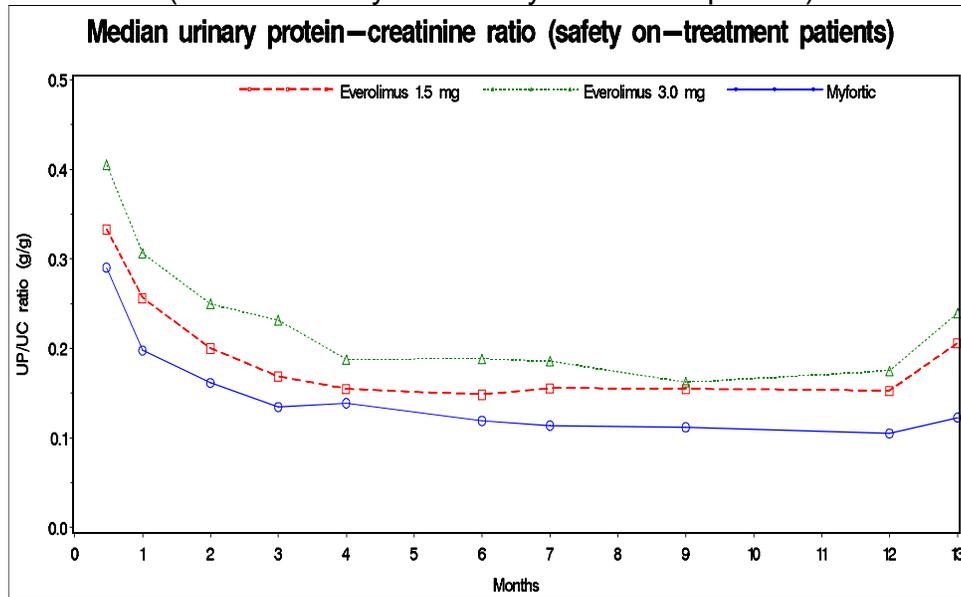
^{*}% relative to Month 12 TEP; ^{**}Wilcoxon rank sum test; ^{***}TEP=treatment endpoint (imputation by LOCF)
 No differences noted between treatment groups at baseline, days 1, 3, 7 and 14 (data omitted from table)

Reviewer's Comment: Although not shown in the Table 41 above Day 1 UP/UC values in the everolimus 1.5 mg group and the Myfortic group were similar to each other with no statistical difference in between. When we look at the values at M12 there is a 40 mg difference in between the everolimus 1.5 mg group and the Myfortic group both with regard to the mean or the median values.

When we look at the Month 12 TEP values which includes a higher number of patients due to the inclusion of the last on treatment value if the patient did not have a M12 value we notice that the gap between the everolimus 1.5 mg group and the Myfortic group increases and goes up to a difference of 100 mg when we look at the median values and increases even further when we look at the Month 12 TEP values (210 mg/g) and raises concerns about the further increases in this gap with longer follow-up.

As can be noticed starting Month 6 the differences between the two treatment groups become statistically significant. These differences become even higher when we consider the male patients only since the subset analysis (explained later in the text) shows that this higher levels of proteinuria in the everolimus 1.5 mg group is driven by the male population.

Figure 11. Median Urinary Protein/Creatinine (Safety On-treatment Population)
 (Source: Safety Review by John S. Yap Ph.D)



Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

UP/UC ratios falling into clinically relevant categories at each visit window are presented in Table 42 below. These data suggest that there were more patients whose UP/UC ratios were less than 2.0 in the Myfortic group than the everolimus 1.5 mg group over time. This result is consistent with what was previously observed when assessing median ratios. *Note also, that there was an increasing number of missing data as study follow-up time increased.* At Day 14, about 90% of data were collected compared to only about 70% at Month 12, as shown in Table 43.

Table 43. Categorized UP/UC Ratios
(Source: Safety Review by John S. Yap Ph.D)

Visit Window	Treatment Group	n (%)*	UP/UC Ratio, n (%)					
			≤0.2	>0.2 to <0.5	0.5 to < 1	1 to < 2	2 to < 3	≥3
Baseline	Ever 1.5 mg	145 (54)	4 (3)	23 (16)	33 (23)	35 (24)	19 (13)	31 (21)
	Myfortic	134 (50)	3 (2)	18 (13)	27 (20)	42 (31)	16 (12)	28 (21)
Day 1	Ever 1.5 mg	235 (87)	7 (3)	56 (24)	80 (34)	56 (24)	14 (6)	22 (9)
	Myfortic	235 (87)	2 (1)	53 (23)	72 (31)	64 (27)	21 (9)	23 (10)
Day 14	Ever 1.5 mg	241 (89)	61 (25)	111 (46)	40 (17)	22 (9)	3 (1)	4 (2)
	Myfortic	244 (90)	78 (32)	104 (43)	34 (14)	16 (7)	5 (2)	7 (3)
Month 1	Ever 1.5 mg	246 (91)	87 (35)	109 (44)	34 (14)	11 (4)	3 (1)	2 (1)
	Myfortic	244 (90)	125 (51)	84 (34)	20 (8)	10 (4)	2 (1)	3 (1)
Month 3	Ever 1.5 mg	219 (81)	132 (60)	63 (29)	16 (7)	4 (2)	3 (1)	1 (0)
	Myfortic	224 (83)	146 (65)	59 (26)	11 (5)	4 (2)	1 (0)	3 (1)
Month 6	Ever 1.5 mg	188 (69)	124 (66)	48 (26)	12 (6)	2 (1)	1 (1)	1 (1)
	Myfortic	207 (77)	147 (71)	39 (19)	13 (6)	5 (2)	1 (0)	2 (1)
Month 9	Ever 1.5 mg	188 (69)	120 (64)	48 (26)	14 (7)	5 (3)	1 (1)	.
	Myfortic	198 (73)	149 (75)	34 (17)	8 (4)	5 (3)	1 (1)	1 (1)
Month 12	Ever 1.5 mg	183 (68)	110 (60)	49 (27)	16 (9)	4 (2)	2 (1)	2 (1)
	Myfortic	192 (71)	143 (74)	32 (17)	8 (4)	4 (2)	1 (1)	4 (2)
Month 12 TEP**	Ever 1.5 mg	271	135 (50)	80 (30)	31 (11)	11 (4)	6 (2)	8 (3)
	Myfortic	270	175 (65)	52 (19)	15 (6)	14 (5)	3 (1)	11 (4)

*% relative to Month 12 TEP; **TEP=treatment endpoint (imputation by LOCF), Ever=everolimus

The proportions of patients with a UP/UC ratio falling into a specific range at month 12 according to the month 1 ratio are presented below in Table 43. These results show that at month 1, 88% of patients in the Myfortic group had a ratio < 0.5 compared to only 81% of patients in the everolimus 1.5 mg group. Of these patients, 40% and 56% in the everolimus 1.5 mg and Myfortic groups, respectively, had ratios below 0.2 at month 1 and about 76% and 85% of these maintained that level at month 12. For month 1, ratios in the > 0.2 to < 0.5 category, the month 12 levels were either maintained at that range or improved to the ≤ 0.2 category for 90% and 85% of the everolimus 1.5 mg and Myfortic patients respectively. In general, there were proportionately more patients in the Myfortic group with lower ratios at month 12 than in the everolimus 1.5 mg group. Note that Table 43 consists of data from patients who had both months 1 and 12 UP/UC measurements, representing only about 70% of the month 12 TEP sample size.

Table 44 Categorized UP/UC Ratios at Month 12
 (6 different grades of UP/UC ratios consolidated into 4 grades)
 (Source: Safety Review by John S. Yap Ph.D)

Visit Window	Treatment Group	Total #	Normal ≤ 0.2 n (%)	Mild > 0.2 to < 1.0 n (%)	Sub-nephrotic ≥ 1.0 to < 3.0 n (%)	Nephrotic ≥ 3.0 n (%)
Month 12	Eve. 1.5 mg Myfortic	183	110 (60)	65 (36)	6 (3)	2 (1)
		192	143 (74)	40 (21)	5 (3)	4 (2)
Month 12 TEP*	Eve. 1.5 mg Myfortic	271	135 (50)	111 (41)	17 (6)	8 (3)
		270	175 (65)	67 (25)	17 (6)	11 (4)

Reviewer's comment: In Table 43 above which gives the 12 Month values only, the 7 different ranges of proteinuria in Table 44 are consolidated into 4 consecutive ranges for easy interpretation. Regardless of the method utilized (M12 or M12 TEP) there are 15% more patients in the normal range in the Myfortic group compared to the everolimus 1.5 mg group. At the other end of the spectrum although we see an opposite trend, the number of patients are too small to make any meaningful comparisons at the nephrotic range. Also according to the Applicant's analysis which utilized a higher cut-off level, nephrotic range proteinuria (≥ 3.0 gm/gm) was reported for 0.7% of everolimus 1.5 mg treated patients, 1.4% of everolimus 3.0 mg treated patients, and by 0.4% of Myfortic treated patients during the 12 month study period.

Table 45 below shows the progression of patients at different ranges of proteinuria at month 1 to different stages of proteinuria at month 12.

Table 45. Categorized UP/UC Ratios (Months 1 and 12)
(Source: Safety Review by John S. Yap Ph.D)

Treatment	Proteinuria Range (Month 1)	n (%)	Proteinuria Range (Month 12), n (%)*					
			≤0.2	>0.2 to <0.5	0.5 to <1	1 to <2	2 to <3	≥3
Everolimus 1.5 mg (n=181)	≤0.2	72 (40)	55 (76)	14 (20)	2 (3)	1 (1)	0 (0)	0 (0)
	>0.2 to <0.5	75 (41)	45 (60)	22 (30)	4 (5)	1 (1)	1 (1)	2 (3)
	0.5 to <1	24 (13)	7 (29)	5 (21)	9 (38)	2 (8)	1 (4)	0 (0)
	1 to <2	7 (4)	2 (29)	4 (57)	1 (14)	0 (0)	0 (0)	0 (0)
	2 to <3	2 (1)	0 (0)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)
	≥3	1 (1)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Everolimus 3.0 mg (n=163)	≤0.2	46 (28)	36 (78)	7 (15)	0 (0)	2 (5)	1 (2)	0 (0)
	>0.2 to <0.5	82 (50)	43 (53)	28 (34)	3 (4)	5 (6)	2 (2)	1 (1)
	0.5 to <1	19 (12)	4 (21)	9 (47)	2 (11)	1 (5)	0 (0)	3 (16)
	1 to <2	13 (8)	6 (46)	6 (46)	0 (0)	0 (0)	0 (0)	1 (8)
	2 to <3	2 (1)	1 (50)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)
	≥3	1 (1)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Myfortic (n=187)	≤0.2	104 (56)	88 (85)	12 (11)	2 (2)	1 (1)	1 (1)	0 (0)
	>0.2 to <0.5	60 (32)	41 (68)	10 (17)	5 (8)	1 (2)	0 (0)	3 (5)
	0.5 to <1	14 (7)	6 (43)	7 (50)	0 (0)	1 (7)	0 (0)	0 (0)
	1 to <2	6 (3)	2 (33)	3 (50)	0 (0)	1 (17)	0 (0)	0 (0)
	2 to <3	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
	≥3	2 (1)	1 (50)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)

* % of row total

Table 46 below which is a simplified version of Table 46 shows the progression of patients at mild and subnephrotic ranges of proteinuria at month 1 to different stages of proteinuria at month 12.

Table 46 Shift Table of UP/UC Ratio Comparing Month 1 and 12
 (Simplified version of Table XX with 6 ranges of UP/UC ratios consolidated into 4 ranges)
 (Source: Safety Review by John S. Yap Ph.D)

Treatment	UP/UC and Proteinuria Range at Month 1	n (%)	UP/UC and Proteinuria Range at Month 12			
			Normal ≤ 0.2 n (%)	Mild > 0.2 to < 1.0 n (%)	Sub-Nephrotic ≥ 1.0 to < 3.0 n (%)	Nephrotic ≥ 3.0 n (%)
Everolimus 1.5mg (N=274)	> 0.2 to < 1.0 Mild	99	52 (53)	40 (40)	5 (5)	2 (2)
	≥ 1.0 to < 3.0 Sub-nephrotic	9	2 (22)	7 (78)	0 (0)	0 (0)
Myfortic (N=273)	> 0.2 to < 1.0 Mild	74	47 (63)	22 (30)	2 (3)	3 (4)
	≥ 1.0 to < 3.0 Sub-nephrotic	7	2 (29)	3 (43)	1 (14)	1 (14)

Reviewer's comment:

One important point to consider before interpreting the results in Table 45 is the baseline stratification of the patients are done according to the month 1 values at which there already is a statistically significant difference between the everolimus groups and the Myfortic group with regard to proteinuria so month 1 values are not the baseline values. Nevertheless, this data may still give us an idea of the time course of development of proteinuria in these patients.

In Tables 45 and 46 above of the patients who are initially in the mild proteinuria range (> 0.2 to < 1.0 gm/gm) approximately 10% more patients move down to the normal range in the Myfortic group compared to the everolimus 1.5 mg group.

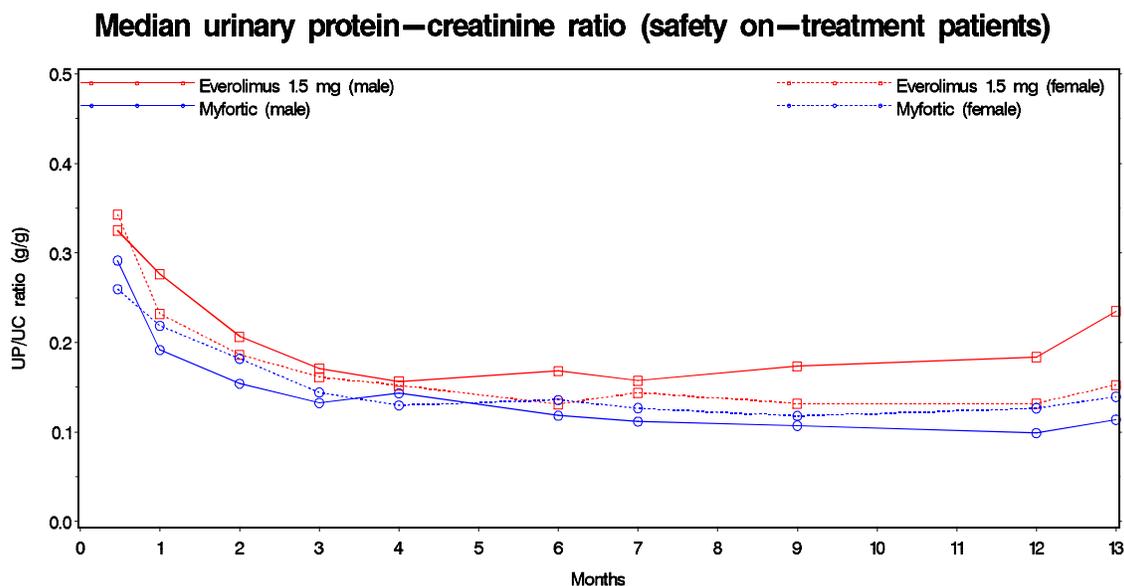
At the nephrotic range (≥ 3.0 gm/gm) we again see the opposite trend with numerically more patients moving up to this range (4 patients) in the Myfortic group compared to the everolimus 1.5 mg group (2 patients). Also at the nephrotic range the patient numbers are too small to make any meaningful comparisons. Also when we look at the total number of patients followed for this period it is only a fraction of the total: 108 patients in the everolimus 1.5 mg group and 81 patients in the Myfortic group.

Subgroup Analyses of Proteinuria by Gender, Race, Age and Diabetes Status
 (FDA analysis by John S. Yap Ph.D.)

Median UP/UC ratios among males in the everolimus 1.5 mg group were consistently higher than among males in the Myfortic group and the treatment groups were found to be statistically different at all time points except at baseline, days 7 and 14 and at month 4, as shown in Figure 8. These differences between the everolimus 1.5 mg and Myfortic groups were not observed among female patients. Thus, it appears that the differences that were seen earlier in the overall population between the everolimus 1.5 versus Myfortic groups may have been driven by the male population.

Reviewer’s Comment: *The fact that the proteinuria is driven by the male population indicates that the magnitude of the proteinuria is larger for male patients. Also it is known from the literature that proteinuria is associated with worsened graft and patient survival and is a risk factor for cardiovascular morbidity. Also it is known from the literature that in general men are at increased risk for atherosclerotic heart disease compared to women. This differential effect across the gender will probably further increase the risk of graft failure and death in the male patients relatively more compared to female patients treated with everolimus.*

Figure 12 . Median Urinary Protein/Creatinine by Gender
 (Source: Safety Review by John S. Yap Ph.D)



Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

Use of ACEI/ARBs

An exploratory analysis was performed by the Applicant to examine the potential effect of the introduction of any angiotensin converting enzyme inhibitor (ACEI) or any angiotensin receptor blocker (ARB) on the level of proteinuria. ACEI or ARBs were used in approximately 50% of the patients across all groups in the new study. However, looking at the effect of the introduction of any ACEI or any ARB on proteinuria at least 30 days after the introduction was limited to approximately 20% of the entire study population. Nonetheless, there was a small yet similar reduction in the median urine protein to creatinine ratios for all groups (-38.9, -49.5 and -44.2 mg/g, respectively). In addition to the small number of patients, the analysis is also limited by the lack of data on the doses used of these agents, which is directly related to their known effect on proteinuria.

Clinical Significance

Proteinuria is not only a manifestation of renal disease, but is also a predictor of survival in most renal diseases. According to the published literature even low levels of proteinuria may adversely affect both the graft and patient survival in kidney transplant recipients.^{8,9} The following graphs show the association between patient and graft survival by degree of proteinuria at one year.

8 Fernández-Fresnedo G, Plaza JJ, Sánchez-Plumed J, Sanz-Guajardo A, Palomar-Fontanet R, Arias M. Proteinuria: a new marker of long-term graft and patient survival in kidney transplantation. *Nephrol Dial Transplant*. 2004 Jun;19 Suppl 3:iii47-51.

9 Roodnat JI, Mulder PG, Rischen-Vos J, van Riemsdijk IC, van Gelder T, Zietse R, IJzermans JN, Weimar W. Proteinuria after renal transplantation affects not only graft survival but also patient survival. *Transplantation* 2001 Aug 15;72(3):438-44.

Figure 13. Patient and Graft Survival by Degree of Proteinuria

(Source: Reference No: 10)

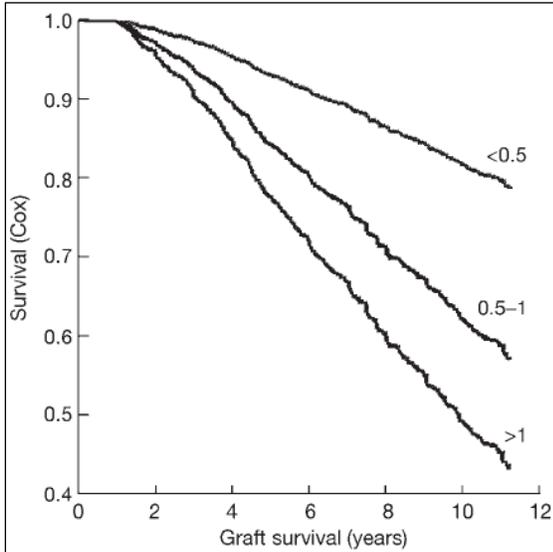


Fig. 1. Graft survival depending on 1 year proteinuria.

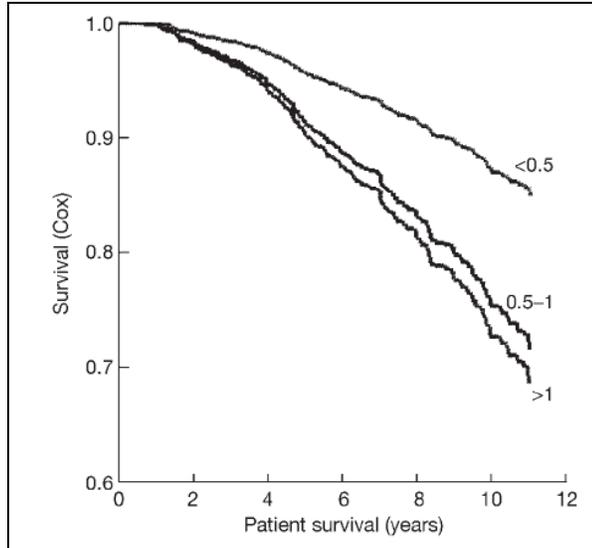


Fig. 2. Patient survival depending on 1 year proteinuria.

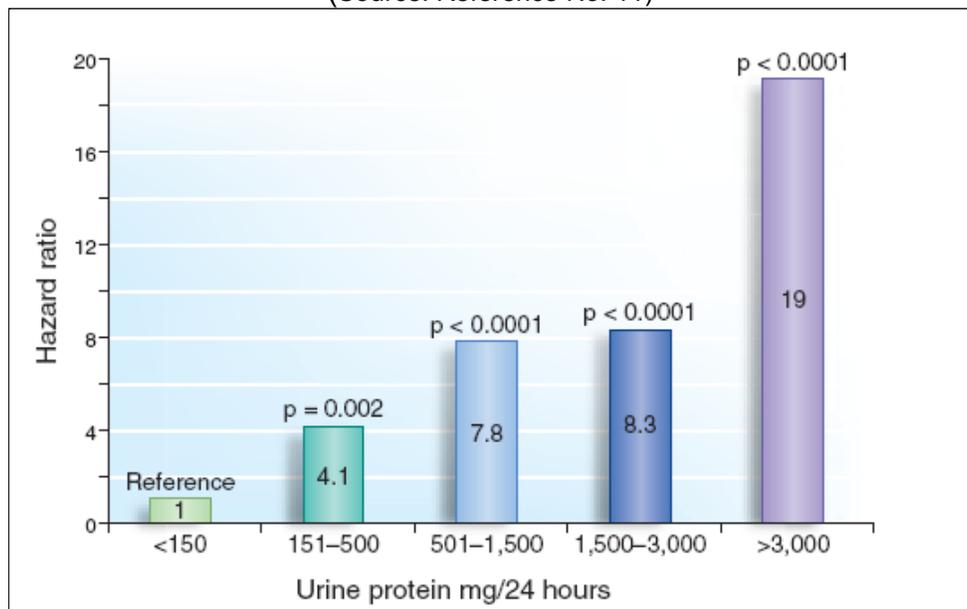
Some recently published data shows that even minimal proteinuria is a risk factor for graft survival.^{10,11} The figure (Figure 14) below shows the association between different levels of post-transplant proteinuria at 1 year and the risk of graft loss.

10 Kang NR, Lee JE, Huh W, Kim SJ, Kim YG, Kim DJ, Oh HY. 10. Minimal proteinuria one year after transplant is a risk factor for graft survival in kidney transplantation. J Korean Med Sci. 2009 Jan;24 Suppl:S129-34.

11 Amer H, Cosio FG. Significance and management of proteinuria in kidney transplant recipients. J Am Soc Nephrol. 2009 Oct 9. [Epub ahead of print]

Figure 14. Relationship between increasing levels of proteinuria at 1 year post-transplant and subsequent graft survival

(Source: Reference No: 11)



In absolute terms, 3.9%, 9.9%, 20%, 33.3%, and 41.2% of kidney allografts were lost during a period of 46 ± 20 mo of follow up in patients who at 1 yr had proteinuria <150 (n = 337), 151 to 500 (n= 182), 501 to 1500 (n= 50), 1500 to 3000 (n= 27), and >3000 (n= 17) mg/d, respectively.

Reviewer's comment: When the Month 12 TEP mean values are taken into consideration there is a difference of 210 mg/g between the everolimus 1.5 mg group and the Myfortic group in favor of the Myfortic group and this difference is even higher for the male patients since the overall higher levels of proteinuria in the everolimus 1.5 mg group is driven by the male patients. The fact that the differences between the two treatment groups became significant starting at Month 6 raises concerns that the gap may continue to widen in favor of the Myfortic group with longer follow-up and may be more severe for the male patients.

Proteinuria is a well known effect of M-TOR inhibitors. Currently a number of studies are being conducted to ameliorate the high levels of proteinuria associated with M-TOR inhibitors in transplant patients by use of concomitant usage of ACEIs/ARBs. Concomitant use of these medications may cause additional problems like chronic coughing and increased incidence of angioedema. Finally, ACEIs/ARBs may adversely affect the kidney graft function by reducing GFR and also by not clearly defined effects. It is also known that even small differences in the level of proteinuria may adversely affect kidney graft survival. Higher levels of proteinuria affect both the patient and graft survival (as explained above), as well as contributing to hyperlipidemia, which is already a

problem in transplant patients and was observed with higher severity in patients receiving everolimus, as will be discussed below.

7.3.4.3 Lipid Elevations

Earlier studies have shown an increased frequency of hyperlipidemia with M-TOR inhibitors and everolimus, predominantly associated with an increase in total cholesterol and triglycerides which can increase cardiovascular risk. Thus, the Applicant evaluated serum lipid profiles, rates of associated lipid-related events and use of lipid-lowering agents.

According to the study protocol patients who have severe hypercholesterolemia (> 350 mg/dL; > 9 mmol/L) or hypertriglyceridemia (> 500 mg/dL; > 8.5 mmol/L) were excluded from the study. Lipid lowering medications such as HMG CoA reductase inhibitors were to be administered according to local practice for the management of hyperlipidemia. According to the study protocol lovastatin and simvastatin were not allowed because of confirmed interaction between these drugs and CsA. Cerivastatin was also strongly discouraged because of insufficient data available. Lipid-lowering therapy was to be optimized before dose reduction of study medication was considered.

Hyperlipidemia was reported as a SAE was reported in only one patient in the study and was in the everolimus 1.5 mg group.

Dyslipidemia, (dyslipidemia, hypercholesterolemia and hyperlipidemia combined together) led to study drug discontinuations in two patients in each of the everolimus groups and one patient in the Myfortic group. Total numbers of patients with drug discontinuations or dose adjustments due to dyslipidemias are 4 (1.4%) patients in the everolimus 1.5 mg group, 7 (2.5%) patients in the everolimus 3.0 mg group compared to one (0.3%) patient in the Myfortic group.

Hyperlipidemia was reported as an AE in 57 (20.8%) patients in the everolimus 1.5 mg group, 60 (21.6%) patients in the everolimus 3.0 mg group, and 43 (15.8%) patients in the Myfortic group. Hypercholesterolemia was reported in 47 (17.2%) patients in the everolimus 1.5 mg group, 50 (18.0%) patients in the everolimus 3.0 mg group, and 34 (12.5%) patients in the Myfortic group as an AE in the 12 month safety population.

Lipid lowering agents were taken by a higher percentage of patients in the everolimus treatment groups (64.6%, 72.3% and 57.5% of patients in the everolimus 1.5 mg, 3.0 mg and Myfortic groups, respectively).

Among patients with high baseline cholesterol values before the statin treatment was initiated, 27.4% (17/62) in the everolimus 1.5 mg group compared to 13.9% (5/36) in the Myfortic group did not move down to the normal range despite the statin treatment. A similar trend was also observed for triglycerides in a similar analysis. Among patients

with high baseline triglyceride values before the statin treatment was initiated, 49% (22/45) in the everolimus 1.5 mg group compared to 26% (5/19) in the Myfortic group did not move down to the normal range despite the statin treatment.

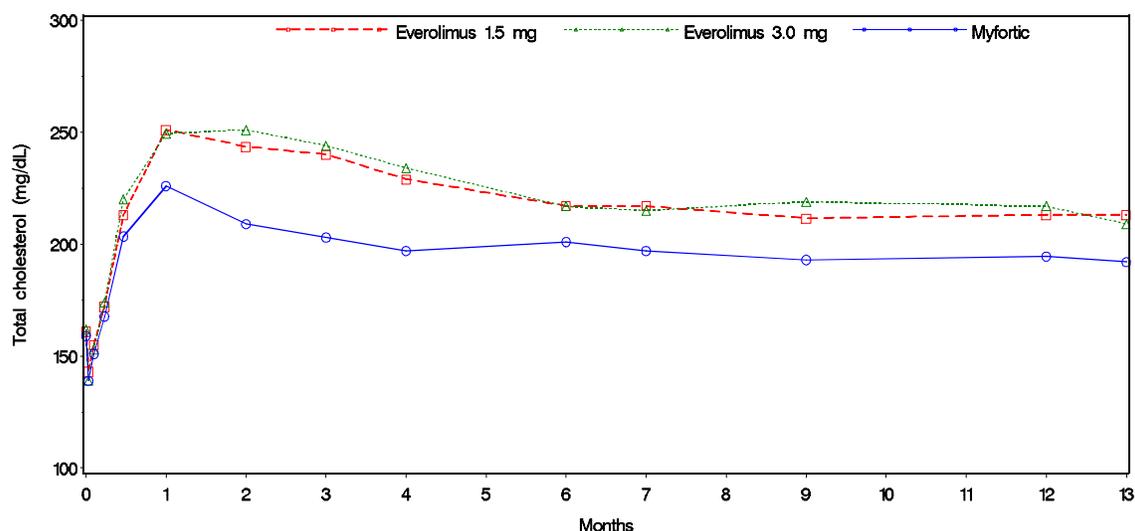
Creatine kinase levels measured in both of the everolimus groups at all time points throughout the 12 month study period were significantly higher compared to the Myfortic group which may be an early sign of rhabdomyolysis although the mean and median levels in both groups stayed within the normal range.

Lipids were assessed in the safety on-treatment population focusing on the following clinical parameters: total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and total cholesterol-HDL ratio. The data presented in the figures below are given in mg/dL units. Since the distributions of the lipid measurements at each visit window are skewed, medians were plotted and the treatment groups were compared using the Wilcoxon rank-sum test.

As illustrated in Figure 15, the median total cholesterol was consistently higher in both everolimus groups compared to the Myfortic group and statistically significant differences were found from month 1 post-transplant through month 12 TEP (Month 13 in the figure).

Figure 15. Median Total Cholesterol
(Source: Safety Review by John S. Yap)

Median total cholesterol (safety on-treatment patients)

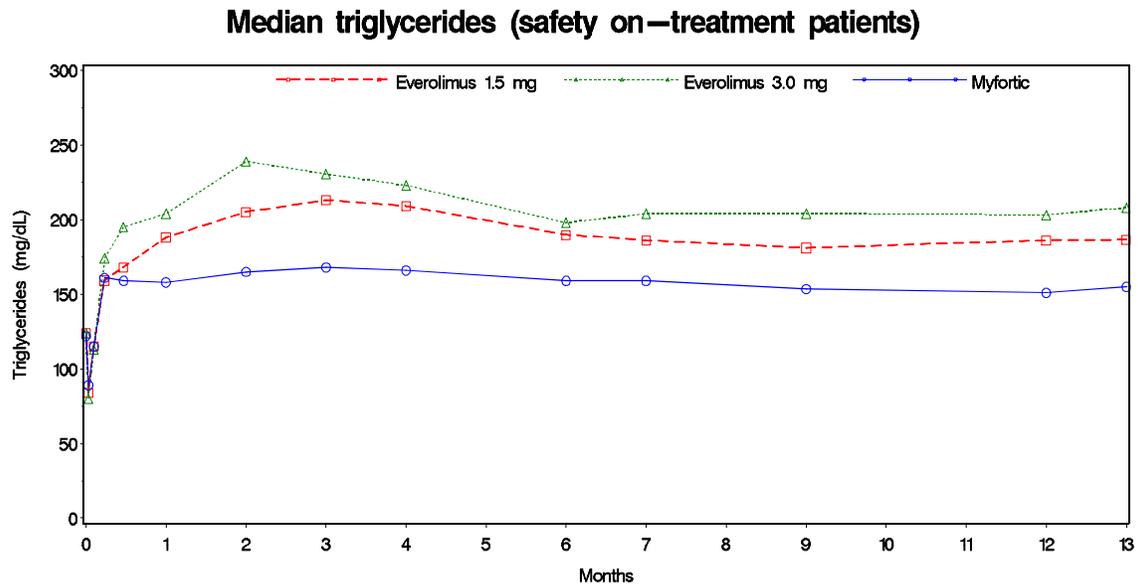


Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

Reviewer's Comment: As shown in Figure X above, starting at Month 9 the median values in the Myfortic group overlap with the upper bound of normal range (200 mg/dL) while the median values in both of the everolimus groups continue to stay well above the normal range. There is also a statistically significant difference in between the everolimus groups and the Myfortic group

Median triglycerides, shown in Figure 12, were consistently higher in both everolimus groups compared to the Myfortic group from month 1 through end of the 12 month follow-up period. Differences between the everolimus 1.5 mg and Myfortic groups were statistically significantly different at month 1 and onwards, including the month 12 TEP.

Figure 16. Median Triglycerides
(Source: Safety Review by John S. Yap Ph.D)



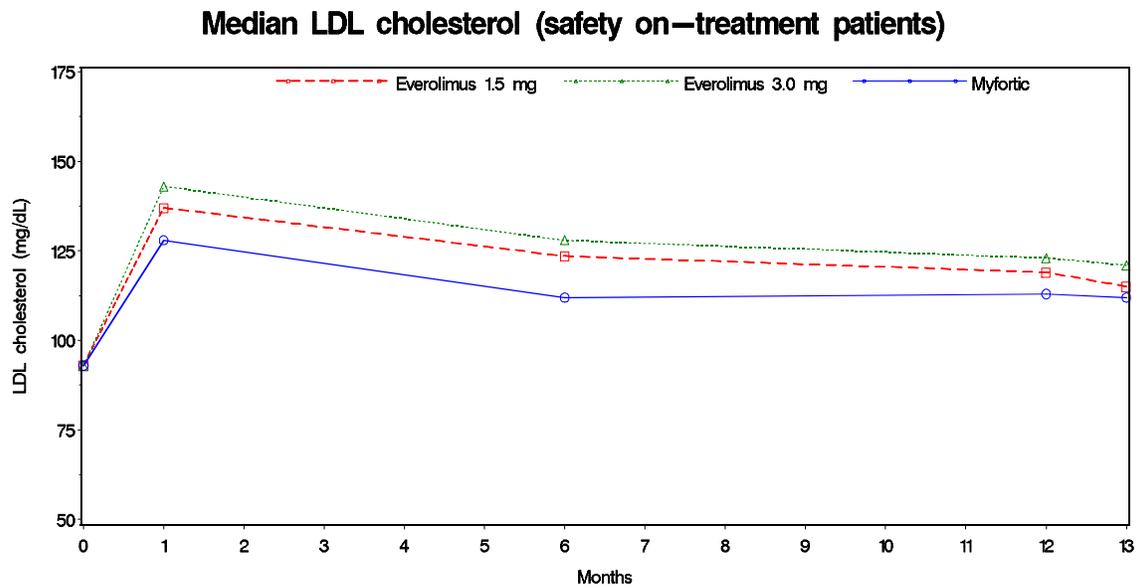
Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

Reviewer's Comment: We see a similar trend with triglyceride values to the trend we have seen with cholesterol values. As shown in Figure X, starting at Month 9 the median values in the Myfortic group overlap with the upper bound of normal range (150 mg/dL) while the median values in both of the everolimus groups continue to stay well above the normal

range. There is a statistically significant difference between both of the everolimus treatment groups and the Myfortic group.

LDL, HDL and total cholesterol to HDL ratio were assessed at baseline, months 1, 6 and 12. Few measurements were obtained at other study visits and were therefore excluded in the analysis. At baseline, no differences were noted among treatment groups. Post-baseline LDL and HDL levels were statistically significantly different between everolimus 1.5 mg and Myfortic at month 1 (p-value=0.0086) and at month 12 TEP (p-value=0.0158) for LDL (Figure 17) and month 6 (p-value=0.0013) and at month 12 TEP (p-value = 0.0002) for HDL (data not shown). Post-baseline total cholesterol to HDL ratio medians in the everolimus 1.5 mg group were greater than in the Myfortic group except at month 6, though treatment differences were not statistically significant.

Figure 17. Median LDL Cholesterol
(Source: Safety Review by John S. Yap Ph.D)



Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

Table 47 LDL Cholesterol Levels at Month 12 and Month 12 TEP (mmol/L)*
 (Source: Table 14.3-2.6a page 980, CSR)

Visit	Treatment Group	n	mean	s.d.	median	min	max	p-value of Wilcoxon Rank-Sum test	
								vs Myfortic	vs RAD 3.0mg
Month 12	RAD 1.5mg	185	3.20	1.089	3.08	0.9	7.2	0.143	0.095
	RAD 3.0mg	175	3.43	1.250	3.18	1.0	9.1	0.002	
	Myfortic	201	3.05	1.149	2.92	0.8	9.4		
Month 12 TEP	RAD 1.5mg	259	3.25	1.174	2.97	0.9	7.7	0.015	0.390
	RAD 3.0mg	259	3.36	1.283	3.13	0.7	9.1	0.001	
	Myfortic	260	2.98	1.186	2.90	0.6	9.4		

* mmol/L values need to be multiplied by 38.6 to convert into mg/dL values. Hence at M12 TEP mean LDL values are 125 mg/dL (3.25x38.6) in the everolimus 1.5 mg group and 115 mg/dL (2.98x38.6) in the Myfortic group.

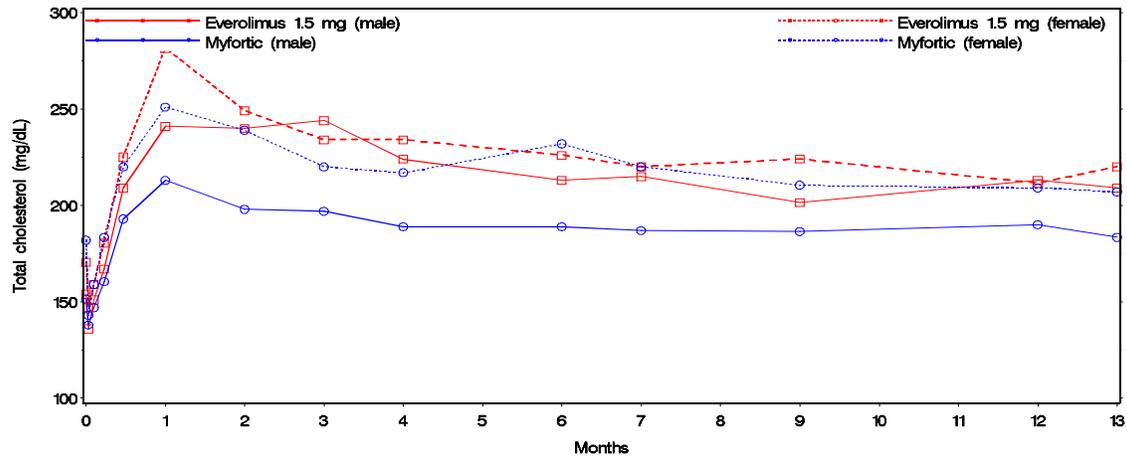
Reviewer's Comment: According to the more recent research and KDIGO¹² LDL is better correlated with cardiovascular risk compared to total cholesterol values. According to both the FDA's analysis and the Applicant's analysis, LDL values in the everolimus 1.5 mg group were significantly higher than the same values in the Myfortic group both at Month 12 and Month 12 TEP.*

Subgroup Analyses of Hyperlipidemia by Gender, Race, Age and Diabetes Status

The following analyses were performed by John Yap PhD, FDA statistical Reviewer. Median total cholesterol levels among males in the everolimus 1.5 mg group were consistently higher than those among males in the Myfortic group and the treatment groups were significantly different at all visit windows except at baseline and day 1. Among females, differences between the everolimus 1.5 mg and Myfortic groups were only observed at months 1 (p-value 0.0449), 2 (p-value 0.0215) and 3 (p-value 0.0420), as shown in Figure 18. Thus, it appears that the statistical differences that were seen earlier between the everolimus 1.5 versus Myfortic groups may have been driven by the subset of males in the study. *Note: These comparisons are unadjusted.*

12 KDIGO, American Journal of Transplantation 2009; 9 (Suppl 3): S71–S79

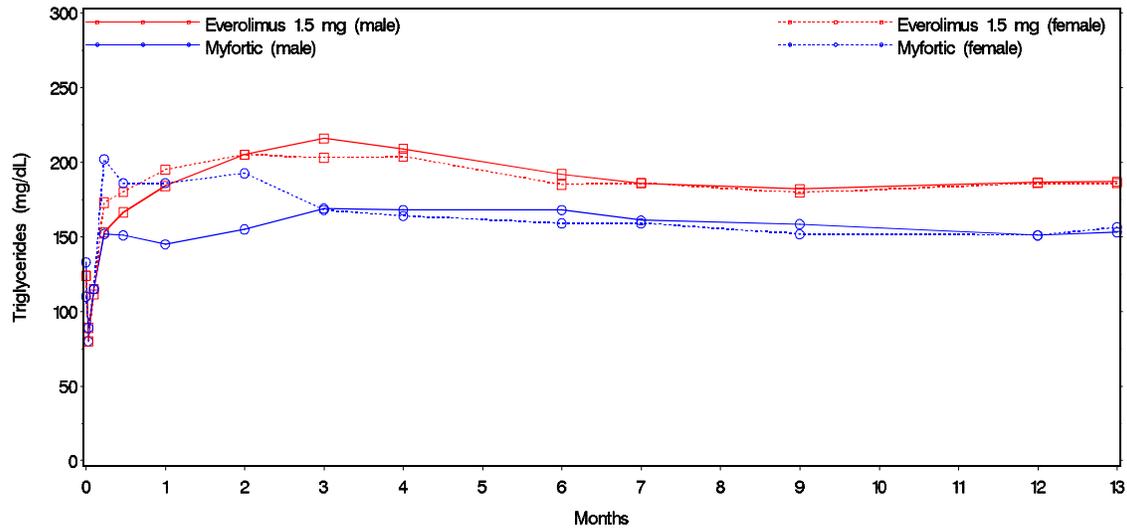
Figure 18 Median Total Cholesterol by Gender
(Source: Safety Review by John S. Yap Ph.D)
Median total cholesterol (safety on-treatment patients)



Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

Median triglyceride levels among males in the everolimus 1.5 mg group were consistently higher than among males in the Myfortic group. The differences between treatment groups were statistically significant at all visit windows except at baseline and days 1, 3, 7 and 14. A similar trend was found among females, with statistically significant differences noted between the everolimus 1.5 mg and Myfortic groups at months 3, 6, 7, 9 and 12, including the month 12 TEP (Figure 19). Thus, for triglyceride levels, it appears that the differences between the everolimus 1.5 versus Myfortic groups in the overall population are also seen when looking at each subgroup by gender.

Figure 19. Median Triglycerides by Gender
 (Source: Safety Review by John S. Yap Ph.D)
Median triglycerides (safety on-treatment patients)



Note: Month 13 represents the month 12 treatment endpoint consisting of the last post-baseline on-treatment observation up to and including the month 12 visit.

There were no notable treatment by gender effects or trends observed in subgroup analyses of LDL, HDL and total cholesterol to HDL ratio.

Table 48 showing the percentage of patients with notably high levels of cholesterol and triglyceride values and the patients with notably high Cholesterol/LDL ratios in the study. Notably high levels, as defined in the protocol by the Applicant, were < 350 mg/dL for cholesterol and 500 mg/dL for triglycerides. According to the 12 month on-treatment analysis, 15.7% of the patients in the everolimus 1.5 mg group have total cholesterol levels > 350 mg/dL compared to 6.3% of the patients in the Myfortic group. The same trend is seen for for serum triglycerides.

Normal ranges in mmol/L:
 Cholesterol (total): 2.2 - 5.2 (Notable Range: GT 9)
 Cholesterol (LDL): 1.6 - 3.3
 Cholesterol (HDL): 1 - 1.9
 Triglycerides: 0.3 - 1.7 GT 8.4
 Cholesterol/HDL (Ratio): 1 - 5 GE 5 and LE 7 or GT 7

Table 48 Patients with Notably High Lipid Values at Month 12*
 (Source Table 14.3-2.7, on page 1267 of CSR)

Table 14.3-2.7 (Page 6 of 8) Incidence Rates of Patients with Post-baseline Laboratory Abnormalities Based on Notable Criteria (Safety Population - 12 Month On-treatment Analysis)					
Variable	Notable Criteria	RAD 1.5mg N=274 n (%)	RAD 3.0mg N=278 n (%)	Myfortic 1.44g N=273 n (%)	Difference/95%CI for RAD 1.5mg-Myfortic RAD 3.0mg-Myfortic RAD 1.5mg-RAD 3mg
Lipids					
- Cholesterol (total) [mmol/L]	High: GT 9.0 mmol/L	43 / 274 (15.7%)	46 / 278 (16.5%)	17 / 272 (6.3%)	9.4% (4.3, 14.6) 10.3% (5.1, 15.5) -0.9% (-7.0, 5.3)
- Triglycerides [mmol/L]	High: GT 8.4 mmol/L	12 / 274 (4.4%)	17 / 278 (6.1%)	7 / 272 (2.6%)	1.8% (-1.3, 4.9) 3.5% (0.2, 6.9) -1.7% (-5.5, 2.0)
- Cholesterol/HDL (Ratio)	High: GE 5 but LE 7	68 / 259 (26.3%)	95 / 259 (36.7%)	81 / 261 (31.0%)	-4.8% (-12.5, 3.0) 5.6% (-2.5, 13.8) -10.4% (-18.4, -2.5)
	Very High: GT 7	20 / 259 (7.7%)	13 / 259 (5.0%)	17 / 261 (6.5%)	1.2% (-3.2, 5.6) -1.5% (-5.5, 2.5) 2.7% (-1.5, 6.9)

* Values in the table are reported in mmol/L. A value of 9.0 mmol/L total cholesterol is approximately equal to 350 mg/dL of total cholesterol (conversion factor: multiply by 38.67 for total, HDL and LDL cholesterol: multiply by 88.57 for serum triglycerides).

Reviewer's Comment: In the everolimus 1.5 mg group almost three times as many patients (16% vs. 6%) have total cholesterol levels above 350 mg/dL and almost twice as many patients (4.4% vs. 2.6%) have triglyceride values above 500 mg/dL compared to the Myfortic group.

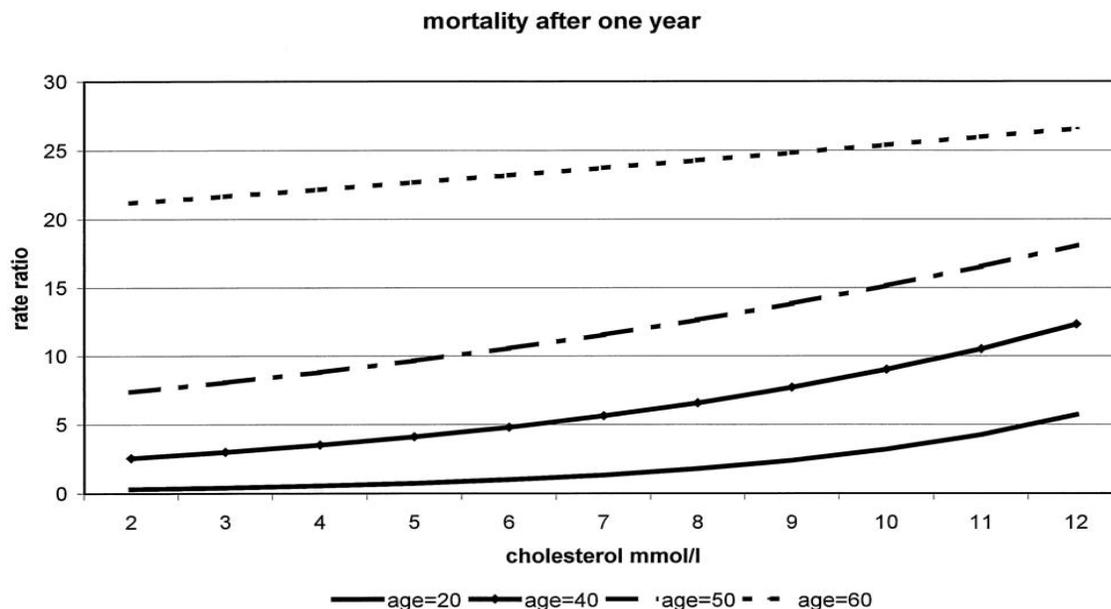
It is important to remember that the upper levels of normal range are 200 mg/dL for cholesterol and 150 mg/dL for triglycerides. Therefore the Applicant's notably high levels can be considered very high values, potentially with serious cardiovascular clinical consequences. This is a very concerning finding for the everolimus 1.5 mg group, especially in light of the 39 year old patient with normal pre-transplant lipid values who developed hyperlipidemia after the transplant and died on Day 85 due to myocardial infarction.

Clinical Significance

Hyperlipidemia is common in chronic kidney disease patients and the incidence increases after kidney transplantation. Various immunosuppressants, including CsA, corticosteroids, and M-TOR inhibitors, have been recognized as a major contributor to dyslipidemias seen after transplant.

Both serum cholesterol and recipient age are independent variables influencing the RR (relative risk) for patient death, adjusted for all other variables in the model.¹⁴ The variables included in the study were cholesterol, creatinine, proteinuria, and hypertension at 1 year after transplantation, recipient and donor age and gender, HLA-mismatches on A and B locus, recipient race, original disease, and transplantation period. The simultaneous risk is defined as a continuous function of serum cholesterol for four ages (20, 40, 50, and 60 years). It is expressed relative to a cholesterol level of 6 mmol/L (240 mg/dL) and a 20-year-old patient. Figure 20 shows the influence of the interaction of cholesterol and recipient age relative to the rate of a 20-year-old with cholesterol of 6 mmol/L (240 mg/dL). The negative influence of high serum cholesterol is largest in the youngest patients. In the elderly, the rate increase caused by cholesterol is outweighed by the larger rate caused by other factors associated with advanced recipient age.¹³

Figure 20. Simultaneous Influence of Serum Cholesterol and Recipient Age on the Relative Risk of Death. (Source: Reference No.15)



The solid line is the regression line obtained with the regression equation when the RR for recipient age is 1. The influence of other recipient ages on the influence of cholesterol on the RR is plotted according to the regression equation.

Table 49 below compares the relative risk of developing ischemic heart disease in the kidney transplant recipients compared to the control group in relation to the presence of various known risk factors like hypercholesterolemia and diabetes. (Control subjects are from the Framingham Heart Study).

13 Roodnat JI, Mulder PG, Zietse R, Rischen-Vos J, van Riemsdijk IC, IJzermans JN, Weimar W. Cholesterol as an independent predictor of outcome after renal transplantation. *Transplantation* 2000 Apr 27;69(8):1704-10

Table 49. Relative Risk of Developing Ischemic Heart Disease in Kidney Transplant Recipients¹⁴
 (Source: Reference No.14)

Risk factor	Relative risk			
	Men		Women	
	Control	Transplant recipient	Control	Transplant recipient
Age	1.05	1.06 ^a	1.40	1.10
Cholesterol (mg/dL)				
<160	0.52	0.00 ^b	0.77	0.00 ^b
160–199	1.00 ^c	1.00 ^c	1.00 ^c	1.00 ^c
200–239	1.19	2.39	1.23	2.07
240–279	1.66	2.02	1.28	2.44
>280	1.93	2.25	1.71	1.84
Blood pressure (mm Hg)				
<120 and <80	1.00	0.25	0.59	0.56
120–129 or 80–84	1.00 ^c	1.00 ^c	1.00 ^c	1.00 ^c
130–139 or 85–89	1.33	1.05	0.93	1.26
140–159 or 90–99	1.68	1.19	1.30	1.63
≥160 or ≥100	1.86	1.47	1.59	0.31
Diabetes mellitus	1.53	2.78 ^a	1.82	5.40 ^a
Smoking	1.69	1.95 ^a	1.34	1.82

Reviewer’s Comment: As shown in Table 48 above even mild elevations in cholesterol levels may double the risk of developing ischemic heart disease in kidney transplant recipients unlike the milder increase of risk in the general population. Also as mentioned in the article by Roodnat published in *Transplantation*¹¹ the effect is even bigger in younger patients.

14 Davidson J, Wilkinson A, Dantal J, et al. New-onset diabetes after transplantation: 2003 International Consensus Guidelines. *Transplantation* 2003; 75: SS3.

The analysis shows that in Study A2309 the median values for both the total cholesterol and triglycerides are well above the upper bound of the normal range while the median values in the Myfortic group overlap or come down to the normal range especially towards the end of the 12 month study period. The differences between the Myfortic group and the everolimus groups are statistically significant.

Also the data shows that more patients fail to respond adequately to statin treatment in the everolimus 1.5 mg group compared to the Myfortic group with significantly higher CK values although the median and the mean CK values are within the normal range. High cholesterol and lipid values in general are well established risk factors for developing cardiovascular disease in the general population.

There is a substantial number of publications including the ones referenced in this review that shows that this adverse effect of high lipid levels is also valid for the transplant patients as well. Recently published Kidney Disease Guidelines (KDIGO) by the AST (American Society of Transplantation) also recommends lowering the serum lipid levels in kidney transplant patients for the same reasons⁷:

“Observational studies suggest that hypercholesterolemia and increased LDL-C are independently associated with CVD events in KTRs (Kidney Transplant Recipients)”
Chapter 16, page S76

In this study a 39 year old male patient (0124-00076) whose death was attributed to acute myocardial infarction developed severe dyslipidemia (hypercholesterolemia) after the transplant which gradually worsened until his death on Day 85. His total cholesterol increased from 147 mg/dL to 432 mg/dL and his LDL cholesterol increased from 81 mg/dL to 212 mg/dL (normal levels: up to 129 mg/dL) during the course of the study. Although this patient had a history of hypertensive heart disease the rapid rise of all lipid levels from normal range to very high values in a short period of time might have contributed to his death.

As mentioned above in the everolimus 1.5 mg group it is 2-3 times more likely to have cholesterol levels above 350 mg/dL and triglyceride levels above 500 mg/dL compared to the Myfortic group.

As explained in the text above LDL values (which is claimed to correlate better with cardiovascular risk in recent literature) in the everolimus 1.5 mg group are also significantly higher than the same values in the Myfortic group both at M12 and M12 TEP.

Hypertriglyceridemia observed in association with M-TOR inhibitors may also contribute to the already high incidence of pancreatitis observed in these patients (over 1% according to Novartis database).

7.3.4.4 Wound Healing

The applicant identified AEs related to wound healing events through a retrospective search of the AE and infectious events databases. Identified terms were reviewed by their clinical team to determine relevance and then paper CRFs were dispatched to the sites for further information regarding the events prior to database lock.

Based on the applicant's analysis of all the relevant preferred terms, including lymphocele, seroma, hematoma, dehiscence, incisional hernia and others; the overall incidence of wound events was 35% in the everolimus 1.5 mg group, 38.8% in the everolimus 3.0 mg group, and 25.6% in the Myfortic group.

As shown in Table 50, incisional wound complications were more frequent in the two everolimus groups compared to the Myfortic group with the highest number occurring in the 3.0 mg group. In each of the Dehiscence, Hernia and Infection categories, more patients required surgical intervention (i.e., intraoperative repair or debridement/drainage) in the everolimus groups compared to the Myfortic group. The total number of surgical interventions was nine in the everolimus 1.5 mg group, 22 in the everolimus 3.0 mg group, and nine surgical interventions in the Myfortic group. (See *shaded rows in the table*)

Wound dehiscence and impaired healing resulted in study drug discontinuations in one patient in the everolimus 1.5 mg group, six patients in the everolimus 3.0 mg group, and none in the Myfortic group.

Wound-related SAEs were reported in six patients in the everolimus 1.5 mg group, seven in the everolimus 3.0 mg group, and three in the Myfortic group. A higher incidence of wound-related SAEs in the everolimus groups is consistent with the known adverse effect of M-TOR inhibitors on the wound-healing process.

Table 50. Management for Patients with Any Incisional Wound Complications
(Source: Applicant's analysis submitted upon request)

Type of Incisional Wound Complication	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
Total Number of Patients	37 (13.5)	48 (17.3)	28 (10.3)
Dehiscence	19 (6.9)	27 (9.8)	13 (4.7)
Non-surgical observation	3 (1.1)	6 (2.2)	3 (1.1)
Intraoperative repair	6 (2.2)	7 (2.5)	3 (1.1)
Local wound care	10 (3.6)	16 (5.7)	7 (2.5)
Hernia	10 (3.6)	11 (3.9)	6 (2.2)
Non-surgical observation	3 (1.1)	5 (1.7)	4 (1.4)
Intraoperative repair	7 (2.5)	6 (2.2)	2 (0.7)
Infection	20 (7.2)	23 (8.2)	15 (5.4)
Intravenous antibiotics	10 (3.6)	12 (4.3)	7 (2.5)
Local wound care	13 (4.7)	17 (6.1)	12 (4.3)
Intraoperative debridement/drainage	6 (2.2)	9 (3.2)	4 (1.4)
Oral antibiotics	12 (4.3)	16 (5.7)	9 (3.2)
Other	1 (0.4)	3 (1.1)	3 (1.1)

Similar to the incidence of wound-related events, fluid collections (lymphoceles and seromas) were also more commonly reported in the everolimus groups compared to the Myfortic group, as shown in Table 51. Hematoma and urinomas are not included in this table since their mechanism is related to surgical technique, coagulation defects (hematomas); or distal ureteral necrosis or in some cases due to poor healing of the uretero-neocystostomy anastomosis (urinomas). On the other hand, seromas and lymphoceles have a common mechanism of development. Both usually develop as a result of excessive transudation of fluids across the membranes or due to failure of the transected lymphatics to heal following surgery.

Lymphocele led to drug discontinuations in three patients in the everolimus 1.5 mg group, four patients in the everolimus 3.0 mg group, and none in the Myfortic group. (See Table 50 above)

The number of surgical or percutaneous interventions (i.e., percutaneous drainage or intraoperative drainage) required for seromas and lymphoceles is also higher in the everolimus groups compared to the Myfortic group (24, 43, and 15 interventions, respectively). (See shaded rows in the table)

Table 51. Management of Fluid Collections
 (Source: Applicant's analysis submitted upon request)

Type of Fluid Collection	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic N=273 n (%)
Total Number of Patients	28 (10.2)	48 (17.2)	17 (6.2)
Seroma	8	13	3
Observation	3 (37.5)	4 (30.8)	2 (66.7)
Percutaneous drainage	5 (62.5)	6 (46.2)	1 (33.3)
Intraoperative drainage	1 (12.5)	2 (15.4)	0
Intravenous antibiotics	1 (12.5)	2 (15.4)	0
Other	1 (12.5)	4 (30.8)	0
Lymphocele	20	35	14
Observation	9 (45.0)	14 (40.0)	9 (64.3)
Percutaneous drainage	11 (55.0)	22 (62.9)	7 (50.0)
Intraoperative drainage	7 (35.0)	13 (37.1)	7 (50.0)
Intravenous antibiotics	6 (30.0)	4 (11.4)	6 (42.9)
Other	0	2 (5.7)	1 (7.1)

Reviewer's Comments:

As shown in Figure 17 and Figure 18 below in graphical form more patients required surgical and non surgical (mainly percutaneous drainage for fluid collections) interventions in the everolimus 1.5 mg group compared to the Myfortic group for the treatment of their wound related complications. This higher requirement of surgical and non-surgical interventions in the everolimus 1.5 mg group shows that not only the number of wound related complications was higher in number but they were also more severe in nature in the everolimus 1.5 mg group.

Figure 21. Surgical Intervention Rates for the Treatment of Wound Complications

Source: Produced by the Clinical Reviewer from the data in Table 50

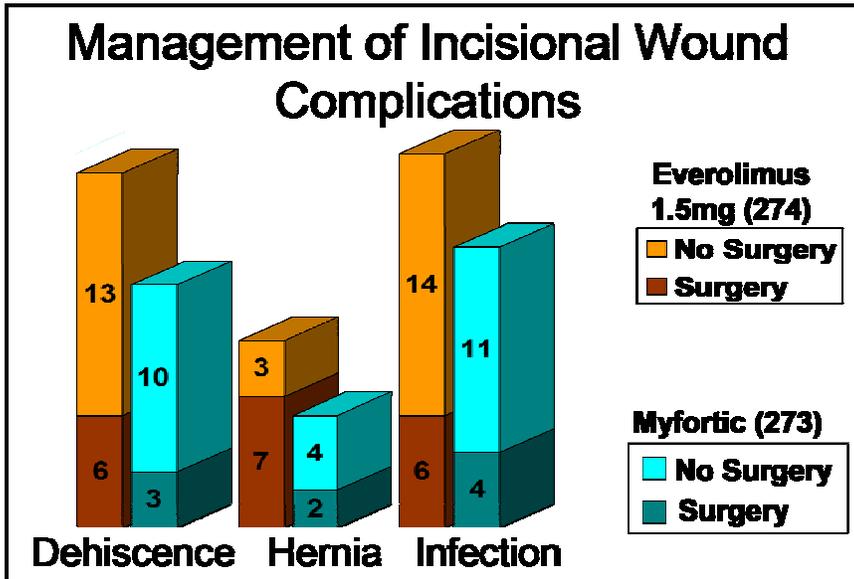
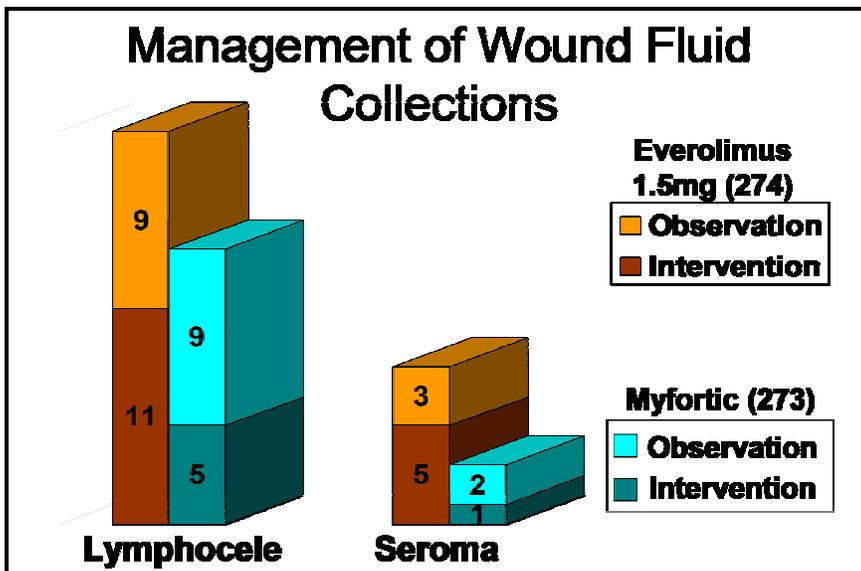


Figure 22. Intervention (Surgery and Percutaneous) Rates for the Treatment of Wound Fluid Collections

Source: Produced by the Clinical Reviewer from the data in Table 51



Reviewer's Comments: *In conclusion, the analyses performed by the Applicant and summarized above show that in the everolimus 1.5 mg group there is an increased incidence and severity complications (as measured by the requirement for surgical and non-surgical interventions) of overall wound related complications compared to the Myfortic group which is also statistically significant.*

Lymphocele and lymphorrhoea led to drug discontinuations in 2.6% of the patients in the everolimus 1.5 mg group and in 2.2% of the patients in the everolimus 3.0 mg group while no patient discontinued the study drug due to wound events in the Myfortic group.

Among all the patients who died during the 12 month period wound related problems (mainly infections and dehiscences and lymphoceles) were noted in 5 patients in the everolimus 1.5 mg group, 4 patients in the everolimus 3.0 mg group and in 1 patient in the Myfortic group:

Everolimus 1.5 mg Group:

1-0125-00002: Lymphocele on Day 16, died on Day 22 due to septic shock

2-0115-00020: Day 16 graft nephrectomy, infection abdominal sepsis, died on Day 28

3-0100-00008: Day 74, ureteral necrosis, urinoma, wound infection, cellulitis, died on Day 148

4-0516-00002: Day 48 incisional hernia, Day 102 edema, died on Day 156

5-0118-00012: Day 15 lymphocele surgical debridement and drainage died due to malignant melanoma on Day 122

Everolimus 3.0 mg group:

1-0100-00002: Day 16: perinephric collection-urinary fistula, D30: recurrence urinary fistula, Day 50 : recurrence urinary fistula, died on D269 due to septic shock

2-0114-00001: Day 30: wound infection, died on Day 243 due to pneumonia

3-0532-00008: Day 24: Wound dehiscence Day 175: severe renal abscess, died on day 175 due to renal abscess and heart failure

4-0173-00003: Day 17: urine leak, infection Day 89: purulent discharge in the wound, died on D185 due to fluid overload (no access to hemodialysis)

Myfortic group:

1-0521-00007: Lymphocele on Day 9 (treated with percutaneous drainage), died on day 356 due to road traffic accident on the scene.

It is not possible to associate the deaths with the wound complications observed in these patients especially for the cases with a long interval between the wound complication and the death of the patient. In both of the everolimus groups deaths tended to be due to multiple factors at least one of which was due to M-TOR

class toxicities. On the contrary in the Myfortic group there is only one wound related event: a lymphocele which did not require surgery for treatment and this patient died on Day 356 due to road traffic accident. In this patient since it is almost certain that the death is not associated with the study drug it may not be relevant to count the lymphocele in this patient among the other cases mentioned here.

Although it is difficult to explain the association between this high occurrence of wound complications among the patients who died in both of the everolimus groups and the death event it is almost certain that there is a trend. In the everolimus 1.5 mg group, five of the 7 patients who died, in the everolimus 3.0 mg group 4 of the 10 patients who died developed wound related complication sometime after the transplant surgery compared to 1 out of 6 patients who died in the Myfortic group. Wound complications observed in the everolimus groups may be a surrogate for the patient's intolerance to the study drug.

As a conclusion although wound related complications reported as adverse events may not reach high percentages their high occurrence among the patients who died in both of the everolimus groups is very concerning and may be a surrogate for M-TOR toxicity.

7.3.4.5 *Fluid Accumulation, Including Peripheral Edema, Ascites, and Pleural Effusions*

At month 12, (Table 51) the incidence of edema related events was statistically significantly higher in both everolimus groups than in the Myfortic group (55.5% and 54.7% versus 45.1%, p-value was 0.02 and 0.03 respectively, Fisher's exact test).

Table 52. Summary of Edema Related Event by Preferred Term and Treatment Group (Safety Population – 12 Month Analysis)

(Source: Applicant's analysis submitted upon request)

	Everolimus 1.5 mg (N=274)	Everolimus 3.0 mg (N=278)	Myfortic 1.44 gm (N=273)
Any edema related event	152 (55.5%)	152 (54.7%)	123 (45.1%)
Edema peripheral	123 (44.9%)	121 (43.5%)	108 (39.6%)
Fluid overload	20 (7.3%)	16 (5.8%)	17 (6.2%)
Edema	20 (7.3%)	16 (5.8%)	14 (5.1%)
Generalized edema	6 (2.2%)	6 (2.2%)	3 (1.1%)
Fluid retention	3 (1.1%)	7 (2.5%)	4 (1.5%)
Pitting edema	3 (1.1%)	2 (0.7%)	6 (2.2%)
Gravitational edema	1 (0.4%)	0 (0%)	0
Localized edema	1 (0.4%)	5 (1.8%)	3 (1.1%)
Edema due to renal disease	1 (0.4%)	0	0
Lymphedema	0	1 (0.4%)	0
95% CI (everolimus versus Myfortic) P-value*	(2.1%, 18.8%) p=0.02	(1.3%, 17.9%) p=0.03	N/A

Preferred terms were sorted by descending order of frequency in the everolimus 1.5 mg group

A patient with multiple occurrence of an event was counted only once in an event category.

* P-value for Fisher's exact test

Table 52 shows the incidence of AEs due to major fluid collections such as edema and other types of fluid collections was 44.9% in the 1.5 mg everolimus group, 43.2% in the 3.0 mg everolimus group and 39.6% in the Myfortic group. SAEs due to peripheral edema and pleural effusions were observed in three patients in the everolimus 1.5 mg group, six patients in the everolimus 3.0 mg group, and none in the Myfortic group. Fluid accumulation is a known effect of the class of M-TOR inhibitors and can cause an increased incidence of pleural and pericardial effusions and can also increase the permeability of serosal membranes in the body to proteins and fluids. Pericardial effusions and ascites were rarely reported.

Table 53. Types of Major Fluid Collections and Outcome
 (Source: Applicant's analysis submitted upon request)

Type of Fluid Collection	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
Peripheral edema (AE)	123 (44.9)	120 (43.2)	108 (39.6)
Severe peripheral edema	8 (2.9)	4 (1.4)	0
SAE	1 (0.4)	5 (1.8)	0
Drug discontinuation	3 (1.1)	1 (0.4)	0
Pleural effusions (AE)	7 (2.6)	5 (1.8)	5 (1.8)
SAE	2 (0.7)	1 (0.4)	0
Drug discontinuation	0	0	0
Pericardial effusions (AE)	1 (0.4)	1 (0.4)	1 (0.4)
SAE	0	0	0
Drug discontinuation	0	0	0
Ascites (AE)	1 (0.4)	0	0
SAE	0	0	0
Drug discontinuation	0	0	0

Reviewer's comment: *Peripheral edema possibly contributed to the death of one patient in Study A2309 in the everolimus 1.5 mg group. This patient (0516-00002) was treated with furosemide because of edema on day 102 and died on day 156 due to congestive heart failure. This patient already had a history of congestive heart failure at the time of transplant but this might have worsened due to everolimus treatment.*

7.3.4.6 Major Cardiac Adverse Events

A specific case report form was designed in order to capture information on the occurrence of major cardiac events (MACE) in the study. The applicant collected information on the following AEs:

- acute myocardial infarction
- congestive heart failure
- percutaneous coronary intervention
- coronary artery bypass graft
- automatic internal cardiac defibrillator
- cerebrovascular accident
- peripheral vascular disease

The total number of patients with MACE was similar in the everolimus 1.5 mg group and the Myfortic groups (2.6% and 2.9%), but the incidence was higher in the everolimus 3.0 mg group (5.8%), as shown in Table 53. There were more patients with acute

myocardial infarction, congestive heart failure and percutaneous cardiac intervention in the 3.0 mg group. The rates of drug discontinuations due to cardiac events were two in the everolimus 1.5 mg group, four in the everolimus 3.0 mg group and one in the Myfortic group.

Table 54. Number (%) of Patients with Major Cardiac Adverse Events (MACE)
 (Source: Table 12-30 on page 222 of CSR)

MACE Terms	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic N=273
Any MACE	7 (2.6)	16 (5.8)	8 (2.9)
Acute myocardial infarction	2 (0.7)	9 (3.2)	4 (1.5)
Congestive heart failure	3 (1.1)	6 (2.2)	2 (0.7)
Percutaneous cardiac intervention	1 (0.4)	3 (1.1)	0 (0.0)
Coronary artery bypass grafting	1 (0.4)	0 (0.0)	0 (0.0)
Automated implanted cardiac defibrillator	0 (0.0)	0 (0.0)	1 (0.4)
Cerebral vascular accident	1 (0.4)	0 (0.0)	0 (0.0)
Peripheral vascular disease	0 (0.0)	1 (0.4)	1 (0.4)

Reviewer's comment: Although the overall incidence of MACE events were much higher in the everolimus 3.0 mg group compared to the other two groups in the study, the everolimus 1.5 mg group and the Myfortic group look similar to each other except for the numerically higher number of MIs in the Myfortic group (4 vs. 2). The reviewer decided to look into the MI events occurring during the study more closely and the results are shown in Table X below.

Table 55 Myocardial Infarctions Reported as MACE events

Source: Produced by the Clinical Reviewer from the information in Table 12-31 on page 223 of the CSR

Age, Sex	Day of MI	Day D/C Med	Outcome	Treatment Group
0532/0003 (49, M, C,)	326	46	Unknown	Everolimus 1.5 mg
0124-00076 (39, M, C)	85	85	Death (Hx. Of HTN)	Everolimus 1.5 mg
0544/00012 (61, M,C)	34	33	Death (Hx. of DM, quadruple bypass and MI)	Myfortic
0502/00016 (58, M, B,)	251	6	Death (On Sirolimus)	Myfortic (cardiac arrest at home)
0528/00014 (69, M,B)	2	4	Resolved (Hx. of DM, CAD, HTN, Gout)	Myfortic
0540/00007 (67M,B)	74	74	Resolved (Hx. of DM, HTN)	Myfortic (No MI on record?)

Clinical Reviewer's Comments: *The following is a more detailed discussion of the patients in Table 55 above.*

Everolimus 1.5 mg group:

Patient 0532/0003: This patient was lost to follow up after he had myocardial infarction, which raises doubts about his survival after the event. The MI is most likely not be associated with the study medication (everolimus) since the MI occurred 278 days after stopping the study medication.

Patient 0124-00076: This 39 year old patient had high lipid levels at the time of death as explained in Section 7.3.1., Deaths.

Myfortic group:

Patient 0544/00012: This patient had a history of quadruple coronary bypass, which was a very important risk factor for a subsequent MI

Patient 0502/00016: This patient was on Sirolimus starting Day 4 until his death on Day 251 so the MI and his death due to MI is probably associated with sirolimus.

Patient 0528/00014: This patient had the MI on the second day after transplant and had been on study medication for only one day. Therefore, due to the early occurrence of the MI, factors other than the study medication may have contributed to the event.

Patient 0540/00007: In this patient's narrative there is no record of MI. On Day 73 this patient had surgery (resection of distal transplant ureter with neoureterocystostomy) and on Day 74 the patient had a cardiac arrest but according to the records the event resolved on the same day. There may be various other reasons which may possibly cause cardiac arrest including electrolyte abnormalities so it is not possible to attribute the event of cardiac arrest to myocardial infarction in this patient. This patient was probably reported as a mistake.

In the reviewer's assessment only one case, 39 year old male patient (0124-00076) in the everolimus 1.5 mg treatment group can be associated with the study medication (everolimus). In this patient who had normal lipid levels before the transplant there is a clear association with the extremely high lipid levels observed after the transplant and the study medication which might have contributed to the MI and explained in more detail in the section about the deaths.

It may also be relevant to note here that according to Novartis's assessment of relevant medical histories performed by standard MEDDRA query (SMQ) (narrow search) reported on page 1784 of the CSR, there were twice as many patients with a prior history of myocardial infarction in the Myfortic group compared to the everolimus 1.5 mg group, 18 (6.6%) vs. 9 (3.3%) which probably was an unintentional imbalance of the baseline characteristics since having a prior MI increases the risk of having a second MI.

Considering the differences in baseline characteristics (twice as many prior MIs in the Myfortic group), the assessment of drug relatedness, the higher incidence of graft thromboses in the everolimus treatment groups (as discussed in Section 7,3,2,1), and unintentional mistakes in event reporting there seems to be a higher association between everolimus and the occurrence of MI compared to the possible association between Myfortic regimen and MI. Another confirmation of this trend is the unusually high incidence of MIs in the higher dose everolimus 3.0 mg group of 9 cases.

7.3.4.7 *Other Thromboembolic Events*

Thromboembolic events reported as AEs, other than graft thrombosis, are shown in Table 56. There were 13 (4.7%) in the 1.5 mg everolimus group, 16 (5.8%) in the 3.0 mg everolimus group and 9 (3.3%) in the Myfortic group. Two patients with HUS (Hemolytic Uremic Syndrome) and one each with TTP (Thrombotic Thrombocytopenic Purpura) and TMA (Thrombotic Microangiopathy) were reported in the everolimus 1.5 mg group.

The number of SAEs related to thrombotic events was: eight in the everolimus 1.5 mg group and four in each of the everolimus 3.0 mg and Myfortic groups. (Table 55)

Deep vein thrombosis (DVT) was reported in eight patients in the everolimus 1.5 mg group, seven patients in the everolimus 3.0 mg group, and five patients in the Myfortic group. Pulmonary embolism (PE) was reported in one, two, and two patients in the everolimus and Myfortic groups, respectively. Although there is a trend of increasing DVTs in the everolimus 1.5 mg and the 3.0 mg groups, there is no similar trend for PE. The trend seen with the DVTs is compatible with thrombogenic potential of the M-TOR inhibitor class of drugs.

Table 56. Incidence Rates of Thromboembolic Adverse Events
 (Source: Applicant's analysis submitted upon request)

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
Any Thromboembolic AE	13(4.7)	16(5.8)	9(3.3)
Blood and Lymphatic System Disorders -Total	4(1.5)	0	0
Hemolytic uremic syndrome	2(0.7)	0	0
Microangiopathic hemolytic anemia	0	0	0
Thrombotic microangiopathy	1(0.4)	0	0
Thrombotic thrombocytopenic purpura	1(0.4)	0	0
Acute myocardial infarction	2 (0.7)	9 (3.2)	4 (1.5)
Respiratory, Thoracic and Mediastinal Disorders - Total	1(0.4)	2(0.7)	2(0.7)
Pulmonary embolism	1(0.4)	2(0.7)	2(0.7)
Vascular Disorders - Total	8(2.9)	7(2.5)	5(1.8)
Deep vein thrombosis	8(2.9)	7(2.5)	5(1.8)

Reviewer's Comment: *Thromboembolic events, other than MIs (which were discussed previously in Section 7.3.4.6), were primarily DVTs and were reported*

more frequently in both of the everolimus groups compared to the Myfortic group. This is an expected trend knowing the thrombogenic effects of M-TOR.

Also TTP, TMA and HUS were only observed in the everolimus 1.5 mg group. These adverse events may be fatal although they are relatively uncommon. In the everolimus 1.5 mg group, TTP contributed to the graft loss in one patient (0192-00002) on Day 116.

TMA/TTP/HUS are also known to be associated with M-TOR inhibitors and the sirolimus label carries a warning regarding these AEs.

7.3.4.8 *Hematologic Abnormalities, Including Thrombocytopenia, Neutropenia, and Anemia*

Hematological events reported as AEs and SAEs are summarized in Table 56. The overall incidence of AEs was 33.9% in the 1.5 mg group, 40.3% in the 3.0 mg group, and 40.7% in the Myfortic group. SAEs were reported in eleven patients in the everolimus 1.5 mg group, ten in the everolimus 3.0 mg group, and eight patients in the Myfortic group.

One SAE each of hemolytic anemia, hemolysis, and HUS was seen in the everolimus 1.5 mg group. There were two cases of pancytopenia reported as SAEs in the Myfortic group while none were observed in the everolimus groups. Thrombocytopenia cases seem to be distributed equally across the three groups but potentially serious TTP and TMA were reported only in the everolimus group (Table 56 and 57). This is a class effect of immunosuppressants like M-TOR inhibitors and CsA as well.

Table 57. Incidence Rates of Selected Hematological Adverse Events
 Source: Table 14.3.1-1.1 on page 1325 of CSR

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 gm N=273 n (%)
Blood and Lymphatic System Disorders AEs	99 (33.9)	112 (40.3)	111 (40.7)
Anemia	70 (25.5)	86 (30.9)	68 (24.9)
Pancytopenia	2 (0.7)	4 (1.4)	4 (1.5)
Leucopenia	8 (2.9)	6 (2.2)	33 (12.1)
Neutropenia	1 (0.4)	3 (1.1)	6 (2.2)
Thrombocytopenia	3 (1.1)	10 (3.6)	6 (2.2)
Blood and Lymphatic System Disorders SAEs	11 (4.0)	10 (3.6)	8 (2.9)
Anemia	2 (0.7)	5 (1.8)	2 (0.7)
Pancytopenia	0	0	2 (0.7)
Leucopenia	2 (0.7)	1 (0.4)	3 (1.1)
Neutropenia	0	1 (0.4)	1 (0.4)
Thrombocytopenia	2 (0.7)	3 (1.1)	2 (0.7)
Blood and Lymphatic System Disorders AEs leading to Drug Discontinuations	7 (2.6)	2 (0.7)	3 (1.1)
Anemia	1 (0.4)	0	0
Pancytopenia	0	0	0
Leucopenia	1 (0.4)	0	2 (0.7)
Neutropenia	0	0	0
Thrombocytopenia	0	0	1 (0.4)
Blood and Lymphatic System Disorders AEs leading to Dose Adjustment/Interruption	10 (3.6)	12 (4.3)	31 (11.4)
Anemia	1 (0.4)	3 (1.1)	4 (1.5)
Pancytopenia	2 (0.7)	0	2 (0.7)
Leucopenia	4 (1.5)	4 (1.4)	23 (8.4)
Neutropenia	0	1 (0.4)	2 (0.7)
Thrombocytopenia	3 (1.1)	5 (1.8)	3 (1.1)

Thrombocytopenia

Thrombocytopenia was reported as an AE in three patients in the everolimus 1.5 mg group, ten in the everolimus 3.0 mg group, and six in the Myfortic group. Notably low platelet counts (defined as $< 50 \times 10^9 /L$ by the Applicant) were not reported for any patient in the everolimus 1.5 mg group, but were reported for three patients in the everolimus 3.0 mg group, and one in the Myfortic group.

Reviewer's Comment: *Thrombocytopenia was thought to contribute to one patient's death in the everolimus 3.0 mg group.*

Patient No. 0549-0001: This 55 year old male had a laparotomy on Day 16 for suspected intestinal obstruction was found to have retroperitoneal hematoma. His baseline platelet count was 165,000. On Day 3 platelet count was down to 128,000, and on Day 14 it was down to 38,000. Between Day 7 and Day 14 his hemoglobin level also dropped from 15.4 gm/dL down to 11.4 gm/dL. On Day 16 he had a laparotomy which disclosed the retroperitoneal hematoma. On Day 18 his platelet count was 16,000 and everolimus was discontinued because of thrombocytopenia. In this patient who also had a history of abdominal aortic aneurysm, thrombocytopenia probably contributed to the retroperitoneal bleeding.

Neutropenia

Neutropenia reported as an AE was highest in the Myfortic group: one, three, and 6 patients in the everolimus 1.5 mg, 3.0 mg and Myfortic gm groups, respectively. In a systematic review of absolute neutrophil counts, notably low values (defined by the Applicant as segmented plus band forms totaling $< 1.1 \times 10^9$ cells/L) were reported by a higher percentage of patients in the Myfortic than everolimus groups: 1.8%, 3.6% and 6.3% of patients in the everolimus 1.5 mg, 3.0 mg and Myfortic groups, respectively.

Anemia

Anemia was reported as an AE at a similar rate in the everolimus 1.5 mg (25.5%) and Myfortic 1.44 gm groups (24.9%), but the incidence was higher in the everolimus 3.0 mg group (30.9%). Notably low values for hemoglobin (as defined by the applicant as < 60 g/L) were reported in the everolimus groups, but not the Myfortic group: four and one in the everolimus 1.5 mg and 3.0 mg groups, respectively.

Reviewer's Comment: *Although overall hematologic events reported as AEs were higher in number in the Myfortic group, when we look at the number of events reported as SAEs or events that led to drug discontinuations they are similar to each other. The main difference in the number of AEs between the two groups is due to the increased incidence of leukopenia observed in the Myfortic group which hardly rose to the level of SAE in Study 2309.*

There is only one death in the study associated with a hematologic event and that is the patient 0549-0001 in the everolimus 3.0 mg group who died because of hemorrhagic shock associated with severe thrombocytopenia.

7.3.4.9 *Interstitial Lung Disease, Lung Infiltration, and Pneumonitis*

A total of six patients were reported to have interstitial lung disease identified by the Applicant using the related preferred terms (*acute interstitial pneumonitis, allergic granulomatous angiitis, alveolar proteinosis, alveolitis, alveolitis allergic, alveolitis fibrosing, alveolitis, necrotizing bronchiolitis, diffuse alveolar damage, eosinophilia myalgia syndrome, eosinophilic pneumonia, eosinophilic pneumonia acute, eosinophilic*

pneumonia chronic, interstitial lung disease, lung infiltration, necrosis of bronchioli, obliterative bronchiolitis, pneumonitis, progressive massive fibrosis, pulmonary fibrosis, pulmonary necrosis, pulmonary radiation injury, pulmonary toxicity, pulmonary vasculitis, radiation alveolitis, radiation fibrosis – lung, radiation pneumonitis, transfusion-related acute lung injury). Two cases were in the everolimus 1.5 mg group, three in the everolimus 3.0 mg group, and one is in the Myfortic group.

According to the Applicant’s assessment, one of these six cases had a biopsy confirmed diagnosis of alveolar proteinosis in the everolimus 1.5 mg group. The investigator reduced the dosage of everolimus; however, the patient died of pneumonia and sepsis two months later (0304-00016). See Section 3.3 Deaths and Table 58 below.

Table 58 Patients Reported to Have Non-infectious Lung Infiltration According to the Applicant’s Assessment
 (Source: Produced by the Clinical Reviewer from patient narratives)

Patient	Diagnosis	Outcome	Treatment
47, M 0304-00016	Alveolar Proteinosis Sepsis	Died on Day 436	Everolimus 1.5 mg
21, F 0537-00008	Interstitial lung disease (Coding error?)	Resolved	Everolimus 1.5 mg
69, M 0507-00019	Pneumonitis , MI	Died on Day 243	Everolimus 3.0 mg
61, C 0124-00072	Pneumonitis (Staph. Coag. Neg.), PE	Resolved	Everolimus 3.0 mg
68, M 0136-00002	Lung infiltration, sepsis due to unknown virus	Resolved	Everolimus 3.0 mg
66, M 0537-00005	No record of lung related pathology in narrative	Completed study	Myfortic 1.44 gm

Non-infectious pneumonitis, including pulmonary alveolar proteinosis, is a rare but serious adverse event because of the mortality risk associated with it. It can be due to different etiologies and is listed among the adverse events associated with M-TOR inhibitors. Alveolar proteinosis is a diffuse lung disease that is characterized by the alveolar and interstitial accumulation of a periodic acid-Schiff (PAS) stain-positive phospholipoprotein that is derived from surfactant. The clinical course of the disease is variable, ranging from respiratory failure to spontaneous resolution. An important feature of the disease is susceptibility to pulmonary infections. Alveolar proteinosis is also among the class effects of M-TOR inhibitors and although observed rarely may have a

fatal outcome. The suggested therapy is discontinuation of the M-TOR inhibitor and treatment of the superimposed infections.

Reviewer's Comment: *A detailed discussion of the cases in Table X follows:*

Everolimus 1.5 mg group:

Patient 0304-00016: This 47 year old male patient had a biopsy confirmed diagnosis of alveolar proteinosis and died due to pneumonia and septic shock 60 days after the diagnosis (see also Section 7.3.1, Deaths)

Patient 0537-00008: The Applicant claims that this patient was reported to have interstitial lung disease probably due to a coding error which replaced "renal interstitial fibrosis," with interstitial lung disease since the patient presented with an increased serum creatinine and was diagnosed with acute tubular necrosis.

Everolimus 3.0 mg group:

Patient 0507-00019: This 69-year-old Caucasian male who died on Day 243. According to the applicant the primary cause of death was myocardial infarction. However, the patient was also noted to have staphylococcal pneumonitis and according to the FDA's assessment, the pneumonia was felt to contribute to his death. (See also Section 7.3.1, Deaths).

Patient 0124-00072: This 61-year-old, Caucasian male who presented with fever and dyspnea and was hospitalized. A culture from the bronchoscopy grew coagulase negative staphylococcus and he was noted to have opacification and alveolar infiltration in the upper lobe of the right lung. He was treated with antibiotics and the dose of everolimus was also decreased. The patient developed a pulmonary embolism, which subsequently completely resolved along with the pneumonitis. In this case it may not be possible to completely rule out the possibility of interstitial lung disease, since this term is mentioned in the narrative and the bronchoscopy culture grew coagulase negative staphylococcus. Also, it is known from the published literature that interstitial lung disease may be superimposed by bacterial infection.

Patient 0136-00002: This 68 year old Asian male in the everolimus 3.0 mg group (0136-00002) was reported to have "sepsis due to unknown virus" in the narrative. The infiltration resolved, but it was not clear if the resolution was due to antibiotics or due to the dose reduction of everolimus or both.

Myfortic group:

Patient 0537-00005: In this 66 year old Caucasian male patients narrative there is no record of any type of lung infiltration or any other lung related pathology or suspicion of any lung or respiratory tract disease.

Five of the reported 6 cases with a possible interstitial lung disease are in the everolimus groups. The patient claimed to have interstitial lung disease in the Myfortic group does not have any record of lung disease in the patient narrative. The association between the M-TOR inhibitors and interstitial lung disease is well established and also mentioned in the Rapamune (Sirolimus) label. In study 2309 there was one death due to alveolar proteinosis and this patient was in the everolimus 1.5 mg group and the death was reported after the 12 month study period. This patient is explained in more detail in the section about deaths.

7.3.4.10 *Benign and Malignant Neoplasms*

Malignant neoplasms reported as AEs were uncommon and evenly distributed across treatments. Total neoplasms (which include non-malignant growths, such as cysts and polyps) were less frequent with both doses of everolimus than Myfortic, as shown in Table 58. The most frequently reported neoplasms in the Myfortic group were basal cell carcinoma, squamous cell carcinoma, skin papilloma and seborrhoeic keratosis, which are generally either benign or very slowly progressing tumors.

Only one patient died due to malignancy (metastatic melanoma) in the study and occurred in the everolimus 1.5 mg group. There was one patient with Epstein-Barr virus-associated lymphoproliferative disorder, also known as post-transplant lymphoproliferative disorder (PTLD) in the everolimus 3.0 mg group.

The incidence of malignancies reported as SAEs are slightly higher in the Myfortic group (1.8%, n=11) compared to the everolimus 1.5 mg group (1.5%, n=8) and everolimus 3.0 mg group (1.1%, n=4). Types of tumors reported as SAEs:

Everolimus 1.5 mg group:

Basal cell carcinoma (3), Squamous cell carcinoma (3), metastatic melanoma,

Everolimus 3.0 mg group:

Basal cell carcinoma, Squamous cell carcinoma (2), Post-transplant lymphoproliferative disorder (PTLD)

Myfortic group:

Basal cell carcinoma (5), Squamous cell carcinoma (5), Transitional cell carcinoma

Two patients discontinued study medication due to a neoplasm, one in each of the everolimus groups: malignant melanoma in the everolimus 1.5 mg group and Epstein-Barr virus associated lymphoproliferative disorder (PTLD) in the everolimus 3.0 mg group. The absence of discontinuations in other cases of neoplasms is partly indicative of the relative benign nature of these other tumors.

**Table 59. Number of Patients Reporting Neoplasms
 Safety Population 12 Month Analysis**
 (Source: Table 12-9 on page 178 of CSR)

Preferred Term	Everolimus 1.5 mg N=274, n (%)	Everolimus 3.0 mg N=278, n (%)	Myfortic 1.44 g N=273, n (%)
Total	9 (3.3)	8 (2.9)	16 (5.9)
Basal cell carcinoma	2 (0.7)	0 (0)	5 (1.8)
Benign breast neoplasm	1 (0.4)	0 (0)	0 (0)
Benign renal neoplasm	0 (0)	1 (0.4)	0 (0)
Dysplastic nevus syndrome	1 (0.4)	0 (0)	0 (0)
Epstein-Barr virus associated lymphoproliferative disorder	0 (0)	1 (0.4)	0 (0)
Fibrous histiocytoma	0 (0)	1 (0.4)	0 (0)
Hair follicle tumor benign	0 (0)	0 (0)	1 (0.4)
Lip neoplasm malignant	0 (0)	0 (0)	1 (0.4)
Lipoma	1 (0.4)	0 (0)	0 (0)
Malignant histiocytosis	0 (0)	1 (0.4)	0 (0)
Melanocytic nevus	2 (0.7)	0 (0)	2 (0.7)
Metastatic malignant melanoma	1 (0.4)	0 (0)	0 (0)
Myelodysplastic syndrome	0 (0)	1 (0.4)	0 (0)
Oral papilloma	0 (0)	0 (0)	1 (0.4)
Seborrheic keratosis	1 (0.4)	0 (0)	2 (0.7)
Skin papilloma	1 (0.4)	1 (0.4)	3 (1.1)
Squamous cell carcinoma	0 (0)	0 (0)	1 (0.4)
Squamous cell carcinoma of skin	1 (0.4)	3 (1.1)	3 (1.1)
Transitional cell carcinoma	0 (0)	0 (0)	1 (0.4)

Reviewer's comment: *The numerically higher occurrence of neoplasms in the Myfortic group compared to the everolimus groups are due to the higher incidence of basal cell, squamous cell carcinomas and benign conditions like skin papillomas and seborrheic keratosis in the Myfortic group.*

Most important tumors with regard to the associated mortality one case of malignant melanoma and one case of PTLD (Post Transplant Lymphoproliferative Disorder) listed as EBV associated lymphoproliferative disorder occurred in the everolimus groups. The patient with malignant melanoma died due to this malignancy. The reviewer's conclusion is although the number of neoplasms in the Myfortic group are higher the type of neoplasms in the everolimus groups are

more serious in nature and resulted in the death of one patient in the everolimus 1.5 mg group.

7.3.4.10 New Onset Diabetes Mellitus

According to the study protocol, new onset diabetes (NODM), was defined as diabetes post-transplantation and identified by one of the following:

1. Diabetes was reported as an adverse event;
2. Glucose (random) \geq 11 mmol/L [198 mg/dL] post-transplantation;
3. Diabetes was recorded as reason for a medication given post-transplantation,
4. In patients who were not diabetic at the time of transplantation, identified by all of the following:
 - a. Reason for transplantation was not diabetes;
 - b. Diabetes was not included in medical history;
 - c. Glucose (random) $<$ 11 mmol/L at the time of transplantation;
 - d. Diabetes was not recorded as reason for any medication given prior to transplantation.

This is the standard definition of NODM, as defined by ADA (American Diabetes Association) and WHO (World Health Organization), with one of the criteria missing (fasting plasma glucose \geq 126 mg/dL (7.0 mmol/L)), which is part of the standard definition for NODM.¹⁵

Reviewer's Comment: *Absence of this pivotal screening criterion for diabetes among the criteria utilized by the Applicant resulted in very low NODAT incidences in all of the treatment groups in Study A2309.*

The incidence of NODM was 9.1% in the everolimus 1.5 mg group, 12.2% in the everolimus 3.0 mg group, and 6.6% in the Myfortic group, as shown in Table 59. This trend is reflective of the known diabetogenic effects of M-TOR inhibitors. Although diabetes-related AEs were reported at similar rates in the everolimus 1.5 mg and the Myfortic groups, more events were reported as serious in both of the everolimus groups compared to the Myfortic group.

There were no discontinuations of study medication due to diabetes-related AEs in any of the treatment groups.

¹⁵ Davidson J, Wilkinson A, Dantal J, et al. New-onset diabetes after transplantation: 2003 International Consensus Guidelines. *Transplantation* 2003; 75: SS3.

Table 60. Disturbed Glucose Metabolism
 (Source: Table 5-24 on page 55 of the Clinical Overview)

	Everolimus 1.5 mg N=274 % (n)	Everolimus 3.0 mg N=278 % (n)	Myfortic 1.44 gm N=273 % (n)
New Onset Diabetes	9.1 (25)	12.2 (34)	6.6 (18)
SAEs			
diabetes mellitus	1.1 (3)	1.1 (3)	0.4 (1)
hyperglycemia	0.4 (1)	2.5 (7)	0.4 (1)
type 2 diabetes mellitus	0	0	0
AEs			
hyperglycemia	12.4 (34)	15.5 (43)	13.9 (38)
diabetes mellitus	5.1 (14)	7.9 (22)	7.0 (19)
type 2 diabetes mellitus	1.5 (4)	0.4 (1)	0.7 (2)
glucose tolerance impaired	0.4 (1)	0.4 (1)	0.4 (1)
impaired fasting glucose	0	0	0.4 (1)

Clinical Importance of NODAT:

According to one published article¹⁴, (Table 60) male kidney transplant recipients with diabetes have a risk factor of 2.78 and female kidney transplant recipients with diabetes have a risk factor of 5.4 for developing ischemic heart disease compared to a risk factor of 1.5 in male diabetic patients without a transplant and a risk factor of 1.8 female diabetic patients without a transplant.¹⁴ These numbers suggest that diabetes in a kidney transplant patient brings a higher risk for developing ischemic heart disease compared to non-transplant diabetic patients. The following paragraph is excerpted from the KDIGO guidelines recently published in the American Journal of Transplantation¹²:

“A number of other risk factors for diabetes have not been rigorously studied in KTRs (Kidney Transplant Recipients), but there is little reason to believe that they would not also be risk factors after transplantation. These risk factors include: family history (type 2 diabetes), gestational diabetes, impaired fasting glucose, impaired glucose tolerance and dyslipidemia (high fasting triglycerides and/or low HDL-C. ...Data from observational studies have shown that NODAT (New Onset Diabetes After Transplantation is the new term for NODM= New Onset Diabetes Mellitus) is associated with worse outcomes, including increased graft failure, mortality and CVD)”⁷

As suggested in the paragraph above, hypertriglyceridemia may also increase the risk of developing NODAT in kidney transplant patients and NODAT is associated with poor

graft and patient survival as expected according to the vast research data available from non-transplant patients with diabetes.

Reviewer's Comment: NODAT which is a major area of concern in transplant patients in general has not been assessed adequately in this study mainly because of omitting the pivotal criteria of FPG (Fasting Plasma Glucose) > 126 mg/dL in the screening criteria. This omission was probably the reason for the low incidence of NODM in all of the treatment groups when compared to the published literature related to NODAT. In the United States, the cumulative incidence of NODAT (all organs) among 11,659 patients is around 16%, at 12 months.¹⁵

In another recently published international, randomized trial NODAT or impaired fasting glucose at 6 months, occurred in 26.0% of the CsA treated patients and 33.6% of the tacrolimus treated patients.¹⁶ It is important to note that these are only six month incidences and the incidence of NODAT increases over time¹⁶.

The reviewer believes that the actual NODAT incidences in the treatment groups in Study A2309 should have been at least 3 times higher than reported (9.1% in the everolimus 1.5 mg group and 6.6% in the Myfortic group) if the NODAT screening had been performed according to the ADA guidelines and would be more compatible with the literature data.

As a crude estimate of the actual incidence of NODAT in this study we can multiply the reported 12 month incidences by 3 and have an incidence of 27.3% (9.1x3) for the everolimus 1.5 mg group and an incidence of 19.8% (6.6x3) for the Myfortic group. As we see the difference in between the two groups come up to 7.5% as opposed to an initial difference of 2.5%. Also it is known from the literature that M-TOR inhibitors have diabetogenic properties¹⁷ like tacrolimus and CsA. However, MPA derivatives are not associated with diabetes. 7.5% more NODAT in the everolimus 1.5 mg group compared to the Myfortic group at the end of 12 months would still be a conservative estimate since the final figures are only comparable to the reported 6 month incidence for NODAT in the recent literature.

7.3.4.11 Gastrointestinal Adverse Events and Oral Ulcers/Stomatitis

¹⁶ Vincenti F, Friman S, Scheuermann E, Rostaing L. et.al Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. Am J Transplant. 2007 Jun;7(6):1506-14

¹⁷ Fraenkel M, Ketzinel-Gilad M, Ariav Y, M-TOR inhibition by rapamycin prevents beta-cell adaptation to hyperglycemia and exacerbates the metabolic state in type 2 diabetes. Diabetes. 2008 Apr;57(4):945-57.

Events in the gastrointestinal SOC were reported as SAEs most frequently in the everolimus 3.0 mg group (28 patients), followed by the 1.5 mg group (21 patients), and the Myfortic group (18 patients). The preferred terms of diarrhea and vomiting were more common in the everolimus 3.0 mg group compared to the other groups [diarrhea, six (2.2%) patients in the everolimus 3.0 mg group compared to one (0.4%) patient in each of the other groups; and vomiting in seven (2.5%) patients in the everolimus 3.0 mg group compared to two (0.7%) patients in the everolimus 1.5 mg group and four (1.5%) patients in the Myfortic group]. Two cases of hemorrhagic esophagitis in the everolimus 1.5 mg group and one case of mesenteric vessel thrombosis in the everolimus 3.0 mg group were reported as SAEs, which may be associated with the ulcerative and thrombogenic class effects of M-TOR inhibitors.

As shown in Table 60, ulcerations of the gastrointestinal (GI) tract were reported as AEs in three patients in the everolimus 3.0 mg group (one duodenal, one gastric, and one esophageal), two in the Myfortic group (one duodenal and one ileal) . No patient in the everolimus 1.5 mg group had GI ulcers reported. Regarding upper GI lesions, overall there was a higher incidence of aphthous stomatitis, stomatitis, mouth ulceration, tongue ulceration in both of the everolimus groups compared to the Myfortic group.

Aphthous stomatitis was reported as a SAE in six patients in the everolimus 1.5 mg group, five patients in the everolimus 3.0 mg group, and in two patients in the Myfortic group. There were additional three patients in the everolimus 1.5 mg group and two patients in the everolimus 3.0 mg group who reported as stomatitis compared to none in the Myfortic group. None of gastrointestinal ulcers, except for the ones shown in Table 35 below, were reported as SAEs.

One patient in the everolimus 3.0 mg group discontinued study medication due to stomatitis and another patient in the everolimus 1.5 mg group discontinued study medication because of esophageal ulceration (necrotic, ulcerative grade D reflux esophagitis on EGD).

Table 61. Gastrointestinal Lesions (Ulcers, Stomatitis)

Source : Table 5-21 on page 51 of the Clinical Overview

GI Disorders Preferred term	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 gm N=273
AE - % (n)			
aphthous stomatitis	2.2 (6)	1.8 (5)	0.7 (2)
stomatitis	1.1 (3)	0.7 (2)	0
mouth ulceration	3.3 (9)	5.0 (14)	1.8 (5)
lip ulceration	0	0	0.4 (1)
tongue ulceration	1.8 (5)	0	0
duodenal ulcer	0	0.4 (1)	0.4 (1)
peptic ulcer	0	0	0
esophageal ulcer	0	0.4 (1)	0
rectal ulcer	0	0	0
ileal ulcer	0	0	0.4 (1)
SAE - % (n)			
mesenteric vessel thrombosis	0	0.4 (1)	0
intestinal ulcer	0	0	0.4 (1)
esophagitis ulcerative	0.4 (1)	0	0
discontinued for AE			
aphthous stomatitis	0	0	0
mouth ulceration	0	0.4 (1)	0
esophagitis ulcerative	0.4 (1)	0	0

Reviewer's Comment: Mouth ulcerations and gastrointestinal tract ulcerations are among the AEs known to be associated with M-TOR inhibitors. In this study we see the same trend. They can be painful and may prevent patient's adequate food and liquid intake, although it is not clear from this study how much the ulcerations impacted the patient. The mechanism is thought to be delayed healing prevention of mucosal regeneration.

7.3.4.12 Endocrine Effects (Male Patients)

As a part of the study protocol FSH, LH and testosterone levels were checked in male patients, at baseline and periodically throughout the study. In the initial 12 months of the study, the latest time point was at month 9.

For reference, normal testosterone levels in this study were reported to be < 10 nmol/L (if age < 50 years) and < 7 nmol/L (if age ≥ 50 years).

Tables 62 through 64 show the testosterone, LH, and FSH levels at baseline and again at month 9 for patients in the everolimus 1.5 mg and Myfortic groups. Data from the

everolimus 3.0 mg group is not presented. At month 9 all three hormone levels (testosterone, LH and FSH) in the everolimus 1.5 mg group were significantly different than the corresponding hormone levels in the Myfortic group, although the baseline values were similar in the two treatment groups. The everolimus 1.5 mg group had a lower mean testosterone level and higher mean LH and FSH levels than the Myfortic group. The difference between the testosterone levels across the two treatment groups at 9 months is thought to be caused by the decrease of testosterone levels in the everolimus 1.5 mg group throughout the study period. During this time period testosterone levels in the Myfortic group stayed the same. Month 9 mean testosterone levels are still within the normal range in both groups despite the significant decrease in the everolimus 1.5 mg group.

Table 62. Comparison of Testosterone Levels at Baseline and at Month 9 (Males Only)

(Source: Table 14.3-2.6.1b on page 1184 of CSR)

	Mean Testosterone, nmol/L	
	Baseline	Month 9
Everolimus 1.5 mg	15.1 ± 8	12.1 ± 5
Myfortic	15.6 ± 9	15.2 ± 6
p-value of Wilcoxon Rank-Sum test	0.949	0.000

Table 63. Comparison of LH Levels at Baseline and at Month 9 (Males Only)

Source: Table 14.3-2.6.1b on page 1184 of CSR)

	Mean LH, U/L	
	Baseline	Month 9
Everolimus 1.5 mg	10.3 ± 19	7.6 ± 11
Myfortic	9.0 ± 8	5.3 ± 4
p-value of Wilcoxon Rank-Sum test	0.29	0.025

Table 64. Comparison of FSH Levels at Baseline and at Month 9 (Males Only)

Source: Table 14.3-2.6.1b on page 1184 of CSR

	Mean FSH, U/L	
	Baseline	Month 9
Everolimus 1.5 mg	7.6 ± 9	11.1 ± 9
Myfortic	8.4 ± 8	7.9 ± 9
p-value of Wilcoxon Rank-Sum test	0.107	0.000

The mean FSH levels in the everolimus 1.5 mg group increased and rose up to the upper limit of the normal range (11.1 ± 9 U/L) at 9 months which may be indicative of decreased sperm production. (Figure 19).

Low testosterone as an AE was reported in 26/137 (19%) patients in the everolimus 1.5 mg group compared to 24/160 (15%) patients in the Myfortic group. Erectile dysfunction as an AE was reported in 9/137 (6.5%) patients in the everolimus 1.5 mg group compared to 4/160 (2.5%) patients in the Myfortic group (Source: Table 14.3.1-1.1 on page 1375 of CSR).

The baseline medical information for patients in the study indicates that twice as many patients in the Myfortic group had erectile dysfunction compared to the everolimus 1.5 mg group, as shown in Table 65 below. Despite this imbalance in the baseline characteristics in favor of the everolimus 1.5 mg group, there is almost a three times higher incidence of erectile dysfunction in the everolimus 1.5 mg group when compared to the Myfortic group during the 12 month study period (6.5% and 2.5%, respectively).

Table 65. Relevant Medical Histories (Erectile Dysfunction)

Source: Table 14.1-3.3, Page 385 of CSR

	Everolimus 1.5 mg N=277 (n, %)	Everolimus 3.0 mg N=279 (n, %)	Myfortic N=277 (n, %)
Erectile Dysfunction prior to transplant	5 (1.8)	9 (3.2)	10 (3.6)

Reviewer's comment: Male hypogonadism including azoospermia associated with M-TOR inhibitor usage is well established in the published literature¹⁸ The possible risk of male hypogonadism with everolimus treatment is also included in the foreign labels of everolimus. The findings in Study A2309 are consistent with the published literature.

In general, gonadal function is expected to improve after renal transplantation parallel to a number of other endocrine and metabolic functions. In this study we see an opposite trend in the everolimus group with regard to the endocrine part (testosterone levels) of the gonadal function at 9 months after the transplant in male patients whereas the mean testosterone levels in the Myfortic group did not change during the same period.

Despite the changes in the everolimus group, mean testosterone levels in both groups stayed within the normal range at this time point.

Although sperm counts were not included in this study protocol the rise in mean FSH levels in the everolimus 1.5 mg group to the upper bound of normal range at 9 months is suggestive of a decrease in sperm counts which is also parallel to the findings reported in the literature and the non-clinical studies.

Maintaining normal levels of sperm counts and normal gonadal function is important for patients who plan on having children. Also maintaining normal levels of testosterone is important from a quality of life point of view. Testosterone plays important roles in maintaining bone density and erythropoiesis. It is important to remember that in study 2309 we only have the month 9 results and immunosuppressive therapy is a life long therapy.

¹⁸ Huyghe E, Zairi A, Nohra J, Kamar N, Gonadal impact of target of rapamycin inhibitors (sirolimus and everolimus) in male patients: an overview. Transpl Int. 2007;20(4):305-11

There are also published articles recommending that male patients should be warned about this possible male hypogonadism associated with M-TOR inhibitors.¹⁹

7.3.4.13 *Delayed Graft Function*

Delayed graft function (DGF) was defined by the Applicant as the need for dialysis within the first 7 days after transplantation. The frequency of DGF, which is important as it is known to be associated with a higher rate of efficacy failure, was only minimally higher in the everolimus groups compared to the Myfortic group: 10.2% (28/274) in the everolimus 1.5 mg group, 10.4% (29/278) in the everolimus 3.0 mg group, and 9.2% (25/273) in the Myfortic group.

The onset of DGF was categorized as occurring between 1-2, 3-4, or 5-8 days post-transplant and did not differ between treatments (data not shown). The duration of DGF was mostly <21 days, occasionally longer and only rarely continued, and did not appear to vary between everolimus and Myfortic groups.

The overall rate of efficacy failure in patients who experienced DGF was greater than in those who did not experience DGF, but equally so for all treatments, so that the rate of efficacy failure was similar across the treatment groups (data not shown).

7.3.4.14 *Biopsy Evaluation of Chronic Allograft Nephropathy*

Chronic allograft nephropathy (CAN), also known as chronic allograft injury (CAI), is the main cause of kidney graft loss in the long term and one of the main reasons for decreasing, or eliminating, the use of calcineurine inhibitors (CNIs) in immunosuppressive regimens. CNIs contribute to the development of CAN mainly by increasing graft fibrosis through TGF- β activation.

The main safety endpoint for Study A2309 was a comparison of GFR at 12 months between the treatment groups, which is also an indicator of the degree of CAN. Another, and possibly more important indicator of CAN, is tissue biopsy because GFR can be altered by other factors, like the reversible afferent arteriole vasoconstriction also caused by CNIs.

According to the study protocol, renal biopsies were to be performed at Month 12 in all patients with significant proteinuria (defined as > 0.5 g/day) or with suboptimal renal function (defined as estimated MDRD GFR of < 50 mL/min/1.72m²) to assess the frequency and severity of biopsy-proven chronic nephropathy and the rate of chronic

¹⁹ Skrzypek J, Krause W. Azoospermia in a renal transplant recipient during sirolimus (rapamycin) treatment. *Andrologia*. 2007 Oct;39(5):198-9

sclerosing nephropathy. The data for all biopsies performed at 12 months are shown in Table 66 below. The percent of patients who met the protocol criteria for a biopsy was 37% in the everolimus 1.5 mg group, 43% in the everolimus 3.0 mg group, and 44% in the Myfortic group. However, it should be noted that the proportion of all patients who actually underwent this Month 12 biopsy is low in all groups (11 to 16% of the total population) and limits the interpretation of the findings.

The chronic allograft damage index (CADI) showed small, statistically insignificant differences in the mean and medians across the treatment groups. The rate of chronic sclerosing nephropathy also showed a small insignificant difference between the everolimus 1.5 mg group and the Myfortic group with the everolimus 3.0 mg group having the highest degree of sclerosis.

Table 66. Frequency of Biopsy and Rate and Severity of Chronic Allograft Nephropathy

(Source: Table 5-10, page 38, of Clinical Overview section of NDA resubmission)

Table 5-10	Frequency of biopsy and rate and severity of chronic nephropathy		
	Everolimus 1.5 mg N=277	Everolimus 3 mg N=279	Myfortic 1.44 g N=277
patients who met criteria for 12 month biopsy (n) (proteinuria >0.5 g/d or GFR <50 mL/min/1.72m ²)	102	119	121
patients in whom a biopsy was performed - % (n/N)	13.7 (38/277)	15.8 (44/279)	10.8 (30/277)
chronic allograft damage index - mean (SD)	4.4 (3.15)	4.4 (2.48)	4.9 (2.89)
chronic allograft damage index – median (range)	4.0 (0-13)	4.3 (0-12)	4.5 (0-10)
rate of chronic sclerosing nephropathy - % (n/N) ^a	8.5 (17/201)	13.9 (27/194)	9.0 (18/200)
^a Subgroup population for CAN: ITT patients with biopsy at baseline or Month 12 used for rate calculation (N=201, 194, 200 for 1.5 mg, 3 mg everolimus and Myfortic, respectively) Month 12 window covers Month 9 and Month 12 Source: [Study A2309 – Table 14.2-2.12 (chronic allograft damage index), [Study A2309 – Table 14.2-2.13] (incidence of chronic sclerosing nephropathy)			

The proportion of all patients who underwent this Month 12 biopsy, however, is low in all groups and limits any interpretation.

Biopsies were taken slightly more often with everolimus than Myfortic, with less difference to 1.5 mg everolimus. The chronic allograft damage index (CADI) showed small, statistically insignificant differences in the mean and medians across the treatment groups. The rate of chronic sclerosing nephropathy also showed a small insignificant difference between the everolimus 1.5 mg group and the Myfortic group with the everolimus 3.0 mg group having the highest degree of sclerosis.

Reviewer's Comment: *Decreasing CAN or CAI is one of the most important goals in order to decrease the rates of long term graft loss and is the reason for decreasing, or even eliminating, the CNI component of immunosuppression over time.*

In Study A2309 it is not possible to make any solid conclusions about the comparison of the study groups with regard to CAN since the percentage of patients with available biopsy findings is very limited and the duration of follow-up is only 12 months, which is a relatively short time to see any outstanding differences. Nevertheless, with the available limited data, the everolimus 1.5 mg group did not appear to have any significant benefit in terms of CAN at 1 year. The relatively higher level of sclerosing nephropathy in the everolimus 3.0 mg group is concerning since it points to a trend as to what might happen if higher trough levels of everolimus is targeted for the purpose of increasing immunosuppression level such as in high immunologic risk patients.

7.3.5 Submission Specific Primary Safety Concerns

Submission specific safety concerns are already discussed in other sections

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events are shown by SOC in Table 66, and by PT for the most common events ($\geq 20\%$) in Table 67. Almost all patients experienced at least one AE in all treatment groups. The most frequently affected organ classes were metabolism and nutrition disorders, and gastrointestinal disorders. More than 70% of patients per treatment group reported AEs in these organ classes.

Generally the incidence of AEs by SOC between treatment groups was similar. SOCs where there appeared to be a higher percentage of patients with AEs in the everolimus treatment groups were; general disorders and administration site conditions, metabolism and nutrition disorders, and reproductive system and breast disorders.

Reviewer's Comment: *In the evaluation of AEs according to SOCs the Reviewer refrains from making any comparisons across the treatment groups by SOC or placing too much emphasis on this type of comparisons unless there is a major*

difference. SOCs may include a variety of preferred terms which may not be always clinically related and may also fit under different SOCs.

As an example: graft loss is a PT under Injury, Poisoning and Procedural complications, whereas a renal infarct, which may be the cause of graft loss, is a PT under Renal and Urinary Disorders.

Table 67 Number (%) of Patients Experiencing Adverse Events/infections by System Organ Class (SOC) and Treatment Group (Safety population – 12 Month Analysis)
(Source: Table 12-5, page 173, CSR)

System organ class	Everolimus 1.5 mg	Everolimus 3.0 mg	Myfortic 1.44 g
	N=274 n (%)	N=278 n (%)	N=273 n (%)
Any system organ class	271 (98.9)	276 (99.3)	270 (98.9)
Blood and lymphatic system disorders	93 (33.9)	112 (40.3)	111 (40.7)
Cardiac disorders	43 (15.7)	39 (14.0)	42 (15.4)
Congenital, familial and genetic disorders	7 (2.6)	4 (1.4)	2 (0.7)
Ear and labyrinth disorders	13 (4.7)	4 (1.4)	14 (5.1)
Endocrine disorders	11 (4.0)	10 (3.6)	20 (7.3)
Eye disorders	29 (10.6)	22 (7.9)	28 (10.3)
Gastrointestinal disorders	196 (71.5)	208 (74.8)	207 (75.8)
General disorders and administration site conditions	181 (66.1)	185 (66.5)	160 (58.6)
Hepatobiliary disorders	7 (2.6)	8 (2.9)	8 (2.9)
Immune system disorders	14 (5.1)	9 (3.2)	11 (4.0)
Infections and infestations	169 (61.7)	178 (64.0)	185 (67.8)
Injury, poisoning and procedural complications	163 (59.5)	174 (62.6)	163 (59.7)
Investigations	137 (50.0)	120 (43.2)	133 (48.7)
Metabolism and nutrition disorders	222 (81.0)	233 (83.8)	199 (72.9)
Musculoskeletal and connective tissue disorders	112 (40.9)	104 (37.4)	105 (38.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (3.3)	8 (2.9)	16 (5.9)
Nervous system disorders	92 (33.6)	96 (34.5)	109 (39.9)
Pregnancy, puerperium and perinatal conditions	1 (0.4)	0 (0.0)	0 (0.0)
Psychiatric disorders	90 (32.8)	76 (27.3)	72 (26.4)
Renal and urinary disorders	112 (40.9)	143 (51.4)	124 (45.4)
Reproductive system and breast disorders	50 (18.2)	51 (18.3)	23 (8.4)
Respiratory, thoracic and mediastinal disorders	86 (31.4)	108 (38.8)	93 (34.1)
Skin and subcutaneous tissue disorders	92 (33.6)	103 (37.1)	102 (37.4)
Social circumstances	0 (0.0)	1 (0.4)	1 (0.4)
Surgical and medical procedures	0 (0.0)	2 (0.7)	0 (0.0)
Vascular disorders	122 (44.5)	137 (49.3)	124 (45.4)

The most commonly reported PTs were constipation, nausea and anemia, as shown in Table 68. Nausea was reported by a similar percentage of patients in each treatment group. Anemia and constipation were most common in the 3.0 mg everolimus treatment group. Peripheral edema, hyperlipidemia and anemia were more frequent with everolimus than Myfortic, other AEs occurring at similar rates.

Hyperlipidemia was reported by at least 5% more patients in the everolimus groups than the Myfortic group.

Table 68 Incidence Rates of Most Frequent (≥ 20% in any Treatment Group) Adverse Events/Infections by Primary System Organ Class and Preferred Term (Safety population - 12 Month Analysis)
 (Source: Table 12-6, page 174, CSR)

Primary System Organ Class Preferred term	Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic N=273 n (%)
Any AE/Infection	271 (98.9)	276 (99.3)	270 (98.9)
Blood and lymphatic system disorders	99 (33.9)	112 (40.3)	111 (40.7)
Anemia	70 (25.5)	86 (30.9)	68 (24.9)
Gastrointestinal disorders	196 (71.5)	208 (74.8)	207 (75.8)
Constipation	105 (38.3)	122 (43.9)	117 (42.9)
Nausea	79 (28.8)	80 (28.8)	85 (31.1)
Vomiting	40 (14.6)	48 (17.3)	60 (22.0)
General disorders and administration site conditions	181 (66.1)	185 (66.5)	207 (75.8)
Edema peripheral	123 (44.9)	120 (43.2)	108 (39.6)
Infections and infestations	169 (61.7)	178 (64.0)	185 (67.8)
Urinary tract infection	60 (21.9)	57 (20.5)	63 (23.1)
Investigations	137 (50.0)	120 (43.2)	133 (48.7)
Blood creatinine increased	48 (17.5)	52 (18.7)	59 (21.6)
Metabolism and nutrition disorders	222 (81.0)	233 (83.8)	199 (72.9)
Hyperkalemia	49 (17.9)	58 (20.9)	48 (17.6)
Hyperlipidemia	57 (20.8)	60 (21.6)	43 (15.8)
Vascular disorders	122 (44.5)	137 (49.3)	124 (45.4)
Hypertension	81 (29.6)	76 (27.3)	82 (30.0)

Reviewer's comment: The PT of "blood creatinine increased" was reported more frequently in the Myfortic group (21.6%) compared to the everolimus 1.5 mg group (17.5%). During the review process the reviewer discovered that 5 patients in the Myfortic group who were reported to have blood creatinine increased or toxic nephropathy were actually receiving sirolimus (another M-TOR inhibitor) as

a concomitant immunosuppressant in addition to the study regimen which may affect the validity of the comparison in between the groups.

For the majority of PTs there was little difference in the incidence between treatment groups. Terms which were reported by at least 5% more patients in the everolimus 3.0 mg than 1.5 mg group were; anemia, constipation and acne. Where the incidence of preferred terms was at least 5% greater in the 1.5 mg everolimus group than in the 3.0 mg group was; tachycardia, abdominal pain, back pain, myalgia, pain in extremity and anxiety.

AEs reported with a 5% or more difference between the everolimus groups and the Myfortic group are shown in Table 69. PTs more common in the everolimus 1.5 mg compared to the Myfortic group were: peripheral edema, dyslipidemia, and hyperlipidemia. PTs more common in the everolimus 3.0 mg group than the Myfortic group were: anemia, dyslipidemia, hypercholesterolemia, hyperlipidemia, proteinuria, acne and lymphocele. In the Myfortic group, leukopenia, abdominal pain upper, dyspepsia, vomiting, CMV infection and tremor were more common than the everolimus 1.5 mg group. At least 5% more patients in the Myfortic group experienced leukopenia, abdominal pain, abdominal pain upper, CMV infection and tremor, than in the everolimus 3.0 mg group.

Table 69. Incidence Rates of Adverse Events/infections with a 5% or Greater Difference in Incidence Between Everolimus and Myfortic treatment Groups, by Preferred Term, Safety population – 12 month analysis
 (Source: Table 12-7, page 175, CSR)

Preferred term	Everolimus 1.5 mg	Everolimus 3.0 mg	Myfortic 1.44 g
	N=274 n (%)	N=278 n (%)	N=273 n (%)
Abdominal pain upper	9 (3.3)	14 (5.0)	30 (11.0)
Anaemia	70 (25.5)	86 (30.9)	68 (24.9)
Acne	26 (9.5)	41 (14.7)	23 (8.4)
Cytomegalovirus infection	2 (0.7)	0 (0.0)	16 (5.9)
Dyslipidemia	41 (15.0)	36 (12.9)	24 (8.8)
Hypercholesterolaemia	47 (17.2)	50 (18.0)	34 (12.5)
Hyperlipidaemia	57 (20.8)	60 (21.6)	43 (15.8)
Leucopenia	8 (2.9)	6 (2.2)	33 (12.1)
Lymphocele	21 (7.7)	34 (12.2)	16 (5.9)
Oedema peripheral	123 (44.9)	120 (43.2)	108 (39.6)
Proteinuria	25 (9.1)	36 (12.9)	20 (7.3)
Tremor	23 (8.4)	22 (7.9)	38 (13.9)

Severity

Investigators graded the severity of AEs as mild moderate or severe. The majority of AEs were reported as mild to moderate in severity by the investigators, with severe AEs reported for approximately one third of patients (32.1%, 39.9% and 35.9% of patients in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 groups, respectively)

There were few differences between treatment groups with regard to the proportion of patients for whom AEs were judged as being mild, moderate or severe. Infections and infestations was the only SOC where at least 10% of patients in any treatment group were reported as having experienced a severe AE (5.8%, 10.1% and 7.3% of patients in the everolimus 1.5 mg, 3.0 mg and Myfortic groups, respectively). There was no difference between treatment groups with regard to the severity of upper respiratory tract infections or urinary tract infections.

Peripheral edema, headache, and hyperlipidemia were reported as severe only for patients in the everolimus treatment groups (edema peripheral: 2.6% in the 1.5 mg group, and 1.4% in the 3.0 mg group; headache: 1.1% and 0.4% for the 1.5 mg and 3.0 mg groups, respectively; hyperlipidemia: 0.7% and 0% for the 1.5 mg and 3.0 mg groups, respectively). Lymphocele was reported as severe for 2.2% of patients in the everolimus 3.0 mg treatment group, and as severe for 0.7% in the 1.5 mg group and 0.4% in the Myfortic group.

Leukopenia was more frequently reported as moderate or severe in the Myfortic treatment group (1.1%, 1.4% and 8.1% of patients had moderate leukopenia in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm treatment groups, respectively). In the Myfortic treatment group, BK virus infections were more frequently severe (by at least 1.5%), while the proportion of patients experiencing mild, moderate and severe CMV infection, CMV viremia and HSV infection were similar across the treatment groups.

CsA-Associated AEs

Focusing on AEs commonly associated with CsA use, a reduction in these AEs was observed for both everolimus groups compared to the Myfortic group. However, the renal and urinary AEs were lower only for the everolimus 1.5 mg group as shown in Table 70.

Table 70. Frequency of CsA-associated AEs,
 (Source: Table 5-13, page 42, Clinical Overview section of NDA
 resubmission)

	Everolimus 1.5 mg N=274	Everolimus 3.0 mg N=278	Myfortic 1.44 g N=273
AEs - % (n)			
tremor	8.4 (23)	7.9 (22)	13.9 (38)
gingival hyperplasia	0.7 (2)	0.4 (1)	2.9 (8)
gingival hypertrophy	1.1 (3)	0.7 (2)	2.2 (6)
hirsutism	2.9 (8)	4.0 (11)	5.5 (15)
renal and urinary disorders	40.9 (112)	51.4 (143)	45.4 (124)
Notably high values % (n)			
notable high values for uric acid			
females	17.2 (17)	22.7 (20)	22.6 (19)
males	1.1 (2)	4.7 (9)	4.3 (8)
notably high values for blood pressure			
diastolic	6.6 (18)	6.1 (17)	8.4 (23)
systolic	2.9 (8)	3.2 (9)	4.4 (12)

Reviewer's Comment: As explained in more detail in Section 7.4.3, the reduction in systolic and diastolic blood pressure over the course of the study was higher in the Myfortic group compared to the everolimus 1.5 mg group and the differences with regard to the SBP were statistically significant. Because of this significant difference in between the SBP changes in favor of the Myfortic group which is not supportive of the reverse finding of higher number of patients with notable values of systolic or diastolic BP in the same group (shown in Table 69), these results need to be interpreted with caution.

7.4.2 Laboratory Findings

7.4.2.1 Biochemistry

Amylase and lipase levels fell from baseline during the first week, after which there was no further change from baseline and mean and median values remained within the normal range.

Creatine kinase levels increased from baseline initially probably due to the effect of surgery, then decreased at Day 14. From Month 1 onwards mean and median levels fluctuated within the normal range although the levels were significantly higher in the everolimus groups compared to the Myfortic group.

Mean and median alkaline phosphatase levels remained within the normal range throughout the study period with an initial decrease from baseline, and subsequent increase from Day 14 to Month 4 after which the levels remained stable.

Bilirubin mean and median levels also remained within the normal range throughout the study period.

Apart from Day 7 and 14 where alanine aminotransferase (ALT) mean values were at or slightly above the upper limit of the normal range in all groups, mean and median aspartate aminotransferase (AST) levels remained within the normal range throughout the study period.

Lipid levels tended to increase from baseline, with the greatest change from baseline at Month 2 or Month 3. Absolute levels at Month 3 were unchanged to Month 12. The change from baseline and the absolute values were greater in the everolimus treatment groups than the Myfortic group, and greater in the everolimus 3.0 mg group than 1.5 mg. *LDL levels increased from baseline by more than HDL levels.* The cholesterol/HDL ratio showed no consistent changes for any treatment group.

Sodium, potassium, chloride, magnesium and calcium mean and median levels remained within the normal range throughout the study period. Inorganic phosphate mean and median values exceeded the normal range at baseline but remained within the normal range afterwards.

As expected, blood urea nitrogen (BUN) values were above the normal range at baseline, decreased during the first two months and remained stable afterwards, with mean and median values within normal range except for the Myfortic group in which the mean values were slightly above range throughout the entire study duration.

Uric acid levels decreased from baseline in all treatment groups. From Month 2 in the Myfortic group the change from baseline became positive and greater than in everolimus groups. This may be related to the higher CsA dose in Myfortic patients.

7.4.2.2 *Endocrinology*

Please refer to Section 7.3.4.12 *Endocrine Effects (Male Patients)*

7.4.2.3 *Hematology*

(Please also refer to section 7.3.4.8)

Total white cell counts increased in the perioperative period (Day 1 and 3), at which time mean and median values were at the upper limit of the normal range in all three groups. A similar pattern was observed for neutrophils. Lymphocyte counts followed an opposing path being low in the perioperative period and within normal range afterwards in all treatment groups.

Red blood cell (RBC) and hemoglobin levels followed a pattern that would be expected following surgery and blood loss. RBC and hemoglobin mean and median levels were low during the first month and normalized afterwards in all groups as expected after the kidney transplantation.

7.4.3 Vital Signs

Vital signs variables included measurements of systolic and diastolic blood pressures, pulse, and body weight.

Mean and median values for weight increased over the treatment period in all groups, with a median increase of 3.7-5.0 kg at Month 12 treatment endpoint.

Systolic blood pressure increased in the 14 days following surgery (the greatest rise was seen in the everolimus 1.5 mg treatment group), after which the change from baseline was negative. At the Month 12 treatment endpoint, median changes from baseline were -1.5, -6.5 and -8.0 mmHg for everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 g, respectively.

Diastolic blood pressure also showed a decrease from baseline from Month 4 onwards which was numerically but not significantly greater in the Myfortic group than everolimus 1.5 mg. At treatment endpoint median change from baseline was -1.0, -2.5 and -4.0 mmHg for the everolimus 1.5 mg, 3.0 mg and Myfortic groups, respectively.

Table 71 Blood Pressure Changes from Baseline

Source: Table 14.3-3.1 on page 1301 of CSR

Change From Baseline	Everolimus 1.5 mg N = 274 Median (mmHg)	Myfortic 1.44 gm N = 273 Median (mmHg)	p-value Wilcoxon Rank-Sum test (Everolimus 1.5 mg vs. Myfortic)
SBP (M 12, TEP)	-1.5	-8.0	0.054
DBP (M 12, TEP)	-1.0	-4.0	NS

Pulse rates increased slightly on Day 1, but showed no overall clinically meaningful trends.

Vital sign abnormalities were predominantly high values for systolic or diastolic blood pressure and were numerically higher in the Myfortic group (Table 72).

Table 72. Number (%) of patients with post-baseline vital sign abnormalities based on notable criteria by treatment group (Safety population - 12 month analysis)
 (Source: Table 12-22, page 205, CSR)

		Everolimus 1.5 mg N=274 n (%)	Everolimus 3.0 mg N=278 n (%)	Myfortic 1.44 g N=273 n (%)
Systolic BP	Low	0/274	2/278 (0.7)	0/273
	High	8/274 (2.9)	9/278 (3.2)	12/273 (4.4)
Diastolic BP	Low	1/274 (0.4)	0/278	0/273
	High	18/274 (6.6)	17/278 (6.1)	23/273 (8.4)

7.4.4 ECGs

ECG assessments were not included in the Assessment Schedule and no findings were reported.

7.4.5 Special Safety Studies/Clinical Trials

The following studies were not reviewed in detail by the Clinical Reviewer. Summaries, provided by the applicant, are included here.

Study No. RAD001A2420 (12 month analysis)

Title of study: A national, multicenter, randomized study comparing the early versus delayed administration of Certican® in de novo kidney transplant recipients at risk of delayed graft function

Study center(s): Seventeen centers in France

Study period

First patient enrolled: 10-Jun-2005

Last patient completed (12 months): 6-Jun-2008

Phase of development: IIIb

Objectives: The objective of this study was to evaluate if the delayed administration of Certican® could reduce the “anti-proliferative complications” (e.g. wound healing disorders) while maintaining efficacy in comparison with the immediate administration in de novo renal transplant patients.

The primary objective was to compare the incidence of the composite criteria combining biopsy proven acute rejection, graft loss, death, DGF and wound healing complications with immediate versus delayed administration of everolimus at 3 months. Secondary objectives were the comparison of immediate versus delayed administration of Certican® for further efficacy and safety variables.

Methodology: This was an open, randomized, parallel-group, multicenter study with two treatment groups, immediate everolimus and delayed everolimus. Patients randomized to immediate everolimus were treated with everolimus from transplantation on, while patients randomized to delayed everolimus were initially treated for one month with MPA and thereafter with everolimus.

Number of patients (planned and analyzed): It was planned to include 142 patients in this study. Actually, 139 patients were randomized, 65 to immediate and 74 to delayed everolimus. All 139 patients were analyzed for safety and efficacy.

Criteria for evaluation

Efficacy: The primary criterion for assessing efficacy was the primary failure endpoint at 3 months, defined as the occurrence of DGF, efficacy failure, or wound healing disorder related to initial transplant surgery within the first 3 months. Efficacy failure was defined as BPAR, graft loss, death, or loss to follow-up. Secondary efficacy endpoints included various components of the primary failure endpoint.

Safety: Main criteria for assessing safety were adverse events, renal function parameters, dialysis, clinical laboratory, and vital signs.

Efficacy results: At 12 months failure was observed for 42 patients (64.6%) in the immediate Certican® group and for 49 patients (66.2%) in the delayed Certican® group, (ITT population, $p=0.8599$, Fisher's exact test). Wound healing disorders had a similar frequency for immediate Certican® (26 patients, 40.0%) and for delayed Certican® (28 patients, 37.8%), and this was not statistically significant ($p=0.8622$). No major differences between treatment groups were seen for other efficacy parameters as well.

Safety results: Adverse events were reported for all patients. Five patients in the immediate everolimus group (7.7%) (two of them had lost the graft previously) and two patients (2.7%) in the delayed everolimus group died. In the immediate Certican® group 45 patients (69.2%) had a serious adverse event and 17 patients (26.2%) had an adverse event leading to discontinuation of study medication. In the delayed everolimus group 57 patients (77.0%) had a serious adverse event and 28 patients (37.8%) had an adverse event leading to discontinuation of study medication.

Conclusion:

1) In patients with risk to develop DGF, immediate vs. delayed introduction of Certican® in combination with reduced Neoral® dose showed a comparable failure rate in the composite primary failure endpoint at Month 12:

- Incidence of DGF as defined by dialysis within 7 days was identical between study groups

and low for this patient population.

- Requirement for dialysis remained low until Month 12 and incidence of dialysis sessions was

comparable between both groups.

- BPAR rates were similar in both treatment groups at 12 months.

- *Graft losses and deaths were slightly higher in the group with immediate introduction of everolimus (of the six patients with graft failure, two patients died).*

- Wound healing events related and unrelated to initial surgery were comparable and nearly unchanged from Month 3 onward.

Study No. RAD001A2421

Title of study: A prospective, open label, controlled, multicenter trial to assess the efficacy and safety of an induction regimen of Neoral®, Myfortic® and corticosteroids, followed by administration of Certican® together with withdrawal of Neoral® and Myfortic® or corticosteroids and Myfortic® in *de novo* kidney transplant recipients.

Study centre(s): TBA

Study No. RAD001A2426

Title of study:

A twelve-month, multicenter, open-label, randomized study of the safety, tolerability and efficacy of Certican® with Simulect®, corticosteroids and two different exposure levels of tacrolimus in *de novo* renal transplant recipients.

Study purpose:

This study is designed to evaluate whether tacrolimus dose reduction in *de novo* renal recipients receiving everolimus can preserve renal function while maintaining efficacy.

Primary objective

The primary objective is to determine whether tacrolimus dose reduction can preserve renal function in *de novo* renal recipients receiving tacrolimus in addition to everolimus Simulect®, and corticosteroids. This objective will be assessed by comparing renal function evaluated by calculated glomerular filtration rate (GFR) (MDRD formula) at 12 months post-transplant between two groups of patients receiving two different exposure levels of tacrolimus.

Study No. RAD001AES05

Title of study: A multicenter, randomized, open-label, 2-year follow-up study to evaluate the effect of calcineurin inhibitor withdrawal and early introduction of everolimus on graft function in patients with a kidney transplant.

Planned dates: first subject dosed: 01-Nov-2006 last subject completed: 01-Nov-2009

Primary objective(s):

The primary objective of the study is to investigate whether early introduction of everolimus combined with CNI withdrawal can improve renal function in recipients of a kidney transplant of at least 3 months duration. This objective, which will be compared between both groups in Month 15 post-transplant, will be evaluated by calculating creatinine clearance according to the MDRD formula.

Safety:

- Evaluation of safety parameters based on the following variables: physical examination, vital signs, including incidence of hypertension, laboratory test results for assessment of hyperlipidemia, diabetes mellitus/glucose intolerance, anemia, leukopenia, thrombocytopenia, as well as evaluation of adverse effects related to immunosuppression (infections, especially viral and fungal, and neoplasms) at 5, 6, 9, 15, 21 and 27 Months post-transplant.

Reviewer's Comment: *No results have been submitted for this study.*

Study No. RAD001ANL02

Title of study:

A prospective, open, randomized, multicenter study comparing the effects of everolimus versus mycophenolatesodium (MPS) as compared to ciclosporin as maintenance therapy in renal allograft recipients, on chronic allograft damage and cardiovascular parameters

Objectives: prospective, open randomized multicenter trial, in which we aim to achieve optimal immune suppression after renal transplantation with maximal reduction of side effects, especially of vascular injury.

Methodology: Induction therapy for renal transplant recipients will consist of quadruple immune suppression consisting of prednisolone, MPS, ciclosporin and basiliximab. After 6 months, patients will be randomized to one of three groups: in the first group MPS will be tapered and patients will continue on double therapy with prednisolone and ciclosporin, in the second group ciclosporin will be stopped and patients will continue on prednisolone and MPS and in the third group, ciclosporin and MPS will be stopped and

everolimus will be started. In this group patients will continue on everolimus and prednisolone .

Number of centers & patients: Three of the seven transplant centers of the Netherlands will participate:

Amendment:

Based on the recommendations of the Study Safety Board, randomization to the experimental MPSprednisolone maintenance therapy group was stopped effective 1-Jul-2007, due to a late acute rejection rate of 22% in this group. The late acute rejection rate, at that time point in the Ciclosporin prednisolone group was 2 %, in the everolimus-prednisolone group 0%.

7.4.6 Immunogenicity

Everolimus is administered orally and is not expected to be immunogenic.

7.5 Other Safety Explorations

None.

7.5.1 Dose Dependency for Adverse Events

The Applicant performed analyses to describe the relationship between blood trough levels of everolimus and various safety events of special interest. Using the pooled data from both everolimus dose groups, these safety events were at various categories of everolimus blood trough levels.

Note: Pharmacometrics reviewer Kevin Krudys Ph.D did his own exposure/response analyses and these results are discussed in Section 7.2.2 and other relevant sections.

7.5.1.1 *Metabolic changes, wound healing, stomatitis and oral ulcers, edema*

Relationship between everolimus C_{min} and adverse events

The PK/safety population consisted of all safety patients who had either everolimus trough levels or CsA C0 levels post randomization.

The incidence of selected AEs, lipid profile and hormone changes, by everolimus C_{min} values is shown in Table 71 and Table 72. There was a tendency for higher everolimus dose levels (especially those greater than 9 ng/mL) to result in a higher percentage of patients reporting events, except for low testosterone. However, the low numbers of patients in the higher C_{min} categories hinder accurate analysis.

When combined dose groups were studied for the median effect there was no statistically significant relationship between C_{min} and the selected AEs. For diabetes and hypercholesterolemia the relationship (positive) approached significance ($p=0.053$ and $p=0.083$, respectively).

Everolimus C_{min} concentrations and low testosterone showed a significant (negative) relationship in the 1.5 mg and 3.0 mg treatment groups, but when the groups were combined the relationship was no longer significant ($p=0.172$).

Table 73. Selected Adverse Events by Average Everolimus Trough Concentration in Combined Everolimus Dose Groups; PK/safety Population
 (Source: Table 12-28, page 220, CSR)

Everolimus C _{min} *	Wound healing events	Peripheral edema	Stomatitis and oral ulcers	New onset diabetes ¹
RAD001	182/528 (34.5%)	242/504 (48.0%)	41/548 (7.5%)	52/543 (9.6%)
<3 ng/mL	20/45 (44.4%)	24/46 (52.2%)	2/38 (5.3%)	2/37 (5.4%)
3 – <4 ng/mL	23/73 (31.5%)	32/74 (43.2%)	5/74 (6.8%)	9/78 (11.5%)
4 – <5 ng/mL	30/102 (29.4%)	50/104 (48.1%)	7/113 (6.2%)	6/105 (5.7%)
5 – <6 ng/mL	26/84 (31.0%)	42/75 (56.0%)	8/87 (9.2%)	5/85 (5.9%)
6 – <7 ng/mL	18/63 (28.6%)	28/58 (48.3%)	6/72 (8.3%)	7/76 (9.2%)
7 – <8 ng/mL	17/56 (30.4%)	15/49 (30.6%)	5/60 (8.3%)	5/61 (8.2%)
8 – <9 ng/mL	14/40 (35.0%)	13/36 (36.1%)	3/48 (6.3%)	5/41 (12.2%)
9 – <10 ng/mL	11/24 (45.8%)	14/24 (58.3%)	4/24 (16.7%)	5/25 (20.0%)
10 – <11 ng/mL	5/13 (38.5%)	9/16 (56.3%)	0/12 (0.0%)	3/14 (21.4%)
11 – <12 ng/mL	9/13 (69.2%)	8/8 (100%)	1/7 (14.3%)	3/6 (50.0%)
12 – <13 ng/mL	3/4 (75.0%)	2/4 (50.0%)	0/3 (0.0%)	1/4 (25.0%)
≥13 ng/mL	6/11 (54.5%)	5/10 (50.0%)	0/10 (0.0%)	1/11 (9.1%)
3 – <6 ng/mL	79/259 (30.5%)	124/253 (49.0%)	20/274 (7.3%)	20/268 (7.5%)
6 – <8 ng/mL	35/119 (29.4%)	43/107 (40.2%)	11/132 (8.3%)	12/137 (8.8%)
8 – <12 ng/mL	39/90 (43.3%)	44/84 (52.4%)	8/91 (8.8%)	16/86 (18.6%)
≥12 ng/mL	9/15 (60.0%)	7/14 (50.0%)	0/13 (0.0%)	2/15 (13.3%)
Myfortic	70/273 (25.6%)	120/273 (44.0%)	8/273 (2.9%)	18/273 (6.6%)

* Average trough levels calculated up to event or censored at cut-off day

¹ Diabetes post-transplantation, identified by any of the following:

- a. Diabetes was reported as an adverse event;
- b. Glucose (random) ≥ 11 mmol/L (≥ 198 mg/dL) post-transplantation;
- c. Diabetes was recorded as reason for a medication given post-transplantation.

In patients who were not diabetic at the time of transplantation, identified by all of the following:

- a. Reason for transplantation was not diabetes;
- b. Diabetes was not included in medical history;
- c. Glucose (random) < 11 mmol/L at the time of transplantation;
- d. Diabetes was not recorded as reason for any medication given prior to transplantation.

Table 74. Lipid Profile and Hormone Changes by Average Everolimus Trough Concentration in Combined Everolimus Dose Groups; PK/safety Population
 (Source: Table 12-29, page 221, CSR)

Everolimus C _{min} [*]	Hypercholesterolemia ₁	Hypertriglyceridemia ²	Low Testosterone ³ – male –
RAD001	375/544 (68.9%)	106/549 (19.3%)	63/287 (22.0%)
<3 ng/mL	39/55 (70.9%)	5/32 (15.6%)	2/8 (25.0%)
3 – <4 ng/mL	55/87 (63.2%)	16/70 (22.9%)	11/32 (34.4%)
4 – <5 ng/mL	66/94 (70.2%)	21/107 (19.6%)	10/59 (16.9%)
5 – <6 ng/mL	48/86 (55.8%)	13/91 (14.3%)	8/44 (18.2%)
6 – <7 ng/mL	40/58 (69.0%)	15/82 (18.3%)	14/40 (35.0%)
7 – <8 ng/mL	36/48 (75.0%)	9/59 (15.3%)	9/44 (20.5%)
8 – <9 ng/mL	35/48 (72.9%)	9/45 (20.0%)	4/26 (15.4%)
9 – <10 ng/mL	18/22 (81.8%)	5/21 (23.8%)	3/13 (23.1%)
10 – <11 ng/mL	15/17 (88.2%)	5/18 (27.8%)	1/9 (11.1%)
11 – <12 ng/mL	7/9 (77.8%)	5/8 (62.5%)	1/6 (16.7%)
12 – <13 ng/mL	5/6 (83.3%)	1/4 (25.0%)	0/1 (0.0%)
≥13 ng/mL	11/14 (78.6%)	2/12 (16.7%)	0/5 (0.0%)
3 – <6 ng/mL	169/267 (63.3%)	50/268 (18.7%)	29/135 (21.5%)
6 – <8 ng/mL	76/106 (71.7%)	24/141 (17.0%)	23/84 (27.4%)
8 – <12 ng/mL	75/96 (78.1%)	24/92 (26.1%)	9/54 (16.7%)
≥12 ng/mL	16/20 (80.0%)	3/16 (18.8%)	0/6 (0.0%)
Myfortic	141/272 (51.8%)	22/272 (8.1%)	24/160 (15.0%)

Metabolic alterations (hypercholesterolemia, hypertriglyceridemia, new onset diabetes) appeared to be more frequent with everolimus than Myfortic and rates increased as trough levels rose from <3 ng/mL to 8 to <12 ng/mL. For average everolimus troughs ≥12 ng/mL, the number of patients was too small for the incidence rates to be reliably estimated.

Wound healing events, stomatitis and oral ulcers were also more frequent with everolimus than Myfortic, with rates of stomatitis and oral ulcers (but not wound healing) also increased slightly as trough levels rose from <3 ng/mL to 8-<12 ng/mL.

Fluid retention from peripheral edema tended to be more common with everolimus than Myfortic and showed little relation to everolimus trough levels.

Table 75 Relation of Everolimus Trough Concentrations to Rates of Events,
(Source: Table 5-28, page 59, Clinical Overview section of NDA resubmission)

Table 5-28 Relation of everolimus trough levels to rates of events						
% (n/N)	Everolimus (ng/mL)					Myfortic (all)
	<3	3 – <6	6–<8	8–<12	≥12	
Metabolic changes:						
Hypercholest.	70.9 (39/55)	63.3 (169/267)	71.7 (76/106)	78.1 (75/96)	80.0 (16/20)	51.8 (141/272)
Hypertriglycer.	15.6 (5/32)	18.7 (50/268)	17.0 (24/141)	26.1 (24/92)	18.8 (3/16)	8.1 (22/272)
new onset diabetes	5.4 (2/37)	7.5 (20/268)	8.8 (12/137)	18.6 (16/86)	13.3 (2/15)	6.6 (18/273)
Wound healing and oral ulcers:						
wound healing	44.4 (20/45)	30.5(79/259)	29.4 (35/119)	43.3(39/90)	60.0 (9/15)	25.6(70/273)
stomatitis and oral ulcers	5.3 (2/38)	7.3 (20/274)	8.3 (11/132)	8.8 (8/91)	0 (0/13)	2.9 (8/273)
Fluid retention:						
peripheral edema	52.2 (24/46)	49.0 (124/253)	40.2 (43/107)	52.4 (44/84)	50.0 (7/14)	44.0 (120/273)

7.5.1.2 Renal function

The potential relationship between blood trough levels of everolimus and of CsA and the frequency of renal function related outcomes was explored. Using the pooled data from both everolimus dose groups, the frequencies of these events at various ranges of everolimus blood trough level are summarized in Table 74.

No consistent conclusions could be drawn for the relationship between everolimus exposure and all these events.

Table 76. Relation of everolimus trough levels to low renal function,
(Source: Table 5-29, page 60, Clinical Overview section of NDA resubmission)

Table 76. Relation of everolimus trough levels to low renal function						
% (n/N)	Everolimus (ng/mL)					Myfortic (all)
	<3	3 – <6	6–<8	8–<12	≥12	
Renal function:						
low GFR	42.9 (6/14)	12.4 (29/234)	18.3 (26/142)	15.0 (12/80)	16.7 (2/12)	15.4 (38/247)
decr. GFR (MDRD)	28.6 (4/14)	30.5 (73/239)	27.9 (38/136)	28.4 (23/81)	33.3 (4/12)	32.8 (81/247)
decr. GFR (Nankivell)	26.7 (4/15)	21.4 (50/234)	15.9 (21/132)	20.3 (16/79)	27.3 (3/11)	25.9 (63/243)
decr. creat. clearance	28.6 (4/14)	19.4 (46/237)	19.3 (27/140)	20.3 (16/79)	33.3 (4/12)	19.8 (49/247)
high creatinine	42.9 (6/14)	17.9 (42/234)	23.1 (33/143)	16.5 (13/79)	16.7 (2/12)	23.9 (59/247)
high UP/UC	66.7 (12/18)	51.7 (120/232)	53.0 (71/134)	63.9 (53/83)	92.3 (12/13)	39.0 (96/246)

7.5.1.3 Relationship between everolimus Trough Concentration and Renal Function

The PK/efficacy population was used for this analysis (those patients in the ITT population who had a post randomization everolimus trough, or CsA C0 levels). The incidence of renal function impairment assessed using absolute GFR (MDRD), decrease in GFR (MDRD or Nankivell), decrease in creatinine clearance (Cockcroft-Gault), absolute creatinine levels or urinary protein-creatinine ratio by everolimus Cmin levels is shown in Table 77. The incidence of renal impairment did not show a statistical correlation with everolimus exposure when data across treatment groups were pooled.

Table 77. Renal Function Impairment by Average Everolimus Trough Concentration in Combined Everolimus Dose Groups; PK/Efficacy Population
(Source : Table 12-25, page 212, CSR)

Everolimus C _{min} *	Low GFR ¹	Decreased GFR (MDRD) ²	Decreased GFR (Nankivell) ²	Decreased creatinine clearance ³	High creatinine ⁴	High UP/UC ⁵
RAD001	75/482 (15.6%)	142/482 (29.5%)	94/471 (20.0%)	97/482 (20.1%)	96/482 (19.9%)	268/480 (55.8%)
<3 ng/mL	6/14 (42.9%)	4/14 (28.6%)	4/15 (26.7%)	4/14 (28.6%)	6/14 (42.9%)	12/18 (66.7%)
3-<4 ng/mL	8/48 (16.7%)	17/51 (33.3%)	8/45 (17.8%)	9/49 (18.4%)	15/50 (30.0%)	28/55 (50.9%)
4-<5 ng/mL	10/107 (9.3%)	31/104 (29.8%)	20/104 (19.2%)	19/106 (17.9%)	14/107 (13.1%)	52/101 (51.5%)
5-<6 ng/mL	11/79 (13.9%)	25/84 (29.8%)	22/85 (25.9%)	18/82 (22.0%)	13/77 (16.9%)	40/76 (52.6%)
6-<7 ng/mL	12/74 (16.2%)	20/74 (27.0%)	10/73 (13.7%)	10/73 (13.7%)	18/75 (24.0%)	43/81 (53.1%)
7-<8 ng/mL	14/68 (20.6%)	18/62 (29.0%)	11/59 (18.6%)	17/67 (25.4%)	15/68 (22.1%)	28/53 (52.8%)
8-<9 ng/mL	6/42 (14.3%)	12/40 (30.0%)	10/40 (25.0%)	8/40 (20.0%)	8/42 (19.0%)	21/38 (55.3%)
9-<10 ng/mL	3/18 (16.7%)	5/21 (23.8%)	3/19 (15.8%)	5/20 (25.0%)	3/19 (15.8%)	21/28 (75.0%)
10-<11 ng/mL	2/14 (14.3%)	5/15 (33.3%)	2/14 (14.3%)	2/14 (14.3%)	1/12 (8.3%)	6/10 (60.0%)
11-<12 ng/mL	1/6 (16.7%)	1/5 (20.0%)	1/6 (16.7%)	1/5 (20.0%)	1/6 (16.7%)	5/7 (71.4%)
12-<13 ng/mL	0/4 (0.0%)	0/4 (0.0%)	0/4 (0.0%)	0/4 (0.0%)	0/4 (0.0%)	1/1 (100%)
≥13 ng/mL	2/8 (25.0%)	4/8 (50.0%)	3/7 (42.9%)	4/8 (50.0%)	2/8 (25.0%)	11/12 (91.7%)
3 - <6 ng/mL	29/234 (12.4%)	73/239 (30.5%)	50/234 (21.4%)	46/237 (19.4%)	42/234 (17.9%)	120/232 (51.7%)
6 - <8 ng/mL	26/142 (18.3%)	38/136 (27.9%)	21/132 (15.9%)	27/140 (19.3%)	33/143 (23.1%)	71/134 (53.0%)
8 - <12 ng/mL	12/80 (15.0%)	23/81 (28.4%)	16/79 (20.3%)	16/79 (20.3%)	13/79 (16.5%)	53/83 (63.9%)
≥12 ng/mL	2/12 (16.7%)	4/12 (33.3%)	3/11 (27.3%)	4/12 (33.3%)	2/12 (16.7%)	12/13 (92.3%)
Myfortic	38/247 (15.4%)	81/247 (32.8%)	63/243 (25.9%)	49/247 (19.8%)	59/247 (23.9%)	96/246 (39.0%)

* Average trough levels calculated up to event or censored at date of last dose + 2 days

1 GFR (MDRD) < 30 mL/min/1.73m²

2 Decrease in GFR (MDRD or Nankivell) > 30% from Month 1

3 Decrease in creatinine clearance (Cockcroft Gault) > 30% from Month 1

4 Creatinine ≥ 200 μmol/L

5 Urine protein-creatinine ratio ≥ 300 mg/g

7.5.2 Time Dependency for Adverse Events

Not applicable due to various reasons including the fact that immunosuppression is a life-long treatment and some of the adverse events are related to the extent of

immunosuppression hence to the level of drug exposure rather than the duration of treatment. In transplant patients some adverse events like CMV infections show a time dependency but this may be more related to the general course of the transplant patients rather than the type of immunosuppression. Multitude and etiological diversity of adverse events may not always permit a time dependency analysis or yield meaningful results.

7.5.3 Drug-Demographic Interactions

The drug-demographic interactions in this study are mentioned in relevant sections such as the differential severity of proteinuria in relation to gender.

7.5.4 Drug-Disease Interactions

Please refer to Ike Lee's Clinical Pharmacology Review with original NDA submission.

The half-life estimates from 12 maintenance renal transplant patients who received single doses of everolimus capsules at 0.75 mg or 2.5 mg with their maintenance cyclosporine regimen indicated that the pharmacokinetics of everolimus are linear over the clinically-relevant dose range. Results indicate the half-life of everolimus in maintenance renal transplant patients receiving single doses of 0.75 mg or 2.5 mg everolimus during steady-state cyclosporine treatment was 30 ± 11 hours (range 19-53 hours).

7.5.5 Drug-Drug Interactions

Please refer to 7.2.5. for a listing of the DDI studies conducted for Clinical Pharmacology.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable

7.6.2 Human Reproduction and Pregnancy Data

Cumulatively, until March 31, 2009, 21 reports of drug exposure during pregnancy were received by the Applicant, including 9 reports of drug exposure to the father. This included 18 prospective cases and 3 retrospective.

An abnormal outcome was reported in 3 cases: 2 reports of spontaneous abortions/intrauterine death (PHHO2004AU16391, PHHO2004US09505, both retrospective, and PHHO2008MX08628, prospective) and 1 prospective report of a live birth with congenital anomalies. The anomaly was described as follows: reduced amniotic fluid consistent with "preterm premature rupture of fetal membranes", dilatation of cerebral ventricles inferiorly without midline falx, kidney abnormalities and two vessel cords. The newborn died shortly after delivery. The investigator suspected a relationship between this event and the study medication (PHHO2005AU08081 baby case, PHHO2004AU16391 mother case, clinical trial).

7.6.3 Pediatrics and Assessment of Effects on Growth

(b) (4)

Given that the application is being issued a CR letter, a final decision on the pediatric plan has not been made. The Division is considering a deferral or waiver for the development pediatric program but due to the CR action, consensus was not reached within the Division and with the Pediatrics and Maternal Health Staff. Once the labeling and REMS program for everolimus in adult patients is addressed, a decision about the information needed in pediatric patients, and whether the studies conducted to date by Novartis are adequate, will be determined, in consultation with the Pediatric and Maternal Health Staff.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is very little information on overdose. During clinical development, single doses of up to 25 mg given to transplant recipients and multiple weekly doses of up to 70 mg given to oncology patients resulted in no major acute tolerability issues.

7.7 Additional Submissions / Safety Issues

None.

7.8 Safety Summary

Primary Safety Endpoint – Renal Function:

At the end of 12 month study period the calculated GFR with the MDRD formula was similar in the everolimus 1.5 mg and the Myfortic (control) groups

Deaths

A total of 23 patients died during the first 12 months of the study, 7 (2.5%) in the everolimus 1.5 mg group, 10 (3.6%) in the 3.0 mg everolimus group, and 6 (2.2%) in the Myfortic control group. The most common causes of death across the study groups were related to cardiac conditions and infections. The reviewer evaluated the narratives and Case Report Forms (CRFs) for the patients who died in this study and, after excluding five deaths because of lack of any discernable association between the cause of death and the study medication, concluded a probable association between the other 18 deaths and the study medication as follows:

- 7 deaths in the 1.5 mg everolimus group
- 8 deaths in the 3.0 mg everolimus group
- 3 deaths in the Myfortic (control) group

According to this final assessment of study drug attributability of patient deaths there are more than twice as many deaths in both of the everolimus groups compared to the Myfortic group that shows a probable association with the study medication.

Although a direct comparison is not possible because of the differences in the study designs and treatment regimens, it may be relevant to mention that in both of the previous studies of fixed dose everolimus with standard dose CsA (Studies B201 and B251) there were numerically more deaths in both of the everolimus groups compared to the MMF control group.

Serious Adverse Events (SAEs)

SAEs in the following MedDRA System Organ Classes (SOCs) were reported at a higher rate in the everolimus 1.5 mg group compared to the Myfortic group:

- Blood and lymphatic system disorders, (4% vs. 2.9%)
- Gastrointestinal disorders (7.7% vs. 6.6%)
- General disorders and administration site conditions (5.5% vs. 4.4%)
- Injury, poisoning and procedural complications (14.2% vs. 11.7%)
- Investigations (8.4% vs. 8.1%)
- Metabolism and nutrition disorders (7.3% vs. 4.8%)
- Musculoskeletal and connective tissue disorders (1.8% vs. 0.4%)
- Nervous system disorders, psychiatric disorders (2.2% vs. 1.8%)
- Psychiatric disorders (1.1% vs. 0%)

- Reproductive system and breast disorders (1.1% vs. 0%)
- Respiratory, thoracic and mediastinal disorders (3.3% vs. 2.9%)
- Vascular disorders (9.5% vs. 7.3%)

SAEs in the following SOCs were higher in the Myfortic group compared to the everolimus 1.5 mg group:

- Infections and infestations (25.3% vs. 19.7%)
- Neoplasms (1.8% vs. 1.5%)
- Renal and urinary disorders (13.2% vs. 10.2%)

The higher incidence in the Myfortic group is mainly due to the higher number of cases with hydronephrosis and ureteric obstruction which are usually due to poor surgical technique. Also 5 patients who were reported to have toxic nephropathy or blood creatinine increase in the Myfortic group were concomitantly receiving sirolimus in addition to the Myfortic study regimen

Graft Losses and Graft Thromboses

Another M-TOR inhibitor, sirolimus, has a Boxed Warning regarding the increased incidence of hepatic artery thromboses in liver transplant patients, so this is a recognized class effect. The number of graft losses was 12 (4.3%) in the everolimus 1.5 mg group, 14 (5.0%) in the everolimus 3.0 mg group and 8 (2.9%) in the Myfortic group over the 12 month study period. One of the patients with renal vein thrombosis in the everolimus 1.5 mg group died later as a result of the events started by this complication (patient 0114-0001).

The Reviewer and the applicant agreed on the assessment of the number of patients who developed graft thrombosis (artery and vein) and consequently lost their grafts:

- 6 graft thromboses (4 renal artery and 2 renal vein) in the everolimus 1.5 mg group
- 4 graft thromboses (4 renal artery) with another probable 5th patient again with renal artery thrombosis according to the narrative in the everolimus 3.0 mg group
- 2 graft thromboses (2 renal artery) in the Myfortic group.

In the everolimus 1.5 mg group the incidence of early graft thromboses (within 30 days of transplant) is 1.8% and we see the same trend in the everolimus 3.0 mg group with an incidence of 1.4% which are both above the national average of 0.9% and in line with the well known thrombogenic effect of M-TOR inhibitors.

Dropouts and/or Discontinuations

Significantly more patients prematurely discontinued study medication due to adverse events in the everolimus group (18.1%) compared to the Myfortic group (9.4%) (p-value=0.004). This difference was primarily driven by significant differences between treatment groups among female patients.

Significant Adverse Events

Infections reported as AEs had a lower incidence in the everolimus 1.5 mg group compared to the Myfortic group (62% vs. 68%) which is mainly due to the more frequent CMV, BK virus and other herpes virus infections in the Myfortic group. When we look at the infections reported as SAEs the only notable differences between the two groups are 9 CMV infections and 4 herpes zoster infections in the Myfortic group vs. no CMV infection and 1 herpes zoster infection in the everolimus 1.5 mg group. All the CMV and herpes zoster infections reported as SAEs were successfully treated without any patient or graft losses.

There are no deaths due to infections in the Myfortic group whereas 2 deaths in the everolimus 1.5 mg group and 5 deaths in the everolimus 3.0 mg group are due to infections. Although numerically there were more infections in the Myfortic group the infections in the everolimus group were more serious and resulted in at least two deaths.

Proteinuria

The median UP/UC ratios over the 12 months of the study in the safety on-treatment population, which was defined as the population of safety patients whose assessments were obtained on and after day 1 but no later than two days after the discontinuation of randomized study medication. The median ratios in the everolimus 1.5 mg group were consistently higher than those of Myfortic throughout the study including the Month 12 TEP²⁰, as shown as Month 13. The differences between the groups became significant starting at Month 6 onwards.

There is a difference of 210 mg/g between the everolimus 1.5 mg group and the Myfortic group in favor of the Myfortic group using the Month 12 TEP values and this difference is even higher for the male patients since higher levels of proteinuria in the everolimus 1.5 mg group is driven by the male patients. The biological mechanism for higher levels of proteinuria in males is not known. Therefore, the Reviewer believes there is an augmented risk for the male patients over female patients. The fact that the differences between the two treatment groups became significant starting Month 6 raises concerns that the gap may continue to widen in favor of the Myfortic group with longer follow-up and may be more severe for the male patients. Proteinuria is a known risk factor for

²⁰ TEP=treatment endpoint (imputation by LOCF)

cardiovascular disease, diabetes and may contribute to hyperlipidemia at high levels. It has also been shown to decrease patient and graft survival in kidney transplantation.

Hypertriglyceridemia, diabetes and proteinuria (at the microalbuminuria level) are all components of the metabolic syndrome, which is linked to adverse patient and graft outcomes^{21,22} and they occur with higher incidence and severity in both of the everolimus treatment groups compared to the Myfortic group. It is not unreasonable to assume that this coexistence of hyperlipidemia, NODAT and proteinuria with higher severity or higher incidence compared to the control group will result in higher cardiovascular morbidity and mortality in this high cardiac risk population in the long term if not during shorter periods of follow-up like one year.

Hyperlipidemia

Hyperlipidemia was reported as an AE in 57 (20.8%) patients in the everolimus 1.5 mg group, 60 (21.6%) patients in the everolimus 3.0 mg group, and 43 (15.8%) patients in the Myfortic group.

All through the 12 month study period mean total cholesterol and triglyceride values were significantly higher in both of the everolimus groups compared to the Myfortic group. Generally, after the 9 month time point, the mean values of both total cholesterol and triglycerides came down to the normal range in the Myfortic group, whereas the mean values in both of the everolimus groups stayed above the upper limit of normal ranges. LDL values in the everolimus groups were also significantly higher in the everolimus groups compared to the Myfortic group.

In the everolimus 1.5 mg group almost three times as many patients (16% vs. 6%) have total cholesterol levels above 350 mg/dL and almost twice as many patients (4.4% vs. 2.6%) have triglyceride values above 500 mg/dL compared to the Myfortic group.

Lipid lowering agents were taken by a higher percentage of patients in the everolimus treatment groups (64.6%, 72.3% and 57.5% of patients in the everolimus 1.5 mg, 3.0 mg and Myfortic 1.44 gm treatment groups, respectively).

Among patients with high baseline cholesterol values before the statin treatment was initiated, 27.4% (17/62) in the everolimus 1.5 mg group compared to 13.9% (5/36) in the Myfortic group did not move down to the normal range despite the statin treatment. A similar trend was also observed for triglycerides in a similar analysis. Among patients with high baseline triglyceride values before the statin treatment was initiated, 49% (22/45) in the everolimus 1.5 mg group compared to 26% (5/19) in the Myfortic group did not move down to the normal range despite the statin treatment.

21 de Vries et al. Metabolic Syndrome Is Associated with Impaired Long-term Renal Allograft Function; Not All Component criteria Contribute Equally. *American Journal of Transplantation* 2004; 4: 1675–1683
22 Sharif. Metabolic Syndrome and Solid-Organ Transplantation. *American Journal of Transplantation* 2009; 9: 1–6

Usage of statins in the everolimus groups also resulted in significantly higher levels of CK (Creatine kinase) levels which may indicate excessive muscle tissue breakdown despite the mean levels stayed within the normal range.

A 39 year old male patient (0124-00076), whose death was attributed to acute myocardial infarction, developed severe dyslipidemia (hypercholesterolemia) after the transplant which gradually worsened until his death on Day 85. His total cholesterol increased from 147 mg/dL to 432 mg/dL and his LDL cholesterol increased from 81 mg/dL to 212 mg/dL (normal levels: up to 129 mg/dL) during the course of the study. Although this patient had a history of hypertensive heart disease the rapid rise of all lipid levels from normal range to very high values in a short period of time might have contributed to his death.

Hyperlipidemia is common in chronic kidney disease patients and the incidence increases after kidney transplantation. Various immunosuppressants, including CsA, corticosteroids, and M-TOR inhibitors, have been recognized as a major contributor to dyslipidemias seen after transplant. According to published research above even mild elevations in cholesterol levels may double the risk of developing ischemic heart disease in kidney transplant recipients unlike the milder increase of risk in the general population and the associated increase in mortality affects the younger recipients more than the older recipients.

Wound Healing and Wound Fluid Collections

Incisional wound complications were more frequent in the two everolimus groups compared to the Myfortic group with the highest number occurring in the 3.0 mg group. In each of the Dehiscence, Hernia and Infection categories, more patients required surgical intervention (i.e., intraoperative repair or debridement/ drainage) in the everolimus groups compared to the Myfortic group. The total number of surgical interventions was 19 in the everolimus 1.5 mg group, 22 in the everolimus 3.0 mg group, and 9 in the Myfortic group.

Similar to the incidence of wound-related events, fluid collections (lymphoceles and seromas) were also more commonly reported in the everolimus groups compared to the Myfortic group

Among all the patients who died during the 12 month period wound related problems (mainly infections and dehiscences and lymphoceles) were noted in 5 patients in the everolimus 1.5 mg group, 4 patients in the everolimus 3.0 mg group and in 1 patient in the Myfortic group. Although it is difficult to explain the association between this high occurrence of wound complications among the patients who died in both of the everolimus groups it is almost certain that there is a trend.

Fluid Accumulation, Including Peripheral Edema, Ascites, and Pleural Effusions;

At Month 12 the incidence of edema related events was statistically significantly higher in both everolimus groups than in the Myfortic group (55.5% and 54.7% versus 45.1%). Peripheral edema possibly contributed to the death of 1 patient in study 2309 who was in the everolimus 1.5 mg group. This patient (0516-00002) was treated with furosemide because of edema on day 102 and died on day 156 due to congestive heart failure.

MACE (Major Cardiac Adverse Events)

Although the overall incidence of MACE events are much higher in the everolimus 3.0 mg group compared to the other two groups in the study, everolimus 1.5 mg group and the Myfortic group look similar to each other except for the numerical increase in myocardial infarctions in the Myfortic group (2 vs 4). When those cases with myocardial infarctions are analyzed in the reviewer's assessment only one case, 39 year old male patient (0124-00076) in the everolimus 1.5 mg treatment group can be associated with the study medication (everolimus).

Hematologic Adverse Events including Thrombocytopenia

The overall incidence of hematologic?? AEs was 33.9% in the 1.5 mg group, 40.3% in the 3.0 mg group, and 40.7% in the Myfortic group. The higher incidence in the Myfortic group was mainly driven by the higher incidence of leucopenia. Leucopenia associated with mycophenolic-acid (MPA) is very common in clinical practice and is usually responsive to dose reductions or interruptions. Hematologic events reported as SAEs were reported in eleven patients in the everolimus 1.5 mg group, ten in the everolimus 3.0 mg group, and eight patients in the Myfortic group.

Thrombocytopenia contributed to one patient's death in the everolimus 3.0 mg group (patient 0549-0001).

Other Thromboembolic Events

There were 13 (4.7%) in the 1.5 mg everolimus group, 16 (5.8%) in the 3.0 mg everolimus group and 9 (3.3%) in the Myfortic group. Two patients with HUS and one each with TTP and TMA were reported in the everolimus 1.5 mg group. The number of SAEs related to thrombotic events was: eight in the everolimus 1.5 mg group and four in each of the everolimus 3.0 mg and Myfortic groups.

TMA/TTP/HUS

Thrombotic microangiopathies [TMA (Thrombotic Microangiopathy), TTP (Thrombotic Thrombocytopenic Purpura) and HUS (Hemolytic Uremic Syndrome)] are rare events traditionally associated with calcineurin inhibitors (CNIs), like CsA, until the recent discovery that they are also associated with M-TOR immunosuppression and the combined usage of M-TOR inhibitors and CNIs may increase the incidence. In Study A2309 a total of 4 TMA cases (1 TMA, 1 TTP and 2 cases of HUS) were reported all in the everolimus 1.5 mg group. TTP reported in the everolimus 1.5 mg group also contributed to one graft loss (patient 0192-00002).

Non Infectious Pneumonitis, Including Alveolar Proteinosis

Non infectious pneumonitis, including alveolar proteinosis, is a class effect of M-TOR inhibitors. It is relatively rare but may have a fatal outcome, especially if it is not recognized or treated appropriately. The diagnosis must be considered in every patient who develops dyspnea especially if they are on an M-TOR inhibitor. Infectious pneumonia is also commonly superimposed. Treatment includes discontinuation of the M-TOR inhibitor and steroids.

A total of six patients were reported to have interstitial lung disease identified by the applicant. Two cases were in the everolimus 1.5 mg group, three in the everolimus 3.0 mg group, and one is in the Myfortic group. The patient in the Myfortic group had no record of lung related pathology in narrative.

One patient developed alveolar proteinosis (0304-00016) in the everolimus 1.5 mg group following the initial 12 months of the study and died due to pneumonia and septic shock 60 days after the diagnosis.

Neoplasms

Neoplasms, benign and malignant, were reported at a lower incidence in the everolimus 1.5 mg group compared to the Myfortic group (9 patients compared to 16 patients, respectively) but the only malignancy death in the study (malignant melanoma) was also reported in the everolimus 1.5 mg group and the only lymphoma (PTLD) was observed in the everolimus 3.0 mg group.

New Onset Diabetes after Transplantation (NODAT)

Fasting plasma glucose \geq 126 mg/dL (7.0 mmol/L), which is part of the standard definition for NODAT by the ADA (American Diabetes Association) was not included as part of the other screening criteria for NODAT in this study. Therefore, the Reviewer believes the resulting estimation of NODAT in all three study groups is lower than

anticipated. The incidence of NODAT was 9.1% in the everolimus 1.5 mg group, 12.2% in the everolimus 3.0 mg group, and 6.6% in the Myfortic group.

The reported incidence of NODAT among kidney transplant recipients with standard immunosuppression in the literature is around 30% though it may be higher depending on the type of CNI inhibitor utilized and in some publications it is reported to be as high as 50%. The numbers reported in Study A2309 are not compatible with the published literature. If the screening criteria had been more stringent (ADA recommended criteria) the incidences would be higher in all treatment groups with a possible increase of the difference between the everolimus group and the Myfortic group in favor of the Myfoertic group.

Gastrointestinal Adverse Events

Gastrointestinal adverse events like nausea vomiting and diarrhea are commonly observed with MPA treatment. However, in the study gastrointestinal adverse events overall had a similar incidence in the everolimus 1.5 mg and the Myfortic groups (72% compared to 76%, respectively).

Gastrointestinal events reported as SAEs were more frequent and tended to be more severe, as described below, in the everolimus 1.5 mg group. The everolimus 3.0 mg group had the highest incidence of SAEs in the SOC of Gastrointestinal Disorders (28 patients) followed by the 1.5 mg group (21 patients) and the Myfortic group (18 patients), respectively.

Two cases of hemorrhagic esophagitis in the everolimus 1.5 mg group and one case of mesenteric vessel thrombosis in the everolimus 3.0 mg group were reported as SAEs, which may be associated with the ulcerative and thrombogenic class effects of M-TOR inhibitors.

Male Endocrine Effects

At 9 months patients in the everolimus 1.5 mg group displayed a lower mean testosterone level and higher mean LH and FSH levels when compared to the Myfortic group. The mean values for all three hormones were still within the normal ranges with FSH level in the everolimus 1.5 mg group being at the upper level of normal,. The difference between the testosterone levels across the two treatment groups at 9 months appeared to be caused by a decrease of testosterone levels in the everolimus 1.5 mg group throughout the 9 month period during which the testosterone levels in the Myfortic group stayed the same. Month 9 mean testosterone levels are still within the normal range in both groups despite the significant decrease in the everolimus 1.5 mg group.

The mean FSH levels in the everolimus 1.5 mg group increased and rose up to the upper limit of the normal range (11.1 ± 9 U/L) at 9 months which may be indicative of

decreased sperm production. Sperm counts were not performed as part of the protocol in Study A2309. However, oligospermia or azospermia, which is usually reversible, is reported in the literature for other M-TOR inhibitors and documented in the non-clinical studies for everolimus. The effect is partly due to the anti-proliferative effects of M-TOR inhibitors.

Other Concerns: Drug-Drug Interactions

Both everolimus and CsA are metabolized through the CYP3A4 enzyme system in the liver. On the other hand, MPA is mainly metabolized through glucuronidation.

For both everolimus and CsA, concurrent treatment with strong 3A4 inhibitors, such as azole antifungals (ketoconazole, itraconazole, voriconazole) and macrolide antibiotics (clarithromycin, telithromycin) gives rise to significant increases in the concentrations of these drugs and concurrent use is not recommended. In addition, CsA also has a significant drug interaction with some of the HMG-CoA reductase inhibitors and use with lovastatin and simvastatin is also not recommended.

In addition, co-administration of CsA with everolimus significantly increases the concentrations of everolimus. Therefore, if the dose of CsA is increased, everolimus toxicity is possible if everolimus concentrations are not carefully monitored and the dose of everolimus adjusted. Another difficulty with the TDM regulation of the everolimus is the relatively long plasma half life which is around 30 hours in kidney transplant recipients. At least 5 days need to elapse before a meaningful trough concentration can be obtained every time either the everolimus or the CsA dose is changed

On the other hand, there is no CYP3A4 interaction between MPA and CsA. In fact, there is a small effect of CsA on the enterohepatic circulation of MPA such that an increase in CsA exposure decreases MPA exposure and reduces the possibility of increased toxicity due to this interaction.

Non-Clinical Findings and Possible Risk of Cataracts

Eye examinations were not included in the study protocol so it is not known if there is an increased incidence with everolimus treatment but in non-clinical studies (in rats) everolimus at clinically relevant doses caused fibrillar degeneration in the lens (see section 4.3).

Conclusion

The efficacy results from Study A2309 showed that both everolimus treatment regimens were non-inferior to the Myfortic control regimen at 12 months with regard to the primary efficacy composite endpoint consisting of the first occurrence of treated BPAR, graft loss, death or loss to follow-up. Although the incidence rate of death, graft loss and loss to follow-up was similar between both everolimus groups and Myfortic group,

numerically these events were more frequent in the everolimus groups and displayed a clear association with everolimus treatment.

In terms of GFR, there were no statistically significant differences between any of the treatment groups at month 12.

However, there were significant safety findings in the everolimus 1.5 mg group compared to the Myfortic control specifically:

- Numerically increased mortality with more causality associations,
- Numerically increased graft losses with an increased incidence of graft thromboses one of which resulted in death.
- More hyperlipidemia
- More NODAT
- More proteinuria
- More wound healing problems with more patients requiring surgical or non-surgical interventions for treatment
- Interstitial lung disease which contributed to the death of one patient
- TMA/TTP/HUS one of which contributed to the graft loss in one patient
- Severe thrombocytopenia which contributed to the death of one patient in the everolimus 3.0 mg group. It is not known if this adverse effect is exposure dependent. Thrombocytopenia has been frequently associated with M-TOR inhibition in the literature, although it may also be encountered with MPA treatment it is usually milder in nature.
- Adverse effects on the male gonadal function.
- -More study drug discontinuations due to adverse events which may partly due to the difficulty of managing the regimen.

Therefore, it is the Reviewer's opinion that the safety findings with the everolimus 1.5 mg regimen far outweigh the benefits of the regimen and probably will result in increased mortality both in the short term and the long term when compared to the comparator Myfortic regimen or other similar immunosuppressive regimens currently being used. The higher morbidity and mortality associated with everolimus may become more noticeable in the long term since some of the associated risks like hyperlipidemia, NODAT and proteinuria continue to exert their effects over the course of the years and immunosuppression is a life long treatment unlike many other treatments.

8 Postmarket Experience

The following post-marketing experience is a summary of the Applicant's Post-Marketing Periodic Safety Updates with details of labeling changes from the NDA resubmission:

The post-marketing experience is derived from the periodic safety update reviews

(PSURs) and updates to the Company Core Data Sheet (CDS), this being the document prepared by the pharmaceutical manufacturer, containing among other things all relevant safety information, such as adverse drug reactions, which are required to be listed for the drug in all countries where the drug is marketed (CIOMS 1996). The CDS for Certican is identical to the Summary of Product Characteristics (SmPC) used in the European Union.

Adverse drug reactions (ADRs) were attributed to Certican in the SmPC based on an imbalance in their frequency relative to active, non-everolimus CsA-based controls, as seen in the initial phase 3 studies and the frequencies quoted are the absolute frequencies for the combination of everolimus and CsA.

Safety issues previously subject to close monitoring, now the subject of routine pharmacovigilance without change

ADRs included in initial SmPC

The following disorders, included as ADRs in the initial SmPC and subject to cumulative reviews in successive PSURs after approval, have since reverted to routine pharmacovigilance without change to their initial characterization in the SmPC: *acute tubular necrosis* (uncommon ADR), *biliary disorders/hepatotoxicity disorders* (uncommon ADR), *lymphocele* (common ADR), *malignancies* (warning), *myotoxicity* (myalgia is uncommon ADR), *thromboembolic events* (venous thromboembolism common ADR), *thrombotic thrombocytopenic purpura* (common ADR).

ADRs not included in SmPC

The following disorders have been the subject of cumulative reviews in past PSURs and have reverted to routine pharmacovigilance without their inclusion into the SmPC: *bronchial/vascular dehiscence*, *hemorrhagic events*, *toxicoderma*, *urinary leak*, *right heart failure*, *pulmonary hypertension*, *cardiac failure*, *pancytopenia*.

ADRs added to SmPC since the Initial Approval in Mexico in 2003

The following disorders related to use in kidney transplant were not included in the initial SmPC but have been added subsequently as a result of later experience:

Angioneurotic edema was the subject of an assessment in November 2005 after receipt of literature reports of tongue swelling in Certican²³-treated patients with subsequent inclusion of the disorder in the Certican SmPC as a common disorder reported predominantly in patients receiving concomitant therapy with ACE inhibitors. A cumulative search until the period of PSUR 6 identified 25 reports (described as angioedema or as edema/swelling evoking the diagnosis) in the Novartis safety database. In all but three cases patients were receiving concomitant therapy with an ACE inhibitor or angiotensin receptor blocker. When outcome was documented,

²³ Certican is the applicant's trade name for everolimus in the countries in which the drug is approved.

complete recovery was apparent in all cases after treatment (steroids, antihistamines and, in one case, tracheostomy). Negative rechallenge was reported in two patients with reintroduction of everolimus following withdrawal of the ACE inhibitor. The experience during the review period being compatible with the description of this adverse reaction in the SmPC, it was concluded that the disorder should be subject to routine pharmacovigilance procedures.

Pancreatitis was reviewed in PSURs 1-2. The topic was re-assessed during the period of PSUR 6. It was noted that although the incidence in the initial phase 3, double-blind clinical trials had not been more elevated than that in the control groups (azathioprine, mycophenolate mofetil) pancreatitis was included as drug-related disorder in the labels of both these drugs. With one case rechallenge positive among those documented, the disorder was included into the Certican SmPC (common disorder, frequency just above 1%).

Safety issues currently subject to close monitoring

Interstitial lung disease (ILD)

Included as an uncommon adverse drug reaction (ADR) in the first SmPC, ILD has been continuously monitored since PSUR 1.

In May-2007, the topic was the subject of a cumulative review (PSUR 6 - Appendix 4) which resulted in modification of the SmPC with further description of the disorder including the existence of fatal cases, the insertion of a warning into the SmPC and the identification also of *pulmonary alveolar proteinosis* as a distinct but rare ADR.

Among transplant recipients, the frequency of ILD appears to be 3 times more frequent in heart transplant patients than in renal transplant patients (1.6% v. 0.5% in clinical trial patients, PSUR 7). Until 31-Mar-2009, there had been 11 reports of ILD with fatal outcome. In only 1 case (spontaneous report in a heart transplant recipient) did this occur in a patient with no evidence of confounding lung disorders. Otherwise, in almost all cases, outcome has been favorable after discontinuation of everolimus with or without steroids.

Rhabdomyolysis/creatinine kinase increase

The accumulated data on reports of rhabdomyolysis and elevated CPK does not suggest Certican to be a causal agent. Rather, the limited number of cases observed appear to be essentially an extension of the known effect of statins prescribed to oppose the lipid-raising effects of everolimus and calcineurin inhibitors including cyclosporine. A small number of cases accompany infectious episodes. Warnings are carried already on the labels of statins, cyclosporine, everolimus and strong 3A4 inhibitors such as itraconazole which can interact with those statins which are 3A4 substrates.

Safety issues identified as requiring review and possible inclusion in the SmPC but pending completion of Study A2309

Stomatitis

There have been numerous reports of stomatitis in everolimus patients in both transplant and oncology indications. A dose-relationship was established for everolimus as regards the incidence and severity of stomatitis in studies in cancer patients (which employ everolimus as monotherapy with significantly higher exposures than in transplant patients). It remains to be assessed whether this disorder is related to everolimus therapy when administered at the lower exposures employed post-transplantation.

Polyomavirus infections

With recent requests from health authorities to include information on the risk of polyomavirus infections in transplant recipients receiving immunosuppressant drugs, the Novartis safety database was searched for evidence of polyomavirus infections in everolimus treated patients. BK virus (BKV) had been reported only in clinical trial patients, almost exclusively in renal transplant recipients, with a crude overall reporting frequency of 0.29%. The reporting of proven BKV-associated nephropathy (BKVAN) in renal transplant recipients is 0.14%. No reports of progressive multifocal leukoencephalopathy (PML) were found.

9 Appendices

9.1 Literature Review/References

Relevant references are given in the text as footnotes.

9.2 Labeling Recommendations

DSPTP will give the Applicant a Complete Response pending submission of an acceptable REMS and revised package insert. Below are portions of the revised package insert to be attached to the CR letter. The Medication Guide, as part of REMS, will be reviewed with the Complete Response letter.

8 Page(s) of Draft Labeling have been withheld in full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21560	ORIG-1	NOVARTIS PHARMACEUTICA LS CORP	CERTICAN (EVEROLIMUS) TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HUSEYIN E VELIDEDEOGLU
12/23/2009
ZORTRESS NDA 21-560 CLINICAL REVIEW

JOETTE M MEYER
12/23/2009

CLINICAL REVIEW

Application Type:

AMENDMENT TO A PENDING NEW DRUG APPLICATION

NDA 21-560 (adult tablets – Kidney transplantation)

NDA 21-628 (adult tablets – Heart transplantation)

(Each tablet contains 0.25/0.5/0.75/1.0 mg everolimus)

Submission Number: 000
Submission Code
(Supplement Modification Type): BZ
Letter Date: February 27, 2004
Reviewer Name: Arturo Hernandez (HFD-590)
Review Completion Date: July 30, 2004
Established Name: Everolimus
Trade Name: Certican®
Therapeutic Class: Immunosuppressant
Applicant: Novartis Pharmaceuticals Corporation
Formulation: Tablets
Proposed Dose Regimen: 1.5 mg p.o. bid
Intended Population: Adult Renal and Heart transplant recipients
Indication:

Prophylaxis of Organ Rejection in Allogeneic Kidney and Heart Transplantation

Team Leader: Marc CavailJ-Coll (HFD-590)
Medical Reviewer: Arturo Hernandez (HFD-590)
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HFD-590/RRO/RAnderson
HFD-590/PMTL/EMolinaro
HFD-590/PM/ ANabakowski
HFD-880/BphTL/Pcolangelo
HFD-880/Bph/JLee
HFD-725/StatTL/KHiggins
HFD-725/Stat/RDavi
HFD-725/Stat/LTracy

HFD-590/Original NDAs 21-560 and
21-628.

1 LIST OF ABBREVIATIONS AND DEFINITIONS.

1.1 LIST OF ABBREVIATIONS.

AC	Active controlled,
AE	Adverse Events, Adverse reaction
AR	Acute rejection
ATG	Anti-thymocyte globulin
ATN	Acute tubular necrosis
AZA	Azathioprine
BCI	Blood Creatinine Increased
BPAR	Biopsy Proved Acute Rejection
BPCAN	Biopsy Proved Chronic Allograft Nephropathy
b.i.d	Twice daily (bis in die)
BSA	Body surface area
CAD	Coronary Artery Disease
CadD	Cadaveric Donor
CAN	Chronic Allograft Nephropathy
CsA	Cyclosporine (Neoral®)
CI	Confidence interval
CI _{inh}	Calcineurin inhibitor
CIT	Cold Ischemia Time
CI _{inh}	Calcineurin Inhibitor
CMH	Cochran-Mantel-Haenszel test
CMV	Cytomegalovirus
CR	Chronic Rejection = allograft vasculopathy
CrCl	Creatinine Clearance
CS	Corticosteroids
CsA	Cyclosporine A
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
HBD	Heart Beating Donor
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
LD	Living Donor

LRD	Living related donor
KM	Kaplan-Meier
KRS	Key Renal Studies (B201 and B251)
KRS-MMF	Key Renal Studies MMF arms pooled data
KHS	Key Heart Study (B253)
MC	Multicenter
MD	Multiple dose
MHRA	Medicines and Healthcare products Regulatory Agency
MMF	Mycophenolate Mofetil
NCEP-ATPIII	National Cholesterol Education Program - Adult Treatment Panel III
NHBD	Non-Heart Beating Donor
NSAE	Non-Fatal Serious AEs
NYHAC	New York Heart Association Classification
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™
RAD 1.5	Certican™ 1.5 mg dose group (given as 0.75mg twice daily [bid])
RAD 3	Certican™ 3 mg dose group (given as 1.5 mg twice daily [bid])
R	Randomized
S-	Study e.g. S-B253
SAE	Serious adverse event
NSEA	Non-Fatal Serious Adverse Event
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
TEP	Treatment End Point = Last Observation Carried Forward
TMA	Thrombotic Microangiopathy (HUS and TTP)
TTP	Thrombotic thrombocytopenic purpura
WBC	White Blood Cells

1.2 DEFINITIONS

Everolimus (40-O-[2-hydroxyethyl]-rapamycin), SDZ-RAD or RAD001: Is a Rapamycin derivative known also as Certican®. We may use all these synonyms but we will use the term RAD primarily.

Antibody treated acute rejection: Only *suspected* rejections (treated with antibodies) where *final clinical diagnosis = acute rejection* will be considered *antibody treated acute rejections*. *Antibody treated acute rejections* are thus a subset of *clinically confirmed acute rejections*.

Chronic Rejection: Also referred as allograft vasculopathy

Clinically confirmed acute rejection episodes: include 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 = rejections diagnosed as chronic on clinical grounds. Do not include biopsy-proven chronic rejection.

DAE: Adverse Event Leading to Discontinuation

HDC (Hemodynamic compromise) was 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.

Efficacy failure in study B253 (Key Heart Study): 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

NDAs: 21-560, and 21-268

Transplantation (ISHLT) \geq grade 3A or any clinically suspected acute rejection episode associated with hemodynamic compromise [HDC]

Efficacy failure in studies B251 and B201 (Key Renal Studies): Defined as the incidence of the composite efficacy endpoint (biopsy-proven acute rejection, graft loss, death, loss of follow-up)

Hypogonadism (Laboratory-defined): Low (age adjusted) testosterone level **and** LH >15 IU/L in an adult male.

Key Renal Studies: B251 (USA study) and B201 (EU study)

Non-significant, was not significant, etc.: This term is used to denote "not statistically significant"

Notable events include Deaths, NSAEs (Non-Fatal Serious AEs) and ADOs (Adverse dropouts). ADOs were patients with primary discontinuation reasons: AEs or abnormal laboratory values or abnormal test procedure result.

Novartis Pharmaceuticals Corporation: In the review we will use the words "sponsor", "applicant" and "Novartis" interchangeably.

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.

Subclinical rejections: acute rejection found on "protocol" [surveillance] biopsies performed [in the absence of clinical symptoms]. Protocol biopsies were required only at selected sites in study 251 at 6, and 36 months. In study 201 surveillance biopsies at 6, 12 and 36 were optional

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

Treatment Endpoint (TEP) was used as a synonym of the last observation carried forward (LOCF)

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

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2 EXECUTIVE SUMMARY

2.1 Recommendation on Approvability

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 profile was observed with the original RAD fixed dose regimen and Full Dose Neoral (FDN) explored in the Key Renal studies (B201 and B251) and Key Heart Study (B253).

The analyses presented by the sponsor on non-controlled studies A2306 and A2307, which explored TDM Certican® with Reduced Dose Neoral (RDN), were not convincing due to fundamental deficiencies in these cross study comparisons. Furthermore, important differences in the donor / recipient baseline characteristics do not allowed using pooled data from KRS without introducing significant potential for bias.

These analyses were able to generate hypothesis that will require to be tested prospectively in randomized well control studies. We believe that TDM Everolimus plus CsA minimization strategy is a promising approach that appears to optimize efficacy and minimize the degree of renal function impairment. However, we were not able to identify an appropriate TDM RAD plus reduced dose neoral regimen for the kidney or heart indication that will allow maintaining efficacy while minimizing toxicity in both early and maintenance periods after transplantation.

We recommend a second approvable letter for this resubmission.

2.2 Summary of Clinical Findings

2.2.1 Brief Overview of Clinical Program

Everolimus (RAD) is a macrolide immunosuppressant derived from rapamycin that bind to FKBP¹. The RAD-FKBP complex binds and inhibits the action of mTOR² suppressing the 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 an original NDA for the prophylaxis of organ rejection in allogeneic kidney and heart transplant patients in December 19, 2002.

In the initial submission Novartis presented two key phase III *de novo* renal allograft trial (B201 and B251) for the kidney indication and one key *de novo* heart study (B253) for the heart indication. However, unacceptable safety profile was observed with the original RAD fixed dose regimen and Full Dose Neoral (FDN) explored in the Key Renal studies (B201 and B251) and Key Heart Study (B253)

In an attempt to decrease nephrotoxicity while maintaining efficacy, the KRS and KHS were

¹ FK binding protein

² Mammalian Target Of Rapamycin.

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unblinded and the RAD fixed dose regimens were changed to RAD TDM (> 3 ng/mL). The full dose Neoral® regimen was changed to CsA minimization and the TDM for CsA was also modified from C0 trough levels to C2.

These protocol amendments had a limited effect in improving renal function and fail to revert chronic renal deterioration in both heart and renal key studies. An approvable letter was issued on October 17, 2003.

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 with out approved control regimen and full reports were not available during the first review cycle (See initial clinical review, October, 2003). We acknowledge that the revised proposed label submitted by Novartis (b) (4)

In this re-submission, the sponsor relied completely on efficacy and safety analysis from studies A2306 and A2307 based on cross study comparisons using historical controls (studies B201/B252 and study B156, respectively). The main safety and efficacy analysis derived from studies A2306 versus key renal studies (B201 / B251) and the recommended regimen relied heavily on these analyses.

The use of historical controls for these open label studies presents important difficulties in this case due to significant differences in study design (Open label vs. double blind), method used for CsA dose adjustments (C₂ vs. C₀) and significant differences in donor /recipient baseline characteristics.

2.2.2 Comparability of patient populations

2.2.2.1 Patient Demographics

- ***The USA study, B251 included more black patients (17%) compared to studies B201 (4%) or A2306 (6%).***
- ***Pooled data from KRS-MMF arms, presented higher rates in black and older recipients³ (12% and 39%) compared to study A2306 (6% and 33%, respectively).***

2.2.2.2 Donor Source

- ***The percentage of cadaveric donors in S-B201-MMF arm was higher (91%) compared to the MMF arm in S-B251 (46%).***
- ***Pooled data showed higher rates of cadaveric donors in the KRS-MMF compared to study A2306 (69% versus 63%, respectively). NHBD kidneys were excluded from study A2306***

³ Recipient age =>50 years

2.2.2.3 Donor and Recipient Baseline Characteristics

- *The European study B201- MMF arm included more cadaveric donors and as expected more higher rates of DFG were observed in S-B201 compared to USA study B-251 (20% versus 6%, respectively). Mean/median donor age was also higher in the EU trial compared to USA trial, which is also a contributing factor for DGF.*
- *Pooled data showed similar rates of DFG across studies, 13% and 16% for KRS-MMF arms and A2306, respectively.*
- *Study A2306 included higher proportion of Living Donors (LD), lower proportion of donors with prolonged cold ischemia time (CIT), and Reduced Dose Neoral® (RDN). Furthermore, functional grafts at randomization were required as inclusion criteria in this study. Despite of all the mentioned favorable conditions the DGF rates were higher in study A2306 compared to KRS-MMF arms (16% vs. 13%). The rate difference is small, but under these circumstances it becomes relevant.*
- *Study B156, compared 3mg RAD fixed dose with either FDN or RDN. The FDN arm presented twice the incidence of GFR (15%) compared to the RDN arm (7%). These results suggest a potential deleterious effect of the RAD plus FDN regimen on immediate renal function.*
- *High risk CMV mismatch (D+/R-) rates from KRS-MMF arms, were higher (18%) compared to study A2306 (11%).*
- *Pre-existing Diabetes Mellitus was 4 times higher in USA study B251-MMF arm (25%) compared to EU study B201-MMF arm (6%). Pooling data from both KRS-MMF arms still shows higher rates of baseline DM versus study A2306 (15% versus 8%, respectively)*
- *High-risk⁴ patients rates in study B201-MMF arm, were higher (69%) compared to B251-MMF arm (37%). This difference was driven by the higher proportion of cadaveric donors and prolonged CIT enrolled in the EU study B-201.*
- *The causes of ESRD leading to transplantation presented imbalances across MMF arms in studies B251 and B201. Diabetes Mellitus and Hypertension/nephrosclerosis presented significantly higher rates in the USA study B251 (18% and 20%, respectively) compared to the European study B201 (4% and 8.5%, respectively) or A2306 (5% and 14%, respectively). The pooled data showed that the rates of DM related ESRD leading to transplantation in study A2306 were less than half compared to B201/B251-MMF arms (5% versus 12.5%, respectively).*

⁴ Recipients of a cadaveric donor plus one of the following characteristics:

a) black, b) PRA >50%, c) cold ischemic time >24 hours, d) total number of HLA mismatches >=3

2.2.2.4 Risk Factors for Cardiovascular Disease

- *Coexisting Medical Conditions known as risk factors for atherosclerotic cardiovascular disease (Obesity, smoking, hypertension, DM, etc.) presented higher incidence rates in the USA study B251 compared to the EU study B201. Similarly, the presence of coronary artery disease, and previous myocardial infarction were higher in USA study B251 compared to the EU study B201. These differences were present across the MMF arms.*
- *Study A2306, considered the presence of cardiac disease as exclusion criteria.*
- *Risk factors for cardiovascular events post-transplantation presented higher rates in the pooled KRS-MMF arms versus RAD arms in study A2306 favoring study A2306 for a better long term outcome.*

2.2.3 Appropriateness for Pooling Data from Key Renal Studies (B251 and B201) as Historical Control for Study A 2306

The differences across MMF arms mentioned in the previous section delineate two different populations, and pooling data is considered inappropriate. Even though, analyses were conducted to adjust for obvious covariates (i.e. donor type, race, DGF), many differences in donor / recipient baseline characteristics and pre-existing condition were not addressed. Furthermore, the potential for bias due to unknown covariates is still present.

Pooled data from studies B201/ B251-MMF arms showed higher rates compared to study A2306 (respectively) in the following donor /recipient baseline characteristics:

- *Cadaveric donors (68.5 vs. 63%),*
- *NHBD (7.5% vs. 0),*
- *CIT >24 hours (13 vs. 7%),*
- *Blacks (11.5 vs. 6%),*
- *Recipient age \geq 50 years (39% vs. 33%)*
- *CMV mismatches, (18 vs. 11%),*
- *Pre-existing DM, (15 vs. 8%),*
- *Tobacco use (6 vs. 2%),*
- *Pre-existing Hypertension (88 vs. 82%),*
- *Pre-existing Coronary Artery Disease (6.5 vs. 2%) and*
- *Pre-existing Anemia (33.5 vs. 29%)*

We conclude that pivotal renal studies, B251 and B201 had different donor and recipient background characteristics. Therefore, pooling data from these studies is inadequate. Using pooled data from KRS as an historical control for A2306 is considered inappropriate due to the fact that these analyses have a high probability to lead to spurious conclusions.

Pooled data (KRS-MMF arms) showed worst profile in the donor /recipient baseline characteristics favoring study A2306 for better outcomes. In these circumstances we would predict a worst long term outcome in the KRS-MMF arms due to the worst baseline characteristic in this population. We consider these cross study comparison invalid.

2.2.4 Efficacy Conclusions:

The efficacy analyses presented by the sponsor were performed pooling data from Key Renal Studies (KRS) EU B201 and USA B251, as an historical control for study A2306. We consider inappropriate to pool data from KRS due to important differences in donor /recipient baseline characteristics. Therefore, the results from these cross study comparisons should be taken with caution.

- *Primary and co-primary efficacy failure rates at 12 months were comparable between study A2306 (RAD 1.5 and RAD 3 dose groups) and MMF groups in studies B251/B201.*
- *Biopsy-proven chronic allograft nephropathy⁵ (CAN) at 12 month was almost the double in the A2306-1.5 arm compared to the control MMF arms (13% versus 7%, respectively). This striking difference raises concerns whether alloantigen dependent causes (i.e. sub-clinical rejection), alloantigen independent causes (i.e. DM, Hyperlipidemia, syndrome X, etc.) or both are involved in this difference. This important difference at one year raises concerns regarding the safety and efficacy of the proposed regimen. We consider, that regarding BPCAN efficacy endpoint the proposed regimen failed compared to the historical control. We do not know the potential consequences of this difference in BPCAN on long term renal function.*
- *Efficacy failure rates in study A2307 (reduced-dose Neoral with Simulect) were lower compared with full-dose Neoral arm and Simulect in study B156. The significance of these results is difficult to evaluate due to:*
 - *Small number of patients included in these studies,*
 - *Cross study comparison with a historical control, and*
 - *Different regimens (RAD TDM regimen versus RAD fixed doses)*

The use of antibody induction therapy is an interesting approach with the theoretical advantage to protect against rejection in early phase post-transplantation which will allow the use of low dose neoral while maintaining efficacy. This approach requires to be tested prospectively in an adequately designed trial.

- *Study A2306 baseline Donor/Recipient characteristic are different from those in the USA transplant population. Therefore, any comparison with UNOS registry needs to be taken with caution. We acknowledge that the proportion of cadaveric donor and living donors in study A2306-RAD 1.5 arm is similar to the UNOS registry donor data reported in the last years. However, other demographic and baseline characteristics do not reflect the rates observed in the USA transplant population (OPTN/SRTR).*
- *The adjusted data for donor type, recipient race, and DGF appeared very similar without any advantage for A2306 versus KRS-MMF arms. Other baseline characteristics favoring study A2306 for better outcomes were not taken in*

⁵ CAN in the most important cause of late graft failure in renal transplantation.

consideration for these analyses. Under these circumstances, a non-inferiority margin is not considered a relevant result.

- *The overall biopsy rates in the European study B201 were higher across arms compared to USA study B251 arms. Differences observed in the baseline donor / recipient characteristics of the populations involved. (e.g. donor type) may explain these differences*

2.2.5 Safety Conclusions:

2.2.5.1 Adverse Events:

- *RAD plus CsA in study A2306 did not showed any advantage compared to historical MMF control in KRS with respect to the rates of discontinuation rates from study medication.*
- *Adverse events were the main cause for discontinuation from study medication in the all studies and across arms. It is interesting to note that, in study A2306, the RAD 1.5 arm presented higher rates of discontinuation from study medication compared to the RAD 3 mg arm (29.5% vs. 24% respectively). Similarly, the incidence of DAE at 12 months, were higher in the RAD 1.5 mg group compared with the RAD 3 mg group (25% vs. 18%, respectively).*
- *Dose related AE for Certican® has been observed in the KRS and KHS. Similarly, in study A2306 the Certican dose effect was observe in a difference of $\geq 5\%$, (RAD 1.5 versus RAD3) in Blood creatinine increased , Hypercholesterolemia , Diabetes mellitus NOS, Hypertension NOS, Hyperglycemia NOS, Anemia NOS , Tremor, Peripheral edema, and Hypokalemia*
- *Anemia rates were very different between MMF arms, studies B251 and B201 (20% and 34%, respectively).*
- *Trombocytopenia showed a RAD dose related effect, the RAD 3 arm presented twice the rate compared to the B251-MMF and B201-MMF arms (12% versus 7% and 6%). The thrombocytopenia RAD1.5 rates were similar to the MMF arms.*
- *Leucopenia showed approximately three times higher rates in the KRS-MMF arms versus study A2306 RAD arms.*

2.2.5.2 Renal Related Adverse Events:

- *Allograft dysfunction total ⁶ rates showed a RAD dose related effect in study A2306.(43% and 32% in the RAD 3 and RAD 1.5, respectively) and were approximately four times higher rates compared to the MMF arms in studies B251 and B201 (8 % and 10%, respectively).*
- *Thrombotic Microangiopathy was reported in seven cases out of 237 patients (3%) in study A2306 versus one case out of 392 transplant patients in the KRS-MMF arms (0.2%). We consider this difference clinically relevant.*

⁶ Allograft dysfunction total includes: Blood creatinine increased, Renal Function, Abnormal Renal impairment NOS, Primary Graft Dysfunction or graft dysfunction, Renal Tubular Necrosis, Renal failure acute.

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- *In study A2306, 12 cases (5%) were reported by the investigator as AE because of cyclosporine toxicity. Half of these cases (6/237) were considered NSAE (2.5%), which is proportionally higher than 6/392 (1.5%) in the KRS-MMF arms. These rates are really small to draw any valid conclusion; however, given the fact that patients in study A2306 were receiving approximately half of the CsA dose compared to the MMF arms, we wonder if the CsA enhanced toxicity by RAD is still an issue with RDN regimens. Long term follow up is recommended.*

2.2.5.3 Renal Function:

RAD plus full dose CsA combination showed early post-transplant deleterious effects on renal function. Chronic use of fixed dose RAD plus FDN may lead to irreversible nephrotoxic changes. Therefore, the regimen of either RAD 0.75mg bid or RAD 1.5 mg bid with FDN is considered unacceptable.

- *The RAD arms in studies A3206/07 showed comparable CrCl to the KRS-MMF arms that used FDN. However we do not consider this fact a real advantage of the RAD plus RDN regimen and it may only reflect a better quality of donors / recipients included in studies A2306/07.*
- *We should expect lower creatinine clearance in EU study 201 compared to the other studies due to the following reasons:*
 - *Study B201-MMF arm included a significantly higher proportion of CAD donors, NHBD, High risk patients⁷ and transplanted kidney with CIT >24 hours compared to studies B251, A2306 and A2307.*
 - *At 12 month, mean GFR was similar between RAD arms (A2306/07) and MMF-B251 arm.*
 - *mean GFR continue to improve (beyond 12 months) in both KRS-MMF arms, showing a superior mean GFR at 36 month of 71 ml/min in the B251-MMF arm.*
 - *From 12 to 36 months, the GFR in the MMF arms in both KRS continue to improve by 5 and 7 mL/min in the MMF arms studies B251 and B 201, respectively.*
 - *We speculate if RAD arms in studies A2306 and A2307 will show GFR improvement beyond 12 month. The long term GFR improvement in the RAD plus RDN regimen remains to be seen.*

⁷ Recipients of a cadaveric donor with one of the following:

a) black, b) PRA >50%, c) cold ischemic time >24 hours, d) total number of HLA mismatches >=3

NDAs: 21-560, and 21-268

- *Biopsy Proven Chronic allograft nephropathy presented higher rates in study 2306 compared to the KRS-MMF arms. We should expect consequences on long term renal function from these differences in BPCAN.*
- *Renal function from older donor allografts remained stable from 12 to 36 month post-transplantation in the KRS-MMF arms.*

2.2.5.4 Lipid Related Adverse Events

- *Hyperlipidemia related AE's, New onset of Hypercholesterolemia, and New onset of Hypertriglyceridemia presented higher incidence rates in study A2306 compared to the KRS-MMF arms. An important RAD dose related effect was observed*
- *The mean cholesterol and triglycerides level in both RAD arms, in study A2306 were higher compared to the MMF arms of both KRS and a RAD dose related effect was observed in the mean triglyceride levels in study A2306.*
- *both RAD arms in study A2306 presented higher mean cholesterol levels at all measurement points (≥ 6.2 mmol/L, High cholesterol lower limit) compared to KRS-MMF arms (≤ 6 mmol/L).*
- *Despite intensive therapeutic intervention to treat related dyslipidemias, the A2306/07 RAD arms mean cholesterol and triglyceride values persisted at higher level all measurement points when compared to the KRS-MMF arms.*
- *Hyperlipidaemia is a well known risk factor for cardiovascular disease and chronic allograft nephropathy. The long term consequences of higher lipid levels and higher incidence of new onset hyperlipidemia in the RAD regimen in study A2306 compared to the approved regimen used in the MMF arms from both KRS are unknown.*

2.2.5.5 Infections

- *Viral infections were significantly lower in study A2306 compared to the MMF arms of the KRS (3% versus 19%, respectively). Even though these results are intriguing, we cannot make any reliable conclusions.*
- *Bacterial, fungal and the total of infections regardless etiologic agent were similar in both study A2306 and KRS-MMF arms from.*

In our primary review of the KRS and KHS, we observed a higher incidence of bacterial infection and pneumonic processes, regardless of etiology, in the RAD1.5 and RAD 3 arms in each study compared to their control arms.

These increased rates in pneumonias and bacterial infection were no longer observed in studies A2306 using RDN.

2.2.5.6 Wound Complications:

- *Wound dehiscence complications were more frequently observed in study A2306 compared to KRS-MMF arms (5% versus 0.2%, respectively)*
- *Lymphocele was reported as AE in 12%(29/237) and 10% (38/392) in study A2306 and B251/B201-MMF arms*
- *Urinary tract fistulas were postoperative complications present in 2% (5/237) and 0.5% (2/392) in study A2306 and MMF arms respectively.*

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- *In general, wound dehiscence, lymphocele and urinary tract fistulas have been related to the antiproliferative effects of mTOR inhibitors and concomitant use of corticosteroids.*

The small differences and the fundamental limitations of cross study comparison; we cannot draw any valid conclusion. However, the fact that the investigator considered in most instances to be Certican® related, it warrant a close follow-up for this kind of drug related complications.

2.2.5.7 Gastrointestinal Adverse Events

Gastrointestinal AE were more commonly observed in the MMF arms (72%) versus RAD arms study A2306 (62%). Epigastric pain was the most important contributor for this difference

2.2.5.8 Malignancies:

The incidence of malignancies was equally distributed across arms (2% in each arm) no PTLD were reported during one year follow up.

2.2.5.9 Deaths:

Cardiovascular disease and infections were the leading causes of death. No differences were observed

2.2.6 Dosing Regimen and Administration

We were not able to identify an appropriate TDM RAD plus reduced dose neoral regimen for the heart or kidney indication that will allow maintaining efficacy while minimizing toxicity in both early and maintenance periods after transplantation.

Please see section 3.1 Product Information and proposed regimens

2.2.7 Special Populations:

Data on special populations is very limited. Black population was under represented in studies A2306 and A2307. Higher incidence of biopsy-proven acute rejection episodes in blacks compared with non-blacks was observed in the Key renal and heart studies, and study A2306.

(b) (4)

2.2.8 Heart transplantation

Extrapolation of safety or efficacy data from the kidney studies to the heart indication or to other organs is inappropriate. (Please see section 12 Heart indication)

2.2.9 Overall Benefit/Risk Assessment and Conclusions

- *It is clear that RAD plus full-dose CsA leads to enhanced CsA nephrotoxicity that is not acceptably outweighed by any increase in immunosuppressive efficacy.*

- *The obvious weakness of the application is that the finally recommended regimen has not been evaluated in a prospective well controlled study.*
- *Trials B201, B251 provided clear evidence of efficacy for the RAD plus FDN and CS regimen which is comparable with the MMF plus FDN and CS regimen.*
- *Retrospective concentration/efficacy and concentration/safety modeling from trials B201, B251 created support for an acceptable efficacy/risk relationship within the therapeutic window for RAD C0 of \Rightarrow 3-8 ng/ml, even at low CsA exposure.*
- *The data available for RAD suggest that the recommended regimen of RAD with RDN would entail risk of nephrotoxicity of the same order of magnitude as a regimen of MMF plus full-dose CsA in de novo renal transplant recipients at low to moderate immunological risk.*

2.2.9.1 Conclusions

- *We have concluded that the Sponsor has not provided sufficient justification for:*
 - *Cross study comparisons,*
 - *Pooling of study arms from studies B251 and B201 (Key Renal Studies) to compare against treatment arms in studies A2306⁸,*
 - *Basing new efficacy claims on exposure-response analyses⁹,*
 - *Applying results of studies A2306/2307 to re-analyze study B253 (Key Heart Study) and*
 - *Extrapolation of safety and efficacy results from kidney studies to the heart indication.*

The non-inferiority approach that the sponsor took for these post-hoc analyses do not sufficiently account for population differences and the bias introduced by the cross study comparisons. Therefore, these analyses are not adequate to draw reliable conclusions.

In summary, cross study comparisons, pooling of studies and analyses by achieved exposure are fundamentally incorrect and increases the probabilities of spurious results.

The analyses presented by the sponsor were able to generate new hypothesis that will require to be tested in a prospective, randomized and well controlled studies for both heart and kidney indications.

⁸ and ²The Agency's concerns regarding this type of analyses were noted in comment #1 and # 3 sent to the Sponsor on 18 February 2004.

3 INTRODUCTION AND BACKGROUND

3.1 Product Information and proposed regimens:

Everolimus (40-O-[2-hydroxyethyl]-rapamycin) is a macrolide immunosuppressant derived from rapamycin known also as SDZ-RAD, RAD001 or Certican®.

Everolimus binds to FKBP¹⁰ and the RAD-FKBP complex inhibits the action of mTOR¹¹ suppressing the 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.

On February 27, 2004, Novartis Pharmaceuticals Corporation submitted an amendment to a pending NDA for the prophylaxis of organ rejection in allogeneic kidney and heart transplant patients.

The proposed regimen considers the use of Certican® (everolimus) (oral use only) for the prophylaxis of organ rejection in adult patients receiving an allogeneic kidney or heart transplants. It is recommended that Certican be administered concurrently with reduced doses of Neoral® (cyclosporine, USP) MODIFIED and corticosteroids.

The applicant proposes an initial dose regimen of 0.75 mg p.o. b.i.d. for the kidney and heart recipients administered as soon as possible after transplantation and consistently either with or without food at the same time as Neoral® (cyclosporine, USP MODIFIED).

Therapeutic drug monitoring (TDM) is recommended targeting whole blood trough levels ≥ 3.0 ng/mL in both renal and heart allograft recipients prior to dose reduction of cyclosporine. The upper limit to the therapeutic range is recommended at 8 ng/mL.

3.1.1 Cyclosporine dose recommendation in renal transplantation

The applicant recommends that CsA exposure reduction should be started after 1 month post-transplantation. Cyclosporine TDM is recommended using C2 blood concentrations, as follows:

(b) (4)

The use of Simulect® basiliximab as induction therapy in combination with Certican® and Neoral® was explored in study A2307. However, there was not enough information in this trial to make dose recommendations. (See table 3.1.1)

3.1.2 Cyclosporine dose recommendation in cardiac transplantation

(b) (4)

¹⁰ FK binding protein

¹¹ Mammalian target of Rapamycin

¹² Study A2306, also measured cyclosporine trough blood concentrations (C0: mean \pm SD, ng/mL) were: month 1: 239 \pm 114; month 3: 131 \pm 85; month 6: 82 \pm 60; month 12: 61 \pm 28.)

(b) (4)

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(b) (4)

[Redacted]	[Redacted]	[Redacted]

3.2 Pharmacologically Related Products.

TOR inhibitors (Sirolimus and Everolimus) are pharmacologic related immunosuppressants with similar mechanism of action and with significant anti-proliferative effects on different cell lines including but not restricted to T cell and smooth muscle cells.

Rapamune® (Sirolimus) is an mTOR inhibitor that shares many characteristics with Everolimus. Rapamune® was FDA-approved on April, 2003 for the prevention of rejection in allogeneic kidney transplantation. Sirolimus is used in combination with CsA and steroids early after transplantation followed by the elimination of CsA in conjunction with concentration-controlled sirolimus maintenance therapy. When used in combination with cyclosporine, sirolimus has been associated with a dose-dependent increased risk of renal function impairment.

The approved regimen for sirolimus in kidney transplant recipients who are at low to moderate risk for rejection involves cyclosporine withdrawal at 2 to 4 months after transplantation¹³. There are no other approved mTOR inhibitors in the USA market.

In the original submission and review, Certican® showed a similar toxicity profile as Sirolimus. The most important concern with TOR inhibitors is derived from the

¹³ See approved Package Insert for Rapamune®.

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enhanced nephrotoxicity when TOR inhibitors are used concurrently with calcineurin inhibitors (CInh). Additionally, the antiproliferative effect of these drugs on different cell lines is implicated in other well recognized toxicities.

3.3 State of Armamentarium for Indication(s)

Proposed indication: “Prophylaxis of allograft rejection in renal and heart transplantation”

Until now, no consensus has been established on what would constitute the optimal immunosuppressive regimen for prevention of renal and heart allograft rejection. The FDA has approved several biologic and drug products for these indications.

In renal transplantation, cyclosporine, azathioprine, tacrolimus, mycophenolate mofetil, sirolimus, basiliximab, daclizumab, and thymoglobulin have been approved for this indication.

In cardiac transplantation, cyclosporine and mycophenolate mofetil has been approved.

Although azathioprine does not have an approved indication of prevention of rejection in allogeneic heart transplantation, it has been used successfully in combination with cyclosporine and corticosteroids for this indication. Azathioprine was the active comparator versus mycophenolate-mofetil in non-inferiority studies supporting the approval of Cellcept® for its indication in cardiac transplantation.

In general, a combination of three immunosuppressive agents is used in most transplant programs. Induction therapy could also be added as a fourth agent according to the organ and patient requirements and center preferences.

Patient and graft survival have improved significantly¹⁴; however, there is still a need for safer, less toxic immunosuppressant drugs and regimens. With regards to Certican®, there have been no Emergency INDs applications for the use of this product in solid organ transplantation in the US.

3.4 Important Issues with Pharmacologically Related Products

TOR inhibitors (Rapamycin and Everolimus) are pharmacologic related immunosuppressants with similar mechanism of action and with significant anti-proliferative effects on different cell lines including but not restricted to T cell and smooth muscle cells.

Rapamune® was FDA-approved for the prevention of rejection in allogeneic kidney transplantation in October, 1999. When used in combination with cyclosporine, sirolimus has been associated with a dose-dependent increased risk of renal dysfunction.

The approved regimen for sirolimus was granted for kidney transplant recipients who are at low to moderate risk for rejection. It involves Rapamycin TDM and cyclosporine withdrawal at 2 to 4 months after transplantation¹⁵.

¹⁴ Cadaveric kidney graft survival is 88.4% at one year and 78.5% at three years post transplantation. Among recipients of kidneys from living donors, graft survival is 94.4% at one year and 88.3% at three years post transplantation.

Patient survival is 94.0% at one year and 88.4% at three years post transplantation in recipients of cadaveric kidneys, while it is 97.7% and 94.7%, respectively, in recipients of kidneys from living donors. (Source: OPTN/SRTR Data as of August, 2002)

¹⁵ See approved Package Insert for Rapamune®.

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In the original submission and review, Certican® showed a similar toxicity profile as Rapamycin.

The most important concerns with TOR inhibitors are a).- The enhanced nephrotoxicity of CI when used concurrently with TOR inhibitors and b).- The antiproliferative effects of these drugs on different cell lines when used at doses recommended for organ rejection prophylaxis.

3.5 Pre-submission Regulatory Activity

Novartis Pharmaceuticals Corporation (Novartis or applicant) submitted the original IND 52,003 application for everolimus Tablets on November 15, 1996¹⁶.

We have antecedents of three pre-NDA meeting conducted on December 3, 1999; February 6, 2001; and March 25, 2002 in which the FDA-DSPIDP discussed the applicant's proposed marketing applications for this drug product.

The initial proposed indication for Certican (first pre-NDA meeting, December 3, 1999) was limited to kidney transplantation and it was supported by two randomized, double-blind, double dummy, multicenter trials (Key Renal Studies B201 and B251).

The study designs of these trials were drastically modified by amendment # 3 converting the DB, DD design to open label at 12 months post randomization.

These drastic changes were made as a result from the key renal studies interim analyses which indicated RAD001 groups presented significant nephrotoxicity with significantly worst SCr and CrCl compared to MMF control groups.

In 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 (EU) and B251 (USA). By that time, the European study (EU) had been already unblinded. (See teleconference minutes October 20, 2000).

In the third 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 (b) (4) kidney transplantation.

(b) (4)

The data presented at this meeting showed worst renal function and a 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 a lower CsA though blood level (50 – 75 ng/mL) and Novartis' hope was that this change would help alleviate the nephrotoxicities associated with RAD plus Neoral ® combination.

On December 19, 2002, Novartis submitted NDAs 21-560 and 21-628 for Certican® (everolimus) Tablets (0.25mg, 0.5mg, 0.75mg, 1.0mg) for prophylaxis of allograft rejection in adult renal and cardiac transplantation, respectively.

On January 31, 2003, NDAs 21-561 and 21-631 were submitted for Certican® tablet for oral suspension (0.1 mg, 0.25mg) were submitted for the same indications. (b) (4)

¹⁶ 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 those dates.

The initial submission contained efficacy and safety data from 2 key renal studies (B252 and B201), one key heart studies (B253), and other supportive studies. The most important studies (design, duration and number of patients) are summarized in table 3.5.1.

Table 3.5.1. Key and Supportive Studies.

Study no.	Design	Duration	No. of patients
B253 Key heart study	R, DB, DD, AC, MC, MD, E, S, PK, <i>de novo</i>	3 years (1-year DB /1 year OL by amendment) + 1-year OL extension	Total – 634 RAD 1.5 mg – 209 RAD 3 mg – 211 AZA 1-3 mg/kg/day – 214
B251 Key renal study	R, DB, DD, AC, MC, MD, E, S, PK, <i>de novo</i>	3 years (1 year DB / 2 years OL by amendment)	Total - 583 RAD 1.5 mg – 193 RAD 3 mg – 194 MMF 2 g – 196
B201 Key renal study	R, DB, DD, AC, MC, MD, E, S, PK, <i>de novo</i>	3 years (1 year DB/ 2 years OL)	Total - 588 RAD 1.5 mg – 194 RAD 3 mg – 198 MMF 2 g – 196
B156 Renal supportive study	R, OL, MC, MD, E, S, <i>de novo</i> , w/Simulect	3 years	RAD 3 mg – 111 (full dose Neoral – 53 & reduced dose Neoral – 58)
B157 Renal supportive study	R, DB, MC, MD, S, T, PK, <i>de novo</i>	3 years (1 year DB/ 2 years OL ext.)	Total - 103 RAD 1 mg – 34 RAD 2 mg – 34 RAD 4 mg – 35
B351 Renal pediatric study	OL, MC, MD, E, S, T, PK, <i>de novo</i>	1 year	Total -19 RAD 0.8 mg/m ² BSA bid (maximum of 1.5 mg independent of BSA)

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 1.1-1 Summary of key and supportive studies, NDA Amendment/Final Safety Update, page 20.

At the initial NDA filing application on December 19, 2002, Novartis submitted incomplete data from on ongoing Phase IIIb studies A2306 and A2307. The subsequent 120 day safety update only included 6-month analyses. The final 12 months analyses were not submitted for the initial NDA application. After review, the Division issued an **approvable letter on October 20th, 2003**.

On November 25th, 2003, a Teleconference with Novartis was held to address Novartis' plans for resubmission for NDAs 21-560 & 21-628 [Certican® (everolimus) Tablets]

The applicant proposed to submit the completed 12-month clinical study reports from studies A2306 and A2307 to demonstrate improved renal function while maintaining adequate protection against graft rejection, graft loss, or death in de novo renal transplantation.

The Division accepted this proposal; however, we expressed our concerns regarding studies A2306 and A2307, specifically:

- Small number of subjects,
- Lack of an approved comparator,

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- Difficulties in assessing biopsy-proven rejection due to the potential for bias in these open-label trials, and
- Cross-study comparisons

The Division stated their intention to be flexible and not arbitrarily discounting other types of data and analyses that might address these deficiencies. However, the Division strongly expressed its concerns regarding cross-study comparisons. Novartis acknowledged and agreed that the cross study comparisons could be systematically biased.

3.6 Evaluation of Certican® by other Medical Authorities.

Certican® received a favorable review in Sweden and was approved for prevention of rejection in renal and cardiac transplantation (18 July 2003).

The recommended immunosuppressive regimens, involve cyclosporine minimization and concentration controlled everolimus. Such regimens have not yet been prospectively compared versus an approved regimen in a randomized, parallel group, controlled studies. On December, 2003, Certican® received a **positive recommendation** by the following Member States of the European Mutual Recognition Procedure:

Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Italy, Netherlands, Norway, Portugal, Spain, and Sweden.

The Assessment Reports from the Swedish Medicinal Product Authority (SMPA) were based on the KRS (B201 and B251), Key Heart study B253 and 6-month data from studies A2306 and A2307. The SMPA concluded that “**RAD plus full dose CsA should not be considered an acceptable option for immunosuppression after renal transplantation**”.

(b) (4)

Certican® (everolimus) is not currently marketed for commercial use in any county and only Mexico has authorized commercial use of Certican® tablets in kidney and heart transplantation (08 July 2003).

4 SIGNIFICANT FINDINGS FROM PREVIOUS REVIEW.

4.1 Previous Clinical Review.

Relevant safety concerns associated with Certican® Fixed Dose plus FDN regimen observed in the key renal and Heart studies were the following:

- Certican® and CsA interaction with enhance nephrotoxicity : Early renal impairment
- Infectious: Increased rate of pneumonia and bacterial Infections
- Metabolic: Lipid abnormalities and new onset Diabetes Mellitus.
- Hematologic: Anaemia and thrombocytopenia, TMA / HUS.
- Increased incidence of gastrointestinal haemorrhage and lymphocele
- (b) (4)

4.2 Chemistry (please refer to the Chemistry Review for the initial submission)

4.3 Animal Pharmacology/Toxicology (please refer to the Pharmacology/Toxicology review for the initial submission)

5 REVIEW STRATEGY

The applicant presented 12 months efficacy and safety results from renal studies A2306 and A2307 in the resubmission package. The sponsor chose not to conduct the suggested “new kidney and heart studies”; instead he presented new analyses based on cross study comparisons.

The proposed regimen in the proposed labeling is based on the regimen used in study A2306 which was compared with studies B251 / B201 (pooled data). Therefore, the core of our review is focused on these studies.

Since study A2306 did not have an approved regimen as a control group, the sponsor proposed to use the KRS (B201 and B251) as historical control group. These analyses relied on pooling data from the MMF arms in the KRS and compare these results to the study A2306 RAD arms (RAD 1.5 and RAD 3). Similarly, study A2307 lacked of an approved regimen as a control group and explored the use of induction therapy with basiliximab, reduced dose Neoral® and RAD (RAD 1.5 and RAD 3).

Induction therapy was also explored in supportive study B156, this study also lacked of an approved regimen as a control group and tested a regimen of basiliximab, RAD 3 mg/day (1.5 mg bid), plus either full dose Neoral® (FDN) or reduced dose Neoral® (RDN). Despite of the differences in study design and small number of patients included, this study was used as an historical control for study A2307.

A more detail description of study designs and differences between A2306 versus KRS and A2307 versus B156 is presented in detail in the RENAL STUDIES sections.

The data was reviewed with special emphasis on donor and recipients baseline characteristic to determine the feasibility to pool data from KRS-MMF arms and perform a fair comparison to study A2306. We pay special attention to factors that may influence patient and graft survival such as graft type, race, ESRD leading to transplantation and risk factors for cardiovascular disease with special interest in DM. Other well known risk factors were also reviewed.

Safety laboratory evaluations (hematology, urinalysis, biochemistry, endocrinology, and pregnancy test), and adverse events including incidence of infections were also performed.

We acknowledge that the potential for bias in making cross study comparisons was addressed by the sponsor in the following areas:

- patient populations,
- enrollment criteria,
- drug regimens, and

- end points measured.

Despite of these efforts the potential for bias still remained since other known and unknown covariates were not taken into consideration.

5.1 Certican Resubmission Deficiencies

After the preliminary review, the following deficiencies were identified:

- The Integrated Safety Summary (ISS) presents updated analyses without clear delineation between the heart and kidney indications or between efficacy and PK/PD analyses.
- The sponsor's analyses were presented in summary form with minimal information, without rationale or other explanation that would allow us to understand the appropriateness of such analyses.
- The organization of the resubmission is complex and presents multiple inconsistencies.
- The information presented appears biased, in the sense that the positive aspects of the study results are emphasized while the negative aspects are difficult to find or ignored. i.e. In the Foreign Marketing History document the sponsor includes a TOC which presents five points: Point 1.0 "List of Country Registrations with Positive Recommendations" is easy to identify on the top of the list. However, it excludes a point for the "List of Country Registrations with negative Recommendations" from the TOC. The list of countries with a negative recommendation is included under point 4.0 "Other Health Authorities and Regulatory Action".

6 CLINICAL PHARMACOLOGY

The mTOR inhibitors (SRL and RAD) and FK506 (tacrolimus) interact with a family of immunophilins termed FKBP (FK Binding Proteins). The mTORi-FKBP complex inhibits the activation of the kinase mTOR (mammalian target of rapamycin). This results in the modulation of the signal transduction pathways and the inhibition of cell cycle progression from G1 to S phase in different cell lines including but not limited to T cells, B cells, osteosarcoma cells, myogenic cell lines and smooth muscle cells.

In summary mTOR inhibitors arrest human T and B lymphocyte proliferation and antibody production but have only limited effects on cytokine production.

FK506-FKBP affects the phosphatase activity of calcineurin blocking of IL-2 transcription and inhibition of T cell proliferation in the G0-G1 phase of the cell cycle. (For further details please refer to previous clinical and clinical pharmacology reviews.)

6.1 Cyclosporine C2 monitoring

Single sampling point at 2 hours post-dose (C₂) has been proposed as an accurate surrogate marker of AUC₀₋₄ in kidney transplant patients.

The sponsor claims that cyclosporine (CsA) C₂ measurement was used to reduce variability in CsA exposure among patients receiving concurrently RAD in studies A2306 and A2307. However, the hypothesis is that C₂ correlates better than C₀ with AUC 1-4 is still controversial and this may not be true for all patients, especially in diabetics.

There is not consensus on the advantages / disadvantages on C2 monitoring and has been reported that C2 was no better than C0 in predicting outcome¹⁷. C2 measurements are greatly limited by the variability at this sample time and the potential impact on C2+/- 15 min measurements.

Lastly, Centers using C2 monitoring find it feasible during the immediate post-operative period but challenging during the follow up period.

6.1.1 Neoral regimens in de novo kidney studies A2306 and A2307

Table 6.1.1-1 shows the target CsA C2 concentration levels and the incidence rates of patients within and above Neoral C2 target ranges.

Table 6.1.1-1. Incidence rates of Patients within and above Neoral C2 Target Ranges (ITT Population - 12 Month Analysis) (Local and Central Laboratory Data)

Study	Target C2 BL (ng/mL)	RAD 1.5 % Within / Above range	RAD 3 % Within / Above range	Historical control
A2306	Weeks 0 – 4 (1000 – 1400)	(56.3%)/ (25.9%)	(56.8%)/ (24.0%)	B201 / B251 RAD Fixed doses
Total – 237¹⁸	Weeks 5 – 8 (700 – 900)	(8.0%)/ (52.7%)	(15.2%)/ (44.8%)	
RAD 1.5 mg – 112	Weeks 9 – 12 (550 – 650)	(9.8%)/ (57.1%)	(8.8%)/ (57.6%)	
RAD 3 mg – 125	Months 4 – 12 (350 - 450) ¹⁹	(13.4%)/ (67.9%)	(17.6%)/ (64.0%)	
A2307	Weeks 0 – 8 (500 – 700)	(41.9%) / (53.8%)	(44.6%)/ (47.5%)	B156 Induction with Simulect® (RAD 3 plus FDN vs. RAD 3 plus RDN)
Induction with Simulect®	Months 3 – 12 (350 – 450)	(25.6%)/ (59.8%)	(28.8%)/ (53.2%)	
Total -256²⁰				
RAD 1.5 mg – 117				
RAD 3 mg – 139				

Data source:

Post-text Table 8.1-12d (Page 1 of 1) for both studies A2306 and A2307 Incidence rates of Patients within, above and below Neoral C2 Target Ranges Both Local and Central Laboratory Data (ITT Population - 12 Month Analysis)

A2306 Neoral C2 Target Ranges

- In study A2306, 56% to 57% of patients were within target C2 CsA range during the first 4 week after transplantation.
- From week 5 to 12 months, **82% to 92%** were out of target range.
- The historical control (KRS) for A2306 used CsA trough blood concentrations to adjust CsA dosing.

¹⁷ ATC, Boston 2004.

¹⁸ A total of 222 non-Black patients were randomized (112 and 110 in the RAD 1.5 and 3 mg groups, respectively). All 15 Black patients enrolled in the study were assigned to the RAD 3 mg group.

¹⁹ C2 is reduced to about half to one-third of typical CsA exposure by week 13.

²⁰ A total of 243 non-Black patients were randomized (117 and 126 in the RAD 1.5 and 3 mg groups, respectively). All 13 Black patients were assigned to the RAD 3 mg group.

A2307 Neoral C2 Target Ranges

- The incidence of patients with in target C2 CsA range was similar for both RAD 1.5 and RAD 3 arms.
- From weeks 1-8, 42% to 45% were with in target C2 CsA range in both RAD dose arms. However, from 3 to 12 months, **74 % and 71%** of the patients were out of C2 CsA target range in the RAD 1.5 and RAD 3 arms, respectively.
- In study B156 the CsA C₂ levels over time averaged 845 ng/mL (N = 33) in the full-dosed arm and 550 ng/mL (N = 35) in the reduced-dose arm.

Reviewer's comments:

Neoral® C2 TDM in studies A2306 and A2307 failed to appropriately guide Neoral® dosing in order to achieve CsA target ranges. In study A2306, 82 to 92% of the patients were out of the target concentration from 5 weeks to 12 months.

There is no consensus regarding the best method to TDM CsA. Currently most of the transplant centers still rely heavily in C0 monitoring arguing that C2 measurements are difficult obtain with accurate timing. This becomes a real issue after the patients are discharged from the hospital. Furthermore, it has been observed that C2 monitoring in patient with delayed gastric emptying (i.e. diabetic gastro-paresis) may lead to CsA overdosing.

Studies A2306 and A2307 achieved a 33 to 50% reduction in Neoral exposure. This reduction levels maintained efficacy comparable to historical controls. However, we consider that pooling data from two studies with different donor/recipient baseline characteristic is inadequate and cross-study comparison is fundamentally incorrect.

Given the limitations of using historical controls minor differences in baseline characteristics may lead to spurious conclusions (Please see statistical review).

6.1.2 CsA trough concentrations and Cross Study comparison between A2306 vs. studies B251 and B201

The sponsor presented table 3.3-1 with a summary of CsA trough levels over time from the RAD 1.5mg and 3 mg arms from studies B201, B251 and A2306 (ITT population – 12-month analysis). The CsA concentrations from the MMF arms were excluded from the sponsor's table. We include the MMF arms CsA trough levels since these arms are considered the historical control in subsequent analyses comparing A3206 RAD arms to MMF arms from the KRS (See table 6.1.2-1).

Table 6.1.2-1.CsA trough levels (ng/mL) in study A2306 (ITT population – 12-month analysis) – and KRS B201 and B251 (ITT population – 12-month analysis)

	A2306		B201			B251		
	RAD 1.5 mg	RAD 3 mg	RAD 1.5 mg	RAD 3 mg	MMF	RAD 1.5 mg	RAD 3 mg	MMF
Day 28	239	278	231	231	227	290	269	246
Month 3	131	140	192	218	177	202	209	207
Month 6	82	83	173	158	170	178	175	178
Month 9	84	71	167	165	158	126	135	159
Month 12	61	71	144	156	157	140	121	167

Post-text Tables 10.7-13b, 10.7-13b and Summary Statistics of the CsA Trough Level [ng/mL] (ITT Population - 36 Month Analysis), Studies B251 and B201.

Table 3-1 Everolimus and cyclosporine trough concentrations over 3 years Study CRAD001 B201: Appendix 8.2 3607

The serial cyclosporine trough evaluations months 1,3,6,9 and 12 showed that similar cyclosporine exposure were achieved among the RAD and MMF arms in studies B201 and B251. However, in the KRS, slightly lower cyclosporine doses were used in the everolimus-treated patients in order to achieve similar cyclosporine troughs levels as in MMF arms.

The mean trough CsA levels decreased over time in studies A2306, B251, and B201. However, the decrements CsA levels in study A2306 were larger, reflecting the reduced CsA dose. At 12 months, CsA trough concentration in study A2306 RAD arms were approximately 35% to 45% of the through CsA concentrations achieved in the in the MMF arms in the KRS .

The cyclosporine trough levels for studies A2307 and B156 are presented in the table 3.3-2 (below) from the application.

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Table 3.3-2 Summary of CsA trough levels in study A2307 (ITT population – 12-month analysis) – Comparison with data from study B156 (ITT population – 36-month analysis)

Visit	Study A2307		Study B156	
	RAD 1.5 mg (N=117)	RAD 3 mg (N=139)	RAD 3 mg + Full Dose Neoral (N=53)	RAD 3 mg + Reduced Dose Neoral (N=58)
	Mean (median) ± SD		Mean (median) ± SD	
Day 7	(N=111) 136 (111) ± 95	(N=135) 118 (93) ± 94	(N=35) 169 (152) ± 88	(N=35) 101 (78) ± 67
Day 28	(N=106) 137 (105) ± 119	(N=127) 129 (102) ± 91	(N=43) 209 (182) ± 166	(N=51) 109 (80) ± 113
Month 2	(N=105) 116 (91) ± 90	(N=122) 117 (93) ± 79	(N=36) 158 (139) ± 83	(N=40) 119 (90) ± 116
Month 3	(N=97) 87 (74) ± 47	(N=116) 92 (74) ± 73	(N=41) 156 (131) ± 90	(N=46) 96 (78) ± 75
Month 4	(N=97) 72 (62) ± 34	(N=116) 79 (65) ± 54	(N=41) 141 (121) ± 109	(N=41) 76 (71) ± 25
Month 6	(N=96) 64 (54) ± 32	(N=115) 68 (53) ± 59	(N=35) 147 (134) ± 74	(N=38) 73 (71) ± 26
Month 9	(N=90) 65 (58) ± 31	(N=111) 62 (51) ± 46	(N=32) 149 (142) ± 73	(N=48) 77 (75) ± 32
Month 12	(N=88) 60 (55) ± 30	(N=101) 58 (46) ± 54	(N=32) 135 (135) ± 56	(N=44) 84 (74) ± 35

Source: [Post-text tables 8.3-2 and 10.7-13c of the 12-month CSR for study A2307]

After six months the mean CsA trough levels were moderately higher (10 to 20 ng /ml higher) in study B156-RDN arm compared to the RAD arms in study A2307. RAD arms in study A2307 showed mean CsA trough levels of approximately 50% to 60% lower compared with the FDN arm in study B156.

Reviewer's comments:

Studies A2306 and A2307 achieved a 33 to 50% reduction in Neoral exposure. These CsA reduced levels plus Certican® maintained comparable efficacy, with respect to the primary endpoint, compared to historical control (CsA+MMF+Pred). However, biopsy-proven chronic allograft nephropathy²¹ (CAN) at 12 month was almost the double in the A2306-1.5 arm compared to the control MMF arms (13% versus 7%, respectively). This striking difference raises concerns whether alloantigen dependent causes (i.e. sub-clinical rejection), alloantigen independent causes (i.e. DM, Hyperlipidemia, syndrome X, etc.) or both are involved in this difference. We consider, that regarding BPCAN efficacy endpoint the proposed regimen failed compared to the historical control.

²¹ CAN in the most important cause of late graft failure in renal transplantation.

Table 6.1.2-2. Important Factors for Renal Function.

	MMF	RAD 1.5	
	arms		
	B201/ B251 (N= 392)	A2306 (N=112)	A2307 (N=117)
GFR at 12 mo,mL/min	62	65	63
Cadaveric donors	69%	60%	68%
NHBD	8%	0	2%
CIT >24 hours	13%	5%	8%
CsA Trough levels @ 1yr	162	61	60
Primary efficacy failure 12 month analysis	29%	28%	16%
Biopsy-proven chronic allograft nephropathy	7%	13%	5%
DGF	13%	14%	20%

Data source: See Comparability of patient populations and Integrated review of efficacy section.

The mean calculated GFR at 12 months in the study A2306 -RAD1.5 arms was 3ml per minute higher compared to the KRS-MMF arms. We do not see any advantage in GFR since the KRS-MMF arms included more cadaveric and NHBD, and more patients with prolonged CIT. Furthermore, the CsA related AE's (TMA, Allograft dysfunction, CsA toxicity) were numerically higher in the RAD arms compared to the KRS-MMF arms. It only required ½ or 1/3 of CsA concentrations in the CsA+ RAD combination, S- A2306 to achieve the same or higher degree of CsA related toxicities presented in the FDN plus MMF regimen.

7 STUDY DESIGNS AND CROSS STUDY COMPARISON

7.1 Renal Study CRAD001 A2306 versus Key Renal Studies, B201 and B251

Study CRAD001 A2306 was a one year multicenter, randomized, open label, parallel group study of the safety, tolerability and efficacy of two doses (1.5 and 3 mg/day) of Certican® (RAD001) with steroids and optimized administration of Neoral® in de novo renal transplant recipients (12-month analysis).

This study was compared to the KRS, B201 (EU) and B251 (USA) which were A 3-year randomized, multicenter studies. One year double-blind, double-dummy and 2 year open-label (by amendment # 3), parallel group studies of the efficacy and safety of RAD001 (RAD) tablets versus mycophenolate mofetil (MMF) as part of triple immunosuppressive therapy in de novo renal transplant recipients.

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The study designs comparison and number of patient per arm are displayed in Table 7.1-1 below.

Table 7.1-1. Study designs comparison KRS and A2306

Study no.	Design	Duration	No. of patients/study drug
B201 Key renal study ²²	Double Blind / Open label, R, MC DD, AC,MD, E, S, PK, <i>de novo</i>	3 years (1 year DB and 2 years OL per amendment # 3)	Total - 588 RAD 1.5 mg – 194 RAD 3 mg – 198 MMF 2 g – 196
B251 Key renal study ²³			Total - 583 RAD 1.5 mg – 193 RAD 3 mg – 194 MMF 2 g – 196
A2306 ²⁴	Open Label, R, MC, MD, S, T and E, <i>de novo</i>	12 month	Total – 237 ²⁵ RAD 1.5 mg – 112 RAD 3 mg – 125

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.

7.1.1 Primary Objectives:

The primary objective was similar in both studies B251 and B201:

“To compare the efficacy of 2 oral doses of RAD001 (RAD) (0.75 or 1.5 mg twice daily [bid]) vs. mycophenolate mofetil (MMF) (1 g bid), as measured by the incidence of efficacy failure (i.e. biopsy-proven acute allograft rejection, graft loss, death, or lost to follow-up) during the first 6 months of treatment and the incidence of graft loss, death, or lost to follow-up during the first 12 months of treatment in de novo renal transplant patients.”

7.1.2 Secondary endpoints:

- To compare the efficacy, as measured by allograft and patient survival and the incidence of acute rejection, including antibody-treated and biopsy-proven acute rejections and safety of both doses of RAD vs. MMF at 6, 12, 24 and 36 months post-transplantation.
- To compare the efficacy of both doses of RAD vs. MMF in the prevention of chronic allograft nephropathy at 12, 24 and 36 months post-transplantation.
- To select the preferred dose of RAD based on safety and efficacy data.
- To assess the pharmacokinetics (PK) of RAD during steady-state administration of Neoral® in a subset of patients.

For more details please refer to the primary Medical Officer review.

²² Fifty four (54) centers participated in this study, Australia – 4 centers, Europe – 48 centers, South Africa – 2 Centers.

²³ Forty four (44) centers participated in this study (33 US, 7 Canada, 2 Argentina, and 2 Brazil)

²⁴ Thirty two (32) centers participated in this study, US (11), Italy (6), Brazil (4), Canada and Spain (3 each), Poland and Venezuela (2 each), and Belgium (1).

²⁵ A total of 222 non-Black patients were randomized (112 and 110 in the RAD 1.5 and 3 mg groups, respectively). All 15 Black patients enrolled in the stud were assigned to the RAD 3 mg group.

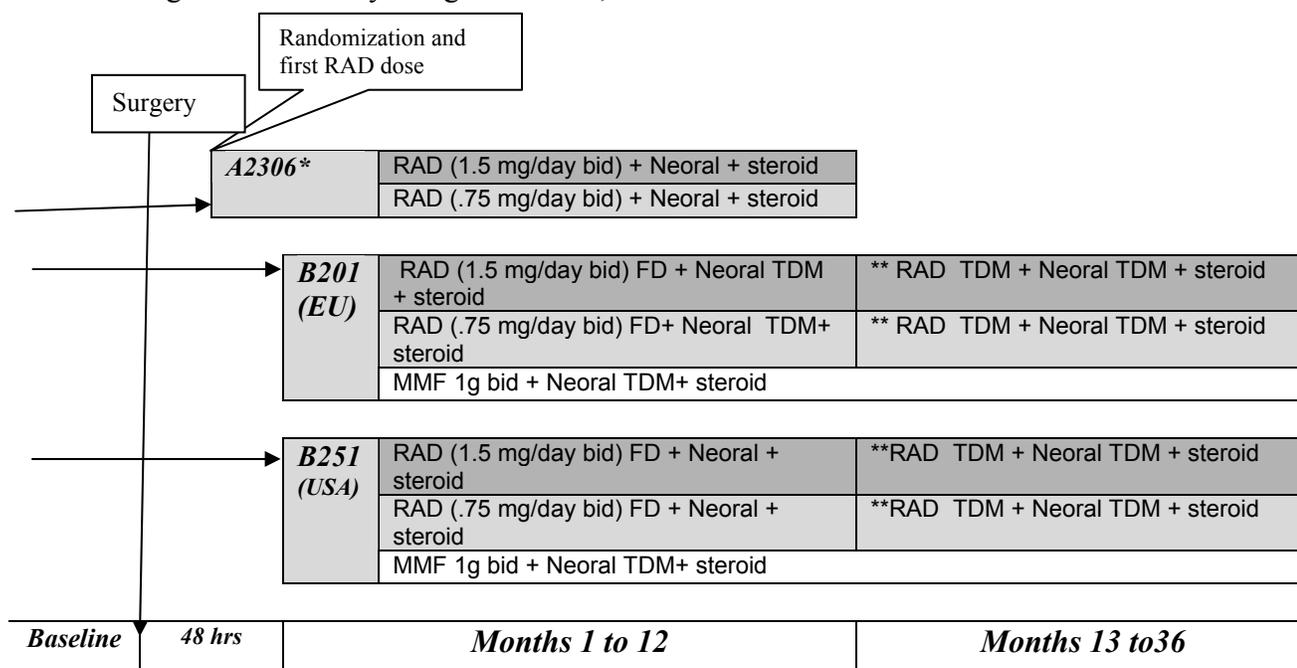
Table 8.1.2. CsA and Everolimus target blood concentration and fixed oral doses.

Time post transplantation		Weeks 0 – 4	Weeks 5 – 8	Weeks 9 – 12	Months 4 - 12	13-36 Months
STUDY	Dose adjustment based on	CsA target blood concentration				
A2306	C2	1000 – 1400 ng/mL	700 – 900 ng/mL	550 – 650 ng/mL	350 – 450 ng/mL	N/A
B201 (EU)	Trough	150 -400 ng/ml	100-300 ng/ml			CsA: 50-75 ng/mL
B251 (USA)	Trough	200-350 ng/ml	100-300 ng/ml			CsA: 50-75 ng/mL
		RAD target blood concentration				
A2306	Trough	RAD: ≥ 3				N/A
B201	Trough	Fixed dose				RAD: ≥ 3
B251	Trough	Fixed dose				RAD: ≥ 3

* At the discretion of the investigator, the Neoral dose may have been further decreased in case of increasing creatinine in study A2306.

In both key renal studies (B201 and B251) and study A2306 all patients were randomized after surgery with the exception of all [15] Black patients in study A2306 which were assigned to the RAD 3 mg group without randomization. RAD dosing was adjusted by doubling the dose, if the RAD trough level was < 3 ng/mL at day 5 or any time later. Dose adjustments were to ensure that a minimum trough level of 3 ng/mL was achieved.

Figure 8.1.2. Study designs: A2306, B201 and B251



*Black patients were not randomized, **RAD TDM: ≥ 3 ng/mL and CsA TDM: 50-75 ng/mL

All patients were to be evaluated at Days 1, 7, 14 and 28 and at Months 2, 3, 4, 6, 9 and 12.

CRAD001 B251: The graft had to be functional at the time of randomization (time of first dose), which was to have occurred within 48 hours post-transplantation.

Reviewer's comments:

Differences in study designs between study A2306 versus KRS (B201 and B 251) were, (respectively):

- ***Time of randomization (24 versus 48 hrs post-transplantation)***
- ***Open label versus double blind design***
- ***No control group versus approved regimen control group (MMF arms)***
- ***Different CsA target concentrations over time***
- ***Different CsA dose adjustment methods (C2 versus C0)***
- ***Different RAD dosing regimens (TDM ≥ 3 mg ml vs. Fixed dose regimen).***

7.2 Renal Study CRAD001 A2307 versus Supportive Renal Study B156

7.2.1 Study A2307

Study A2307 was “A 1 year multicenter, randomized, open label, parallel group study of the safety, tolerability and efficacy of two doses (1.5 and 3 mg/day) of Certican® (RAD001) with Simulect®, corticosteroids and optimized administration of Neoral® in de novo renal transplant recipients (12 month analysis)

Renal transplant recipients initiated immunosuppression with either 0.75mg or 1.5mg everolimus twice daily along with cyclosporine, basiliximab, and corticosteroids. Black patients were all assigned to the RAD 3mg arm.

Everolimus (RAD) dosing was subsequently adjusted based on therapeutic drug monitoring using predose whole blood trough levels (C0).

Cyclosporine levels were monitored using TDM C2 blood concentration and the dose was adjusted according to a protocol-specified down-titration.

(See Neoral regimens in de novo kidney studies A2306 and A2307 and Rationale for cyclosporine C2 monitoring)

The primary endpoint in this study was to compare renal function, as measured by serum creatinine, of 2 doses of RAD (1.5 and 3 mg/day), and to assess whether acceptable renal function (improved creatinine vs. prior trial data [study B156]) can be achieved at 6 months post-transplantation in de novo renal transplant recipients who received either of the 2 doses of RAD, Simulect, corticosteroids, and optimized administration of Neoral.

The secondary endpoints were to evaluate:

- The incidence of biopsy-proven acute rejection episodes, graft loss, death, loss to follow-up, antibody-treated acute rejection, clinically-confirmed acute rejection, clinically-confirmed chronic rejection, and biopsy-proven chronic allograft nephropathy at 6 and 12 months in both groups.
- The incidence of graft loss, death, or loss to follow-up at 12 months.
- Renal function, as measured by serum creatinine, calculated creatinine clearance (Cockcroft-Gault) and calculated glomerular filtration rate (GFR) (Nankivell formula), at 6 and 12 months post-transplantation.
- The safety of 2 oral doses of RAD.

7.2.2 Study B156

Study B156 was a three-year, multicenter, randomized, open-label, parallel-group study of the efficacy and safety of RAD tablets given in conjunction with Simulect, corticosteroids, and either full or reduced dose Neoral in *de novo* renal transplant recipients (12-month analysis). Transplant recipients received an immunosuppressive regimen consisting of basiliximab (20 mg on days 0 and 4), corticosteroids (protocol-specified taper), and everolimus (1.5 mg twice daily) with either full-dose or reduced-dose cyclosporine.

Full-dose cyclosporine was begun at 6-8 mg/kg/day and then individualized in twice-daily regimens to achieve morning trough concentrations of 150-300 ng/ml in months 1 to 2 and 125-250 ng/ml thereafter; **reduced-dose cyclosporine** was begun at 3-4 mg/kg/day and then individualized to achieve trough concentrations of 75-125 ng/ml in months 1 to 2 and 50-100 ng/ml thereafter. Blood samples were obtained prior to the everolimus and cyclosporine morning doses at scheduled clinic visits. (See clinical pharmacology review for further details)

The primary endpoint was to compare the occurrence of efficacy failure (biopsy-proven acute rejection, death, graft loss or lost to follow up at Month 6) and death, graft loss or lost to follow-up at Month 12.

The secondary endpoints were to:

- Compare serum creatinine, calculated creatinine clearance and blood pressure, safety and tolerability, the occurrence of biopsy-proven acute rejection, and graft and patient survival in the 2 treatment groups (either full dose or reduced dose Neoral®) at 6, 12 and 36 months posttransplant.
- To evaluate the pharmacokinetics (PK) of RAD and cyclosporin (CsA) in combination with Simulect®, and the effect of decreasing Neoral dosage on RAD PK.

The main objective in this cross study comparison was to assess whether acceptable renal function (improved creatinine vs. prior trial data [study B156]) can be achieved at 6 months post-transplantation in *de novo* renal transplant recipients who received either of the 2 doses of RAD, Simulect, corticosteroids, and optimized administration of Neoral. Table 8.2-1, shows the target C0 and C2 CsA blood concentration for studies B156 and A2307, respectively.

Table 8.2-1. Target CsA blood concentration for studies B156 and A2307.

	B156		A2307	
	Fixed RAD 3 mg dose plus FDN (N=53)	Fixed RAD 3 mg dose plus RDN (N=58)	Initial RAD 3 mg dose plus RDN (N=139)	Initial RAD 1.5 mg dose plus RDN (N=117)
Starting CsA dose	6-8 mg/kg/day	3-4 mg/kg/day		
Target CsA C0 (1-2 month)	150-300 ng/mL	75-125 ng/mL		
Target CsA C0 (3-36 month)	125-250 ng/mL	50-100 ng/mL		
Target CsA C2 (1-2 month)			500-700 ng/mL	
Target CsA C2 (3-12 month)			350-450 ng/mL*	

RDN= Reduced dose Neoral® FDN= Full dose Neoral® *CsA targets corresponded to mean CsA C0 exposure <100 ng/ml from month 3 onwards (A2307),

Reviewer's comments:

Studies A2307 and B156 (historical control) were both open label design that addressed the use of Simulect® with Certican and CsA.

The use of induction therapy is an interesting approach to maintain efficacy early after transplantation with concurrent RDN. Unfortunately, studies A2307 and B156 lacked of approved control regimen. The difficulties of cross study comparison, limited long term follow up, and the small number of patients enrolled does not allow us to draw reliable conclusions. This approach will require further evaluation in a prospective, well controlled clinical trial.

The main study design differences between studies B156 versus A2307 were, respectively:

- ***Fixed dose RAD 3 mg /day versus TDM C0 \geq 3ng/mL***
- ***C0 CsA TDM versus C2 CsA TDM (dose adjustments)***

7.3 Conclusions

- ***The Agency expressed their concern about the use of historical controls in studies A2306 and A2307 (Pre-NDA meeting held on March 25, 2002).***
- ***The main limitations of studies 2306 and 2307 are the open label design and the lack of an approved comparator arm, cross study comparison and the small study size of these studies.***
- ***The use of historical controls for these open label studies presents important difficulties due to differences in study design, RAD dosing (Fixed dose vs. TDM), CsA target concentrations and method used for dose adjustments (C2 vs. C0).***
- ***The pivotal trials (historical control) were extensively amended and were impacted by numerous other conditions that were present during that study, such as type of population, base line characteristics, concomitant medications, and the timing of the study. These conditions are different for studies A2306 and A2307, so that considering the pivotal trial data as a historical control arm for these studies would not be appropriate.***

8 COMPARABILITY OF PATIENT POPULATIONS

Key Renal Studies (B201 and B251) versus renal study CRAD001 A2306. And Study B156 versus A2307

The sponsor supported the present resubmission with studies A2306 and A2307. Since these studies were open label which did not include an approved control regimen. Novartis relied only on cross study comparisons using historical controls. The core of these analyses were based on pooling data from KRS-MMF arms as a comparator for study A2306. Additionally, The sponsor also submitted analyses comparing study A2307 versus study B156.

Cross study comparison presents fundamental difficulties and potential for bias that may be introduced from imbalances in the known and unknown covariates. In this section of the review we analyzed the donor and recipient background characteristics to assess differences between the MMF arms from the Key Renal Studies (B201 and B251) to evaluate the potential consequences from pooling data from these studies as a control arm for study A2306. Similarly, the same demographic and other baseline donor / recipient covariates were compared across studies. (KRS-MMF arms versus study A2306 and study B156 versus study A2307).

According to registry data²⁶, donor /recipient baseline characteristics are important determining factors for patient and graft survival. Similarly, ESRD leading to transplantation has influence on long term graft survival. Polycystic Kidney disease and Chronic Glomerulonephritis patients have better outcome compared to DM or Hypertension / Nephrosclerosis patients. The effect of the ESRD leading to transplantation, on graft survival is more evident in cadaveric kidneys and black recipient. Therefore imbalances across treatment arms in these recipient and donor characteristics will significantly influence outcomes.

Tables 9-1, 9-2 and 9-3 are based on UNOS Scientific Renal Transplant Registry data from 1995 to 2000. They display half lives and graft survival rates in the USA transplant population comparing Living Donors Vs. Cadaveric Donors and White Recipients Vs. Black Recipients. These tables also show several covariates that patient and graft survival.

²⁶ Primary End Stage Renal Disease (ESRD) Leading to Transplantation in the USA population. (Based on UNOS Scientific Renal Transplant Registry 1995 to 1999)

Table 9-1. Half life and Graft Survival in the USA transplant population. White Recipients VS. Black Recipients. (Modified from Clinical Transplants 2000²⁷).

1995-1999	<i>Blacks (23%)²⁸</i>			<i>White (61%)</i>		
	<i>T_{1/2}</i>	<i>5yr GS</i>	<i>5yr PS</i>	<i>T_{1/2}</i>	<i>5yr GS</i>	<i>5yr PS</i>
<i>HLA identical</i>	27.2	88%		41.7	88%	
<i>Living Donors</i>	9.6	65%	90%	20.4	80%	93%
<i>Cadaveric Donors</i>	7	55%	83%	13	70%	85%
<i>No Rejection</i>	7.2	55%		13.9	72%	
<i>Early Rejection</i>	5.8	45%		8.1	50%	
<i>IF</i>	7.6	60%		14.8	75%	
<i>DGF</i>	5.8	42%		8.8	52%	
<i>R> 60yr</i>	7.6	58%		10	62%	
<i>D> 60yrs</i>	4.4	35%		7.8	58%	

Table 9-2. Half life and Graft Survival in the USA transplant population. Living Donors VS. Cadaveric Donors. (Modified from Clinical Transplants 2001²⁹).

1996-2000	<i>Living Donors n=19,721</i>			<i>Cadaveric Donors n=33,327</i>		
	<i>T_{1/2}</i>	<i>1-yr GS</i>	<i>5yr GS</i>	<i>T_{1/2}</i>	<i>1-yr GS</i>	<i>5yr GS</i>
<i>HLA identical</i>	31.8	94-96%	86	14.5	96-98%	70%
<i>Blacks (23%)</i>	10.6	93%	68	7.1	87%	58%
<i>Caucasian (61%)</i>	20.6	95%	80	12.8	89%	72%
<i>IF & No Rejection</i>	19.6		82	11.8		72%
<i>DGF & Rejection</i>	4.5		44	6.3		44%
<i>Donor > 60yrs³⁰</i>	11.9	94%	84%	6.3	80%	50%

Table 9-3. Half life and Graft Survival in the USA transplant population. Living Donors VS. Cadaveric Donors. (Modified from Clinical Transplants 2001³¹).

1996-2000	<i>Living Donors n=19,721</i>			<i>Cadaveric Donors n=33,327</i>		
	<i>T_{1/2}</i>	<i>1-yr GS</i>	<i>5yr GS</i>	<i>T_{1/2}</i>	<i>1-yr GS</i>	<i>5yr GS</i>
<i>HLA identical</i>	31.8	94-96%	86%	14.5	96-98%	70%
<i>Blacks (23%)</i>	10.6	93%	68%	7.1	87%	58%
<i>Caucasian (61%)</i>	20.6	95%	80%	12.8	89%	72%
<i>IF & No Rejection</i>	19.6		82%	11.8		72%
<i>DGF & Rejection</i>	4.5		44%	6.3		44%
<i>Donor > 60yrs</i>	11.9	94%	84%	6.3	80%	50%

²⁷ Based on UNOS Scientific Renal Transplant Registry 1995 to 1999.

²⁸ Based on OPTN data as of July 6, 2001.

²⁹ Based on UNOS Scientific Renal Transplant Registry 1995 to 1999.

³⁰ Donor age exerted a striking influence on first cadaver transplant results, also played a role in the early graft function of cadaver, but not living donor grafts.

³¹ Based on UNOS Scientific Renal Transplant Registry 1995 to 1999.

NDAs: 21-560, and 21-268

The sponsor presented table 2-2 (page 26, NDA Amendment/Final Safety Update) comparing pooled data (RAD 1.5 and RAD 3) from KRS to studies A2306, A2307 and data from UNOS registry. No data on donor source regarding the MMF arms (control arm) was presented in this specific table.

We did not find convincing evidence from these comparisons since pooling donor source data from KRS make the result more similar to study A2306 without showing the fundamental differences in donor types between EU study B201 and USA study B251.

We approach this evaluation in a different way. Since donor source is a very important factor that influences graft survival, we compared the rates of cadaveric and living donors for the **MMF arms** (historical control for study A2306) and compared them versus the RAD 1.5 and RAD 3 arms in study A2306. We follow the same approach to evaluate other donor / recipient baseline characteristics.

Table 8.1.1-1, presents the patient demographic rates for the KRS-MMF arms and study A2306.

8.1 Patient Demographics

8.1.1 Patient Demographics - Cross-study Comparison A2306 vs. B251/B201

Table 8.1.1-1. PATIENT DEMOGRAPHICS by treatment group (ITT population)
Studies B251, B201 and A2306 (% of patients)

	RAD 1.5	RAD 3	MMF		Pooled data	
	A2306 (N=112 RDN)	A2306 (N=125 RDN)	B251 (N=196 FDN)	B201 (N=196 FDN)	B201/ B251 MMF arms (N= 392)	A2306 N=237
Male	62.5%	54%	67%	71%	69%	58%
Recipient age =>50 years	32%	34%	36%	43%	39%	33%
Caucasian (61%)	79%	66%	66%	87%	76.5	72%
Black (23%)	0	12%	17%	6%	11.5	6%
Hispanic (11%)	12%	11%	12%	-	6%	11%
Oriental (4%)	0	4%	1%	3%	2%	2%

Data source: Modified from post-text Table 7.4-1 and 7.4-12 Patient Demographics, Studies B251 and B201 (ITT Population - 12 Month Analysis). Percentages are calculated using the ITT population as the denominator

Reviewer's comments: *There were important differences across the KRS-MMF arms in the proportion of older (=> 50yrs) and black recipients.*

In general, the majority of patients included in both KRS and study A2306, were male and Caucasian. The rates of Caucasian recipients included in these studies showed notable differences across studies (66%, 72% and 90% in studies B251, A2306 and B201, respectively). Minorities, including black recipients, were under-represented in these studies. The USA study, B251 included more black patients (17%) compared to studies B201 (4%) or A2306³² (6%).

³² Black patient in study A2306 were not randomized instead they were systematically assigned to the 3mg RAD arm.

Pooled data from KRS-MMF arms, presented higher rates in black and older recipients³³ (12% and 39%) compared to study A2306 (6% and 33%, respectively). These demographic differences favor study A2306 for better outcomes.

8.1.2 Patient Demographics Cross-study Comparison A2307 vs. B156

Table 9.1.2-1. PATIENT DEMOGRAPHICS by treatment group (ITT population) Studies A2307 and B156 (% of patients)

	RAD 1.5	RAD 3	RAD 3	
	A2307 (N=139 RDN)	A2307 (N=117 RDN)	B156 (N=53 FDN)	B156 (N=58 RDN)
Male	69%	63%	57%	65.5%
Recipient age =>50 years	38%	48%	43%	33%
Caucasian (61%)	91%	83.5%	68%	81%
Black (23%)	0	9%	24.5%	17%
Hispanic (11%)	3%	3%	-	-
Oriental (4%)	3%	2%	3.8%	1.7%

Data source: Modified from post-text Table 7.5-1, 7.5-2, and 9.5-3 Patient Demographics, Studies B-156 12 and A2307 (ITT Population - 12 Month Analysis) Percentages are calculated using the ITT population as the denominator

Reviewer's comments:

Study B156 enrolled significantly higher proportion of black recipients (20%) favoring study A2307 (4%) for better outcomes.

8.2 Donor Source

8.2.1 Donor Source Cross-study Comparison A2306 vs. B251/B201

Table 9.2.1-1. Donor Source, n (%) by treatment group (ITT population) Studies B252, B201 and A2306 (% of patients)

Donor source, n (%)	RAD 1.5	RAD 3	RAD 3		Pooled data	
	A2306 (N=112 RDN)	A2306 (N=125 RDN)	B251 (N=196 FDN)	B201 (N=196 FDN)	B201/ B251 MMF arms (N= 392)	A2306 N=237
Cad. HBD	60%	66%	43%	79%	61%	63%
Cad. NHBD	0 ³	0 ³⁴	3%	12%	7.5%	0
Total Cadaveric Donors	60%	66%	46%	91%	68.5%	63%
LRD	35%	31%	40%	7%	23.5%	33%
LURD	5%	3%	14%	3%	8.5%	4%
Total Living Donors	40%	34%	54%	9%	31.5%	37%

³³ Recipient age =>50 years

³⁴ NHBD was an exclusion criterion in study A2306

NDAs: 21-560, and 21-268

Data source: Post-text tables 7.4-1, 7.4-3, and 7.4-12 Study B-251 12 months analysis.

Table 7-3 Baseline demographic characteristics by treatment group (ITT population- 12 month analysis) (Study A2306)

Post-text Table 7.4-3 (Page 1 of 1) Study B201 Primary Disease Leading to Transplantation and Donor Source (ITT Population - 12 Month Analysis). Percentages are calculated using the ITT population as the denominator

Reviewer's comments:

The percentage of cadaveric donors was higher in European study B201 (83%) compared to the American study B251 (47%) or study A2306 (63%). Similarly, the percentage of cadaveric donors in S-B201-MMF arm was higher (91%) compared to the MMF arm in S-B251 (46%). NHBD kidney rates were 8.5%, 3% and 0% in studies B201, B251 and A2306, respectively (NHBD kidneys were excluded from study A2306). On the contrary, living donor rates were higher in study B251-MMF arm (54%) versus study B201-MMF arm (9%).

Similarly, the pooled data showed higher rates of cadaveric HBD and NHBD in the KRS-MMF compared to S-A2306 (69% and 8% versus 63% and 0%, respectively).

Pooling data from KRS is not adequate due to the important differences in the type of donors used in each study.

These differences reflect the better quality of organs included in study A2306, therefore a better outcome is expected in this study compared to KRS-MMF arms. In these circumstances cross-study comparison is also inadequate and may easily lead to spurious conclusions.

8.2.2 Donor Source Cross-study Comparison A2307 vs. B156

Table 9.2.2-1. Donor Source, n (%) by treatment group (ITT population) Studies A2307 and B156

Donor source, n (%)	RAD 1.5	RAD 3	RAD 3	
	A2307 (N=139 RDN)	A2307 (N=117 RDN)	B156 (N=53 FDN)	B156 (N=58 RDN)
<i>Cad. HBD</i>	66%	76%	77%	83%
<i>Cad. NHBD</i>	2%	1%	0%	0%
<i>Total Cadaveric Donors</i>	67.5%	77%	77%	83%
<i>Total Living Donors</i>	32.5%	23%	23%	17%

Data source: Post-text tables 7.4-1, 7.4-3, and 7.4-12 Study B-251 12 months analysis.

Table 7-3 Baseline demographic characteristics by treatment group (ITT population- 12 month analysis) (Study A2306)

Post-text Table 7.4-3 (Page 1 of 1) Study B201 Primary Disease Leading to Transplantation and Donor Source (ITT Population - 12 Month Analysis)

1. Percentages are calculated using the ITT population as the denominator

Reviewer's comments: No major differences in donor type were observed between S-A2307 and B156. However, the RDN in S-B156 higher percentage of cadaveric donors were used. We do not expect a major impact from these differences. Furthermore, the small number of cases in these studies limits our ability to draw conclusions.

8.3 Donor and Recipient Baseline Characteristics

8.3.1 Donor / Recipient Baseline Characteristics Cross-study Comparison A2306 vs. B251/B201

**Table 9.3.1-1. Other Donor /Recipient Characteristics (ITT population) Studies
A2306, B201 and B251**

	RAD 1.5	RAD 3	MMF		Total	
	A2306 (N=112)	A2306 (N=125)	B251 (N=196)	B201 (N=196)	B201/ B251 MMF arms (N= 392)	A2306 N=237
DM at baseline (pre-study)	9%	7%	24.5%	6%	15%	8%
Patient weight (Mean)	69kg	70kg	79kg	71kg	-	-
DGF³⁵	14%	17%	6%	20%	13%	16%
CMV D+/R-	12%	10%	16%	20%	18%	11%
Missing Donor CMV Serology	18%	15%	0.5%	0.5%	0.5%	16%
Donor Age ≥ 50 yrs	33%	28%	-	-	-	-
Mean Donor Age in yrs (Range)Median	42(10, 66) 44	50(10- 67) 43	37(6,66) 36	42(11,72)) 46	-	-

Data source: Post-text Table 7.4-2 (Page 1 of 1), Donor Characteristics, and (Post-text Table 7.4-1 (Page 2 of 3) Patient Demographics (ITT Population- 12 Month Analysis).

Post-text Table 7.4-12 (Page 1 of 1) Pre-Study Diabetes(ITT Population - 12 Month Analysis, B251, B201 and A2306)

Post-text Table 7.4-5a (Page 1 of 1)Recipient Viral Serology Prior to Randomization (ITT Population - 12 Month Analysis A2306)

Post-text Table 7.4-5b (Page 1 of 1) CMV Status: Recipient and Donor(ITT Population - 12 Month Analysis)

Percentages are calculated using the ITT population as the denominator

Reviewer's comments:

USA study B251-MMF arm included higher proportion of diabetic recipients (25%) compared to S-B201 (6%), similarly more overweight patients were included in the American study versus the European study. On the contrary The EU S-B201- MMF arm included more cadaveric donors and as expected more higher rates of DFG were observed in S-B201 compared to B-251 (20% versus 6%, respectively).

8.3.1.1 Delayed Graft Function (DGF):

Type of donor, donor age, vasoconstrictive effects of CsA and tubular damage during ischemia /reperfusion are the major contributing factor for DGF.

Pooled data showed similar rates of DFG across studies, 13% and 16% for KRS-MMF arms and A2306, respectively.

Compared to the KRS-MMF arms, study A2306 included higher proportion of living donors, lower proportion of donors with prolonged ischemia time, and Reduced Dose Neoral® (RDN).

³⁵ Need for dialysis within 7 days posttransplantation

NDAs: 21-560, and 21-268

Furthermore, functional grafts at randomization were required as inclusion criteria. Therefore, we would expect lower rates of DGF in this group; surprisingly, this was not the case.

Results from animal studies suggest that mTOR inhibitors may delay recovery from tubular damage by impairing the required proliferation of renal epithelial cells and, perhaps, by promoting apoptosis³⁶. Additionally it well characterized the RAD enhanced CsA nephrotoxicity.

Study B156, compared 3mg RAD fixed dose with either FDN or RDN. The FDN arm presented twice the incidence of GFR (15%) compared to the RDN arm (7%). These results suggest a potential deleterious effect of the RAD plus FDN regimen on immediate renal function.

8.3.1.2 CMV mismatch (D+ /R-):

High risk CMV mismatch (D+/R-) rates were the higher in both key renal studies (19% and 20%) versus study A2306 (11%). Furthermore, 4% of the (D+/R-) patients in study B251 did not received CMV prophylaxis. Pooling data from KRS-MMF arms, high risk CMV mismatch rates were higher (18%) compared to study A2306 (11%).

8.3.1.3 Preexisting Diabetes Mellitus.

Pre-existing Diabetes Mellitus was 4 times higher in study B251-MMF arm (25%) compared to B201-MMF arm (6%). Pooling data from both KRS-MMF arms still shows higher rates of baseline DM versus S-A2306 (15% versus 8%, respectively). DM is a well known risk factor for cardiovascular disease, which is the main cause for patient death with functioning graft.

The differences across MMF arms mentioned above delineate two different populations and pooling data is considered inappropriate. Even though analyses were conducted to adjust for the most obvious donor covariates, many differences in donor / recipient baseline characteristics and pre-existing condition were not addressed. Furthermore, the potential for bias due to unknown covariates is always present.

8.3.1.4 High Risk Patients A2306 vs. B251/B201**Table 9.3.2.1-1. “High risk” patients (Recipients of a cadaveric kidney) by treatment group (ITT population) Studies A2306 and KRS (B201 and B251)**

	RAD 1.5	RAD 3	MMF		Total	
	A2306 (N=112)	A2306 (N=125)	B251 (N=196)	B201 (N=196)	B201/ B251 MMF arms (N= 392)	A2306 N=237
Total High risk patients³⁷	51%	52%	37%	69%	53	51.5%
CIT >24 hours	4.5%	9%	9%	17%	13%	7%
PRA >50%	1%	0	0.5%	0	0.25%	0.4%
Black	0	12%	9%	6%	7.5%	6%
HLA mismatches ≥3	76%	76%	31%	62%	46.5%	75%

Data Source:

Post-text Table 7.4-8 (Page 1 of 1)High Risk Patients (ITT Population - 12 Month Analysis S-A2306)

Post-text Table 7.4-8 (Page 1 of 1) original submission, High Risk Patients Studies B201 and B251 (ITT Population - 12 Month Analyses). Data on recipient from a cadaveric kidney. Percentages are calculated using the ITT population as the denominator.

Reviewer's comments:

Study B201-MMF arm, enrolled higher number of high-risk³⁸ patients (69%) compared to B251-MMF arm (37%). This difference was driven by the higher proportion of cadaveric donors and prolonged CIT enrolled in the EU study B-201 (Table 4A).

The incidence of CIT>24 in the KRS-MMF arms pooled data was higher (13%) than study A2306 (7%) favoring this study for better graft survival.

8.3.2 Donor / Recipient Baseline Characteristics A2307 vs. B156**Table 9.3.2.2-1. Relevant Donor / Recipient Baseline characteristics by treatment group (ITT population) Studies A2307 and B156.**

	RAD 1.5	RAD 3	RAD 3	
	A2307 (N=117 RDN)	A2307 (N=139 RDN)	B156 (N=53 FDN)	B156 (N=58 RDN)
Cadaveric Donors	67%**	77%**	77%*	83%*
CIT >24 hours	8%	7%	28%	15.5%
PRA >50%	0%	1%	2%	0%
Black	9%	5%	24%	17%
HLA mismatches ≥3	72%	73%	57%	64%

Data Source: Post-text Table 7.4-8 (Page 1 of 1)High Risk Patients (ITT Population - 12 Month Analysis S-A2306) Post-text Table 7.4-8 (Page 1 of 1) original submission, High Risk Patients Studies B201 and B251 (ITT Population - 12 Month Analyses). Data on recipient from a cadaveric kidney.. Percentages are calculated using the ITT population as the denominator.;* all were HBD;** Includes 3 cases of NHB

³⁷ Recipients of a cadaveric donor with one of the following:

a) black, b) PRA >50%, c) cold ischemic time >24 hours, d) total number of HLA mismatches >=3

Reviewer's comments:

Study B 156 enrolled higher proportion of black recipients and cadaveric donors with higher CITs .

8.4 Primary ESRD Leading to Transplantation

Table 9.4-1. Primary End Stage Renal Disease (ESRD) Leading to Transplantation Studies A2306 and KRS (B201 and B251)

	RAD 1.5	RAD 3	MMF		Total	
	A2306 (N=112)	A2306 (N=125)	B251 (N=196)	B201 (N=196)	B201/ B251 MMF arms (N= 392)	A2306 N=237
(UNOS data)						
Glomerulonephritis/glomerular disease (22.1%)	27%	30%	22%	40%	31%	29%
Hypertension/nephrosclerosis (16.1%)	11%	17%	17%	13%	15%	14%
Diabetes Mellitus (19.9%)	5%	6%	22%	3%	12.5%	5%
Polycystic disease (8.1%)	14%	12%	15%	17%	16%	13%
Pyelonephritis/interstitial nephritis	3.5%	5%	3%	9%	6%	4%
Unknown	21%	15.2%	-	8.2%	-	-

Table 9.4-2. Primary End Stage Renal Disease (ESRD) Leading to Transplantation Studies A2307 and B156.

	RAD 1.5	RAD 3	RAD 3	
	A2307 (N=117 RDN)	A2307 (N=139 RDN)	B156 (N=53 FDN)	B156 (N=58 RDN)
(UNOS data)				
Glomerulonephritis/glomerular disease (22.1%)	27%	29.5%	24.5%	29%
Hypertension/nephrosclerosis (16.1%)	3%	9%	24.5%	12%
Diabetes Mellitus (19.9%)	8.5%	11%	9%	5%
Polycystic disease (8.1%)	12%	16.5%	13%	15.5%

Source: Post-text Table 7.4-3 (Page 1 of 1), Studies B253 and B201 - Primary Disease Leading to Transplantation and Donor Source
Post-text tables 7.4-1, 7.4-3, 7.4-12, 7.5-1a, 7.5-1b 7.5-2a, 7.5-2b, 9.5-3a, 9.5-3b, 9.3-13, A2306 12 month CSR- (ITT Population - 12 Month Analyses). Percentages are calculated using the ITT population as the denominator.

Reviewer's comments:

The principal causes of ESRD leading to transplantation presented different rates among studies B251(USA), B201(EU) and A2306

Glomerulonephritis / glomerular disease was the most common primary cause of ESRD leading to transplantation across studies. However, higher rates were observed in EU study B201(38%) compared to USA B251(28%) or A2306 (29%).

NDAs: 21-560, and 21-268

In contrast, Diabetes Mellitus (DM) and Hypertension (HTN)/nephrosclerosis presented significantly higher rates in the USA study B251 (18% and 20%, respectively) compared to the European study B201 (4% and 8.5%, respectively) or A2306 (5% and 14%, respectively).

In summary:

- ***The causes of ESRD leading to transplantation presented imbalances across MMF arms in studies B251 and B201.***
- ***Diabetes Mellitus caused ESRD leading to transplantation in 22% and 3%, in the MMF-B251 and MMF-B201 arms, respectively.***
- ***Glomerulonephritis/glomerular disease was the cause of ESRD leading to transplantation in 22% and 40%, in the MMF-B251 and MMF-B201 arms, respectively.***
- ***The pooled data showed that the rates of DM related ESRD leading to transplantation in study A2306 were less than half compared to B201/B251-MMF arms (5% versus 12.5%, respectively).***

DM and HTN are important risk factors for cardiovascular morbidity and mortality. It is obvious that study A2306 underrepresented not only the black population but also the diabetic renal transplant population. These facts clearly give an advantage to study A2306 for better outcomes.

We strongly believe that the imbalances observed in the MMF arms in the KRS introduce additional factors of potential for bias.

8.5 Past/Coexisting Medical Conditions

8.5.1 Risk Factors for Cardiovascular Disease

The leading cause of graft loss is “death with functioning graft” and CVD is the primary cause of death with graft function. Approximately 47% of the graft failures are caused by death from 2 to 12 months after transplantation and thereafter will remain in 40% approximately³⁹.

Risk factors for cardiovascular disease in the general population include age, smoking, diabetes mellitus, obesity, hypertension, hyperlipidemia, and family history.

Among transplant recipients, immunosuppressive therapy is an additional risk factors for heart disease. Immunosuppressants have been associated with worsening of hypertension, diabetes mellitus and hyperlipidemia. Certican® and other mTOR inhibitors have been associated with hyperlipidemia and worsening of calcineurin inhibitors related adverse events when used concurrently.

Cardiovascular morbidity and mortality are high among renal transplant patients. The risk of death due to ischemic heart disease is 6 times higher than the general population and further increases in diabetics (20 times higher)⁴⁰

³⁹ Ojo Ao et. al. Kidney Int. 2000;57:307-313

⁴⁰ Lindholm et. al. Transplantation 1995;60:451.

NDAs: 21-560, and 21-268

Table 9.5.1-1. Past/Coexisting Medical Conditions (ITT Population) Studies A2306, and MMF B201/B251 (Pooled data). Risk Factors for cardiovascular disease.

	RAD 1.5	RAD 3	MMF		Total	
	A2306 (N=112)	A2306 (N=125)	B251 (N=196)	B201 (N=196)	MMF B251/B201 (N=392)	A2306 N=237
<i>Obesity</i>	4%	4%	6%	3%	4.5%	4%
<i>Smokers: Tobacco use or abuse</i>	0.9%	2%	10%	1.5%	6%	2%
<i>Hypertension NOS</i>	83%	82%	95%	81%	88%	82%
<i>Diabetes Mellitus NOS Non-Insulin-Dependent Insulin-Dependent</i>	6%	6%	24%	6%	15%	6%
<i>Lipid abnormalities total⁴¹</i>	12.5%	22%	24%	15%	20%	17%
<i>Coronary Artery Disorder or CAD NOS</i>	1%	4%	10%	3%	6.5	2.5%
<i>Myocardial Infarction / Ischemia</i>	3%	2%	5%	5%	5%	2.5%
<i>Anaemia NOS</i>	31%	26%	37%	30%	33.5%	29%
<i>Hyperparathyroidism NOS Primary / Secondary</i>	9%	5%	8 %	13%	10%	7 %

Data source: Post-text Tables 7.4-9 Past/Coexisting Medical Conditions (ITT Population - 12 Month Analysis) Studies B201, (Pages 1 of 28), B251(Page 1 of 21) and A2306(page 135)

Reviewer's comments:

Cardiovascular disease is the leading cause of death among renal transplant patients with functioning grafts. Coexisting Medical Conditions known as risk factors for atherosclerotic cardiovascular disease (Obesity, smoking, hypertension, DM, etc.) presented higher incidence rates in the USA study B251 compared to the EU study B201. Similarly, the presence of coronary artery disease, and previous myocardial infarction were higher in USA study B251 compared to the EU study B201. These differences were similarly present across the MMF arms in these studies.

USRDS data indicates that cardiovascular event rates are higher in cadaveric compared to LRD transplant recipients. With the exception of coronary revascularization, rates for any cardiovascular event or death rates are higher for patients with cadaveric transplants as compared to those who receive LRD transplants⁴².

In the 30 days following a transplant, the estimated probability of AMI is 1.2 and 0.8% , cardiac arrest, 1.1 and 0.7 %; and for CHF, 5.2 and 4.7% for cadaveric and LRD transplants, respectively⁴³.

⁴¹ Lipid abnormalities includes: Hyperlipidaemia NOS, Hyperlipaemia, Dyslipidaemia, Hypercholesterolaemia, Hypertriglyceridaemia, and Lipid Metabolism Disorder NOS.

⁴² U.S. Renal Data System, USRDS 2000 Annual Data Report, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD. June 2000 www.urds.org/adr

⁴³ U.S. Renal Data System, USRDS 2000 Annual Data Report, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD. June 2000 www.urds.org/adr

Reviewer's comments:

The EU study B201 included a higher proportion of cadaveric donors while the USA study B210 included the higher proportion of patients with pre-existing DM and other risk factors for CVD. Pooled data clearly shows higher rates of cardiovascular risk factors in the KRS-MMF arms compared to study A2306 (See table 9.5.1-1).

Study A2306, considered the presence of cardiac disease as exclusion criteria (Old New York Heart Association Classification Grade 3, elevated creatine phosphokinase [CPK] of muscle band, or any cardiac disease considered to be unsafe by the investigator exclusion criteria).

These differences not only indicates that pooling data from KRS-MMF arms is not adequate but also that cross study comparison in this particular case is very complex.

Cardiovascular risk factors were higher in the MMF arms pooled data favoring study A2306 for a better long term outcome.

In summary:

- *Risk factors for cardiovascular events post-transplantation presented higher proportion in the pooled KRS- MMF arms versus RAD arms in study A2306 (See table 9.5.1-1.)*
- *These important differences between the KRS populations make pooling data from these studies inappropriate.*
- *Cross study comparison using pooled data from KRS-MMF arms will favor study A2306 for better long term outcomes.*

9 APPROPRIATENESS OF POOLING DATA FROM KEY RENAL STUDIES (B251 AND B201) AS HISTORICAL CONTROL FOR STUDY A 2306

The sponsor considered appropriate to pool the data from studies B210 and B251 considering that both studies had “similar study designs” and “similar populations”.

We agree with the sponsor that KRS protocols were similar regarding inclusion/exclusion criteria, treatment schemes, efficacy / safety endpoints.

However, important differences in study design were observed (See reviewers comments sections 8.1 and 8.2, Study Designs and Cross Study Comparison)

The populations included in the European study B201 versus the USA study B251 presented major differences in the donor / recipients baseline characteristics. (See Comparability of patient populations, Past/Coexisting Medical Conditions, and Risk Factors for cardiovascular disease [Studies A2306, and MMF B201/B251 pooled data]). These differences follow the same trends in the respective MMF arms. Therefore, we do not agree with the sponsor that both American study B251 and the European study B201 had similar populations.

9.1 Differences across MMF arms in the European S-B201 and the American S-B251

Study B201-MMF arm showed higher rates compared to study B251-MMF arm, respectively in the following donor /recipient baseline characteristics:

- Recipient age ≥ 50 years (43 Vs 36%),
- Caucasians recipients (87% vs. 66%),
- Cadaveric donors (91% vs. 46),
- NHBD (12 vs. 3%),
- CIT > 24 hrs. (17 vs. 9%),
- DGF (20 vs. 6%),
- High Risk patients (69 vs. 37%),
- HLA mismatches ≥ 3 (62% vs. 31%), and
- Mean donor age (42 vs. 37yrs).

Study B251-MMF arm showed higher rates compared to study B201-MMF arm, respectively in the following donor /recipient baseline characteristics:

- Black recipients (17% vs. 6%),
- Hispanic (12% v. 0%),
- Living donors (54 vs. 9%),
- Pre- existing DM at baseline (24.5% vs. 6%) and
- Patient mean weight (79 Kg vs. 71 kg),
- Obesity 6 vs. 3,
- Tobacco use (10 vs. 1.5),
- Pre-existing Hypertension (95 vs. 81),
- Pre-existing Coronary Artery Disorders (10 vs. 3%), and
- Pre-existing Anemia NOS (37 vs. 30%)

9.2 Pooled Data of MMF arms (B201/B251) versus Study A2306

Pooled data (B201/ B251-MMF arms) showed higher rates compared to study A2306, respectively in the following donor /recipient baseline characteristics:

- Cadaveric donors (68.5 vs. 63%),
- NHBD (7.5% vs. 0),
- CIT >24 hours (13 vs. 7%),
- Blacks (11.5 vs. 6%),
- Recipient age ≥ 50 years (39% vs. 33%)
- CMV mismatches, (18 vs. 11%),
- Pre-existing DM, (15 vs. 8%),
- Tobacco use (6 vs. 2%),
- Pre-existing Hypertension (88 vs. 82%),
- Pre-existing Coronary Artery Disease (6.5 vs. 2%) and
- Pre-existing Anemia (33.5 vs. 29%)

9.3 Conclusions:

We conclude that pivotal renal studies, B251 and B201 had different donor and recipient background characteristics. Therefore, pooling data from these studies is inadequate. Using pooled data from KRS as an historical control for A2306 is considered inappropriate due to the fact that these analyses have a high probability to lead to spurious conclusions.

Pooled data (KRS-MMF arms) showed worst profile in the donor /recipient baseline characteristics favoring study A2306 for better outcomes. In these circumstances we would predict a worst long term outcome in the KRS-MMF arms due to the worst baseline characteristic in this population. We consider these cross study comparison invalid.

10 INTEGRATED REVIEW OF EFFICACY

10.1 Efficacy Analyses for Key Renal Studies (B201 / B251) versus Renal Study A2306 (Cross Study Comparison)

The core efficacy, safety and PK/PD analyses presented by the sponsor, were performed pooling data from Key Renal Studies (KRS) EU B201 and USA B251 as an historical control for study A2306.

The primary endpoint for efficacy for KRS (**B201 and B251**) and study A2306 was the incidence of efficacy failure⁴⁴ at 6 and 12 months post-transplantation.

The secondary efficacy variables were the incidence of biopsy-proven acute rejection episodes, graft loss, death, antibody-treated acute rejection, clinically-confirmed acute and chronic rejection and biopsy-proven chronic allograft nephropathy at 6 and 12 months post-transplantation. For 12-month analyses, the cut-off dates were day 381 for the efficacy evaluations.

The sponsor analyzed studies A2306, A2307, B251, B201, and B156 to compare differences in renal function and rate of biopsy, distribution of biopsies over time, and rejection rates. Pooling data from both MMF arms from the KRS may show similar rates when compared to the study A2306-RAD 1.5 arm. However, pooling data from KRS is inappropriate due to differences observed in the donor / recipient baseline characteristics of the populations involved. (i.e. donor type).

⁴⁴ biopsy-proven acute rejection, graft loss, death, or loss to follow-up

10.2 Composite efficacy endpoints and individual components in kidney transplantation (ITT Population - 12 Month Analyses)

Table 3 Efficacy-related events (ITT Population - 12 Month Analyses) Studies B251, B201 and A2306

Efficacy-related events	RAD 3	RAD 1.5	MMF	
	A2306 (N=125)	A2306 (N=112)	B251 (N=196)	B201 (N=196)
Primary efficacy failure 12 month analysis	32 (25.6%)	31 (27.7%)	54 (27.6%)	61 (31.1%)
BPAR	24 (19%)	29 (26%)	47 (24%)	47 (24%)
Graft loss / death	10 (8%)	6 (5%)	12 (6%)	21 (11%)
Graft loss	4 (3%)	6 (5%)	10 (5%)	18 (9%)
Death	6 (5%)	1 (1%)	4 (2%)	5 (3%)
Loss to F/U	1 (1%)	0	1 (0.5%)	1 (0.5%)
Antibody Treated Acute Rejection	5 (4.0%)	7 (6.3%)	32 (16.3%)	14 (7.1%)
Biopsy-proven chronic allograft nephropathy	14 (11.2%)	15 (13.4%)*	11 (5.6%)*	15 (7.7%)

Source: [Post-text table 9.1-2a of the 6- month CSR for study A2306, Post-text tables 9.1-2a, 9.1-5a, and 9.1-5b of the 12-month CSR for study A2306], and [Post-text tables 9.1-5a-c, 9.1-6a-b, 9.2-4, and 9.4-6 of the 12-month CSRs for studies B251 and B201] Post-text Table 9.2-1 (Page 1 of 9), Comparing Simple Event Rates of an Event Using the Z-Test, (ITT Population - 36 Month Analysis), and 12 month analyses studies B201 and B251.

This analysis includes 12 month data only using the efficacy cut-off Day 381 (ITT Population) Post-text Table 9.1-2a (Page 1 of 1) Components of efficacy failure are generally not mutually exclusive.

Number (%) of Patients with Efficacy Failure Within 12 Months of the Initial Dose of Study Medication (ITT Population - 12 Month Analysis) A2306 Post-text Table 9.3-14 (Page 1 of 1)

1 Patient no. 009 0008 (study A2306) discontinued study medication at Month 2 due to an AE. Since this patient had his 6-month follow-up visit early (at Day 154), and his 12-month follow-up visit was scheduled after the database lock, he was included as a 'lost to follow-up' because of the definition of 'loss to follow-up' used in these analyses.

* 95% C.I (0.7%, 14.9%) p=0.0181

Reviewer's comments:

In study A2306, in the incidence of efficacy failure across arms showed no significant differences at month 12, Similarly, Primary and co-primary efficacy failure rates at 12 months were comparable between study A2306 (RAD 1.5 and RAD 3 dose groups) and MMF groups in studies B251/B201. The individual rates per group are presented in table 3, above.

At month 12, Biopsy-proven chronic allograft nephropathy (CAN) incidence rates were higher in study A2306 (12%) as compared to MMF arms in the KRS (7%). Biopsy-proven CAN was statistically significantly higher in the RAD 1.5- A2306 arm versus B251-MMF arm.

CAN is the leading cause of late graft failure in renal transplantation and it is related to immunologic (AR, Sub-clinical rejection, antibody treated AR etc.), non-immunologic factors (CsA nephrotoxicity, donor factors, etc.) and coexisting medical conditions (DM, hypertension, hyperlipidemia, obesity and syndrome X).

This important difference at one year raises concerns regarding the safety and efficacy of the proposed regimen.

10.3 Efficacy Analyses for Renal Study A2307 versus Supportive Study B156 (Cross Study Comparison)

Table 4 Efficacy-related events (ITT Population - 12 Month Analyses) Studies A2307 and B156

Efficacy-related events	Study A2307 RAD TDM ≥3ng/ml		Study B156 RAD Fixed Dose 3 mg	
	RAD 1.5 mg (N=117)	RAD 3 mg (N=139)	Full Dose Neoral (N=53)	Red. Dose Neoral (N=58)
Primary efficacy failure 12 month analysis	19 (16.2%)	27 (19.4%)	15 (28.3%)	5 (8.6%)
BPAR	16 (13.7%)	22 (15.8%)	9 (17.0%)	4 (6.9%)
Graft loss / death	2 (1.7%)	7 (5.0%)	4 (7.5%)	1 (1.7%)
Graft loss	2 (1.7%)	7 (5.0%)	3 (5.7%)	1 (1.7%)
Death	0	2 (1.4%)	2 (3.8%)	0
Loss to F/U	1 (0.9%)	2 (1.4%)	3 (5.7%)	1 (1.7%)

Source: [Post-text table 9.1-2a of the 6-month CSR for study A2307], [Post-text tables 9.1-1a, 9.1-2a, and 9.1-5a of the 12-month CSR for study A2307], and [Post-text tables 9.1-5a, 9.1-5c, 9.1-6a, 9.1-6b, and 9.2-4 of the 12-month CSR for study B156]

It includes all data as of the cutoff date of Day 381 (Month 12). Components of efficacy failure are generally not mutually exclusive.

1 Patient nos. 505 0010 and 508 0001 (study A2307) discontinued study medication at Months 3 and 1, respectively, due to AEs. Since these patients had their 6-month follow-up visits early, and their 12-month follow-up visits were scheduled after the database lock, they were included as 'lost to follow-up' because of the definition of 'loss to follow-up' used in these analyses.

Reviewer's comments:

Efficacy failure rates in study A2307 (reduced-dose Neoral with Simulect) were lower compared with full-dose Neoral arm and Simulect in study B156.

The significance of these results is difficult to evaluate due to:

- *Small number of patients included in these studies,*
- *Cross study comparison with a historical control, and*
- *Different regimens (RAD TDM regimen versus RAD fixed doses)*

The use of antibody induction therapy is an interesting approach with the theoretical advantage to protect against rejection in early phase post-transplantation which will allow the use of low dose neoral while maintaining efficacy. This approach requires to be tested prospectively in an adequately designed trial.

10.4 Comparisons of efficacy failure, graft loss and death adjusted by risk Factor

The analyses of the baseline donor /recipient characteristics in studies A2306 vs. the composite of B201/251 MMF pooled data, demonstrated an advantage for the experimental arms of A2306. Several risk factors for poor outcomes presented higher rates in the B201/251 MMF pooled data as compared to study A2306.

These imbalances favored study A2306 for better outcomes. However, in the analyses for efficacy failure, graft loss and death, there was no advantage in study A2306 compared to B201/251 MMF arms.

Reviewer's comments:

The adjusted data for donor type, recipient race, and DGF appeared very similar without any advantage for A2306 versus KRS-MMF arms. Other baseline characteristics favoring study A2306 for better outcomes were not taken in consideration for these analyses. Under these circumstances, a non-inferiority margin is not considered a relevant result.

10.5 Assessment of potential bias in the reporting of acute cellular Rejection

Cross study comparison is regarded as an important source of biased conclusions.

Biopsy-proven acute rejection is a major component of the efficacy endpoint in these trials. The investigator's threshold to perform a biopsy in a given patient requires assessment of the clinical status of such patient and it might influence outcome.

The sponsor analyzed studies A2306, A2307, B251, B201, and B156 to compare differences in Renal function and rate of biopsy, Distribution of biopsies over time, and Rejection rates.

Table 11.1-1 Number (%) of patients with biopsies (ITT population – 12-month analyses) – Studies A2306, A2307, B251, B201, and B156

Number (%) of patients with biopsies	RAD 3	RAD 1.5	MMF B251	MMF B201
<i>B201 (N=588)</i>	<i>113 (57%)</i>	<i>102 (53%)</i>		<i>99 /196 (50.5%)</i>
<i>B251 (N=583)</i>	<i>96 (49.5%)</i>	<i>91 (47%)</i>	<i>70 /196 (36%)</i>	
<i>A2306 (N=237)</i>	<i>42/ 125 (34%)</i>	<i>48/ 112 (43%)</i>		
<i>B201/ B251</i>			<i>169 /392 (43%)</i>	
<i>A2307 (N=256)</i>	<i>51 (37%)</i>	<i>39 (33%)</i>		
<i>B156 (N=111)</i>	<i>37 (33%)</i>			

Source: Modified from table 4.1-1 NDA amendment Final Safety Update Page 34.

NDAs: 21-560, and 21-268

The overall biopsy rates in the European study B201 were higher across arms compared to USA study B251 arms. In study A2306, the biopsy rates in the RAD 1.5 and RAD 3 arms were lower compared to the corresponding RAD arms in both KRS.

In clinical settings most renal biopsies are indicated due to graft dysfunction. Therefore, having a higher rate of biopsies in MMF arm, study 201 would suggest either a population at higher risk or a lower clinical threshold to perform biopsies. In either case these differences will affect the data and introduce potential for bias.

Pooling data from studies B201/251- MMF arms will make to appear a similar rates of biopsies as those in study A2306-1.5 mg arm.

Even though, the sponsor claims a valid comparison, we consider cross study comparisons fundamentally incorrect. Furthermore, the differences in biopsy rates observed across study arms in the KRS are clinically relevant due to a higher probability to detect BCAR's (including sub-clinical rejection episodes).

The sponsor's analyses also looked at renal function and rate of biopsy and distribution of biopsies over time, in Studies A2306, A2307, B251, B201, and B156.

We agree that patients with higher creatinine levels (above 200 µmol/l) are more likely to be biopsied than a patient with a lower creatinine. (below 200 µmol/l) and that patients with elevated creatinine levels were similarly likely to be biopsied regardless of the RAD study they participated in.

Reviewer's comments: *The overall biopsy rates in the European study B201 were higher across arms compared to USA study B251 arms. Pooling data from both MMF arms from the KRS may show more balanced rates when compared to the RAD 1.5 arm (proposed initial dose) from the A2306. However, pooling data from KRS is inappropriate due to de differences observed in the baseline donor / recipient characteristics of the populations involved. (e.g. donor type). These differences may explain the higher proportion of renal biopsies observed in the EU study B201.*

10.6 Treatment of Acute Rejection:

Table 11.2-1. N (%) of Patients who had Treated Acute Rejection at 6 Months. (Studies A2306, B201 and B251)

Number (%) of patients with Treated Acute Rejection at 6 Months	RAD 3	RAD 1.5	MMF
B201 (N=588)	65/198 (33%)	69/194 (36%)	69/196 (35.2%)
B251 (N=583)	51/194 (26%)	46/193 (24%)	56/196 (28.6%)
A2306 (N=237)	19/125 (15%)	28/112 (25%)	
B201/ B251	116/392 (30%)	115/387 (30%)	125/392 (32%)

Source: Modified from Post-Text Table 6.1-5 (Page 1 of 1)N (%) of Patients who had Treated Acute Rejection at 6 Months (ITT Population - 12 Month Analysis) This analysis includes 6 month data only using the efficacy cut-off day

Reviewer's comments: *There were higher rates of treated acute rejection episodes across arms in the EU study B201 compared to studies B251 and A2306. This difference may be reflecting the higher number of biopsies in study 201 (See table 11.1-1 above) and the opportunity to detect more rejections episodes. Furthermore, EU study B201 included higher rates of cadaveric donors, HNBD and high risk patients in general, so higher rates of rejection and poorer grafts outcomes are expected in this study.*

These differences between the KRS, also exemplifies the presence of two different populations and the inappropriateness of pooling data from these studies. The effect of the differences in the patient / donor baseline characteristics is clearly reflected on long term renal function between studies B201 and B251. (See CrCl at 1, 2, and 3years post transplantations for both KRS,) which is reasonable expected mainly because of the disproportions in donor type.

Pooling data from KRS makes the rates of treated acute rejection look similar compared to the rates observed in study A2306 arms. We agree with the sponsor that “Acute cellular rejection would not be expected to spontaneously improve, so treatment for acute rejection ultimately would be required.” However, subclinical rejection can only be detected through biopsy or it will manifest itself as chronic allograft dysfunction (i.e. chronic rejection/CAN) if untreated. As a matter of fact, the rates of biopsy-proven chronic allograft nephropathy were higher in both arms of study A2306 compared to the MMF arms in the KRS. Therefore, it is difficult to defend the sponsor's argument. Furthermore, no data on renal function is available from study A2306 beyond one year; therefore, we do not know the potential consequences of this difference in BPCAN on long term renal function (See section 11.1.9 Renal function).

10.7 Patient and graft survival study A2306 versus OPTN/SRTR data in kidney transplantation.

The sponsor claims that “the most recent rates of one year graft survival are somewhat lower than achieved in the Certican clinical trials”

We agree with the sponsor that graft survival rates from OPTN/SRTR⁴⁵ August 1, 2002 numerically are lower than the survival rates observed in the Certican trials. However, the populations studied in A2306 did not reflect important baseline characteristics of the OPTN/SRTR that reflects the USA transplant population⁴⁶. Cross study comparison of these studies with registry data are not valid.

10.8 Efficacy Conclusions

(See Executive Summary)

⁴⁵ Survival rates 88.4% for cadaveric organs and 94.3% for living donor organs

⁴⁶ Study A2306 vs registry data shows differences in DM as leading cause of ESRD (5% vs 20%), Black recipients (6% vs 23%) , Caucasians (72% vs 61%) and NHBD were not included in study A2306.

11 INTEGRATED REVIEW OF SAFETY

11.1 Integrated Review of Safety Key Renal Studies (B201 / B251) versus Renal Study A2306 (Cross Study Comparison)

For 12-month analyses, the cut-off dates were day 450 for the safety evaluations. The safety analyses were performed pooling data from Key Renal Studies (KRS) EU B201 and USA B251 as an historical control for study A2306.

There were obvious differences in the donor / recipient baseline characteristics between both KRS- MMF arms. Therefore, pooling data from both MMF arms as historical control for study A2306 is inappropriate under these circumstances. Due to these deficiencies, the safety analyses have high probability to lead to spurious conclusions. Therefore, we analyzed safety data to explore and define:

- Differences in safety parameters between KRS-MMF arms
- A dose related differences between the RAD 1.5 and the RAD 3 mg arms in the AE's and other safety parameters, and
- New safety signals

We will present pooled data from study A2306 and KRS-MMF arms to illustrate strong safety signals that persist regardless cross study comparisons.

11.1.1 Patient disposition - Patient discontinuation from study medication:

Table 1. Premature Discontinuation from study medication (ITT population - 12 Month Analyses - <450 days) Studies B251, B201 and A2306.

	RAD 3	RAD 1.5	MMF	
	A2306 (N=125)	A2306 (N=112)	B251 (N=196)	B201 (N=196)
Discontinued Study Medication (%)	24%*	29.5%*	25.5%	28%
Adverse event(s)	14%	20%	10%	20%
Abnormal laboratory value(s)	1%	1%	1.5%	0.5%
Unsatisfactory treatment effect	3%	4.5%	7%	4%
Protocol violation	0	2%	2%	2%
Withdrawal of consent	2 %	0	3%	1%
Death	2%	0	1%	0.5%
Graft loss	2 %	3 %	-	-

Source: B-251 Source: [Post-text table 7.1-1](#) and [Post-text table 7.1-2](#), B201 Source: [Post-text table 7.1-1](#) and [Post-text table 7.1-2](#) (Clinical Study Reports)

* Note: The total does not include 2 patients (1 in each group) who discontinued study medication prior to their Month 12 visits. In the investigators' opinion, they had completed the study.

Note: The rate of patients that discontinued study medication and the specific causes for discontinuation represents a proportion of the enrolled patients in each study arm.

Reviewer's Comments:

- *The rates of discontinuation from study medication were similar between studies. RAD plus CsA in study A2306 did not showed any advantage compared to historical MMF control in KRS with respect to the rates of discontinuation rates from study medication.*
- *Adverse events were the main cause for discontinuation from study medication in the all studies and across arms. It is interesting to note that, in study A2306, the RAD 1.5 arm presented higher rates of discontinuation from study medication compared to the RAD 3 mg arm (29.5% vs. 24% respectively). Similarly AE*
- *Adverse event leading to discontinuation from study medication, showed a striking difference between the MMF arms in studies B201 and B251, (20% vs. 10%, respectively). This fact reinforce our view that EU study B201 and USA study B251 enrolled populations with different donor / recipient baseline characteristics (i.e. pre-existing medical conditions) that influence patient outcomes.*

11.1.2 AE Leading To Discontinuation of Study Medication (DAE)

Table 2 includes the renal related DAE. Most of the DAE are discussed in the different sections of the Integrated Safety Review.

Table 2. Incidence Rates of Adverse Event Leading to Discontinuation of Study Medication by Preferred Term (Safety Population - 12 Month Analyses) Studies B251 , B201 and A2306.

DEA	RAD 3	RAD 1.5	MMF	
<i>Preferred Term (Reported term)</i>	A2306 (N=125)	A2306 (N=112)	B251 (N=196)	B201 (N=196)
<i>Any DAE 12 month analyses</i>	23	28	24	42
<i>No (%)</i>	(18%)	(25 %)	(12 %)	(21 %)
<i>Renal Failure Acute</i>	-	-	1(0.5%)	0
<i>Renal Function Abnormal</i>	-	-	1(0.5%)	1 (0.5%)
<i>Renal Tubular Necrosis</i>	-	-	1(0.5%)	
<i>Graft dysfunction /DGF</i>	1 (0.8)	1 (0.9)	1	1
<i>Blood creatinine increased</i>	3 (2.4)	1 (0.9)	2	1
<i>Therapeutic Agent Poisoning o drug toxicity NOS⁴⁷</i>	1(0.8)	1 (0.9)	0	1
<i>TMA, HUS & TTP</i>	1 (0.8%)	4 (3.6%)	1(0.5%) ⁴⁸	0
<i>Pneumonias NOS⁴⁹</i>	3 (2.4)	0	0	1 (0.5%)
<i>Lipid abnormalities⁵⁰</i>	1 (0.8)	2 (1.8)	3(1.5%)	0

⁴⁷ Only cases that the investigator reported as cyclosporin / cyclosporine/ ciclosporin toxicity were included. Other drug toxicities not cyclosporine-related were excluded.

⁴⁸ Includes a case reported as Haemolysis (preferred term) / but the investigator reported as Hemolytic Uremic Syndrome (reported term)

⁴⁹ All pneumonias includes, bronchopneumonia, and any DAE including pneumonia in the preferred term (PCP, CMV etc). A case o recurrent pulmonary infiltrates is also included in this category.

⁵⁰ We include all lipid abnormalities that denoted an increment that lead to discontinuation from study medication including Hyperlipidemia NOS., Lipids Increased NOS, Hypercholesterolemia, Blood cholesterol increased, Hypertriglyceridemia, Blood Triglycerides Increased, and Low Density Lipoprotein Increased.

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Data obtained from: Post-text Table 10.2-1c (Page 1 of 10) and Post-text Table 10.2-1c (Page 1 of 11) Post-text Table 10.2-1c (Page 1 of 5) studies B201, B251, and A2306 reports, respectively. Incidence Rates of DAE by Body System and Preferred Term DAE: Adverse Event Leading to Discontinuation of Study Medication (Safety Population - 12-Month Analysis)

This table summarizes the most relevant DAEs up to the safety cut-off (Day 450), i.e. DAEs reported as occurring after the discontinuation of randomized study medication are not excluded; further, any DAE with onset before Day 450 is also included even if permanent discontinuation of study medication occurred only after Day 450

Reviewer's comments:

- ***In study A2306, the incidence of DAE at 12 months, were higher in the RAD 1.5 mg group compared with the RAD 3 mg group (25% vs. 18%, respectively).***
- ***DAE rates in the pooled data from KRS-MMF arms were lower compared to either the RAD 1.5 arm or the total DAE in study A2306 (17% versus 25% or 21.5%, respectively)***

11.1.3 Adverse Events (AE)

Due to inconsistencies in the “preferred terms” used to categorize the AE’s, more than one term may indicate the same entity e.g. Thrombocytopenia and platelet count decreased. The terms used were mutually exclusive when reported as AE. The post-text listings were reviewed to account for the terms as reported by the investigator. Also the center and patient number were checked to avoid duplicates. We used the “Preferred Terms” in most instances of the review. However, when appropriate we used “Reported Terms”, to reflect the most accurate data. In either case, we clearly specify which “Term” is used in the respective table.

The same approach was taken to analyze Adverse Event Leading to Discontinuation of Study Medication (DAE) and Non-Fatal Serious Adverse Events (NSAE).

Almost all patients experienced any AE’s (97% to 100% across arms) in both RAD arms, study A2306 and KRS-MMF arms.

11.1.4 Certican® Dose-related Adverse Events:

Dose related adverse events were observed in the KRS between the RAD 1.5 and RAD 3 arms. In study A2306, the RAD dose effect was similarly observed. We list below the AE reported with a difference of $\geq 5\%$, in study A2306 (RAD 1.5 versus RAD3):

- Blood creatinine increased (9%vs. 15%)
- Hypercholesterolemia (13%vs. 23%)
- Diabetes mellitus NOS (5% vs. 12%)
- Hypertension NOS (20% vs.27%)
- Hyperglycemia NOS (6% vs. 12%)
- Anemia NOS (20%vs.25%)
- Tremor (12% vs. 18%)
- Peripheral edema (25%vs. 38%)
- Hypokalemia (8%vs. 15%)

Reviewer's Comments:

The interaction of Certican® and CsA is well known. In the Key renal and Heart studies, Certican® showed a dose-related CsA toxicities (Including CsA enhanced nephrotoxicity). These dose-related effects are confirmed in studies A2306 and A2307.

11.1.5 Hematologic Adverse Events

Table 2. Incidence Rate of Hematologic Adverse Events by Preferred Term (Safety Population – 12 Month Analyses Studies B251 , B201 and A2306)

	RAD 3		RAD 1.5		MMF		Total	
<i>Preferred Term</i>	A2306 (N=125)	A2306 (N=112)	B251 (N=196)	B201 (N=196)	MMF B251/B201 (N=392)		A2306 N=237	
<i>Anemia or Anemia NOS</i>	31(25%)	22(20%)	38(19%)	63(32%)				
<i>Anemia Total</i>⁵¹	38(30%)	23(20%)	39(20%)	67(34%)	27%		26%	
<i>Thrombocytopenia</i>	10(8%)	4 (4%)	13 (7%)	10(5%)				
<i>Thrombocytopenia Total</i>⁵²	15(12%)	5(4%)	13(7%)	12(6%)	6%		8%	
<i>Leukopenia NOS, leucopenia</i>	5 (4%)	5 (4.5%)	20 (10%)	31 (16%)				
<i>Leukopenia Total</i>⁵³	6(5%)	5 (4.5%)	24(12%)	35(18%)	15%		5%	

Data obtained from: Incidence Rate of Adverse Events/Infections by Body System and Preferred Term (Safety Population - 12-Month Analysis). Post-text Tables 10.1-1a (Page 2 of 82), Post-text Table 10.1-1a (Page 1 of 58), and Post-text Table 10.1-1 (Page 1 of 30), studies B251, B201, and A2306 respectively.

Reviewer's Comments:

Anemia rates were very different between MMF arms, studies B251 and B201 (20% and 34%, respectively).

Anemia rates in study B251-MMF arm, was similar to the RAD 1.5 arm, and 10% lower than the RAD 3 arm. On the other hand, anemia rates in study B201-MMF arm appear higher than both RAD arms in study A2306. (Pooled data makes these differences disappear and produce factitious similar rates across studies)

Thrombocytopenia showed a RAD dose related effect, the RAD 3 arm presented twice the rate compared to the B251-MMF and B201-MMF arms (12% versus 7% and 6%); while, the RAD1.5 rates were similar to the MMF arms. Thrombocytopenia lead to discontinuation from study medication (DEA) in two cases (2%) in the RAD1.5 and in one case (0.5%) in the MMF arms (B201)

⁵¹ **Includes:** Anemia or Anemia NOS, Hb or Hto Decreased, Iron deficiency anaemia, Normochromic normocytic, Secondary anemia, and Hypochromic anemia,

⁵² **Includes:** Thrombocytopenia, Platelet Count Decreased, and Platelet abnormalities

⁵³ **Includes:** Leukopenia NOS, Leucopenia, WBC decreased, and Granulocytopenia

NDAs: 21-560, and 21-268

Leucopenia showed approximately three times higher rates in the KRS-MMF arms versus study A2306 RAD arms. Leucopenia lead to DEA in four cases in the KRS- MMF arms and one case in study A2306.

11.1.6 Hypertension:

Table 3. Incidence Rate of Adverse Events/Infections by System Organ Classification and Preferred Term (Safety Population – 12 Month Analyses Studies B251 , B201 and A2306)

Preferred Term	RAD 3	RAD 1.5	MMF	
<i>Preferred Term</i>	A2306 (N=125)	A2306 (N=112)	B251 (N=196)	B201 (N=196)
<i>Hypertension NOS</i>	34 (27%)	22 (20%)	48(24.5%)	61 (31%)
<i>Hypertension Aggravated</i>	Not used* -	Not used*-	22(11%)	6 (3%)
Total	27%	20%	36%	34%

Data obtained from: Incidence Rate of Adverse Events/Infections by Body System and Preferred Term (Safety Population - 12-Month Analysis). Post-text Tables 10.1-1a (Page 2 of 82), Post-text Table 10.1-1a (Page 1 of 58), and Post-text Table 10.1-1 (Page 1 of 30), studies B251, B201, and A2306 respectively.

* Preferred term not used in the post-text tables.

Hypertension NOS is a common CsA-related AE, it presented similar rates between the FDN plus MMF arms compared to the RDN plus RAD 1.5 and RAD 3 arms. However, it appears that the aggravation of hypertension was more frequently observed in the FDN plus MMF arms. A RAD dose related effect was observed in the observed rates of hypertension NOS (27% versus 20% for the RAD 3 versus RAD 1.5, respectively).

11.1.7 Renal Related Adverse Events:

The term “Allograft dysfunction Total” was used to include all preferred terms that denoted "abnormal allograft function" that were reported as AE's. The preferred terms used in the KRS-MMF arms and in study A2306 are listed in table 1. Some preferred terms were used in one study and not used in another; however, all preferred terms included in table 1 were systematically and carefully reviewed in both KRS-MMF arms and study A2306.

Thrombotic Microangiopathy (TMA) including Hemolytic uremic syndrome (HUS) and Thrombotic thrombocytopenic purpura (TTP) are consumptive coagulopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia. All preferred terms used are included in table 4..

Allograft dysfunction and microangiopathic hemolytic anemia (including TMA and HUS) are clinically relevant CsA-related adverse events, since these complications require early recognition and immediate treatment in order to preserve allograft survival.

NDAs: 21-560, and 21-268

Table 4. Incidence Rate of Renal Related AE by Preferred Term (Safety Population - 12 Month Analysis - Studies B251, B201 and A2306)

Preferred Term	RAD 3	RAD 1.5	MMF	
Preferred Term	A2306 (N=125)	A2306 (N=112)	B251 (N=196)	B201 (N=196)
<i>Blood creatinine increased</i>	19 (15.2%)	10 (8.9 %)	Not used**	Not used -
<i>Renal Function Abnormal</i>	Not used -	Not used -	4 (2.0%)	14 (7.1%)
<i>Renal impairment NOS</i>	4 (3.2%)	4 (3.6%)	Not used -	Not used -
<i>Primary Graft Dysfunction or graft dysfunction</i>	20 (16.0%)	16 (14.3%)	Not used -	Not used -
<i>Renal Tubular Necrosis</i>	9 (7.2%)	5 (4.5%)	8 (4.1%)	5 (2.6%)
<i>Renal failure acute</i>	2 (1.6%)	1 (0.9%)	4 (2.0%)	1 (0.5%)
<i>Allograft Dysfunction Total</i>	54(43%)	36(32%)	16(8%)	20(10%)
<i>HUS</i>	1 (0.8%)	3 (2.7%)	1 (0.5%) ⁵⁴	0
<i>TMA NOS, TTP</i>	1 (0.8%)	2 (1.8%)	0	0
<i>Total TMA⁵⁵</i>	2	5	1	0
<i>Proteinuria or Albuminuria</i>	3(2%)	5(4.5%)	8 (4%)	4 (2%)
<i>Haematuria</i>	16 (13%)	9 (8%)	31(16%)	7(4%)

Data obtained from: Incidence Rate of Adverse Events/Infections by Body System and Preferred Term (Safety Population - 12-Month Analysis). Post-text Tables 10.1-1a (Page 2 of 82), Post-text Table 10.1-1a (Page 1 of 58), and Post-text Table 10.1-1 (Page 1 of 30), studies B251, B201, and A2306 respectively.

**Not used: means that the preferred term was not used in the Post-text Tables.

Reviewer's Comments:

Allograft dysfunction total⁵⁶ rates showed a RAD dose related effect in study A2306.(43% and 32% in the RAD 3 and RAD 1.5, respectively) and were approximately four times higher rates compared to the MMF arms in studies B251 and B201 (8 % and 10%, respectively).

Thrombotic Microangiopathy is a well recognized CsA-related toxicity. The incidence TMA in renal transplant patients is as low as 5.6 episodes per 1000 person-year⁵⁷ and even lower in de novo TMA cases.

⁵⁴ Includes a case reported as Haemolysis (preferred term) / but the investigator reported as Hemolytic Uremic Syndrome (reported term)

⁵⁵ TMA (Thrombotic Microangiopathy) including HUS (Hemolytic uremic syndrome) and TTP (Thrombotic thrombocytopenic purpura) are consumptive coagulopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia.

⁵⁶ Allograft dysfunction total includes: Blood creatinine increased, Renal Function, Abnormal Renal impairment NOS, Primary Graft Dysfunction or graft dysfunction, Renal Tubular Necrosis, Renal failure acute.

⁵⁷ Reynolds JC, Agodoa LY, Yuan CM, Abbott KC. Thrombotic microangiopathy after renal transplantation in the United States. Am J Kidney Dis. 2003 Nov;42(5):1058-68.

NDAs: 21-560, and 21-268

Seven case out of 237 (3%) were reported in study A2306 versus one case out of 392 transplant patients in the KRS-MMF arms (0.2%). Six out of 7 TMA/HUS cases in study A2306, lead to discontinuation from study medication.

We consider this difference clinically relevant since we would expect 2.1 cases in the KRS-MMF arms versus 1.3 cases in study A2306.

11.1.8 Cyclosporine-Related Toxicity NSAE and DAE:

CsA toxicity Reported as Non-Fatal Serious Adverse Events (NSAE) and Adverse Events Leading to discontinuation from study medication (DAE) (Safety Population - 12 Month Analysis) Studies B251, B201 and A2306).

The incidence of cyclosporine toxicity was obtained from post-text listings of Non-Fatal Serious Adverse Events (NSAE) and post-text listings of Adverse Events Leading to Discontinuation of study medication (DAE). In this analysis, we included all cases in which the investigator used the term cyclosporine toxicity, cyclosporine nephropathy, and neoral toxicity and /or nephropathy. One case was also included with the reported term “cyclosporine tubulopathy”.

The table 11.1.8-1, below includes the preferred terms. Only cases of cyclosporine drug toxicity were included under the preferred term “Drug Toxicity”. To document CsA toxicity all pertinent listing were reviewed. Cases of drug toxicity due to other drugs other than cyclosporine were excluded from this analysis.

Table 11.1.8-1. Incidence Rate of CsA toxicity Related NSAE and DAE by Investigator’s Reported Term (Safety Population - 12 Month Analysis) Studies B251, B201 and A2306).

Investigator’s Reported Term	RAD		MMF		Pooled data	
	3	1.5				
	A2306 (N=125)	A2306 (N=112)	B251 (N=196)	B201 (N=196)	MMF B251/B201 1 (N=392)	A2306 N=237
NSAE CYCLOSPORIN TOXICITY CYCLOSPORINE NEPHROTOXICITY CHRONIC CYCLOSPORIN TOXICITY	4	2	4	2	6 (1.5%)	6 (2.5%)
DAE CYCLOSPORIN TOXICITY CHRONIC CYCLOSPORIN TOXICITY CYCLOSPORINE NEPHROTOXICITY	1	1	0	1	1	2

Data source:

Post-text Listings 10.2-2 Non-Fatal Serious Adverse Events (Including Infections) (Safety Population - 12 Month Analysis), studies A2306, B201 and B251.

Post-Text Listings 10.2-3 Adverse Events (Including Infections) Leading to Discontinuation of SM(Safety Population - 12 Month Analysis)), studies A2306, B201 and B251.

In study A2306 two patients were discontinued due to CsA toxicity one on each arm. In the KRS one patient was discontinued the MMF arms

Reviewer's Comments:

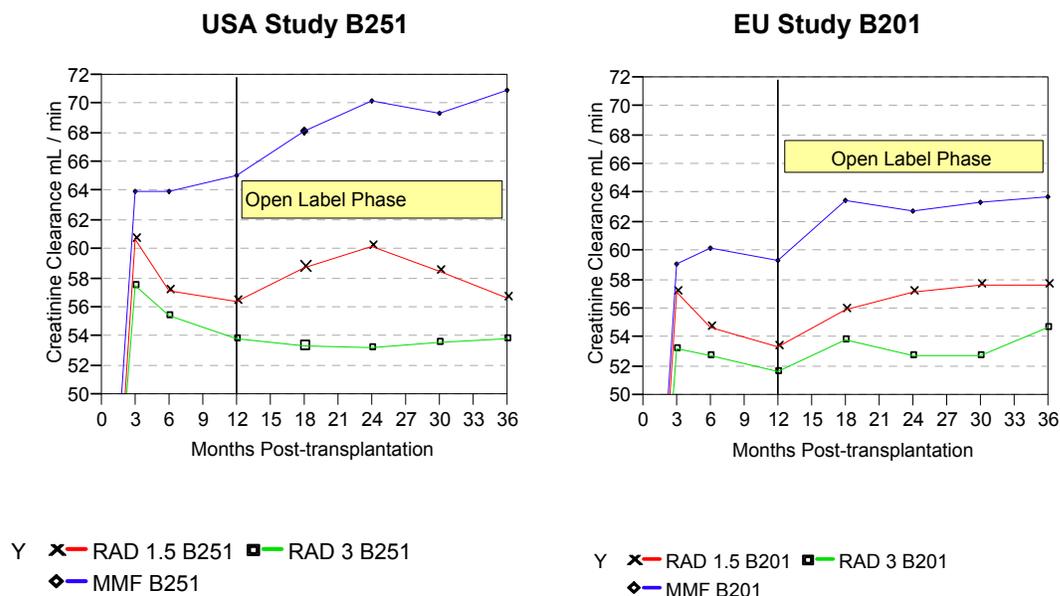
In study A2306, 12 cases (5%) were reported by the investigator as AE because of cyclosporine toxicity.

Half of these cases (6/237) were considered NSAE (2.5%), which is proportionally higher than 6/392 (1.5%) in the KRS-MMF arms. These rates are really small to draw any valid conclusion; however, given the fact that patients in study A2306 were receiving approximately half of the CsA dose compared to the MMF arms, we wonder if the CsA enhanced toxicity by RAD is still an issue with RDN regimens. Long term follow up is recommended.

11.1.9 Renal Function (B201 / B251) versus Renal Study A2306 (Cross Study Comparison)

11.1.9.1 Renal Function in Studies B201 and B251.

Figure 1. Estimated Creatinine Clearance (Nankivell) [ml/min] by visit (Safety Population -36 month analyses, S-B251 and B201)



Datasource: Post-text Tables 10.3-1b (Page 14 of 22) and (Page 13 of 22).

Reviewer's comment:

Zenith mean creatinine clearance values at three months post transplantation were lower and dose related in the RAD arms compared to MMF arms in both original key renal studies. This observation indicates the RAD plus full dose CsA combination has early post-transplant deleterious effects on renal function.

A dose related nephrotoxic effect between the RAD groups was consistent in both key renal studies. The RAD 3 arms, presented numerically or significantly lower calculated CrCl compared with RAD1.5 arms in both key renal studies. These findings suggest a

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significant and sustained nephrotoxic effect that is markedly observed in the RAD plus FDN combination compared with FDN plus MMF.

Amendments for KRS (B201 and B251) and KHS (B253) at one year post transplantation targeted a population con renal dysfunction and provided for Neoral® dose reduction while RAD TDM achieved $\geq 3\text{ng/ml}$.

This regimen modification stabilized renal function in the majority of patients while only a few showed an improvement. From this observation we strongly suspect that chronic use of fixed dose RAD plus FDN may lead to irreversible nephrotoxic changes.

Therefore, the regimen of either RAD 0.75mg bid or RAD 1.5 mg bid with FDN is considered unacceptable.

11.1.10 Renal Function in KRS-MMF arms, Study A2306 and A2307.

RAD with reduced dose Neoral (RDN) was tested in renal studies A2306 and A2307 to improve the renal safety compared to the RAD and FDN combination.

The overall analysis showed a significant benefit in improved renal function against RAD regimens with full dose Neoral (FDN). In contrast with the sponsor's claims; we did not see any advantage in renal function when the RAD+RDN regimens are compared to the MMF arms from the KRS. In other words, same degree in renal function at 12 month was observed in both, RAD 1.5 plus RDN and the historical control MMF plus FDN.

It is important to emphasize that the European (EU) study B201 include a high proportion of cadaveric donors compared to the studies B251, A2307 and A2307. Therefore we should expect lower GFR values in the EU study B201 (See table 6 below).

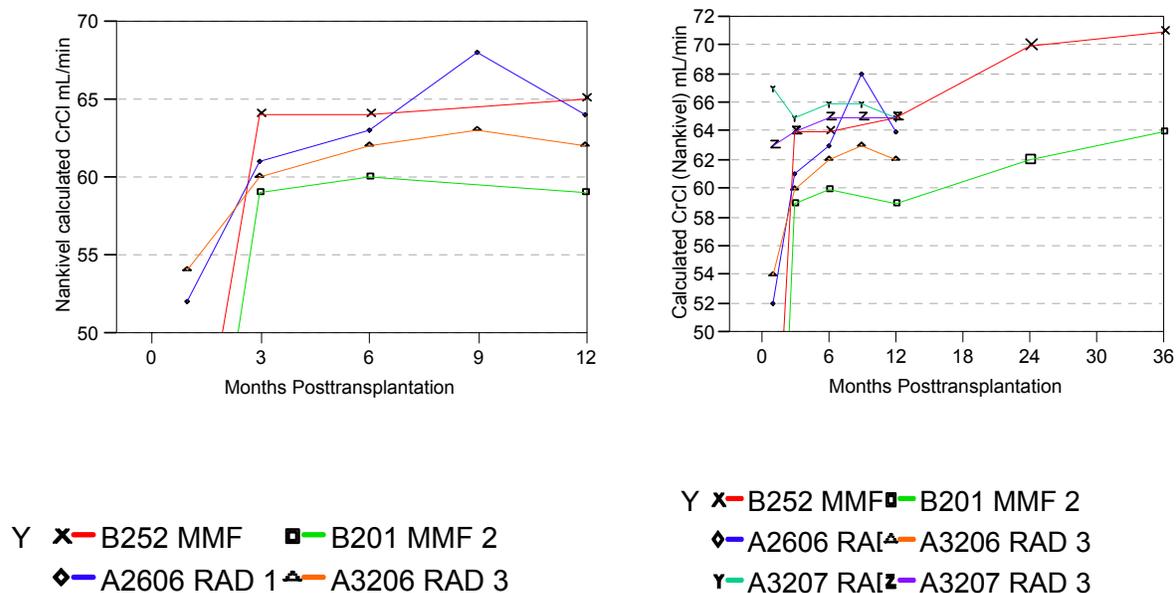
Similarly, when the subgroups of older donors ($\geq 50\text{y/o}$) are compared for GFR in study A2306 versus the MMF arms from the KRS we did not see any advantage on GFR in either group (table 7 and figure 3).

**Table 6. Estimated GFR Nankivell method [mL/min] over time
Studies A2306/07 and KRS-MMF arms**

	MMF		RAD plus low dose CsA			
	B251 (N=196)	B201 (N=196)	A2307 RAD 1.5 mg	A2307 RAD 3 mg	A2306 RAD 1.5 mg	A2306 RAD 3 mg
Day 28			67	63	52	54
Month 3	64	59	65	64	61	60
Month 6	64	60	66	65	63	62
Month 9			66	65	68	63
Month 12	65	59	65	65	64	62
Month 24	70	63				
Month 36	72	64				

Data source: Post-text Tables 10.3-1b S-B251, B201, A2306 and A2307,(ITT Population - 12 Month Analysis)
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.

Fig. 2. Calculated GFR over time (Nankivel) mL / min. KRS-MMF arms, A2306/07



Data source: Post-text Table 10.7-28f (Page 1 of 2) Estimated Creatinine Clearance (Nankivel) [mL/min] at 6 and 12 Months ITT Analysis - Including values observed at follow-up visits (ITT Population - 12 Month Analysis A2307 and 2306) and (ITT Population - 36 Month Analysis B201 and B251)

The graph on the left shows the calculated GFR (nankivel) from the KRS-MMF arms and the RAD 1.5 and RAD 3 arms from study A2306. (12 months ITT data)

The graph on the right shows the calculated GFR (nankivel) in MMF arms from the KRS-MMF arms and the RAD 1.5 and RAD 3 arms from studies A2306 and A2307. (36 and 12 months ITT data, respectively)

Reviewer's comments:

- *All the RAD arms in studies A3206/07 presented better CrCl than the B201-MMF arm. However we do not consider this fact a real advantage of the RAD plus RDN regimen but to a better quality of donors included in studies A2306/07. We should expect lower creatinine clearance in EU study 201 compared to the other studies due to the following reasons:*
 - *It included a significantly higher proportion of CAD donors (91%) compared to studies B251, A2306 and A2307 (50%, 63, and 77% respectively). Similarly, NHBD were in higher proportion in study B201 (8.5%) compared to studies B251, A2306 and A2307 (3%, 0, and 1 % respectively)*

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- **The proportion of High risk patients⁵⁸ was also higher in study B201 (68%) compared to B251, A2306 and A2307 (41%,52% and 56% respectively.)**
- **The proportion of transplanted kidney with CIT >24 hours was also higher in study B201 (16%) compared to B251, A2306 and A2307 (10%, 7% and 7% respectively.)**
- **Mean GFR continue to improve in 201-MMF arm (beyond 12 months) showing similar mean GFR at 36 month (64 ml/min) as compared to the best mean GFR at 12 months among all RAD arms in both studies A2306 and A2307 (62 to 65 ml/min).**
- **At 12 month, mean GFR was similar between RAD arms (A2306/07) and MMF-B251 arm. However, mean GFR continue to improve (beyond 12 months) in both KRS-MMF arms, showing a superior mean GFR at 36 month of 71 ml/min in the B251-MMF arm.**
- **We speculate if RAD arms in studies A2306 and A2307 will show GFR improvement beyond 12 month. The long term GFR improvement in the RAD plus RDN regimen remains to be seen.**

11.1.11 Renal Function in KRS-MMF arms, Study A2306 and A2307 (Donor age =>50 Y/O)

Table 7. Estimated Creatinine Clearance [mL/min] by Donor Age (≥ 50 y/o)

	MMF		RAD plus low dose CsA			
	B251 (N=196)	B201 (N=196)	A2307 RAD 1.5 mg	A2307 RAD 3 mg	A2306 RAD 1.5 mg	A2306 RAD 3 mg
Day 28			55	55	47	45
Month 3	58	52	55	56	52	52.5
Month 6	55	56	55	56	54	54
Month 9			55	56	61	53.5
Month 12	58	56	54	56	55	53
Month 24	58	58				
Month 36	57	56				

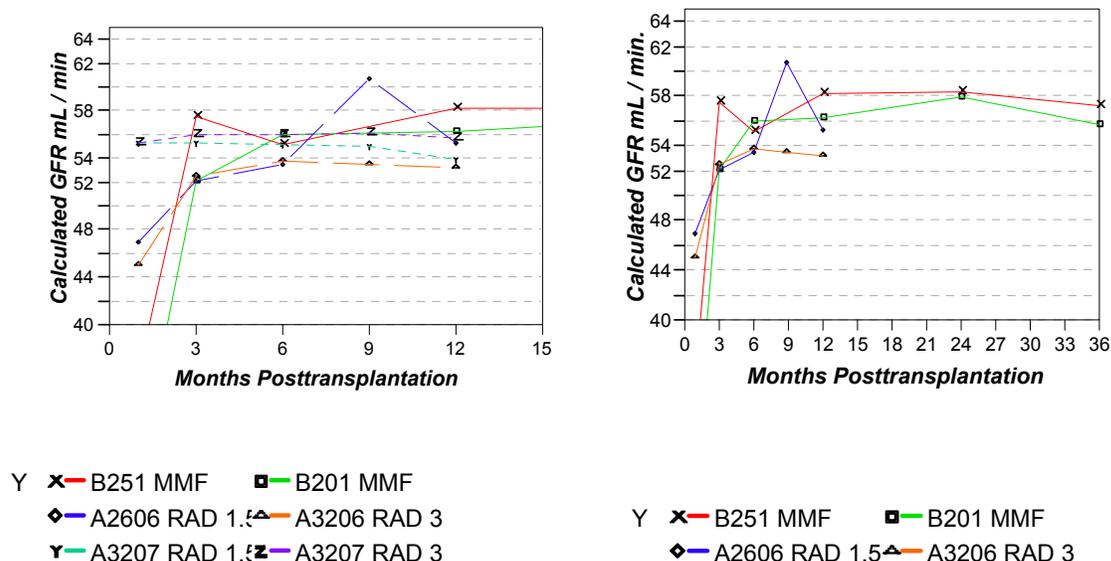
Data source: Post-text Tables 10.7-28fc. Estimated Creatinine Clearance (Nankivell) [mL/min] by Donor Age: ≥ 50 years. This table Includes values observed at follow-up visits (ITT Population - 12 Month Analysis) studies A2306 and A2307

Approximately 30 patient per CrCl calculation were used to determine the mean at each point time in studies A2306 and A2307.

⁵⁸ Recipients of a cadaveric donor with one of the following:

a) black, b) PRA >50%, c) cold ischemic time >24 hours, d) total number of HLA mismatches ≥ 3

Fig. 2. Calculated GFR over time (Nankivel) mL / min by Donor Age (≥50 y/o).



The graph on the left shows the calculated GFR (nankivel) from the KRS-MMF arms and the RAD 1.5 and RAD 3 arms from study A2306 (Donor Age ≥50 y/o).

The graph on the right shows the calculated GFR (nankivel) in MMF arms from the KRS-MMF arms and the RAD 1.5 and RAD 3 arms from studies A2306 and A2307 (Donor Age ≥50 y/o).

Long term outcomes in GFR observed in the KRS-MMF plus FDN combination that remain to be evaluated in the RAD plus RDN regimen:

- *Renal function from older donor allografts remained stable from 12 to 36 month post-transplantation in the KRS-MMF arms.*

11.1.12 Lipid Related Adverse Events

Lipid abnormalities: We have included all types of lipid abnormalities that were reported as AE i.e. hyperlipidemia NOS, Lipids Increased NOS hypercholesterolemia, Blood cholesterol increased, hypertriglyceridemia, Blood Triglycerides Increased, and Low Density Lipoprotein Increased.

There was inconsistency in the preferred terms used for coding, and more than one term may describe a same condition. These terms were mutually exclusive, and each patient was included under one term only.

“Hyperlipidemia Total” includes all the preferred terms denoting an abnormal increment in serum lipids as described in table 6.

Table 6. Incidence Rate of Hyperlipidemia Related AE by Preferred Term (Safety Population - 12Month Analysis Studies B251, B201 and A2306)

<i>Preferred Term</i>	RAD 3		RAD 1.5		MMF		Total Pooled data	
	A2306 (N=125)	A2306 (N=112)	B251 (N=196)	B201 (N=196)	MMF B251/B201 (N=392)	A2306 N=237		
<i>Hyperlipidemia or Hyperlipaemia</i>	35 (28%)	31 (28%)	41 (21%)	24 (12%)	16.5%	28%		
<i>Hypertriglyceridaemia</i>	7 (5.6%)	4 (3.6%)	12 (6%)	13 (7%)	6%	5%		
<i>Hypercholesterolaemia</i> <i>Hypercholesterolemia</i>	29 (23.2%)	14 (12.5%)	48 (24.5%)	35 (18%)	21%	18%		
<i>Lipid Metabolism Disorder NOS</i>	0	1 (1%)	0	2 (1%)	0.5%	0.4%		
<i>Dyslipidaemia</i> <i>Dyslipidemia</i>	11 (9%)	14 (12.5%)	-	-	-	10.5%		
<i>Hyperlipidemia Total</i>⁵⁹	82 (66%)	64 (57%)	101 (51.5%)	74 (38%)	(45%)	(62%)		

Data source: Post-text Table 10.1-1a (Page 1 of 82), Post-text Table 10.1-1a (Page 1 of 58), and Post-text Table 10.1-1 (Page 1 of 30), studies B251, B201, and A2306 respectively.

Table 7. Incidence Rate of New onset Dyslipidemias and Lipid Blood Levels (Safety Population - 12Month Analysis Studies B251, B201 and A2306)

<i>Incidence Rate</i>	RAD 3		RAD 1.5		MMF		Total Pooled data	
	A2306 (N=125)	A2306 (N=112)	B251 (N=196)	B201 (N=196)	MMF B251/B201 (N=392)	A2306 N=237		
<i>No. pts / No. pts at risk</i>								
<i>New onset of Hypercholesterolemia /hyperlipemia</i>	92/125 (74%)	77/112 (69%)	109/153 (71%)	115/159 (72%)	72%	71%		
<i>Cholesterol level \geq 6.2 mmol/L⁶⁰</i>	107/125 (86%)	94/112 (84%)	130/193 (67%)	140/195 (72%)	69.5%	85%		
<i>Cholesterol level \geq 9.1 mmol/L</i>	33/125 (26%)	25/112 (22%)	12/193 (6%)	13/195 (7%)	6%	24%		
<i>New onset of Hypertriglyceridemia/ Hyperlipemia</i>	77/125 (62%)	61/112 (54.5%)	81/159 (51%)	64/169 (38%)	44%	58%		
<i>Triglyceride level \geq 4.5 mmol/L⁶¹</i>	60/125 (48%)	38/112 (34%)	45/193 (23%)	32/195 (16%)	20%	41%		

⁵⁹ It includes: Hyperlipidaemia nos, Hypercholesterolemia, Blood Cholesterol Increased, Hypertriglyceridemia, Blood Triglycerides Increased.

⁶⁰ The reference of 6.2 mmol/L represents the lower limit for the high cholesterol range according to the NCEP.

⁶¹ The reference of 4.5 mmol/L represents the lower limit for the high triglycerides range according to the NCEP.

NDA: 21-560, and 21-268

Triglyceride level \geq 5.6 mmol/L	43/125 (34%)	17/112 (15%)	23/193 (12%)	19/195 (10%)	11%	25%
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Data source: Post-text Table 10.6-3. Rise in Triglyceride Levels and Related Events (Safety Population - 12 Month Analysis) Studies A2306, A2307, B201 and B251.

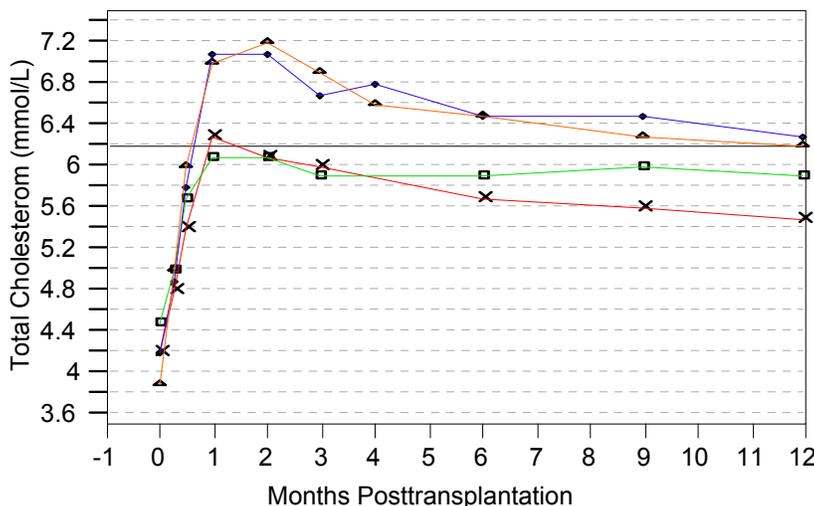
Reviewer's comment:

Hyperlipidemia related AE's, and New onset of Hypertriglyceridemia presented higher incidence rates in study A2306 compared to the KRS-MMF arms. An important RAD dose related effect was observed in the parameters mentioned above, and higher incidence rates were observed in the RAD3 compared to RAD 1.5 (See tables 6 and 7).

11.1.13 Mean Cholesterol and Triglycerides values:⁶²

The figures below show the mean cholesterol and triglyceride values over time. The use of lipid lowering agents was left to the discretion of the investigator in both KRS In study A2306, HMG CoA reductase medication was used per protocol even in patient with normal lipid at enrollment. Ninety percent of the patients in each treatment group were on HMGCoA reductase.

Fig. 1 Mean Total Cholesterol (mmol/L) KRS-MMF arms and study A2306 (Safety Population – 12-Month Analysis)

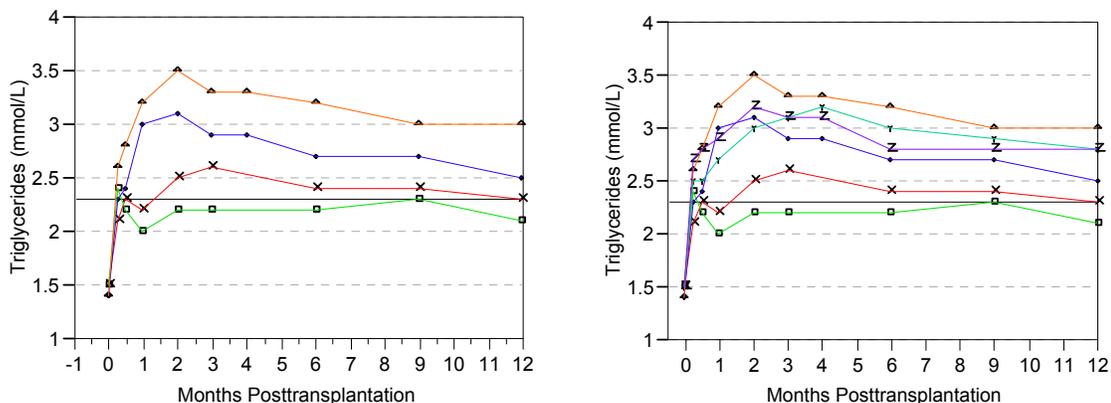


The reference line at 6.2 mmol/L represents the lower limit for the high cholesterol level according to the NCEP. The reference line at 5.1 mmol/L represents the upper limit for the desirable cholesterol level according to the NCEP. Data source: Post-text Table 10.3-1a. Summary Statistics of Change from Baseline by Visit Lipids : Total Cholesterol [mmol/L](Safety Population - 12 Month Analysis) studies B201, B251, and A2306

⁶² NCEP high triglycerides : 4.5 -11.2 mmol/L ,NCEP high total cholesterol : \geq 6.2 mmol/L

Y X— B251 MMF □— B201 MMF
 ◆— A2606 RAD 1.5 ▲— A3206 RAD 3

Fig. 2. Mean Triglycerides (mmol/L) values (Safety Population – 12-Month Analysis) KRS-MMF arms, studies A2306 and A2307 (Right side graph)



The reference line at 2.3 mmol/L represents the lower limit for the normal triglyceride value according to the NCEP. The 200-449 mg/dL or 2.3 to 5.63 mmol/L range indicates high triglyceride values⁶³
 Data source: Post-text Table 10.3-1a. Summary Statistics of Change from Baseline by Visit Lipids :Triglycerides [mmol/L] (Safety Population - 12 Month Analysis) studies B201, B251, A2306 and A2307

Y X— B251 MMF □— B201 MMF
 ◆— A2606 RAD 1.5 ▲— A3206 RAD 3
 Y— A3207 RAD 1.5 Z— A3207 RAD 3

Reviewer's comment:

The mean cholesterol and triglycerides level in both RAD arms, in study A2306 were higher compared to the MMF arms of both KRS.

A dose related effect was observed between the RAD1.5 and RAD 3 arms in study A2306 with respect to hyperlipidemia related AEs, percentage of patients with high cholesterol and triglycerides (NCEP), new onset hypertriglyceridemia, and mean triglyceride levels over time.

Mean cholesterol values over time were similar in both RAD arms in study A2306. However, a dose related effect was reflected in the higher incidence rates of new onset hypercholesterolemia, and hypercholesterolemia related adverse events in the RAD 3 arm versus the RAD1.5 arm. (See tables 6 and 7)

⁶³ NCEP-ATPIII National Cholesterol Education Program - Adult Treatment Panel III

NDAs: 21-560, and 21-268

In both KRS-MMF arms and A2306 RAD arms, mean total cholesterol values were above the desirable range⁶⁴ (<200 mmg/dL, <5.1 mmol/L) in all arms. However, the both RAD arms in study A2306 presented higher mean cholesterol levels at all measurement points (≥ 6.2 mmol/L, High cholesterol lower limit) compared to KRS- MMF arms (See fig. 1)

Despite intensive therapeutic intervention to treat related dyslipidemias, the A2306/07 RAD arms mean cholesterol and triglyceride values persisted at higher level all measurement points when compared to the KRS-MMF arms. Low-density lipoproteins mean values followed the same pattern as cholesterol and triglycerides.

Hyperlipidaemia is a well known risk factor for cardiovascular disease and chronic allograft nephropathy. Intensive therapy for hyperlipidemia in the RAD arms study A2306/07, did not succeed in decreasing cholesterol and triglycerides levels below of what is considered high levels. This fact raises the concern on the long term consequences of higher lipid levels and higher incidence of new onset hyperlipidemia in the RAD regimen used in study A2306 compared to the approved regimen used in the MMF arms from both KRS.

11.1.14 Infections

Table 7. Incidence Rate of Infections by Type of Organism (Safety Population - 12Month Analysis Studies B251 B201 and A2306)

The rates describe the percentage of the enrolled patients that presented infections.

Preferred Term	RAD 3	RAD 1.5	MMF	
	A2306 (N=125)	A2306 (N=112)	B251 (N=196)	B201 (N=196)
<i>Any Infection</i>	81 (65%)	76 (68%)	125 (64%)	132 (67%)
<i>Bacterial</i>	38 (30%)	42 (37.5%)	52 (26.5%)	66 (34%)
<i>Fungal</i>	9 (7%)	5 (4.5%)	7 (4%)	13 (7%)
<i>Viral</i>	6 (4.8%)	2 (1.8%)	21 (11%)	53 (27%)
<i>Unknown</i>	57 (45.6%)	51 (45.5%)	101(51.5%)	79 (40%)

Post-text Tables 10.1-7a and Post-text Table 10.1-7 Summary Statistics for the Number of Infections by Type of Organism (Safety Population - 36 Month Analysis) studies B-201, B251 and A2306.

Reviewer's comments:

- Viral infections were significantly lower in study A2306 compared to the MMF arms of the KRS (3% versus 19%, respectively). Even though these results are intriguing, we cannot make any reliable conclusion, since these studies were not designed to demonstrate differences in viral infections. The fact that CMV mismatches (D+ /R-) were higher in the KRS-MMF arms (18%) compared to study A2306 (11%), makes this interpretation more complex.***
- Bacterial, fungal and the total of infections regardless etiologic agent were similar in both study A2306 and KRS-MMF arms from.***

⁶⁴ NCEP-ATPIII National Cholesterol Education Program - Adult Treatment Panel III

11.1.14.1 Pneumonia:

The incidence rate of Pneumonia rate of pneumonia was similar across arms in both KRS-MMF arms and A2306 arms (approximately 5% in each arm). However, upper respiratory infections in general, were the double in the KRS-MMF arms (22%) compared to study A2306 (9%).

11.1.14.2 Urinary Tract Infections:

Urinary tract infection (UTI) NOS. was the most common AE in A2306 (30% and 31% in the RAD 1.5 and the RAD 3, respectively)

UTI rates were similar across studies 30% in the RAD arms and 26% in the MMF arms.

Reviewer's comments:

In our primary review of the KRS and KHS, we observed a higher incidence of bacterial infection and pneumonic processes, regardless of etiology, in the RAD1.5 and RAD 3 arms in each study compared to their control arms.

These increased rates in pneumonias and bacterial infection were no longer observed in studies A2306 using RDN.

11.1.15 Wound Complications:**11.1.15.1 Major Wound Complications:**

The post- text tables and available post-text listings on adverse events and NSAE were reviewed looking for preferred term or reported term that included the terms: Wound dehiscence, evisceration, breakdown or eventration. Cases of recurrent wound dehiscence were counted only one time. Lymphocele was reviewed separately.

Table 8. Incidence Rate of wound complications by Preferred Term (Safety Population - 12 Month Analysis Studies B251, B201 and A2306)

<i>Preferred Term</i>	RAD 3	RAD 1.5	MMF		Total Pooled data	
	A2306 (N=125)	A2306 (N=112)	B251 (N=196)	B201 (N=196)	MMF B251/B201 (N=392)	A2306 N=237
<i>Lymphocele⁶⁵</i>	11 (9%)	18 (16%)	22(11%)	16 (8%)	10%	12%
<i>Lymphocele Suspected to be drug related</i>	7 (6%)	8(7%)	0	4(2%)	4/38	15/29
<i>DAE Lymphocele</i>	1 (1%)	1 (1%)	0	0	0	2/237
<i>Urinary tract fistulas Ureteric Fistula, Renal pelvis fistula.Vesical fistula</i>	1 (1%)	4 (3.57)	0	2 (1%)	2/392 (0.5%)	5/237 (2%)
<i>Wound Dehiscence, breakdown, evisceration and eventration</i>	7	5	1	0	1 (0.2%)	12 (5%)

1. The dictionary used is the 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

3. Data obtained from: Incidence Rate of Adverse Events/Infections by Body System and Preferred Term (Safety Population - 36-Month Analysis). Post-text Table 10.1-1a (Page 2 of 82) and Post-text Table 10.1-1a (Page 1 of 58) Studies B251 and B201, respectively.

⁶⁵ One case of Renal lymphocele in the RAD 1.5 and one case of Lymphorrhoea in the RAD 3 arm are included.

Reviewer's comments:

Wound dehiscence complications were more frequently observed in study A2306 compared to KRS-MMF arms (5% versus 0.2%, respectively)

Lymphocele was reported as AE in 12%(29/237) and 10% (38/392) in study A2306 and B251/B201-MMF arms. . We should take into consideration that 50% of the lymphocele cases(15/29) in study A2306, were considered to be related to Certican® by the investigator, while only 10%(4/38) were drug related in the MMF arms. In the study A2306 two patients were discontinued from study medication due to severe or recurrent lymphocele (one in each RAD arms). No patients were discontinued due lymphocele in the MMF arms of the KRS.

Urinary tract fistulas were postoperative complications present in 2% (5/237) and 0.5% (2/392) in study A2306 and MMF arms respectively.

In general, wound dehiscence, lymphocele and urinary tract fistulas have been related to the antiproliferative effects of mTOR inhibitors and concomitant use of corticosteroids. These complications are clinically relevant because they require extended hospitalization and /or surgery. However, due to the small differences and the fundamental limitations of cross study comparison, we cannot draw any valid conclusion. However, the fact that the investigator considered in most instances to be Certican® related, it warrant a close follow-up for this kind of drug related complications.

11.1.16 Diabetes Mellitus:

Table 20-18 Incidence rates of Diabetes Mellitus at base line and New onset Diabetes Mellitus (Studies B201 and B251 - 12 month Analyses)

	RAD 3		RAD 1.5		MMF		Total
	A2306 (N=125)	A2306 (N=112)	B251 (N=196)	B201 (N=196)	MMF B251/B201 (N=392)	A2306 N=237	
DM at baseline (ITT Population)	9 (7%)	10 (9%)	48 (24)%	12 (6%)	15%	8%	
New Onset DM⁶⁶ (Safety Population)	9/116 (8%)	4/102 (4%)	7/148 (5%)	2/184 (1%)	9/332 (3%)	13/218 (6%)	
Diabetes Mellitus NOS	15 (12%)	5 (4.5%)	7 (4%)	12 (6%)	4.8	8.4%	
Hyperglycaemia NOS	15 (12%)	7 (6%)	32 (16%)	6 (3%)	9.6%	9.2%	

Data source: Post-text Tables 7.4-12 and 7.4-12, studies B201 and B251, Pre-Study Diabetes (ITT Population - 12 Month Analysis) and Post-text Table 10.2-4 (Page 1 of 1) Incidence of Post-transplant Diabetes Mellitus (PTDM) in first 12 Months (Safety Population - 12 Month Analysis) S-b251 , S-B201 and A2306.

1. Diabetes mellitus (DM) at baseline is based on past medical history database.

⁶⁶ Mayer's definition of PTDM : (1) had no history of insulin or non-insulin dependent diabetes before transplantation, and (2) required insulin after transplantation for 30 or more consecutive days, with fewer than 5 days interruption, to maintain a normal, fasting blood glucose level

Reviewer's comments:

The rates of DM at baseline presented important differences across MMF arms. Study B251-MMF arms was four times higher than B201-MMF arm. Pooled data in the KRS-MMF arms showed twice the rates observed in study A2306.

11.1.17 Gastrointestinal Disorders:

GI disorders reported as AE were more commonly observed in the MMF arms (72%) versus RAD arms study A2306 (62%). Epigastric pain was the most important contributor for this difference 19% versus 9% in KRS-MMF arms versus RAD arms in study A2306, respectively.

11.1.18 Malignancies:

Reviewer's comment: *The incidence of malignancies was equally distributed across arms (2% in each arm) no PTLD were reported during one year follow up.*

11.1.19 Deaths:

Table 9. Primary Reason for Death Reported in ≥ 2 patients in any group (Safety Population - 36 Month Analysis Studies B251 and B201)

Cause of Death	RAD 3	RAD 1.5	MMF	
	A2306 (N=125)	A2306 (N=112)	B251 (N=196)	B201 (N=196)
Any Death	6 (4.8)	1 (0.9)	4 (2.0%)	5(2.6%)
Cardiac Disorders	2	1	2	1
Infections	3	0	1	2

Data obtained from: Post-text Table 10.2-1a (Page 1 of 3) Incidence Rates of Death (Primary Cause) by Body System and Preferred Term (Safety Population - 36-Month Analysis)

Reviewer's comment: *Cardiovascular disease and infections were the leading causes of death.*

11.1.20 Other Safety Evaluations

Other Safety evaluation including vital signs, laboratory evaluations, (hematology, urinalysis, biochemistry, endocrinology and ECG) were performed. We did not detect any new safety signal different from those described in our primary review.

Mean blood systolic and diastolic values were within acceptable range across arms in both studies A2306 and A2307.

11.2 Safety Conclusions**11.3 (Please see Executive Summary)**

1 Page(s) has been withheld in full immediately following this page as B4 (CCI/TS)

13 ADDITIONAL CLINICAL ISSUES

13.1 Dosing Regimen and Administration

We were not able to identify an appropriate TDM RAD plus reduced dose neoral regimen for the heart or kidney indication that will allow maintaining efficacy while minimizing toxicity in both early and maintenance periods after transplantation.

Please see section 3.1 Product Information and proposed regimens

13.2 Special Populations

13.2.1 Pediatrics:

A Pediatric Written Request (PWR) was issued on April 25, 2000 for Certican® (everolimus) Tablets to Novartis Pharmaceuticals Corporation to obtain pediatric information on Certican® (everolimus) for the prophylaxis of acute rejection in allogeneic kidney and liver transplantation in pediatric patients.

Pediatric studies and Pediatric Exclusivity application were reviewed in the original NDA please refer to the Medical Officer Review of the initial submission for Certica®

13.2.2 Black Population:

Black population was under represented in studies A2306 and A2307 and very limited information is available on this subpopulation. Key renal and heart studies using RAD fixed-dose showed a significantly higher incidence of biopsy-proven acute rejection episodes in blacks compared with non-blacks. This observation was also observed in study A2306.

13.2.3 Pregnancy:

Pregnancy data is limited and no data on this subject was presented in this application

13.3 Advisory Committee Meeting

There are no plans for an ACM for this review cycle.

14 OVERALL ASSESSMENT

- *Fixed doses of RAD plus FDN and CS should not be considered an acceptable regimen for immunosuppression after heart or renal transplantation.*
- *Studies A2306 and A2307 investigated TDM-based RAD (1.5 mg and 3 mg initial doses) plus lower doses of CsA, monitored by C2h. These trials did not include an approved control group; therefore, the interpretation of the findings relied on comparison with historical data from trials B201, B251 and B156.*

NDAs: 21-560, and 21-268

- ***Overall, A2306 regimen provides anti-rejection efficacy and graft function comparable with what is achieved with MMF and conventionally dosed CsA (historical data). MMF was an adequate control group with a 10% non-inferiority margin in the KRS; however, using a historical control, non-inferiority is not acceptable, or at least you would expect a significant difference in favor of the treatment group. Given the limitations of using historical controls and the high potential for spurious conclusions, these evaluations should be observed potential hypothesis that will require prospective testing.***
- ***Studies A2307 and B156 explored the use of induction therapy with basiliximab concurrently with RAD, Neoral and CS. The limited data available confirms efficacy of basiliximab in this regimens, but it will require a prospective testing of this regimen to draw a valid conclusion.***
- ***The overall safety profile of TDM RAD plus RDN in renal transplantation is characterized by moderate hematological toxicity, hyperlipidemia, and undesirable effects related to the pronounced antiproliferative properties (delayed wound healing, lymphocele). RAD also enhances CsA nephrotoxicity and, other aspects of CsA toxicity (i.e. risk for TMA)***
- ***No data on renal function is available from study A2306 beyond one year; therefore, we can not corroborate an improvement in renal function beyond one year as observed in the MMF arms in both KRS. The higher proportion of BPCAN in this study 12 months compared to the KRS-MMF arms may preclude a further GFR improvement in study A2306.***

14.1 Recommendation on Regulatory Action

We have completed the review of the re-submission for Certican® (RAD) for the prophylaxis of organ rejection in de novo allogeneic kidney and heart transplantation.

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 profile was observed with the original RAD fixed dose regimen and Full Dose Neoral (FDN) explored in the Key Renal studies (B201 and B251) and Key Heart Study (B253).

Studies A2306 and A2307 explored TDM Certican® (trough concentration ≥ 3 ng/mL) with Reduced Dose Neoral (RDN); however, these studies were open label and did not included an approved control regimen.

To support the proposed regimen of reduced dose Neoral with concentration-guided Certican ® in this resubmission, the sponsor relied completely on efficacy and safety analysis from studies A2306 and A2307 based on cross study comparisons using historical controls.

These studies evaluated only kidney transplant patients and they cannot on their own be used to support a modified (TDM) regimen with low dose cyclosporine in heart transplantation. Furthermore, the sponsor did not presented new data in this re-submission for either the heart or the kidney indication.

NDA: 21-560, and 21-268

The analyses presented by the sponsor were not convincing due to fundamental deficiencies in these cross study comparisons. Furthermore, important differences in the donor / recipient baseline characteristics do not allowed to use pooled data from KRS without introducing significant potential for bias.

These analyses were able to generate hypothesis that will require to be tested prospectively in randomized well control studies. We believe that TDM Everolimus plus CsA minimization strategy is a promising approach that appears to optimize efficacy and minimize the degree of renal function impairment.

In conclusion, the information provided in this and previous submission 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 regimens for the prevention of allograft rejection in heart and kidney proved to be effective with respect to the primary endpoints⁶⁹.

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 were not able to identify an appropriate TDM RAD plus reduced dose neoral regimen for the heart or kidney indication that will allow maintaining efficacy while minimizing toxicity in both early and maintenance periods after transplantation.

We recommend a second approvable letter for this resubmission.

14.2 Comments and Recommendations to Applicant

The provided information suggests that Certican® has the potential to improve the care of renal transplant patients. It appears that CsA minimization strategy should be implemented at early stage post-transplantation to avoid irreversible damage due to CsA nephrotoxicity.

We were unable to identify a CsA minimization /sparing strategy that would minimize toxicity without compromising efficacy in both heart and kidney transplant patients.

The presented cross study comparison analyses and the exposure-efficacy and exposure-safety analysis provided data to delineate a potentially successful regimen. We recommend that this regimen be tested in a prospective well controlled trial in both de novo kidney and heart transplant recipients.

The concentration-controlled regimen 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, produces the desired improvement in renal function.

⁶⁹ **Heart 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.

Kidney Primary endpoint: Composite of Biopsy-proven acute rejection, graft loss, death or loss to follow-up

We recommend that these studies define prospectively target concentration ranges over time for both Certican and CsA and demonstrate 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 this indications, 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 studies A2306/07, additional safety data (duration and number of subjects) might be needed to support approval of the regimen.

In order to design a successful study:

- Randomize at the time the patient are able to take the first medication dose.
- Adequate sample size that would be able to test the hypothesis even though the expected efficacy failure rates were not similar to the expected.
- To be able to reproduce the planed target concentrations (75% of patients with in the target rage) according to a predefine dose adjustment algorithm.
- To have an approved regimen as an active control e.i. CsA+MMF+Prednisone. It would be desirable that the CsA dose adjustments were based in through concentrations, since this was the approach that led to the approval of the control regimen and other related factors discussed in this review (See Discussion of Neoral regimens in study A2306)

15 APPENDIX I - REVIEW OF INDIVIDUAL STUDY REPORTS

15.1 Renal Studies CRAD001 A2306 and CRAD001 A2307

15.1.1 Background:

On March 25, 2002 (last Pre-NDA meeting prior to the original submission on December 19, 2002) the applicant informed to the agency regarding on going studies A2306 and A2307.

Renal studies A2306 and A2307 were open-label, randomized studies, which lacked of an adequate control arm.

In the initial Submission on Dec 19, 2002, the applicant presented a preliminary report on studies A2306 and A2307 (6-month analysis with approximately half of the patients' data was submitted for each study). On September 19, 2003, the **first interpretable results**, on these studies, of the 12 month data, were received.

On November 25, 2003 teleconference, Novartis Pharmaceutical announced the re-submission of NDAs 21-560 & 21-628 [Certican® (everolimus) Tablets] by the end of 2003. In this re-submission, Novartis would provide new analyses using the key renal studies (**B201 and B251**) and renal supportive study **B156** as historical controls for studies A2306 and A2307, respectively.

With this regard, the agency stated that *"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"*

to support the safe and effective dose of Certican® in renal and heart transplantation.

On February 27, 2004, the 12-months results on studies A2306 and A2307 were submitted including new analysis which used the key renal studies (**B201 and B251**) and renal supportive study **B156** as historical controls for studies A2306 and A2307, respectively.

Efficacy and safety analysis on these cross study comparisons are presented to support the proposed regimen of reduced dose Neoral with concentration-guided Certican®.

15.1.2 Study Titles:

A2306

A 1 year multicenter, randomized, open label, parallel group study of the safety, tolerability and efficacy of two doses (1.5 and 3 mg/day) of Certican® (RAD001) with steroids and optimized administration of Neoral® in de novo renal transplant recipients (12-month analysis). First patient enrolled: 22-Nov-2001 Last patient completed: 19-Aug-2003

A2307

A 1 year multicenter, randomized, open label, parallel group study of the safety, tolerability and efficacy of two doses (1.5 and 3 mg/day) of Certican® (RAD001) with Simulect®, corticosteroids and optimized administration of Neoral® in de novo renal transplant recipients (12 month analysis). First patient enrolled: 14-Nov-01 Last patient completed: 19-Aug-03

15.1.3 Study design:

Open label 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).

Studies A2306 and A2307 were designed as "**A 1 year multicenter, randomized, open label, parallel group study of the safety, tolerability and efficacy of two doses (1.5 and 3 mg/day) of Certican™ (RAD001) with steroids and optimized administration of Neoral in de novo renal transplant recipients**, with the variant that study A2307 additionally used Simulect® as induction therapy. Furthermore, CsA exposure over time was different in these studies (See target C₂ blood levels, table 1 and Fig. 1).

15.1.4 Primary Objectives:

The primary objective was similar in both studies A2306 and A2307:

"To compare renal function, as measured by serum creatinine, of 2 doses of RAD (1.5 and 3 mg/day), and to assess whether acceptable renal function (improved creatinine vs. historical data⁷⁰) can be achieved at 6 months post transplantation in de novo renal transplant recipients who received RAD, corticosteroids, and optimized administration of Neoral (Plus induction therapy with Simulect® only in study A2307)".

15.1.5 Main Secondary Objectives:

The main secondary objectives were also similar in both studies:

- Incidence of efficacy failure (biopsy-proven acute rejection, graft loss, death, or loss to follow-up) at 6 and 12 months. Also, clinically-confirmed chronic rejection, and biopsy-proven chronic allograft nephropathy at 6 and 12 months.
- To assess renal function, as measured by serum creatinine, calculated creatinine clearance (Cockcroft-Gault) and calculated glomerular filtration rate (GFR) (Nankivell), at 6 and 12 months post-transplantation.
- To assess the incidence of antibody-treated acute rejection, clinically-confirmed acute rejection, clinically-confirmed chronic rejection, and biopsy-proven chronic allograft nephropathy at 6 and 12 months in both groups.

⁷⁰ Historical controls: Studies B251 and B201 for Study A2306 and B156 for Study A2307

15.1.6 Main inclusion criteria:

- Male or female patients, 18(16 in the US) to 68 years of age, who were *de novo* cadaveric, living unrelated or HLA-mismatched LRD renal transplant recipients. Females were required a negative pregnancy test at baseline and the practice of an approved method of birth control.
- Donor age between 10 to 65 years and CIT < 36(A2307) and < 40 hours(A2306)

15.1.7 Relevant exclusion criteria:

- Previous organ transplantation, A-B-O incompatibility, and T cell positive crossmatch.
- NHBD organs or donor-specific transfusion.
- Cardiac disease (Old NYHAC \geq grade 3), Liver injury with abnormal LFT's
- Chronic active hepatitis C, or who were HIV or hepatitis B surface antigen (HBsAg) positive.
- Presence of severe systemic infections or past or present malignancy (Other than excised basal or squamous cell skin carcinoma).
- Severe uncontrolled hypercholesterolemia (\geq 350 mg/dL, 9.1 mmol/L) or hypertriglyceridemia (\geq 500 mg/dL, 5.6 mmol/L), white blood cell (WBC) count, \geq 4500/mm³, Absolute neutrophil count (ANC) \leq 2000/mm³ or platelet count \leq 100,000/mm³.
- Pregnant or breast-feeding patients.

Table 7.1.1 summarizes the study design, enrolment, and C2 target CsA concentrations over time – Studies A2306 and A2307.

Table 7.1.1.

Study no.	Design	Duration	Target C2 BL (ng/mL)	No. of patients	Historical control
A2306 32 Centers ⁷¹	R, OL, MC, MD, S, T and E, <i>de novo</i>	1 year	Weeks 0 – 4 (1000 – 1400 Weeks 5 – 8 (700 – 900) Weeks 9 – 12 (550 – 650) Months 4 – 12 (350 – 450) ⁷²	Total – 237⁷³ RAD 1.5 mg – 112 RAD 3 mg – 125	B201 B251
A2307 37 Centers ⁷⁴	R, OL, MC, MD, S, T and E., <i>de novo</i>	1 year	Weeks 0 – 8 (500 – 700) Months 3 – 12 (350 – 450) Induction with Simulect®	Total -256⁷⁵ RAD 1.5 mg – 117 RAD 3 mg – 139	B156 (RAD 3 FDN vs. RDN)

MC = multicenter, R = randomized, OL = open label MD= multi dose HC = Historical control, S = safety, and T = tolerability, E = efficacy. From NDA Amendment/Final Safety Update, page 21 , table 1.1-2

⁷¹ US (11), Italy (6), Brazil (4), Canada and Spain (3 each), Poland and Venezuela (2 each), and Belgium (1).

⁷² C2 was reduced to about half to one-third of typical CsA exposure by week 13.

⁷³ A total of 222 non-Black patients were randomized (112 and 110 in the RAD 1.5 and 3 mg groups, respectively). All 15 Black patients enrolled in the study were assigned to the RAD 3 mg group.

⁷⁴ Italy (8), US (7), Australia and France (5 each), Argentina, Germany, and Czech Republic (3 each), and Columbia, Norway, and Switzerland (1 each)

⁷⁵ A total of 243 non-Black patients were randomized (117 and 126 in the RAD 1.5 and 3 mg groups, respectively). All 13 Black patients were assigned to the RAD 3 mg group.

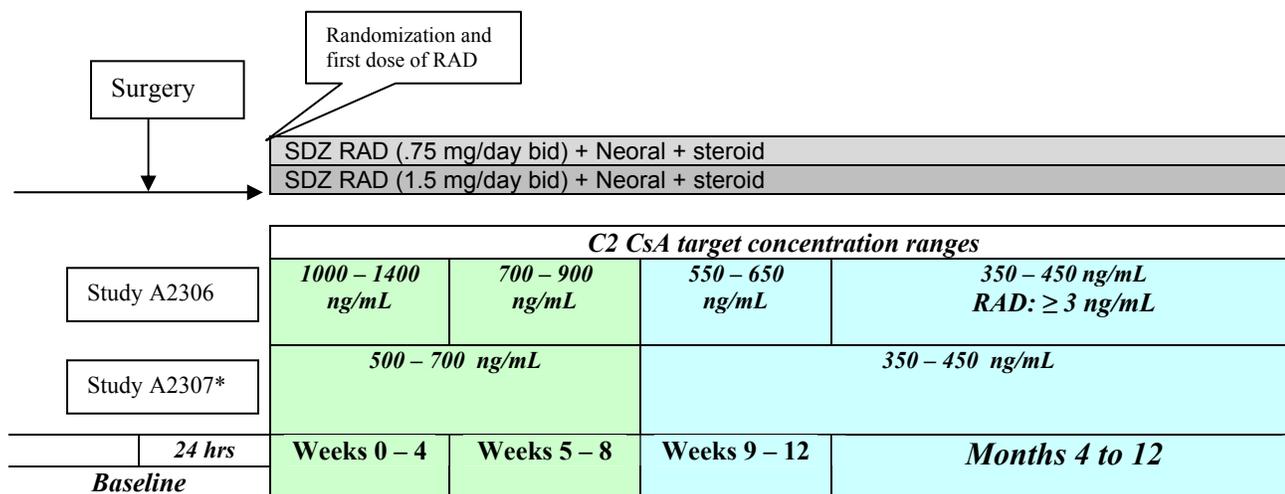
Reviewer’s comments:

Studies A2306 and A2307 were both open label studies with a primary objective to assess renal function of 2 doses of RAD (1.5 and 3 mg/day) in the context of low dose Neoral® and corticosteroids.

The main differences between studies A2306 and A2307 were the use of induction therapy, different CsA taper schemes and lower target C2 blood concentrations early post transplantation in study A2307 (See table 1). These differences make difficult to determine the contribution of study A2307 in terms of safety and efficacy to the proposed regimen that reflects the low dose RAD approach in study A2306.

The USA black transplant population was significantly under represented in both studies. All black transplant recipients were assigned to the RAD 3mg/day arms without randomization. (15 black patients in study A2306 and 13 black patients in study A2307).

Figure 7.1.1. Study designs: A2306 and A2307



Black patients were not randomized and assigned to the RAD 3 mg arms in both studies.

* Induction with Simulect®

All patients were to be evaluated at Days 1, 7, 14 and 28 and at Months 2, 3, 4, 6, 9 and 12.

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this page is the manifestation of the electronic signature.**

/s/

Arturo Hernandez
8/27/04 01:21:23 PM
MEDICAL OFFICER

Marc Cavaille Coll
8/27/04 02:21:59 PM
MEDICAL OFFICER

Renata Albrecht
8/27/04 04:43:16 PM
MEDICAL OFFICER

**Deputy Office Director's and Division Director's Review (addendum)
NDA 21-560 (kidney), NDA 21-628 (heart)**

**Certican[®] (everolimus) for Immunosuppression to Prevent Organ Rejection
in Patients Undergoing Kidney and Heart Transplantation**

Date: August 27, 2004

From: Renata Albrecht, M.D.
Director, DSPIDP, HFD-590

Edward M. Cox, M.D., M.P.H.,
Deputy Director, ODE IV, HFD-104

Re: Certican[®] tablet (everolimus, RAD001, SDZ RAD)
Novartis Pharmaceuticals Corporation

Original Submission Date: December 19, 2002
First Action Due Date: October 20, 2003
First Action: Approvable
Resubmission Date: February 27, 2004
PDUFA Goal Date: August 27, 2004
Second Action: Approvable

Related INDs and NDAs: IND 52,003 (tablets) NDAs 21-561 and
21-631 (dispersible tablet)

Subject:

Review of Complete Response submitted by applicant in response to the October 20, 2003 approvable letter and Addendum to Division Director's Review dated October 17, 2003 for original NDAs 21-560 and 21-628

Recommended Regulatory Action and Outstanding Issues:

Recommend Approvable letters be issued for both indications -- immunosuppression in prevention of organ rejection in patients undergoing kidney and heart transplantation.

The resubmission contained two clinical trials A2306 and A2307 as well as additional analyses that were reviewed by the clinical, statistical and clinical pharmacology reviewers and determined to be insufficient to address the deficiencies itemized in the October 20, 2003 approvable letter. These data from Studies A2306 and A2307 (these studies do not include an approved active control regimen) and the exposure-response analyses from previous studies did not provide data to support a safe and effective regimen for the use of everolimus and the approaches themselves were not valid: use of cross-study comparison to the previously submitted renal studies, B201 and B251, pooling of control arms, retrospective analysis of exposure response based on non-randomized samples.

The extrapolation of efficacy from renal to heart transplantation was not justified in concept, but would still not have been practical given that a safe and effective

dosing regimen utilizing therapeutic drug monitoring (TDM) for renal transplantation was not established.

Therefore, before the applications can be approved, the applicant must establish a safe and effective regimen for prophylaxis of organ rejection for each indication being pursued. This can be done by providing:

1. An adequate and well-controlled study or studies prospectively evaluating concentration-controlled regimens of everolimus in combination with concentration-controlled cyclosporine in *de novo* renal transplant recipients, which would support therapeutic drug monitoring (TDM) schemes for everolimus and cyclosporine.
2. An adequate and well-controlled study or studies prospectively evaluating concentration-controlled regimens of everolimus in combination with concentration-controlled cyclosporine in *de novo* cardiac transplantation, which would support therapeutic drug monitoring (TDM) schemes for everolimus and cyclosporine.

The two renal and one cardiac transplant studies in the original NDA showed the tested regimens to have greater renal toxicity than the comparators (MMF and azathioprine, respectively). The company indicated that ongoing studies A2306 and A2307 would address this by providing results from an everolimus regimen that utilized TDM. Although the division had previously discussed these studies with the company on several occasions and pointed out that a non-comparative study using an unconventional C2 (cyclosporine levels at 2 hours post dosing) for monitoring and adjusting blood levels instead of C0 (trough levels) would be challenging to review. The studies were not ready at the time of the FDA action on October 20, 2003. The approvable letter asked for an adequate and well controlled study to address the deficiency, but left options open for other approaches if such approaches were convincing. Excerpts from the October 20, 2003 Approvable letter are presented below:

1. Provide information supporting a safe and effective dosing regimen for everolimus and cyclosporine that would minimize renal function impairment while maintaining adequate protection against graft rejection, graft loss or death in *de novo* renal transplantation.
 - One approach would be to provide data from an adequate and well-controlled study or studies prospectively evaluating concentration-controlled regimens of everolimus in combination with concentration-controlled cyclosporine in *de novo* renal transplant recipients, which would support therapeutic dose monitoring (TDM) schemes for everolimus and cyclosporine.
 - An alternate approach would be to provide prospective analyses from completed, controlled studies evaluating lower exposures to cyclosporine in combination with everolimus and dosed according to a prospectively defined therapeutic drug monitoring scheme (TDM).
 - Other approaches that may support the definition of a safe and effective regimen for everolimus in the prevention of graft rejection in *de novo* renal transplantation should be discussed with the Division.

The data and analyses that support a therapeutic concentration range in *de novo* renal transplantation need to identify a clinically efficacious and safe concentration range of everolimus (upper as well as lower limits) when used with the proposed cyclosporine concentration range. A safe and effective TDM regimen for everolimus, used in

combination with cyclosporine, would also require a validated assay for everolimus blood levels, and need to be supported by experience with a successful monitoring schedule and dose adjustment scheme, proven capable of maintaining patients within the proposed therapeutic concentration range.

[REDACTED] (b) (4)

[REDACTED]

- [REDACTED] (b) (4)

[REDACTED]

3. Have adequately addressed by Sandoz [formerly Biochimie and the holder of Drug Master File (DMF) 15720] the deficiencies that were communicated to Sandoz's U.S. Agent, Geneva Pharmaceuticals, Inc. DMF 15720 describes the manufacture of sirolimus by fermentation at Kundl, Austria.

You are encouraged to communicate with the Division regarding the option(s) you plan to select before resubmitting your applications. The ultimate suitability of the proposed approaches can only be determined after review of the relevant data.

A teleconference to review the action letter took place on November 25, 2003, and the resubmission arrived on February 27, 2004. There were other teleconferences regarding pharmacokinetic issues, including full characterization and drug-drug interactions. Work on these issues was initiated and is ongoing; these issues can be addressed in labeling and do not at present constitute approvability issues.

The division held a teleconference on April 1, 2004 to discuss preliminary findings in the application as well as problems with both organization (reviewers were having trouble locating information) and transparency of data (information was not clearly presented – for example favorable regulatory actions were highlighted with a header, unfavorable ones were not). At the time, Novartis was told that the review staff did not find convincing new evidence that would support approval of the application.

Prevention of Graft Rejection in Renal Transplant Patients

(b) (4)

In the current resubmission the applicant provides data from two additional open-label studies in patients with *de novo* renal transplantation. The applicant's analyses intended to support the safety and efficacy of everolimus as part of a regimen that includes cyclosporine to prevent graft rejection in renal transplant patients were based primarily upon cross-study comparison of the data from studies in renal transplant patients derived from the original NDA submission (Studies B201, B251, and B156) and the data from studies A2306 and A2307. The applicant's comparison of primary interest was a cross-study comparison of the 1.5 mg everolimus reduced cyclosporine group (C2) to the combined group of patients receiving an MMF based regimen from studies B201 and B251 (196 patients from the MMF arm in Studies B201 and an additional 196 patients from the MMF arm in Study B251). The applicant's proposed analysis of secondary interest was a cross-study comparison of the everolimus 3.0 mg, reduced cyclosporine group (C2) from Study A2307 (n=139) to each of the following groups from Study B156 everolimus 3.0 mg, full cyclosporine (n=53) and everolimus 3.0 mg reduced cyclosporine (n=58).

The populations in B201 and B251 were not comparable because of differences in donor and recipient baseline characteristics that could influence outcomes. For example, B251 had a greater percentage of black patients (17%) compared to Study B201 (4%) and the percentage of cadaveric donors in B201 in the MMF arm was 91% compared to 46% in the MMF arm in B251, among other differences. Additional differences are enumerated in the review by Dr. Hernandez. In addition there were also differences between the study populations in B201 and B251 and the population in A2306. These included several differences in the baseline characteristics of the donor and recipient likely to affect treatment outcomes. The potential impact of these differences on the observed outcomes is illustrated by an exploratory analysis performed and presented in detail by Dr. Davi in her Statistician's Review. This exploratory analysis compares differences in outcome measurements at the 12- and 36-month timepoints for the everolimus 3.0 mg arm from B201 to the everolimus 3.0 mg from B251. B251 and B201 were very similarly designed studies. The table shows that for some of the analyses, there are statistically significant differences in outcomes between the everolimus 3.0 mg arms of the two studies. Given the results of these exploratory analyses, it is highly likely that factors other than study drug are determining the observed patient outcomes. Given the overt differences, one cannot exclude the possibility of unrecognized differences as well and for all these reasons, pooling these populations and performing cross-study comparisons is considered unacceptable. As with the cross-study comparison of primary interest, there are also significant questions about the validity of the applicant's cross-study comparison of secondary interest. In addition Study A2307 also used Simulect (basiliximab) induction.

Table: Cross-Study Comparison of the Certican 3.0 mg groups in Studies B201 and B251 in terms of the Primary and Secondary Efficacy Analyses (ITT Group)			
6 Months Post-Transplant			
Endpoint	Certican 3.0mg in B201 (N=198)	Certican 3.0 mg in B251 (N=194)	95% C.I. for Diff. in Prop.
Biopsy-Proven Acute Rejection, Graft Loss, Death, or Loss to Follow-up Composite	52 (26.3%)	46 (23.7%)	(-11.1%, 6.1%)
Graft Loss, Death, or Loss to Follow-up Composite	24 (12.1%)	13 (6.7%)	(-11.5%, 0.4%)
Biopsy-Proven Acute Rejection (single event)	36 (18.2%)	39 (20.1%)	(-5.9%, 9.8%)
Graft loss (single event)	17 (8.6%)	7 (3.6%)	(-10.1, -0.3%)*
Death (single event)	7 (3.5%)	6 (3.1%)	(-4.4%, 3.5%)
12 Months Post-Transplant			
Endpoint	Certican 3.0 mg in B201 (N=198)	Certican 3.0 mg in B251 (N=194)	95% C.I. for Diff. in Prop.
Biopsy-Proven Acute Rejection, Graft Loss, Death, or Loss to Follow-up Composite	60 (30.3%)	51 (26.3%)	(-12.9%, 4.9%)
Graft Loss, Death, or Loss to Follow-up Composite	33 (16.7%)	15 (7.7%)	(-15.6%, -2.5%)*
Biopsy-Proven Acute Rejection (single event)	39 (19.7%)	43 (22.2%)	(-5.6%, 10.6%)
Graft loss (single event)	21 (10.6%)	8 (4.1%)	(-12.0%, -1.4%)*
Death (single event)	8 (4.0%)	7 (3.6%)	(-4.6%, 3.7%)
36 Months Post-Transplant			
Endpoint	Certican 3.0 mg in B201 (N=198)	Certican 3.0 mg in B251 (N=194)	95% C.I. for Diff. in Prop.
Biopsy-Proven Acute Rejection, Graft Loss, Death, or Loss to Follow-up Composite	77 (38.9%)	66 (34.0%)	(-14.3%, 4.7%)
Graft Loss, Death, or Loss to Follow-up Composite	50 (25.3%)	28 (14.4%)	(-18.7%, -3.0%)*
Biopsy-Proven Acute Rejection (single event)	49 (24.7%)	50 (25.8%)	(-7.6%, 9.7%)
Graft loss (single event)	33 (16.7%)	15 (7.7%)	(-15.6%, -2.5%)*
Death (single event)	18 (9.1%)	13 (6.7%)	(-8.0%, 3.1%)

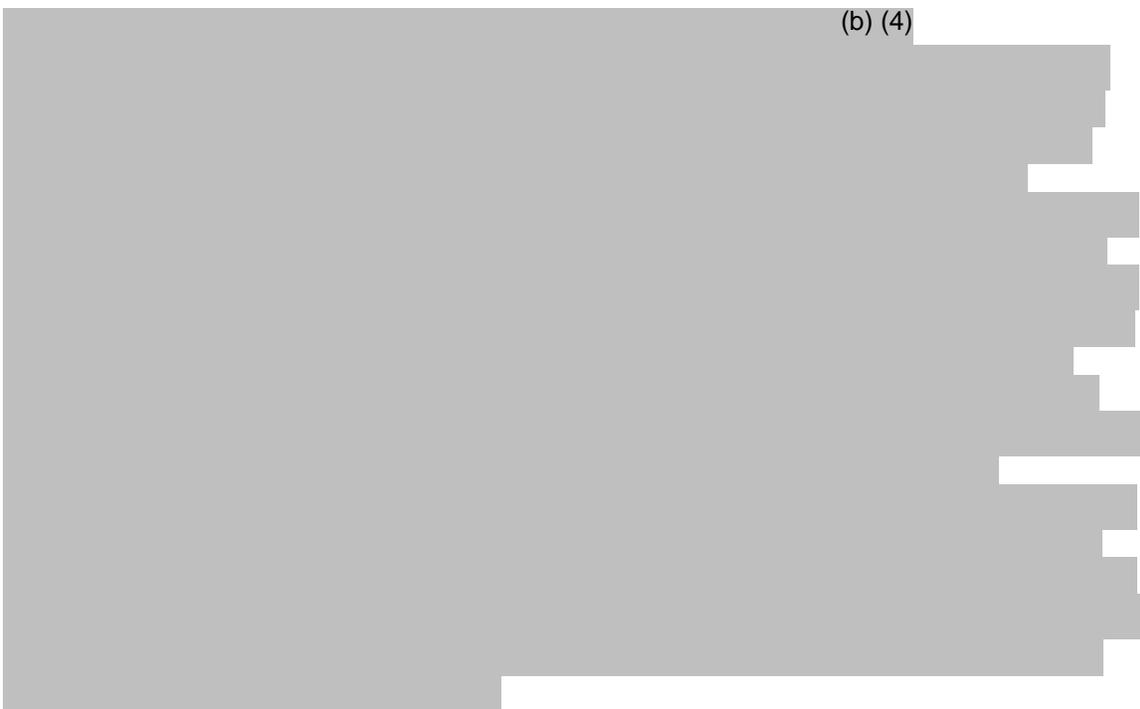
*Yellow shading indicates statistically significantly superior results for Certican 3.0 mg in B251 compared to Certican 3.0 mg in B201.

There were also differences across the studies in the method used to measure cyclosporine blood concentrations. The established method of monitoring whole blood cyclosporine trough concentrations was utilized in B201 and B251 while C2 levels (cyclosporine blood concentration at 2 hours post dose) were utilized in

A2306 and A2307. Also of note is that in Study A2306, cyclosporine dose adjustment did not maintain cyclosporine whole blood concentrations in the protocol specified target ranges in a large proportion of the patients in the study.

The applicant, as well as FDA reviewers, further looked at the data comparing outcomes in A2306 to the pooled B201/B251 control. First of all, the population for A2306, based on demographic characteristics, would be expected to have a better outcome compared to the population in the “pooled” control. A favorable difference in efficacy was not demonstrated. Renal function and safety were also analyzed, but given the populations were not randomized to the two drugs, the similarities and differences between the “arms” cannot be interpreted to show evidence of safety.

(b) (4)



Alternative Approaches

(b) (4)



The evaluation of PK/PD relationships was undertaken by Dr. Ike Lee, Clinical Pharmacology. Although his review provides a great deal of information on the levels, the relationship between the products and the patterns of outcome both for the primary endpoint (efficacy) and safety, he concluded that these data can only be used as hypothesis generating and a prospectively conducted study is needed to evaluate the safety and efficacy of a dosing regimen for everolimus.

The discussion of restricted labeling was confounded by the absence of information on a safe and effective regimen to include in labeling, given that the regimens tested were associated with efficacy mostly on acute rejection as determined histologically, and were not associated with increased graft survival or patient survival. In the studies in renal transplant patients in the original submission, some of the components of the composite endpoint showed favorable outcome, but the findings were not consistent in the two studies). (b) (4)

However, when these demographic and donor elements were stratified based on everolimus compared to control, consistently, the control patients (young, old, living, cadaveric) had better renal function compared to the everolimus patients. Therefore, no practical and acceptable restrictive labeling was written.

Finally, the only regimens tested prospectively were full dose cyclosporine with fixed doses of everolimus, and although dosage adjustments were made in the studies, these did not prevent or resolve the renal toxicity and did not show a clinically-evident benefit such as graft or patient survival that would offset the risk of renal impairment. It is apparent that the applicant recognizes this issue given the applicant's proposal for including dose modification and TDM in labeling (recognizing that the full dose regimens are not safe). However, because of the complex drug interaction between everolimus and cyclosporine, a regimen cannot be based on hypothetical dosage adjustment and prospectively such a regimen has not been studied.

Related Drug Products:

Much of the challenge in the review of this product is analogous to the issues faced during the review of Rapamune (sirolimus), the first product in this class of mTOR (mammalian target of rapamycin) immunosuppressants. Rapamune (sirolimus) was first approved September 15, 1999, following an advisory committee meeting on July 27, 1999. During this meeting, the efficacy as well as the renal toxicity of the product was presented and the committee voted for approval and advised that informative labeling be written. In April 2001, the company submitted results of a "cyclosporine sparing" regimen and again this was discussed before an advisory committee on January 24, 2002 and following additional information, this regimen was approved April 11, 2003. Also in 2003, the sirolimus product labeling was updated to include WARNINGS about its use in liver transplant (due to hepatic artery thrombosis) and lung transplant (anastomotic dehiscence). Information on interstitial lung disease was added:

Interstitial Lung Disease

Cases of interstitial lung disease (including pneumonitis, and infrequently bronchiolitis obliterans organizing pneumonia [BOOP] and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of

Rapamune. The risk may be increased as the trough Rapamune level increases (see **ADVERSE REACTIONS**).

Foreign Regulatory Authorities:

Certican was approved in Sweden in July 2003, and completed the European Mutual Recognition Procedure (MRP) in December 2003, achieving endorsement in the following countries: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Italy, Luxembourg, Netherlands, Norway, Portugal and Spain.

[REDACTED] (b) (4)

Specific details are further summarized in Dr. Cavaille Coll's Team Leader Review.

Advisory Committee meeting

The division has made recommendations of not approving the product with the current studies because the information has not demonstrated a safe and effective regimen. Novartis believes the data are convincing and that there is simply a difference of opinion on the results. Thus, they have requested the option of discussing the application at an FDA Advisory Committee (AC) meeting. The division has left the option open, but has told Novartis that products are typically brought to committee when there is a challenging scientific question to be addressed. In this circumstance, the Division would be in a novel position given the recommendation that the applications should not be approved. Novartis proposed to convene panels of transplant physicians, present their studies and obtain opinions about safety and efficacy. They were sent a series of questions from the Division that could be asked of the panel dealing with regimens for renal transplant, cardiac transplant, C2 monitoring and risk management. The main questions are presented in brief below:

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

(b) (4)

The company has not completed these panel meetings at the time of this action; they are waiting for further advice and comments from their panel meetings. Novartis has also requested the option of meeting with the agency after the action letter for the current review cycle to discuss their plans.

Pediatrics

Regarding the applicant's pediatric drug development, please see the October 17, 2003 Division Director's Review.

(b) (4)

DMF Deficiency noted in the October 20, 2003 Approvable Letter

The deficiency in the DMF noted in the October 20, 2003 approvable letter has been adequately addressed.

Summary

As noted during the initial review of NDAs 21-560 and 21-628, the applicant has shown that everolimus when administered as a fixed dosage regimen as studied is efficacious in preventing rejection, but a sufficiently safe regimen for everolimus when used with cyclosporine has not yet been determined. The additional data provided in the current resubmission and the re-analyses of previously submitted data do not provide adequate information to determine a safe and effective regimen for the use of everolimus in combination with cyclosporine to prevent organ rejection in renal and cardiac transplant patients. The review of the original NDA submission found significant impairment of renal function when everolimus was administered in a fixed dose regimen with

cyclosporine.

Additional clinical data are needed in order to demonstrate safe and effective dosing regimens for everolimus and cyclosporine for the prophylaxis of organ rejection in allogeneic kidney and heart transplant patients. As stated in the Approvable letter for this resubmission, it will be necessary for the applicant to provide the following in order to address the deficiencies in the proposed indications.

1. Provide information supporting a safe and effective dosing regimen for everolimus and cyclosporine that would minimize renal function impairment while maintaining adequate protection against graft rejection, graft loss or death in *de novo* renal transplantation. In order to do this, we believe that it will be necessary for the applicant to provide data from an adequate and well-controlled study or studies prospectively evaluating concentration-controlled regimens of everolimus in combination with concentration-controlled cyclosporine in *de novo* renal transplant recipients, which would support therapeutic drug monitoring (TDM) schemes for everolimus and cyclosporine.

(b)
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(4
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At present, we are unable to identify another approach other than that described in items 1 and 2 above to provide the necessary data to support the safety and efficacy of everolimus. If the applicant proposes an alternative to conducting such a study or studies, we strongly encourage the applicant to discuss the study design with the Division of Special Pathogen and Immunologic Drug Products (DSPIDP) prior to its initiation.

If a non-inferiority study design is chosen, the active control should represent an approved comparator regimen. Target concentration ranges over time for both everolimus and cyclosporine should be prospectively defined, and then demonstrated to be safe and effective in both early stages post transplantation and during the maintenance phase.

A primary analysis at 6 months after the last protocol specified change in target everolimus and cyclosporine concentration ranges (i.e., 6 months into maintenance phase) could support a resubmission of the NDAs for these indications, providing there were a commitment to provide follow-up outcome and

safety data (including renal function, rejection, graft loss, and death) at 12, 24, and 36 months post transplantation.

To demonstrate the safety and efficacy of the proposed everolimus-cyclosporine combination regimens, the applicant will need to adequately determine a starting dose and a target trough concentration (C_{min}) range (upper and lower limits) for both everolimus and cyclosporine for each indication. A safe and effective TDM regimen for everolimus, used in combination with cyclosporine, would also require a validated assay for everolimus blood concentrations and need to be supported by experience with a successful monitoring schedule and dose adjustment scheme proven capable of maintaining patients within the proposed therapeutic concentration range.

If the proposed regimen(s) would require doses and blood concentrations of everolimus that are higher than those observed in studies previously submitted to the NDA, additional safety data of similar duration in an adequate number of subjects would be needed to support approval of the recommended regimen(s). A minimum of 300 transplant patients should have been observed for at least 12 months at the proposed recommended exposure of everolimus with cyclosporine. This might be achieved by simultaneous submission of data from an adequate well-controlled study in *de novo* renal transplantation (b) (4)

The applicant is encouraged to communicate with DSPIDP regarding the option(s) they plan to select before resubmitting NDAs 21-560 and 21-628. The ultimate suitability of the proposed approaches can only be determined after review of the relevant data.

Although not a condition of approval, we strongly recommend that the applicant continue to adequately determine the terminal $t_{1/2}$ of everolimus in the target patient population following the administration of the proposed everolimus-cyclosporine regimen. This everolimus $t_{1/2}$ should be determined at the range of proposed clinical doses and/or concentrations of everolimus and cyclosporine following multiple dose (steady state) administration of the proposed everolimus-cyclosporine combination regimen to transplant patients. We note that *in vivo* drug interaction studies with everolimus are ongoing; we anticipate continued progress and cooperation in identifying significant drug interactions with everolimus.

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/s/

Edward Cox
8/27/04 04:34:23 PM
MEDICAL OFFICER

Renata Albrecht
8/27/04 04:37:10 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Office of Drug Evaluation IV/ Division of Special Pathogen and Immunologic Drug Products

DATE: August 27, 2004

TO: Mark J. Goldberger, M.D, M.P.H.
Director, ODE4, HFD-104

THROUGH: Renata Albrecht, M.D.
Division Director, HFD-590

FROM: Marc W. CavallJ-Coll, M.D., Ph.D.
Medical Officer Medical Team Leader, HFD-590

SUBJECT: NDA 21,560 Certican® (everolimus) Tablet, for prophylaxis or organ rejection in allogeneic kidney transplantation.

NDA 21,628 Certican® (everolimus) Tablet, for prophylaxis or organ rejection in allogeneic heart transplantation.

Please refer to the new drug applications, dated December 19, 2002 and the approvable action letter, dated October 20, 2003, as well as the Medical Officer Team Leader memorandum of the same date, which provides a detailed discussion of the risk and benefit of everolimus based on the original NDAs (see Attachment). The February 27, 2004 submission constituted a complete response to the action letter. The major issues of these NDAs, including the materials submitted above, have been thoroughly discussed in the pre-clinical, statistical and clinical reviews. I concur with the consensus of the reviewers that these NDAs are approvable. This memorandum will describe the relevant deficiencies and comment on a few areas that have been discussed at some length during the review process.

Background:

Everolimus (also known as SDZ RAD) is a member of a new class of immunosuppressants, the mTOR inhibitors, which include Rapamune® (sirolimus), approved for the prevention of graft rejection in allogeneic renal transplantation. The original NDAs 21,560 and 21,628 for the use of Certican® (everolimus) tablet for the prophylaxis of graft rejection in adult allogeneic renal and cardiac transplant recipients, respectively, submitted on December 19, 2002, included two pivotal clinical studies in *de novo* renal transplantation (Studies B201 and B251) and one pivotal clinical study in cardiac transplantation (Study B253). These studies evaluated two fixed doses of everolimus, 1.5 mg and 3 mg per day, in combination with standard, “full dose”, concentration-controlled cyclosporine therapy, and corticosteroids.

In the renal transplantation studies, the active control was an approved regimen of mycophenolate mofetil (CellCept®), cyclosporine and corticosteroids, while a regimen based on azathioprine, cyclosporine and corticosteroids was used as active control in the cardiac transplantation study.

A major concern in the development of everolimus has been the potential for everolimus to increase cyclosporine nephrotoxicity. This concern was expressed by FDA on numerous occasions, including three pre-NDA meetings with the Applicant (December 3, 1999, February 6, 2001 and March 25, 2002). As encountered with other regimens using an mTOR inhibitor with “full dose” cyclosporine, the combination regimens of everolimus, cyclosporine and corticosteroids were associated with unacceptable increases in serum creatinine, and loss of renal function, compared to the control regimens. This is believed to be due, at least in part, to enhancement of cyclosporine nephrotoxicity by concomitant administration of mTOR inhibitors. The general consensus has become that “full dose” cyclosporine regimens, based on target whole blood concentrations believed to be safe and effective when used with corticosteroids and mycophenolate mofetil (MMF) or azathioprine (AZA), do not represent safe regimens when used with mTOR inhibitors.

The increased risk of renal function impairment, associated with the regimens evaluated in Studies B201 and B 251, in *de novo* renal transplantation, was not outweighed by any added benefit, with respect to freedom from acute rejection, graft loss or death, compared to the approved control regimen, of MMF, cyclosporine and corticosteroids. Indeed, when considering the disproportionate premature treatment discontinuation as a failure, neither the 1.5 mg or 3 mg everolimus groups were non-inferior to MMF in either study.

Preservation of renal function is also important in heart transplantation recipients, all the more that impaired renal function is common after successful heart transplant recipients as demonstrated by decreased mean and median baseline glomerular filtrations rates (GFR) in study B253. Based on analysis of transplant registry data, further renal function impairment in recipients of non-renal organ transplants treated with cyclosporine is associated with decreased long term patient and graft survival.

(b) (4)



[REDACTED] (b) (4)

[REDACTED] (b) (4)

[REDACTED] (b) (4)

As a result of these submissions, an NDA approvable action letter was issued on October 20, 2003. The action letter stated “Although you have demonstrated your product to be efficacious, as studied in your clinical trials, you have yet to show a sufficiently safe regimen for everolimus when used with cyclosporine. Before these applications may be approved, you must establish a dosing regimen of everolimus and cyclosporine that is both safe and effective for the prophylaxis of organ rejection in allogeneic renal and cardiac transplant patients”. There is a need to provide information supporting a safe and effective dosing regimen of everolimus and cyclosporine that would minimize renal function impairment while maintaining adequate protection against graft rejection, graft loss or death in *de novo* renal and *de novo* cardiac transplantation. The Applicant was offered the option to provide data from new adequate well controlled studies, which would need to be initiated, or provide analyses from completed, controlled studies evaluating lower exposures to cyclosporine in combination with therapeutic dose monitoring schemes (TDM) for everolimus and cyclosporine. The validity of the chosen approach would ultimately depend on a complete review of the data.

Updated Regulatory Information:

- **US IND and NDA Submissions**

Everolimus (code name: RAD001, SDZ RAD) was evaluated in the US by Novartis Pharmaceutical Corp. under IND 52,003. Additional foreign studies, not conducted under the US IND, have been used to support this application. There have been no applications in the US for Emergency INDs for the use of everolimus in solid organ transplantation.

On December 19, 2002, Novartis submitted an NDA for Certican® (everolimus) Tablet (0.25mg, 0.5mg, 0.75mg, 1.0mg) for prophylaxis or organ rejection in allogeneic renal transplantation and allogeneic cardiac transplantation. For administrative purposes, the

original NDA was separated, by indication, into two NDA's, thus requiring the assignment of two NDA numbers (21-560 for renal transplantation, 21-628 for cardiac transplantation).

Although additional studies had been initiated to evaluate cyclosporine minimization and concentration-controlled everolimus in renal transplantation (Studies A2306 and A2307), full study reports of the completed 12-month studies would not be available before the end of the review cycle. There were and still are no ongoing studies evaluating cyclosporine minimization and concentration-controlled everolimus in cardiac transplantation.

Protocols for Study A2306 entitled "A 1 year multicenter, randomized, open-label, parallel group study of the safety, tolerability and efficacy of two doses (1.5 and 3 mg/day) of Certican™ (RAD001) with steroids and optimized administration of Neoral® in *de novo* renal transplant recipients" and Study A2307 entitled "A 1 year multicenter, randomized, open-label, parallel group study of the safety, tolerability and efficacy of two doses (1.5 and 3 mg/day) of Certican™ (RAD001) with Simulect®, corticosteroids and optimized administration of Neoral® in *de novo* renal transplant recipients" were submitted to IND 52,003 on August 9, 2001. Concerns over the design of these studies were communicated to the sponsor on September 13, 2001:

"We recognize that these phase II studies may provide information that could be used to design subsequent phase III studies. However, we do not believe that these phase II studies could represent adequate well-controlled studies because of the lack of valid controls. By design the studies are unable to reliably exclude an unacceptable decrease in patient or graft survival compared to approved therapy, nor would they be able to support that either dose of the test drug would have beaten placebo. Finally, the open-label designs create a potential for bias that would impair assessment of endpoints including but not limited to biopsy proven rejection [Please refer to 21CFR 314.126(b)(2) and (5)]"

No significant modifications were made to the protocol designs by the sponsor, after receiving these comments.

Following the approvable action issued for NDAs 21-560 and 21-628 on October 20, 2003, and prior to this resubmission no new controlled studies were initiated in renal or cardiac transplantation. Several discussions were held with the Applicant over the approach they wished to use to respond to the deficiencies. The Applicant proposed to support new regimens of concentration controlled everolimus and cyclosporine, using analyses of new data from completed 12-month studies A2306 and A2307, involving comparisons with studies B201 and B251 in kidney transplantation, along with some exposure-response analyses recommended by the FDA Biopharmaceutics reviewer. The applicant further proposed to use extrapolation from analyses in renal transplantation, and exposure-response analyses of data from study B253 to support a similar regimen in heart transplantation. Although some concerns were expressed over such approaches, it was

agreed that the validity of their approach would require a complete review of the information they intended to include in the complete resubmission.

Following the resubmission of NDAs 21-560 and 21-628, the reviewers found these electronic resubmissions to be poorly organized and lacking in adequate written justifications of extrapolations from renal to cardiac transplantation, new cross study comparisons, or discussion of the interpretation of new analyses. In particular, information from new pharmacokinetic and pharmacodynamic analyses were scattered about the electronic resubmission, such that the Biopharmaceutics Reviewer needed to open and search every file to locate the information, which needed to be reviewed. These concerns were expressed to the Applicant early in the review and addressed in part with responses to requests for additional information.

During the review of these resubmissions it became apparent that the utility of taking this application to a Subcommittee of the Antivirals Drug Products Advisory committee was not yet certain enough to justify early mobilization FDA and Applicant resources to create such a subcommittee and prepare for an open public meeting. The Applicant shared this uncertainty and initiated a plan to consult panels of their investigators in heart transplantation and renal transplantation, before committing to presenting before an advisory committee meeting. The FDA Review Team prepared a list of questions, which highlighted some of the scientific issues and concerns, for the Applicant's consideration while consulting their panel of experts. The Applicant's process could not be completed within a reasonable amount of time before the action due date specified by the Prescription Drug User Fee Act III. A preliminary opinion authored by a group of principal investigators from the cardiac transplantation study, B253, was submitted to the NDA, late in the six-month review cycle. It was found to represent a testimonial from the investigators and not a critical independent evaluation by experts not involved in the study. This was not intended to represent a major clinical amendment, which could have allowed the review cycle to be extended an additional three months. Additional discussions as to the utility of creating a Subcommittee for Immunosuppressants and seeking their advice on these applications were deferred, by mutual agreement with Applicant, until after the pending regulatory action.

- **Foreign Marketing Applications**

Certican received its first approval from the Swedish Medical Products Agency (MPA) in July 2003 for the prevention of rejection in heart and kidney transplant patients in combination with Neoral and corticosteroids, using regimens, involving cyclosporine minimization and concentration controlled everolimus, that have not yet been prospectively evaluated, compared to approved therapy, in randomized parallel group controlled studies. Analyses of preliminary six-month data from studies A2306 and A2307 were also considered in the European application.

(European Summary of the Products Characteristics prepared by the Swedish MPA http://www.mpa.se/spc_pil/pdf/enhumspc/Certican%20tablet%20ENG.pdf).

Certican® subsequently completed the European Mutual Recognition Procedure (MRP), December 2003. The following 15 countries endorsed the mutually agreed summary of product characteristics (SmPC): Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, and Sweden. Sweden is the Reference Member State for the Mutual Recognition Procedure. Approval was conditional on the Applicant's commitment to conduct a prospective, randomized, controlled, post-marketing study in cardiac transplantation, evaluating concentration-controlled everolimus with cyclosporine minimization compared to and approved active control regimen of cyclosporine, MMF and corticosteroids. Another condition for the approval in France was a commitment from the Applicant to conduct intensified post-marketing surveillance of the safety of this yet un-tested regimen. (b) (4)



Certican® (everolimus) Tablet, for the prevention of rejection in allogeneic renal transplantation.

The current supplement, submitted by the sponsor on December 19, 2003, in response to the NDA Action letter, contains the 12 month results of two additional studies in *de novo* renal transplantation (Studies A2306 and A2307). These studies were originally designed to compare initial doses of 1.5 mg and 3.0 mg of everolimus, with subsequent dose adjustments based on whole blood concentrations, targeting a whole blood trough concentration greater than 3 ng/mL, and did not include an active control group using an approved regimen for comparison. Cyclosporine was administered based on therapeutic drug monitoring of the whole blood concentration, two hours after dosing (C₂ monitoring), and progressively decreased over time as everolimus doses were adjusted to maintain whole blood concentrations above the minimum threshold of 3 ng/mL. Study A2307 also used induction with Simulect® (basiliximab), which was not used in B201 and B251. Simulect® is approved for the prevention of rejection in renal transplantation, when used as part of a regimen that includes cyclosporine and corticosteroids.

The efficacy and safety analyses were based primarily on cross study comparisons using data from studies in *de novo* renal transplantation in the original NDA submission (studies B201 and B251). Populations from B201 and B251 were pooled together to create comparator groups. This approach is not appropriate and is likely to lead to incorrect conclusions. The populations studied in B201 and B251 differed greatly between themselves and individually with in those studied in A2306, in distribution of important baseline recipient and donor characteristics, which would be expected to influence efficacy and safety outcomes. It should be noted, that beginning at the time of the submission of the A2306 and A 2307 study protocols to the IND, in August 2001, and throughout the pre-NDA and NDA review process, the clinical and statistical concerns regarding the use of external controls (e.g. cross-study comparisons) have been expressed to the Applicant on numerous occasions, as described in greater detail in on page 10 in Section 3 of the FDA's Statistical Review and Evaluation.

While studies B201 and B251 were double-blind for 12 months post-transplantation, studies A2306 and A2307 were open-label. The open-label design creates a potential for bias that would impair the reliability of the assessment of endpoints including but not limited to biopsy-proven acute rejection.

In addition, studies B201 and B251 used cyclosporine whole blood trough concentrations (Cmin), the proven method for therapeutic drug monitoring of cyclosporine and the method used in the clinical studies supporting the approval of Sandimmune® (cyclosporine USP) and Neoral® (cyclosporine USP) MODIFIED, while studies A2306 and A2307 used C2 monitoring. C2 monitoring of cyclosporine therapy is not an established safe and effective method. Common individual differences in time to cyclosporine maximum concentrations (Tmax) and/or small deviations in sampling time from the 2 hour after dosing are a problematic source of variability, since this time point occurs during a steep section of the curve of concentration over time. Populations such as diabetics (who constitute approximately 25% of renal transplant recipients in the US) with delayed cyclosporine absorption due to gastroparesis, and consequently delayed Tmax, would be at increased risk for overdosing if C2 monitoring, and target ranges for C2 were used to adjust cyclosporine dosing.

C2 monitoring and cyclosporine dose adjustment failed to maintain whole blood cyclosporine concentrations within the protocol specified target ranges in study A2306, as demonstrated by mean C2 concentrations that were at or above the upper limit of the targeted ranges at all time points, in this open-label study. Indeed, only approximately 30% (range 15% to 39%) of the patients were within the protocol specified target cyclosporine concentration ranges over the 12 months post transplantation, meaning that therapeutic drug monitoring (TDM) goals could not be met in the majority of patients in the study. Study A2307 used induction with basiliximab and similar target C2 concentrations for cyclosporine dose adjustments. Approximately 50% (range 39% to 72%) were within the specified cyclosporine concentration limits. This still does not represent a successful TDM regimen. There appears to be no scientific justification for using C2 monitoring instead of the standard monitoring of whole blood trough concentrations to guide cyclosporine dosing.

Overall, I concur with the statistical and clinical reviewers, that the cross-study comparisons being proposed are not reliable and that these data do not allow us to identify a safe and effective regimen of everolimus and cyclosporine for the prevention of graft rejection in *de novo* renal transplantation recipients.

(b) (4)

(b) (4)



(b) (4)



(b) (4)



Pediatric Issues:

There are no new pediatric data in this resubmission. The Applicant had a Written Request for Pediatric Studies, which has now expired, and has further indicated they do not intend to seek a pediatric indication. In the future, if a safe and effective regimen of everolimus can be identified in adults, the potential benefits and risks of developing a regimen should be reconsidered in children.

Recommended regulatory action:

There is need for fresh data from new prospective studies. Currently, there are no ongoing clinical trials evaluating everolimus and cyclosporine regimens in renal or cardiac transplantation. We do not believe there is much more that one can derive from additional retrospective analyses of existing data, other than hypothetical regimens whose safety and efficacy need to be prospectively evaluated in adequate well-controlled trials.

These applications remain approvable. Although we continue to believe the Applicant has demonstrated that everolimus is efficacious, they have yet to show a sufficiently safe regimen for everolimus when used with cyclosporine. Before these applications may be approved, safe and effective dosing regimens of everolimus and cyclosporine for the prophylaxis of organ rejection in allogeneic kidney and heart transplant patients must be established. Therefore, before the applications may be approved, it will be necessary to:

1. Provide information supporting a safe and effective dosing regimen for everolimus and cyclosporine that would minimize renal function impairment while maintaining adequate protection against graft rejection, graft loss or death in *de novo* renal transplantation. In order to do this, we believe that it will be necessary to provide data from an adequate and well-controlled study or studies prospectively evaluating concentration-controlled regimens of everolimus in combination with concentration-controlled cyclosporine in *de novo* renal transplant recipients, which would support therapeutic drug monitoring (TDM) schemes for everolimus and cyclosporine.

(b) (4)



At present, we are unable to identify another approach to provide the necessary data to support the safety and efficacy of the Applicant's products. Should the Applicant have another alternative to conducting such a study or studies, we should strongly encourage them to discuss the study design with us prior to its initiation.

If a non-inferiority study design is chosen, the active control should represent an approved comparator regimen. Target concentration ranges over time for both everolimus and cyclosporine should be prospectively defined, and then demonstrated to be safe and effective in both early stages post transplantation and during the maintenance phase.

A primary analysis conducted at least 6 months after the last protocol specified change in target everolimus and cyclosporine concentration ranges (i.e. 6 months into maintenance phase), could support a resubmission of the NDAs for these indications, providing there were a commitment to provide follow-up outcome and safety data (renal function, rejection, graft loss, death) at 12, 24 and 36 months post transplantation.

To demonstrate the safety and efficacy of the proposed everolimus-cyclosporine combination regimens, the Applicant 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. A safe and effective TDM regimen for everolimus, used in combination with cyclosporine, would also require a validated assay for everolimus blood concentrations, and need to be supported by experience with a successful monitoring schedule and dose adjustment scheme, proven capable of maintaining patients within the proposed therapeutic concentration range.

If the proposed regimen(s) would require doses and blood concentrations of everolimus that are higher than those observed in studies previously submitted to the NDA, additional safety data of similar duration in an adequate number of subjects would be needed to support approval of the recommended regimen(s). A minimum of 300 transplant patients should have been observed for at least 12 months at the proposed recommended exposure of everolimus with cyclosporine. This might be achieved by simultaneous submission of data from an adequate well-controlled study in de novo renal transplantation (b) (4)

The Applicant should be encouraged to communicate with the Division regarding the option(s) they plan to select before resubmitting your applications. The ultimate suitability of the proposed approaches can only be determined after review of the relevant data.

In addition, we should strongly recommend that the Applicant continue to adequately determine the terminal T_{1/2} of everolimus in the target patient population following the administration of the proposed everolimus-cyclosporine regimen. This everolimus T_{1/2} should be determined at the range of proposed clinical doses and/or concentrations of everolimus and cyclosporine following multiple dose (steady state) administration of the proposed everolimus-cyclosporine combination regimen to transplant patients. This information would be particularly important in guiding dosing algorithms used in a TDM regimen.

In vivo drug interaction studies with everolimus, requested by FDA and agreed to by the Applicant are ongoing. Continued progress and cooperation in identifying significant drug interactions with everolimus is expected and should be encouraged. Information on important drug interactions would be needed to guide dosage adjustments in regimens based on therapeutic drug monitoring.

ATTACHMENT

MEDICAL OFFICER TEAM LEADER MEMORANDUM
DATED OCTOBER 20, 2003

11 Page(s) have been withheld in full immediately following this page as duplicative

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Marc Cavaille Coll
8/27/04 02:23:03 PM
MEDICAL OFFICER

Marc Cavaille Coll
8/27/04 02:26:44 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation IV/ Division of Special Pathogen and Immunologic Drug Products

DATE: October 20, 2003

TO: Mark J. Goldberger, M.D, M.P.H.
Director, ODE4, HFD-104

THROUGH: Renata Albrecht, M.D.
Division Director, HFD-590

FROM: Marc W. CavailJ-Coll, M.D., Ph.D.
Medical Officer Medical Team Leader, HFD-590

SUBJECT: NDA 21,560 Certican® (everolimus) Tablet, for prophylaxis or organ rejection in allogeneic kidney transplantation.

NDA 21,561 Certican® (everolimus) Tablet for Oral Suspension, for prophylaxis or organ rejection in allogeneic kidney transplantation.

NDA 21,628 Certican® (everolimus) Tablet, for prophylaxis or organ rejection in allogeneic heart transplantation.

NDA 21,631 Certican® (everolimus) Tablet for Oral Suspension, for prophylaxis or organ rejection in allogeneic heart transplantation.

The major issues of this NDA have been thoroughly discussed in the pre-clinical, statistical and clinical reviews. I concur with the consensus of the reviewers that these NDAs are approvable. This memorandum will describe the relevant deficiencies and comment on a few areas that have been discussed at some length during the review process.

Background:

Renal transplantation has become the treatment of choice for end-stage renal disease and offers a better quality of life and survival than hemodialysis. Annually, in the US approximately 8000 renal transplants are performed from cadaveric donors and 6000 from living donors. Among recipients of cadaveric kidneys, graft survival is 88.4% at one year and 78.5% at three years post transplantation. Among recipients of kidneys from living donors, graft survival is 94.4% at one year and 88.3% at three years post transplantation. Patient survival is 94.0% at one year and 88.4% at three years post transplantation in recipients of cadaveric kidneys, while it is 97.7% and 94.7%,

respectively, in recipients of kidneys from living donors. (Source: OPTN/SRTR Data as of August, 2002)

Although, there may be no consensus as to what would constitute the optimal immunosuppressive regimen for prevention of allograft rejection, several biologic and drug products have been approved for this indication in renal transplantation, including but not limited to, cyclosporine, azathioprine, tacrolimus, mycophenolate mofetil, sirolimus, basiliximab, daclizumab, and thymoglobulin. Combination immunosuppressive therapy is the rule including three to four agents with non-overlapping mechanisms of activity or toxicities.

The leading causes of death following renal transplantation, infection and cardiovascular disease, are related to immunosuppression and/or the toxicities associated with the use of these drugs. There is a need for safer, less toxic immunosuppressant drugs and regimens.

Cardiac transplantation has become an important part of the management of end-stage heart disease. Approximately 2,200 heart transplants are performed in the US annually. The most common indications for cardiac transplantation in the US are coronary artery disease, 41% and cardiomyopathy 45.3% (Source OPTN/SRTR 2001). Graft survival at one year and three years post transplantation are 84.4% and 77.5%, respectively. Patient survival at one year and three years are 85.1% and 78.6%. These numbers have remained stable over the past 5 years. (Source OPTN/SRTR August 1, 2002)

Although, there may be no consensus as to what would constitute the optimal immunosuppressive regimen for prevention of allograft rejection, a few products are approved for this indication in cardiac transplantation, including cyclosporine and mycophenolate mofetil. Although azathioprine does not have an approved indication of prevention of rejection in allogeneic heart transplantation, it has been used successfully in combination with cyclosporine and corticosteroids in heart transplantation. Thus, azathioprine was the active comparator against which mycophenolate-mofetil (CellCept®) was compared to in non-inferiority studies supporting the approval of the latter in cardiac transplantation.

The major causes of hospitalization during the first year remain infection alone (16%), infection plus rejection (7%), and rejection alone (11%). Other morbidity after heart transplantation include, drug-treated hypertension (66.5%), hyperlipidemia (60.6%), diabetes (20.3%), malignancy (3.7%), renal dysfunction (12.1%), and coronary artery disease (6.6%). In particular, 7.8% of heart transplant recipients in the US have a serum creatinine > 2.5 mg/dl, and 1.3% are on chronic dialysis. (Source: UNOS/ISHLT Thoracic Registry 2000). Such morbidity reflects the burden associated with achieving adequate immunosuppression, and the acceptable amount of renal function impairment that has been traded off in order to achieve current levels of patient and graft survival with cyclosporine-based immunosuppressive regimens (CBIR). Again, there is a need for safer, less toxic immunosuppressant drugs and regimens.

Everolimus, 40-O-(2-hydroxyethyl)-rapamycin is a macrolide immunosuppressant of the same class as sirolimus (a.k.a. Rapamune®, or rapamycin), immunosuppressants that act via the TOR molecule (target of rapamycin). Rapamune® is approved for the prevention of rejection in allogeneic kidney transplantation. When used in combination with cyclosporine, sirolimus has been associated with a dose-dependent increased risk of renal function impairment. The approved regimen for sirolimus in kidney transplant recipients who are at low to moderate risk for rejection involves cyclosporine withdrawal at 2 to 4 months after transplantation (See approved Package Insert for Rapamune®).

Regulatory Information:

Everolimus (code name; RAD001, SDZ RAD) was evaluated in the US by Novartis Pharmaceutical Corp. under IND 52,003. Additional foreign studies, not conducted under the US IND, have been used to support this application. There have been no applications in the US for Emergency INDs for the use of everolimus in solid organ transplantation.

On December 19, 2002, Novartis submitted an NDA for Certican® (everolimus) Tablet (0.25mg, 0.5mg, 0.75mg, 1.0mg) for prophylaxis or organ rejection in allogeneic renal transplantation and allogeneic cardiac transplantation. For administrative purposes, the original NDA was separated, by indication, into two NDA's, thus requiring the assignment of two NDA numbers (21-560 for renal transplantation, 21-628 for cardiac transplantation).

A separate NDA was submitted, on January 31, 2003, for the dispersible tablet (0.1 mg, 0.25mg). This original NDA was separated for administrative purposes into NDA 21-561 for kidney transplantation and NDA 21-631 for heart transplantation. Although these formulations were intended for pediatric use, the applicant is not seeking a pediatric indication at this time (See **Pediatric Issues** Section of this memo). Nevertheless, such formulations may provide an alternative to patients unable to take the solid tablets.

At three successive pre-NDA meetings with the Applicant concerns were expressed over increased renal function impairment in treatment arms using everolimus with standard dose cyclosporine in both renal and cardiac transplantation. Additional studies are underway to evaluate cyclosporine minimization and concentration-controlled everolimus in renal transplantation (Studies A2306 and A2307). Preliminary synoptic information from 6 month interim data was submitted with the NDA and the 120 day safety update. Full study reports of the completed 12-month studies will not be available before the end of this review cycle.

There are no currently ongoing studies evaluating cyclosporine minimization and concentration-controlled everolimus in cardiac transplantation.

Certican® received a favorable review in Sweden and was approved for prevention of rejection in cardiac transplantation and renal transplantation using regimens, involving cyclosporine minimization and concentration controlled everolimus, that have not yet

been prospectively compared to approved therapy in randomized parallel group controlled studies.

Certican® (everolimus) Tablet, and Certican® (everolimus) Tablet for Oral Suspension, for the prevention of rejection in allogeneic renal transplantation.

The applicant has submitted two controlled Phase 3 studies in support of this indication, studies B201 and B251, each titled “A three year, double-blind, double dummy, randomized, multicenter, parallel group study of the efficacy and safety of SDZ RAD tablets versus mycophenolate mofetil as part of triple immunosuppressive therapy in de novo renal transplant recipients”. Both studies compared two fixed daily doses of everolimus, 1.5 mg and 3 mg, to the approved dose of CellCept® (mycophenolate-mofetil) (MMF) and used standard cyclosporine/corticosteroid regimens.

Strengths of these studies include the randomized, double blind design and use of an approved active control regimen, representative of regimens currently used in the US. A potential weakness, which may limit the extent to which one may generalize these studies to the US renal transplant population is the low proportion of subjects who received kidneys from living donors, a population with a lower risk for rejection and perhaps in need of lesser immunosuppression.

The double blind studies were intended to last 12 months but were extended (open-label) for an additional 24 months. After the last subject had completed 12 months, and unacceptable increase in renal function impairment was found in the everolimus arms compared to the MMF control, which led to a protocol amendment that provided for lower cyclosporine exposure and adjustment of everolimus dose to meet minimum whole blood concentrations. By that time a substantial proportion of subjects had discontinued study drug, more in the 3 mg everolimus treatment group than in the other two. Thus, it may be difficult to draw reliable conclusions past 12 months after transplantation, from this open-label, non-randomly selected subset.

Although everolimus appeared comparable to MMF with respect to the co-primary endpoints of biopsy-proven acute rejection, graft loss, death or loss to follow-up at six months, and incidence of graft loss, death or loss to follow-up at 12 months, the results were not consistent across both studies in that the 1.5 mg everolimus group failed to meet the 12 month non-inferiority endpoint in study B251 while the 3 mg group failed to do so in study B201 [See Table 3: Primary Efficacy Analysis (ITT Group) in the FDA Statistical Review and Evaluation]. In addition, not all results were robust against the disproportionate premature treatment discontinuation. When considering premature treatment discontinuation as a failure, neither the 1.5 mg or 3 mg everolimus groups were non-inferior to MMF in either study [See Table 4: Primary Efficacy Endpoint Analysis with Premature Treatment Discontinuation Considered a Failure (ITT Group) in the FDA Statistical Review and Evaluation].

Outcomes past 12 months are difficult to attribute to randomized treatment assignments, because of disproportionate premature treatment discontinuation and unblinded alteration

of dosage regimens after the protocol was amended based on the 12-month safety information.

In both studies, the 3 mg everolimus group had statistically significantly worse median serum creatinine and calculated creatinine clearance than those of the MMF group, beginning as early as 3 months after transplantation and continuing through month 36 of the study. The 1.5 mg everolimus group demonstrated similar renal function impairment, with statistically significant worse median serum creatinine and calculated creatinine clearance, compared to the MMF group beginning at 6 months and persisting through 36 months, except at two time points in study B201 (30 and 36 months). Efforts to minimize renal function impairment after the dosing regimens were amended are difficult to evaluate, but do not appear to support that loss of renal function was reversible after cyclosporine was lowered and everolimus dose were adjusted to meet minimum whole blood concentrations. The degree of renal function impairment observed in the everolimus treatment groups is in excess of what has been tolerated with currently approved cyclosporine-based immunosuppressive regimens.

Other safety concerns including elevation of serum lipids, despite statin therapy, thrombocytopenia, and potential wound healing complications associated with this class of immunosuppressant were identified in the review.

Retrospective exploratory analyses of relationships between certain measures of observed drug concentrations and various efficacy and safety parameters were performed by the Applicant and the FDA reviewers. At best, these may produce hypotheses that need to be prospectively tested, in an attempt to define a proven regimen of concentration-controlled everolimus and therapeutic drug monitoring that would allow minimization of cyclosporine use and renal toxicity, while maintaining adequate protection against rejection, graft loss or death.

The 120-day safety update, contained a revised proposed label that recommended (b) (4)

We agree that fixed doses of everolimus used with “full dose” cyclosporine are not appropriate to prevent rejection and preserve graft function in renal transplantation. Cyclosporine minimizing strategies should be initiated earlier than 12 months, since the deleterious effect on renal function was demonstrated as early as three months after transplantation.

Overall, although we believe everolimus is active in preventing rejection in renal transplantation, a safe and effective dose of everolimus when used with a cyclosporine-based regimen could not be identified.

Exploratory PK/PD analyses could possibly identify a hypothetical range of everolimus trough concentrations and cyclosporine blood concentrations that would be expected to be associated with better outcome, with respect to both efficacy (less rejection, better patient and graft survival) and a more optimal safety profile (better allograft function, and less renal toxicity). However, such a concentration-controlled regimen (or TDM

algorithm) should be tested prospectively in an adequate, well-controlled clinical trial, using an approved regimen as comparator.

Such a trial should demonstrate that the combination everolimus and cyclosporine A therapeutic drug monitoring regimen is feasible, well tolerated and produces the desired improved outcome with respect to renal function, without compromising efficacy.

One approach would be to show that the proposed corticosteroid, everolimus, and cyclosporine A combination TDM regimen is non-inferior compared to an approved regimen with respect to acute rejection, graft-loss or death, while minimizing renal function impairment. Target concentration ranges over time for both everolimus and cyclosporine A should be prospectively defined, and then demonstrated to be safe and effective in both, early stages post transplantation and during the maintenance phase. A primary analysis at 3 to 6 months post transplantation could support a resubmission of the NDA for this indication, providing there were a commitment to follow-up outcome at 12, 24 and 36 months (allograft-function, rejection, graft loss, any death).

If the proposed regimen would require doses and concentrations of everolimus that were higher than those previously observed in studies B201, B251 and B253 (cardiac transplantation), additional safety data from a similar duration of drug exposure duration in and adequate number of subjects might be needed to support approval of the regimen.

A double-blind study would provide stronger evidence. However, it may be difficult to maintain treatment blinding given the need to measure drug concentrations, and for using different dosing algorithms to meet target concentrations and/or to manage toxicity.

There is particular concern about the potential for bias in comparing rates of acute rejection in an open-label study. The level of concern increases with claims of comparative superiority. The use of protocol biopsies, and blinding the biopsy reading to treatment assignment, could help minimize the potential for bias. However, poor compliance with protocol biopsies could also introduce a potential for selection bias.

Certican® (everolimus) Tablet, and Certican® (everolimus) Tablet for Oral Suspension, for the prevention of rejection in allogeneic cardiac transplantation.

In support of this indication the Applicant has submitted a single study (B253), a prospective, randomized, 1-year with an open-label 1 year extension, multi-center active control, parallel-group, double-blind, double-dummy study in de novo cardiac transplant recipients. A total of 634 patients were enrolled at approximately 40 clinical centers in the US, Canada, and Europe. This study evaluated two daily fixed doses of everolimus, 1.5 mg and 3 mg, compared to azathioprine, 1.0 to 3.0 mg/kg, using conventional cyclosporine/corticosteroids-based immunosuppression. Although the applicant has submitted a single study in support of this indication, efficacy and safety information in renal transplantation may be considered supportive.

A strength of the study is its randomized, double-blind design. A potential weakness that may affect the extent to which one may generalize the results to the US cardiac transplant population, is possibly the lack of adequate representation from certain high risk groups specific to the US transplant population. Although the study was extended to 24 months after transplantation, outcomes past 12 months are difficult to attribute to randomly assigned doses, because of disproportionate premature treatment discontinuation and unblinded alteration of dosage regimens after the protocol was amended based on the 12-month safety information.

Everolimus was found to be superior to azathioprine with respect to the primary endpoint, acute rejection greater than or equal to ISHLT grade 3A, any rejection with hemodynamic compromise (HDC), death or graft loss. However, this difference was due to grade 3A or greater rejection, and not to the more severe components, rejection with HDC, death or graft loss (See Table 3.5: Incidence of Composite and Simple Events at 6, 12, and 24 months, in the FDA Statistical Review and Evaluation). These rejection episodes were largely reversible after treatment with corticosteroids and rarely required additional treatment with antilymphocyte antibodies.

As in the renal transplantation studies, everolimus when used with cyclosporine was associated with an unacceptable increase in renal function impairment, far in excess of what has been tolerated with currently approved cyclosporine-based immunosuppressive regimens in cardiac transplantation. In particular, 25% and 27% of subjects in the 1.5 mg and 3 mg everolimus groups, respectively, had serum creatinine concentrations greater than 2.5 mg/dL, compared to 8% in the azathioprine group (which demonstrated renal function at one year after transplantation which was consistent with one year data in US cardiac transplant registries). Baseline renal function, as measured by calculated creatinine clearance is already abnormally decreased in successful cardiac transplantation, a mean of approximately 64 to 67 mL/min in this study. In the 1.5 mg and 3 mg everolimus groups, respectively, 10% and 20% experienced a 50% decline in creatinine clearance from baseline, compared to only 5% in the azathioprine group. Decreased renal function in non-renal solid organ transplant recipients is a hazard of cyclosporine-based immunosuppressant therapy, and is associated with decreased long term survival.

After the last subject had reached 12 months after transplantation, the protocol was amended to lower cyclosporine exposure while maintaining everolimus blood concentrations above a target minimum concentration, in an unsuccessful attempt to minimize renal toxicity. By that time, disproportionate drop-out rates and an open-label design make it further difficult to draw definitive conclusions, because of the potential for selection bias. It is not known how subjects who discontinued study drug before month 12 would have fared under the modified dosing regimen.

Other safety concerns associated with everolimus included increased dyslipidemia (elevated serum cholesterol and triglycerides) despite the systematic use of statin therapy, and an increased risk of bacterial infections including pneumonia in the everolimus groups that was not out-weighted by the increased rate of viral infections reported as

adverse events in the azathioprine group. The latter events were largely due to “CMV infection”, although there were no significant differences in the incidence of invasive CMV disease.

The NDAs’ 120 day safety update included revised labeling recommending therapeutic drug monitoring for everolimus with cyclosporine minimization. We agree that fixed dose everolimus with full dose cyclosporine is not appropriate in cardiac transplantation; however, the amended regimen has not been prospectively evaluated in de novo cardiac transplantation. In particular, it is uncertain how safe and effective such a proposed regimen would perform during the critical first 3 to 6 months after transplantation. Cyclosporine minimizing strategies need to be initiated earlier than 12 months after transplantation, since the deleterious effect on renal function was demonstrated as early as three months after transplantation.

Intravascular ultrasound (IVUS) was used in study B253 to evaluate post-transplant coronary artery vasculopathy. However, only a non random subset of the subjects (approximately one third), with baseline and follow evaluations, participated in the final analysis of IVUS data. The IVUS is still an investigational method for evaluating intimal thickening in the coronary arteries of the heart allograft. One cannot exclude that events, which occurred after randomization, related or unrelated to treatment assignment, including post-transplant coronary arteriopathy itself, may have interfered with performing the test and influenced which subjects were included in the analysis. Impaired renal function was evoked as a reason in some cases for not performing the test, which required the use of intravenous contrast dye. Thus, renal function impairment due to study regimen (everolimus plus cyclosporine) could also have influenced which subjects were included in the IVUS analyses. These analyses are further confounded by differential rates of treatment discontinuation.

There was no benefit with respect to the most serious efficacy outcomes, death, graft loss or rejection with HDC that could potentially outweigh the degree of increased renal function impairment and other safety concerns. Overall, while everolimus used in combination with steroids and cyclosporine appeared effective in preventing acute rejection in recipients of *de novo* heart allograft, safe and effective doses for the everolimus and cyclosporine combination regimen could not be established in this study.

Exploratory PK/PD analyses could possibly identify a hypothetical range of everolimus trough concentrations and cyclosporine blood concentrations, that would be expected to be associated with better outcome, with respect to both efficacy (less rejection, better patient and graft survival) and safety (less renal toxicity). However, such a concentration-controlled regimen (or TDM algorithm) should be tested prospectively in an adequate, well-controlled clinical trial, to demonstrate that the proposed TDM regimen is feasible, well-tolerated and produces the desired outcome with respect to improved safety without compromising efficacy.

The effect of everolimus in combination with cyclosporine on renal function is detectable at 3 months. This suggests that cyclosporine minimization should be initiated sooner than 12 months.

Ongoing studies A2306 and A2307 evaluating everolimus TDM and reduced exposure to cyclosporine may be supportive of similar regimens in cardiac transplantation, but this could only be determined by a review of the data when the study reports become available. Limitations of these studies, include the lack of an approved comparator regimen and the use of C2 (concentration 2 hours after dosing) monitoring to adjust cyclosporine dosing, an unestablished regimen in cardiac transplantation. In general, while clinical studies in one solid organ transplant may be supportive of safety and efficacy in another type of solid organ transplant, they may not be sufficiently predictive to establish a safe and effective regimen without further evaluation in transplantation of the organ of interest.

One approach would be to show that the proposed corticosteroids, everolimus-cyclosporine A combination TDM regimen is non-inferior compared to an approved regimen, with respect to acute rejection, graft-loss or death, while minimizing renal function impairment. Target concentration ranges over time for both everolimus and cyclosporine should be prospectively defined, and then demonstrated to be safe and effective in both, early stages post transplantation and during the maintenance phase. A primary analysis at 3 to 6 months post transplantation could support a resubmission of the NDA for this indication, providing there were a commitment to provide follow-up outcome and safety data (renal function, rejection, graft loss, any death) at 12, 24 and 36 months.

If the regimen would require doses and concentrations of everolimus that are higher than those observed in studies B253, B201 and B251, additional safety data of similar duration in an adequate number of subjects might be needed to support approval of the regimen.

A double-blind study would provide stronger evidence. However, it may be difficult to maintain treatment blinding given the need to measure drug concentrations, and for using different dosing algorithms to meet target concentrations and/or to manage toxicity.

We have particular concern over the potential for bias in comparing rates of acute rejection. Compliance with protocol surveillance biopsy schedules, and blinding the biopsy reading to treatment assignment, could help minimize the potential for bias.

Pediatric Issues:

The application had a Written Request for Pediatric Studies, which has now expired. Although two single dose PK studies of everolimus in pediatric renal and hepatic transplant recipients have been completed, a third required multi-dose study in pediatric renal transplantation was terminated prematurely by the Applicant after on 19 out of a planned number of 40 subjects had been enrolled. The Applicant, unilaterally chose to terminate enrollment because of concern over laboratory findings in adult transplant

recipients, lower serum testosterone, that the Division had agreed could be addressed in this study with adequate monitoring and informed consent.

The Applicant indicated in the NDAs for the table for oral suspension, that they did not intend to seek a pediatric indication, but did request a determination for pediatric exclusivity. To date, such a determination has not been formally made.

Recommended Regulatory Action:

These applications are approvable. Although the Applicant has demonstrated that everolimus is efficacious, they have yet to show a sufficiently safe regimen for everolimus when used with cyclosporine. Before these applications may be approved, safe and effective dosing regimens of everolimus and cyclosporine for the prophylaxis of organ rejection in allogeneic renal and cardiac transplant patients must be established. Therefore it will be necessary for the Applicant to:

1. Provide information supporting a safe and effective dosing regimen for everolimus and cyclosporine that would minimize renal function impairment while maintaining adequate protection against graft rejection, graft loss or death in *de novo* renal transplantation.
 - One approach would be to provide data from an adequate well-controlled study or studies prospectively evaluating concentration-controlled regimens of everolimus in combination with concentration-controlled cyclosporine in *de novo* renal transplant recipients, which would support therapeutic dose monitoring (TDM) schemes for everolimus and cyclosporine.
 - An alternate approach would be to provide prospective analyses from completed, controlled studies evaluating lower exposures to cyclosporine in combination with everolimus and dosed according to prospectively defined TDM schemes.
 - Other approaches that may support the definition of a safe and effective regimen for everolimus in the prevention of graft rejection in *de novo* renal transplantation should be discussed with the Division.

The data analyses that support a therapeutic concentration range in *de novo* renal transplantation need to identify a clinically efficacious and safe concentration range of everolimus (upper as well as lower limits) when used with the proposed cyclosporine concentration range. A safe and effective TDM regimen for everolimus, used in combination with cyclosporine would also require a validated assay for everolimus blood levels, and need to be supported by experience with a successful monitoring schedule and dose adjustment scheme, proven capable of maintaining patients within the proposed therapeutic concentration range.

2. Provide information supporting a safe and effective dosing regimen for everolimus and cyclosporine that would minimize renal function impairment

while maintaining adequate protection against graft rejection, graft loss or death in *de novo* cardiac transplantation.

- One approach would be to provide data from an adequate well-controlled study or studies prospectively evaluating concentration-controlled regimens of everolimus in combination with concentration-controlled cyclosporine in *de novo* cardiac transplant recipients, which would support therapeutic dose monitoring (TDM) schemes for everolimus and cyclosporine.
- Other approaches that may support the definition of a safe and effective regimen for everolimus in the prevention of graft rejection in *de novo* cardiac transplantation should be discussed with the Division. Information from TDM regimens for everolimus in other solid organ transplantation could be sufficient to support a safe and effective regimen in cardiac transplantation, but that can only be determined by the review of the data.

The data analyses that support a therapeutic concentration range in *de novo* renal transplantation need to identify a clinically efficacious and safe concentration range of everolimus (upper as well as lower limits) when used with the proposed cyclosporine concentration range. A safe and effective TDM regimen for everolimus, used in combination with cyclosporine would also require a validated assay for everolimus blood levels, and need to be supported by experience with a successful monitoring schedule and dose adjustment scheme, proven capable of maintaining patients within the proposed therapeutic concentration range.

Other issues that may continue to require attention include, but are not limited to, characterization of additional potential drug interactions, and characterization of the steady state pharmacokinetics of everolimus in renal and cardiac transplant recipients.

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/s/

Marc Cavaille Coll

10/27/03 03:16:46 PM

MEDICAL OFFICER

Medical Officer Team Leader Memo for Certican® NDAs 21560,21628,21631,21561

**Division Director's Review
NDA 21-560 (kidney), NDA 21-628 (heart)**

**Certican[®] (everolimus) for Immunosuppression to Prevent Organ Rejection
in Patients Undergoing Kidney and Heart Transplantation**

Date: October 17, 2003

From: Renata Albrecht, M.D.
Director, DSPIDP, HFD-590

Through: Edward M. Cox, M.D., M.P.H.,
Deputy Director, ODE IV, HFD-104

Mark Goldberger, M.D., M.P.H.
Director, ODE IV, HFD-104

Re: Certican[®] tablet (everolimus, RAD001, SDZ RAD)
Novartis Pharmaceuticals Corporation

Original Submission Date: December 19, 2002

Action Due Date: October 20, 2003

Related INDs and NDAs: IND 52,003 (tablets) NDAs 21-561 and
21-631 (dispersible tablet)

**Division Director's Recommended Regulatory Action and Outstanding
Issues:**

**Recommend Approvable letters be issued for both indications --
immunosuppression in prevention of organ rejection in patients
undergoing kidney and heart transplantation.**

Fundamentally, the clinical trial program for both indications showed the proposed fixed dose regimens studied were effective or active in preventing rejection, but they were not considered safe, showing an unacceptable rate and degree of renal and other toxicity:

- Efficacy was demonstrated by statistically significant difference favoring the everolimus regimens in the combined endpoint and the difference was due to biopsy-documented acute rejection \geq 3A but not due to significant differences in graft loss or death.
- Safety findings showed statistically significant difference in renal function, where both everolimus doses were more toxic than the comparators
- The finding of renal toxicity resulted in protocol amendments at 12 months (in 2-3 year trials) to allow for conversion from fixed doses to target concentration dosing using therapeutic drug monitoring (TDM) for both

(b) (4)

In discussions with the company over the years -- particularly as more was learned from the fixed dose studies and in view of information that has been published over the years for Rapamune (sirolimus), the first member of this drug class -- the concern about drug toxicity with everolimus and full-dose cyclosporine concentration led to the recommendation that reduced cyclosporine doses should be evaluated and prospective trials to evaluate concentration-controlled dosing using TDM should be undertaken. Because these drugs involve CYP3A, lower cyclosporine doses will likely warrant higher everolimus doses and the resulting efficacy and safety of these doses cannot be predicted without actual data from an adequate and well-controlled clinical study intended to evaluate TDM. Everolimus is not inherently significantly nephrotoxic as shown in animal toxicology studies, but when used in combination with cyclosporine, renal toxicity is observed, most likely due to the drug interaction and enhancement of cyclosporine toxicity.

The company indicated that their initial interest was focused on the everolimus and cyclosporine regimens submitted; although more recently two noncomparative trials testing TDM have been conducted in kidney transplant patients - A2306 and A2307. These trials introduce a new concentration determination for cyclosporine at 2hr after administration "C2." The Division recommended that the protocols be modified to include an approved control regimen arm and TDM should include the conventional cyclosporine trough monitoring. Nevertheless, in these studies patients are prospectively dosed to target everolimus and cyclosporine concentrations. According to the company, the full reports for these studies will be available November 2003, which is after the October 20, 2003, action date for this standard application. Therefore, information from these and other prospective data on TDM will need to be reviewed as part of a resubmission. In addition, there is currently no study evaluating TDM in heart transplantation, therefore, in the absence of such a study, the input of an FDA Advisory Committee may be warranted to discuss whether the results are adequate to support renal transplantation and whether the data may be extrapolated to heart transplantation or whether a TDM heart transplantation study should be conducted prospectively. During telephone conversations with the company in September and October of 2003, some of the Division's outstanding questions and concerns have been discussed and the need for prospective data on patients managed by TDM has been discussed. Although the company believes the data demonstrate that everolimus is safe and effective and would prefer the drug be approved during the first cycle, the company will continue to work with the Division and Office to address the aforementioned questions or deficiencies.

Background

The original NDA for everolimus tablets (also known during development as RAD001 and SDZ RAD) was submitted on December 19, 2002 by Novartis Pharmaceuticals Corporation. The proposed indications were immunosuppression in allogeneic kidney transplantation, NDA 21-560, and heart transplantation, NDA 21-628, in adult patients. The company had three pre-NDA meetings with the Agency: December 3, 1999; February 6, 2001 and March 25, 2002. The company's initial plan was to pursue marketing for kidney transplantation (studies B201 and B251), but because of increased renal toxicity seen during clinical development, the company amended the kidney trials at 12 months to allow therapeutic drug monitoring and continued to follow patients' renal function. As presented in more detail below, the application submission was delayed as the company collected data for 36 months in the kidney studies (B201 and B 251) and for 24 months in the heart study (B253). The initial plan was to seek approval for kidney transplant in adults, this was modified to include a pediatric study and then replaced with proposal for heart transplantation. The company was particularly optimistic about the findings from IVUS (intravenous ultrasound) evaluation of the left anterior descending (LAD) coronary artery showing patency, suggesting this evidence of efficacy may offset the observed adverse effects on renal function. This information was recently been published in NEJM 2003:349:847-58 and reported statistically superior activity of everolimus compared to the azathioprine control arm in incidence of cardiac vasculopathy as represented in LAD intimal thickening. A letter to the editor (reproduced below) commenting on the limitations of the trial design has been sent to the NEJM by our statistical reviewers (check if accepted)

Eisen, et al. concluded everolimus was more efficacious than azathioprine in reducing cardiac-allograft vasculopathy severity, measured by changes in intravascular ultrasonography (IVUS) parameters from baseline to month 12. However, since a majority (67%) of randomized patients was excluded from IVUS analyses (resulting in a non-randomly selected subset), these conclusions may be undeserved.

The authors state that patients were excluded if IVUS procedures posed significant risk, which leaves one speculating about the magnitude of selection bias and if an effect is present in these higher risk patients.

Treatment discontinuation rates were higher in everolimus groups. However, IVUS sub-study eligibility for patients discontinuing treatment was not addressed by the authors. Exclusion of these patients would create serious selection bias. Inclusion would be problematic as effects may then be attributable to differential use of alternate therapy.

In that the authors' conclusion regarding cardiac-allograft vasculopathy was based on analyses of a small, possibly biased subset of patients and confounded by differential rates of treatment discontinuation, judgment regarding attributes of everolimus should be reserved until more sound information is available.

Everolimus is a macrolide immunosuppressive and anti-proliferative agent, produced by modification of rapamycin, a natural product isolated from

Streptomyces hygroscopicus. Two formulations are being developed, the tablet for adults and the dispersible tablet. The latter was initially developed for use in pediatric patients, but a pediatric indication has not been sought to date (see next 3 paragraphs).

The submission of the above two NDAs was followed by two additional NDAs that arrived unexpectedly on January 31, 2003 for the everolimus dispersible tablet; NDA 21-561 for kidney transplantation, and NDA 21-631 for heart transplant. The NDAs contained results of the 3 pediatric trials listed in the company's Pediatric Written Request, including the prematurely-terminated pediatric trial in kidney transplant patients, and the applicant requested a pediatric exclusivity determination. The Pediatric Exclusivity Committee met on May 9, 2003, and based on the deliberations during that meeting the decision to deny exclusivity was made. Specifically, the written request had asked Novartis to conduct three studies:

- Single dose pk study in 19 stable pediatric kidney transplant patients (done)
- Single dose pk study in 24 stable pediatric liver transplant patients (done)
- Multiple dose study to evaluate everolimus along with cyclosporine and steroids in 40 pediatric kidney transplant patients.

The applicant ended the multiple-dose study prematurely after 19 patients were enrolled, citing that reduced testosterone levels in adult patients was a safety concern. The division did not share this concern because the laboratory finding in adults was not associated with clinical findings, and low testosterone levels are also associated with renal failure and tend to go up with successful kidney transplantation. The levels in adult subjects on everolimus did increase post transplantation, but the increase was lower in magnitude compared to the control arm. While the Pediatric Exclusivity determination letter was being finalized (still pending), the company submitted a proposal to amend their WR to continue enrollment to the 40 patient target or ask for a new WR to enroll 21 additional pediatric patient. The company was advised that the WR had expired and could not be amended but that these discussions would need to take place after they received the Pediatric Exclusivity determination letter.

HEART TRANSPLANTATION:

(full discussion in reviews by Drs. Hernandez and Tracy, tables courtesy of reviewers)

The protocol for this trial (B253) was submitted to the agency in 1998. The trial evaluated two fixed dosage regimens of everolimus (0.75 mg PO BID and 1.5 mg PO BID) compared to azathioprine, in a combination regimen that also included cyclosporine and steroids. At 12 months into the study, based on the finding of renal toxicity in both everolimus arms, the protocol was amended to allow patients to be dosed based on "therapeutic drug monitoring" instead of fixed

doses; this amendment was not provided to the agency until the NDA submission.

The primary endpoint of the trial was a composite endpoint consisting of the following

- Biopsy-proven acute rejection histologic grade $\geq 3A$
- Acute rejection with hemodynamic compromise (HDC)
- Graft failure
- Death
- Loss to follow-up

In addition, other analyses were done that included patients who were treated for a rejection episode regardless of its histologic grade, and a composite endpoint that included clinically evident signs of rejection:

- Treated acute rejection
- Acute rejection with hemodynamic compromise (HDC)
- Graft failure
- Death

Efficacy Outcomes:

As seen in the tables below, the statistically significant difference between the everolimus regimens and azathioprine is accounted for by acute rejection of histologic grade ≥ 3 ; this is a histologic finding and may or may not always advance to clinically evident rejection. In comparison, when the other components of the endpoint are evaluated, there is no statistically significant difference between the three arms. There are some observations that are noteworthy. The acute rejection with HDC group is numerically lower in the everolimus groups compared to aza, graft loss, death rates and patient attrition rates are numerically higher in the 3 mg group compared to the 1.5 mg everolimus and aza groups. [Tables and Graphs from Dr. Laree Tracy]

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

Month 6 (up to day 194)	everolimus 1.5 mg (n=209)	everolimus 3 mg (n=211)	AZA (n=214)	95.0% CI	97.5% CI
Primary composite endpoint: (BPAR of grade ≥3A, AR assoc. with HDC, GL, death, or LTFU)	76 (36.5%)	57 (27.0%)	100(46.7%)	(-19.6,-1.0) ^a (-28.5,-10.6) ^b	(-20.9,0.4) ^a (-29.7,-9.3) ^b
BPAR of grade ≥3A	58 (27.8%)	40 (19.0%)	89 (41.6%)	(-22.7,-4.8) ^a (-30.8,-13.8) ^b	(-23.9,-3.5) ^a (-32.0,-12.6) ^b
AR associated with HDC	14 (6.7%)	11 (5.2%)	16 (7.5%)	(-5.89, 4.32) ^a (-7.20, 2.51) ^b	(-6.69, 5.12) ^a (-7.99, 3.26) ^b
Graft loss	4 (1.9%)	8 (3.8%)	6 (2.8%)	(-4.31, 2.36) ^a (-2.68, 4.84) ^b	(-4.94, 2.96) ^a (-3.31, 5.52) ^b
Death	13 (6.2%)	14 (6.6%)	12 (5.6%)	(-4.09, 5.40) ^a (-3.71, 5.88) ^b	(-4.84, 6.18) ^a (-4.47, 6.66) ^b
Loss-to-follow-up	0	0	1 (0.5%)	(-2.60, 1.34) ^a (-2.60, 1.33) ^b	(-3.14, 1.89) ^a (-3.14, 1.86) ^b
Month 12 (up to day 381)	everolimus 1.5 mg (n=209)	everolimus 3 mg (n=211)	AZA (n=214)	95.0% CI	97.5% CI
Primary composite endpoint: (BPAR of grade ≥3A, AR assoc. with HDC, GL, death, or LTFU)	87 (41.6%)	68 (32.2%)	113 (52.8%)	(-20.7,-1.7) ^a (-29.8,-11) ^b	(-22.0,-0.4) ^a (-31.1,-10) ^b
BPAR of grade ≥3A	64 (30.6%)	45 (21.3%)	98 (45.8%)	(-24.3,-6.1) ^a (-33.2,-16) ^b	(-25.7,-4.7) ^a (-34.4,-15) ^b
AR associated with HDC	17 (8.1%)	14 (6.6%)	23 (10.7%)	(-8.2, 3.0) ^a (-9.4, 1.2) ^b	(-9.0, 3.8) ^a (-10.2, 2.0) ^b
Graft loss	7 (3.3%)	11 (5.2%)	10 (4.7%)	(-5.1, 2.3) ^a (-3.6, 4.6) ^b	(-5.7, 2.9) ^a (-4.2, 5.2) ^b
Death	18 (8.6%)	24 (11.4%)	17 (7.9%)	(-4.5, 5.9) ^a (-2.1, 9.1) ^b	(-5.3, 6.7) ^a (-2.9, 9.9) ^b
Loss-to-follow-up	0	0	2 (0.9%)	(-2.2, 0.4) ^a (-2.2, 0.4) ^b	(-2.3, 0.5) ^a (-2.3, 0.5) ^b
Month 24 (up to day 810)	everolimus 1.5 mg (n=209)	everolimus 3 mg (n=211)	AZA (n=214)	95.0% CI	97.5% CI
Primary composite efficacy variable: (BPAR of grade ≥3A, AR assoc. w/HDC, GL, death, or LTFU)	96 (45.9%)	76 (36.0%)	123 (57.5%)	(-21.1,-2.1) ^a (-30.8,-12) ^b	(-22.4,-0.8) ^a (-32.1,-11) ^b
BPAR of grade ≥3A	73 (34.9%)	48 (22.7%)	103 (48.1%)	(-22.4,-3.9) ^a (-34.2,-17) ^b	(-23.8,-2.6) ^a (-35.4,-15) ^b
AR associated with HDC	19 (9.1%)	17 (8.1%)	28 (13.1%)	(-10.0, 2.0) ^a (-10.8, 0.8) ^b	(-10.8,-2.8) ^a (-11.7,1.7) ^b
Graft loss	10 (4.8%)	14 (6.6%)	13 (6.1%)	(-5.6,3.0) ^a (-4.1, 5.1) ^b	(-6.2,3.6) ^a (-4.8,5.8) ^b
Death	21 (10.0%)	29 (13.7%)	24 (11.2%)	(-7.1,4.7) ^a (-3.8,8.8) ^b	(-7.9,5.5) ^a (-4.7,9.7) ^b
Loss-to-follow-up	0	0	2 (0.9%)	(-2.2, 0.4) ^a (-2.2, 0.4) ^b	(-2.3, 0.5) ^a (-2.3, 0.5) ^b

Source: Table 9-1 (b253-12-month.pdf) and Table 2 (b253-34-month.pdf). Values verified by reviewer – AR=acute rejection, BPAR=biopsy-proven acute rejection, HDC=hemodynamic compromise, GL=graft loss, LTFU=lost to follow-up

^a everolimus 1.5 mg vs. AZA, ^b everolimus 3 mg vs. (Sponsor's analyses)

Renal Findings:

While the primary endpoint was evaluated at 6 months and 12 months, patients did have data collected weekly during the first month and monthly thereafter. At the 3 month evaluation, differences are already seen regarding safety; serum creatinine was significantly higher and creatinine clearance was significantly lower; the values go down slightly in the everolimus arms until month 12, and then increase slightly after the 12 month amendment. The reason for the slight increase in creatinine clearance from 12 to 24 months is not clear -- during this time period patients in the everolimus arm could convert to TDM; however, while the creatinine clearance increase is 1-2+ mL/min in the everolimus arms it is almost 3 mL/min in the aza arm, so other factors may be responsible. Some fluctuation is seen in the aza arm; however, the mean values are significantly higher than in either everolimus arm at all time points after baseline. Ojo [NEJM 2003;349:931-40] and Wilkinson [J Am Soc Nephrol 10:1136-1144,1999] write about the incidence of chronic renal failure in patients undergoing non-renal transplants and discuss the increased risk of death associated with chronic renal failure in this population.

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

	Everolimus 1.5 mg (N=209)	Everolimus 3.0 mg (N=211)	AZA (N=214)	p-value everolimus 1.5 vs. AZA everolimus 3.0 vs. AZA
Baseline	64.38(n=204) (m=5)	67.5(n=209) (m=2)	67.18 (n=210) (m=4)	0.2610 0.9053
Month 3	54.59 (n=170) (m=28) (gl/death=11)	55.56 (n=155) (m=46) (gl/death=10)	65.23 (n=168) (m=35) (gl/death=11)	<0.0001 0.0007
Month 6	53.00 (n=158) (m=38) (gl/death=13)	51.75 (n=155) (m=43) (gl/death=13)	62.68 (n=168) (m=34) (gl/death=12)	0.0001 <0.0001
Month 12	52.03 (n=146) (m=47) (gl/death=16)	52.95 (n=137) (m=50) (gl/death=24)	64.83 (n=156) (m=40) (gl/death=18)	<0.0001 0.0001
Month 24	54.46 (n=162) (m=27) (gl/death=20)	53.95 (n=164) (m=19) (gl/death=28)	67.41 (n=169) (m=22) (gl/death=23)	<0.0001 <0.0001

n=number of patients with assessments at time point

m=missed assessment not due to graft loss or death

gl/death=missed assessments due to graft loss or death

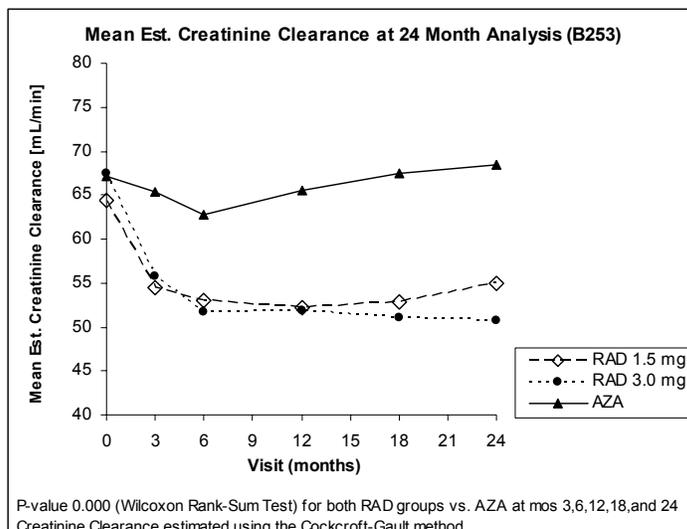
Pair-wise comparisons of treatment groups using Wilcoxon's Rank Sum test

CrCL calculated using the Cockcroft-Gault formula

Data description: All on and off-treatment creatinine measurements (ITT) in safety population.

Data source: Reviewer analyses of additional data requested from sponsor. Sponsor provided dataset located in NDA file [\\Cdsesub1\N21560\N_000\2003-08-06\CRT\Datasets\Heart\derived\crt_b253.xpt](#).

Findings consistent with NDA post-text table 10.7-28d.



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

	everolimus 1.5 mg (n=209)	everolimus 3.0 mg (n=211)	AZA (n=214)
Month 3	-10.9 (n=158)	-12.8 (n=149)	-2.3 (n=159)
Month 6	-12.7 (n=146)	-19.3 (n=149)	-4.8 (n=159)
Month 12	-14.7 (n=132)	-18.7 (n=129)	-2.8 (n=145)
Month 24	-13.4 (n=109)	-17.4 (n=98)	1.2 (n=118)

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

Creatinine Clearance calculated using the Cockcroft-Gault formula

Only patients with matched assessments at baseline and corresponding follow-up visit are included. On and off-treatment assessments (ITT) included from safety population.

Data source: Post-text table 10.3-1a (page 59-60)

Patients with Creatinine Clearance \leq 50% of Baseline Value

	everolimus 1.5 mg (n=209)	everolimus 3.0 mg (n=211)	AZA (n=214)	p-value everolimus 1.5 vs. AZA everolimus 3.0 vs. AZA
Month 3	13/159 (.08)	15/151 (.10)	4/161 (.025)	0.020 0.005
Month 6	15/146 (.10)	23/151 (.15)	7/160 (.044)	0.050 0.001
Month 12	14/136 (.10)	26/133 (.20)	7/148 (.047)	0.070 <0.001
Month 24	21/150 (.14)	26/160 (.16)	10/164 (.061)	0.019 0.004

P-values obtained using the chi-square test

Creatinine clearance calculated using the Cockcroft-Gault Formula

Data description: All on and off-treatment creatinine measurements (ITT) in safety population.

Data source: Reviewer analyses of additional data requested from sponsor. Sponsor provided dataset located in NDA file [\Cdsesub1\N21560\N_000\2003-08-06\CRT\Datasets\Heart\derived\crt_b253.xpt](#)

Mean Serum Creatinine (µmol/L) by Treatment Month

	everolimus 1.5 mg (N=209)	everolimus 3.0 mg (N=211)	AZA (N=214)	p-value everolimus 1.5 vs. AZA everolimus 3.0 vs. AZA
Baseline	139.52 (n=204) (m=5)	135.12 (n=209) (m=2)	134.84 (n=210) (m=4)	0.3868 0.9547
Month 3	163.39 (n=170) (m=28) (gl/death=11)	163.18 (n=155) (m=46) (gl/death=10)	134.24 (n=168) (m=35) (gl/death=11)	<0.0001 <0.0001
Month 6	176.60 (n=158) (m=38) (gl/death=13)	176.30 (n=155) (m=43) (gl/death=13)	149.11 (n=168) (m=34) (gl/death=12)	0.0001 <0.0001
Month 12	182.03 (n=146) (m=47) (gl/death=16)	185.84 (n=137) (m=50) (gl/death=24)	147.91 (n=156) (m=40) (gl/death=18)	<0.0001 <0.0001
Month 24	179.69 (n=162) (m=27) (gl/death=20)	179.52 (n=164) (m=19) (gl/death=28)	147.57 (n=169) (m=22) (gl/death=23)	<0.0001 <0.0001

n=number of patients with assessments at time point

m=missed assessment not due to graft loss or death

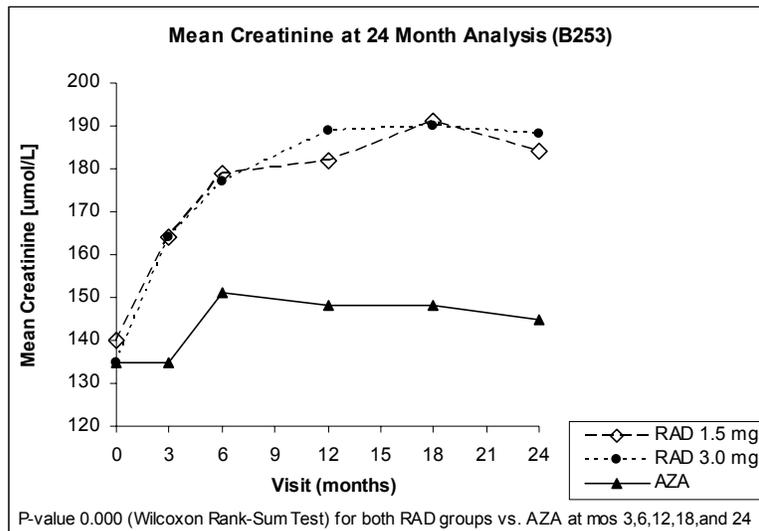
gl/death=missed assessments due to graft loss or death

Amendment 3 added serum creatinine at time of discontinuation and at 3 and 6 months after discontinuation

Pair-wise comparisons of treatment groups using Wilcoxon’s Rank Sum test

Data description: All on and off-treatment creatinine measurements (ITT) in safety population.

Data source: Reviewer analyses of additional data requested from sponsor. Sponsor provided dataset located in NDA file [\Cdsesub1\N21560\N_000\2003-08-06\CRT\Datasets\Heart\derived\crt_b253.xpt](#).



Mean Change from Baseline in Creatinine ($\mu\text{mol/L}$)

	everolimus 1.5 mg (n=209)	everolimus 3.0 mg (n=211)	AZA (n=214)
Month 3	25 (n=165)	28 (n=151)	2 (n=163)
Month 6	40 (n=152)	47 (n=151)	17 (n=163)
Month 12	46 (n=137)	58 (n=131)	14 (n=149)
Month 24	51 (n=115)	56 (n=99)	8 (n=120)

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

Only patients with matched assessments at baseline and corresponding follow-up visit are included.

On and off-treatment assessments (ITT) included from safety population.

Data source: Post-text table 10.3-1a (page 56-57)

Other Adverse Reactions:

While leukopenia and CMV syndrome (viral infection) were more common in the azathioprine arm, there were more bacterial pneumonias, elevated cholesterol and triglycerides reported as adverse events in the everolimus arm.

Furthermore, the 3mg everolimus arm had higher rates of neutropenia, thrombocytopenia, new onset of DM and GI hemorrhage compared to the other two arms. [Table from Dr. Arturo Hernandez]

Incidence rates of AEs/infections at month 24 with relevant differences between groups

	everolimus 1.5 mg (n=209)	everolimus 3 mg (n=211)	AZA (n=214)	p-value (95% CI) everolimus 1.5 vs. AZA everolimus 3.0 vs. AZA
Anemia NOS	70 (33.5%)	93 (44%)	58 (27%)	0.15 (-2.4, 15.1) <0.01 (7.9, 25.8)
Leukopenia NOS	43 (21%)	44 (21%)	63 (29%)	0.04 (-17.0, -61) 0.04 (-16.8, -34)
Neutropenia	1(0.5%)	5(2%)	10(5%)	0.01 (-8.2, -1.5) 0.18 (-6.5, 1.3)
Thrombocytopenia	21 (10%)	37 (17.5%)	16(7.5%)	0.39 (-3.2, 8.1) <0.01 (3.6, 16.4)
TMA ¹	5 (2%)	6 (3%)	0%	0.02 (.61, 5.5) 0.01 (1.1, 6.1)
Pericardial effusion	48 (23%)	49 (23%)	36 (17%)	0.11 (-1.5, 13.8) 0.10 (-1.2, 14.0)
Cardiac tamponade	6 (3%)	10 (5%)	3 (1%)	0.30 (-1.5, 4.9) 0.05 (0.1, 7.3)
CMV infection	15 (7%)	15 (7%)	45 (21%)	<0.01 (-20.5, -7.4) <0.01 (-20.6, -7.5)
Pneumonia NOS	29 (14%)	20 (9.5%)	6 (3%)	<0.01 (6.1, 16.7) <0.01 (2.3, 11.7)
Renal impairment NOS	61 (29 %)	65 (31%)	40 (19%)	0.01 (2.4, 18.6) <0.01 (3.9, 20.2)
Blood creatinine increased	24 (11.5%)	18 (8.5%)	10 (5%)	0.01 (1.7, 12.4) 0.11 (-0.9, 8.9)
Hyperlipidaemia NOS	38 (18%)	29 (14%)	13 (6%)	<0.01 (6.1, 18.5) <0.01 (2.1, 13.6)

Hypercholesterolemia ²	27 (13%)	25 (12%)	20 (9%)	0.24 (-2.5, 9.8) 0.40 (-3.4, 8.5)
Hypertriglyceridemia ³	13 (6%)	21 (10%)	11(5%)	0.63 (-3.5, 5.8) 0.06 (-0.21, 10.2)
Total Lipid Abnormalities	78(37%)	75(35.5%)	44(20.5%)	<0.01 (8.2, 25.2) <0.01 (6.5, 23.3)
Bacterial infection	78 (37%)	85 (40%)	55 (26%)	0.01 (2.8, 20.3) <0.01 (5.7, 23.3)
Fungal infection	18 (9%)	27 (13%)	19 (9%)	0.92 (-5.8, 5.3) 0.19 (-2.0, 10.0)
Viral infection	34 (16%)	39 (18.5%)	69 (32%)	<0.01 (-24.0, -7.9) <0.01 (-21.9, -5.5)
GI hemorrhage NOS	2 (1.0%)	9 (4.3%)	3 (1.4%)	0.67 (-3.2, 2.2) 0.07 (-0.3, 6.7)
New onset post-tx DM ⁴	7/174 (4%)	17/162 (10.5%)	7/178 (4%)	0.97 (-4.4, 4.6) 0.02 (1.2, 12.7)

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

² Includes blood cholesterol increased and hypercholesterolemia aggravated

³ Includes blood triglycerides increased and blood triglycerides abnormal

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

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

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

System Organ Classification or Preferred Term	everolimus 1.5mg (n=209)	everolimus 3.0 mg (n=211)	AZA (n=214)	P-value (95% CI) everolimus 1.5-AZA everolimus 3.0-AZA
Any SAE	127(61%)	137(65%)	117(55%)	0.21 (-3.3, 15.4) 0.03 (0.93, 19.4)
Infections and infestations	30 (14%)	44 (21%)	25 (12%)	0.41 (-3.8, 9.2) 0.01 (2.2, 16.3)
All types of pneumonia*	13(6%)	21(10%)	4(2%)	0.02 (0.67, 8.7) <0.01 (3.9, 13.1)
Renal impairment NOS	13(6%)	12(6%)	4(2%)	0.02 (0.67, 8.7) 0.04 (0.22, 8.1)
Pericardial effusion	12(6%)	11(5%)	6(3%)	0.14 (-1.0, 7.3) 0.22 (-1.5, 6.5)
Cardiac tamponade	3(1.4%)	5(2.4%)	2(1%)	0.63 (-2.1, 3.3) 0.25 (-1.3, 4.5)
Leukopenia NOS	5(2%)	5(2%)	11(5%)	0.14 (-6.9, 0.99) 0.13 (-6.9, 0.95)
CMV infections including: CMV infection, CMV hepatitis, Encephalitis CMV	1(0.5%)	4(2%)	5(2%)	0.11 (-4.9, 0.55) 0.75 (-3.7, 2.7)
Gastric hemorrhage/Gastrointestinal hemorrhage NOS	3(1%)	5(2 %)	1(0.5%)	0.30 (-1.3, 3.7) 0.10 (-0.47, 5.0)

Dyslipidemia including: Hyperlipidaemia NOS, Hypercholesterolemia, Blood cholesterol increased, Hypercholesterolemia aggravated Hypertriglyceridemia, increased blood triglycerides	5(2%)	9(4%)	2(1%)	0.24 (-1.2, 4.7) 0.03 (0.37, 7.1)
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*Adverse events included in this category were coded as any of the following: *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*

The company incorporated intravascular ultrasound (IVUS), a procedure of measuring intimal thickening in coronary arteries to evaluate chronic allograft rejection. Concerns raised by the review team about accepting the conclusions of the results in the table below include:

- Only about one third of the patients in the trial had evaluation
- The one third were not randomly selected; in fact patients who had renal toxicity were not considered candidates for the procedure
- Only one vessel was evaluated (again raising possibility of selection bias)

Despite the limitations identified, the results may be considered encouraging and it is possible that this procedure, if developed further, standardized, and used systematically, may provide useful information in future heart studies.

IVUS Results

	Everolimus 1.5 mg (n=70)	Everolimus 3.0 mg (n=69)	AZA (n=72)
Change (mm) in average maximum intimal thickness from baseline to month 12			
Mean	0.04 p=0.014	0.03 p=0.003	0.10
Range	(-0.36, 0.27)	(-0.20, 0.25)	(-0.44, 0.74)
Allograft vasculopathy			
≥0.5 mm	25 (35.7%) p=0.045	21 (30.4%) p=0.010	38 (52.8%)
<0.5 mm	45 (64.3%)	48 (69.6%)	34 (47.2%)

P-values represent pair-wise comparison against AZA

Wilcoxon's Rank Sum test used to compare change in average intimal thickness

Fisher's Exact Test used to compare incidence of allograft vasculopathy

Differences in the treatment arms were seen in other ways as well. In addition to differences in efficacy (statistically significant histologic difference but not in clinically evident HDC, graft loss of death) and safety (renal toxicity, elevated cholesterol and triglycerides), there were differences in the discontinuation of patients from the three arms. Again, a difference between the 3 mg dose and the others was seen already at month 6 and continued through 12 and 24 months. Interestingly, the rates of discontinuation and lack of therapeutic effect were

similar between the 1.5 mg and azathioprine arms; however the safety profile was more favorable in the azathioprine arm. [Tables from Dr. Laree Tracy]

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

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

^a everolimus 3.0 mg/day vs. AZA: $p=0.036$, 95% CI (0.6, 17.0), Z-test statistic

^b everolimus 3.0 mg/day vs. AZA: $p=0.007$, 95% CI (2.4, 15.2), Z-test statistic

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

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

^a everolimus 3.0 mg/day vs. AZA: $p=0.014$, 95% CI (2.3, 20.2), Z-test statistic

^b everolimus 3.0 mg/day vs. AZA: $p=0.018$, 95% CI (1.5, 16.0), Z-test statistic

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

	Everolimus 1.5 mg (n=209)	Everolimus 3 mg (n=211)	AZA (n=214)
Discontinued treatment up to 24 months	82 (39.2%)	104 (49.3%) ^a	83 (38.8%)
Adverse Event(s)	43 (20.6%)	58 (27.5%) ^b	40 (18.7%)
Abnormal Lab Value(s)	9 (4.3%)	18 (8.5%)	10 (4.7%)
Unsatisfactory therapeutic effect	15 (7.2%)	3 (1.4%)	18 (8.4%)
Death	7 (3.3%)	9 (4.3%)	7 (3.3%)
Withdrawn Consent	6 (2.9%)	11 (5.2%)	3 (1.4%)
Lost to follow-up	0	1 (0.5%)	2 (0.9%)
Protocol Violation	2 (1.0%)	4 (1.9%)	2 (0.9%)

Administration Problems	0	0	1 (0.5%)
Drug taken after study drug discontinuation			
Azathioprine	17 (21%)	29 (28%)	5 (6%)
mycophenolate mofetil	37 (45%)	41 (39%)	41 (49%)
Discontinued study prior to 24 months	23 (11.0%)	33 (15.6%)	31 (14.5%)
Death	21 (10.0%)	29 (13.7%)	24 (11.2%)
Withdrawn Consent	2 (1.0%)	3 (1.4%)	5 (2.3%)
Lost to follow-up	0	1 (0.5%)	2 (0.9%)

^a. everolimus 3.0 mg/day vs. AZA: $p=0.029$, 95% CI (1.1, 19.7), Z-test statistic

^b. everolimus 3.0 mg/day vs. AZA: $p=0.031$, 95% CI (.79, 16.8), Z-test statistic

The applicant did amend the protocol at 12 months and introduced therapeutic drug monitoring. It appears that this modification lead to stabilization in patient course, in that patient discontinuation is approximately 30% in the first 6 months in the 3mg everolimus arm and approximately 20% in the other two arms; from 6-12 months an extra 10% in each arm discontinued treatment and from 12-24 months yet again an additional 10% discontinue treatment, suggesting maintainance on TDM may be effective. The applicant has used this information obtained from months 12-24 to request that TDM be approved for patients in the immediate post-transplant period on. However, while some may hold that pharmacodynamically, this should be acceptable, others, including our clinical pharmacology, statistical and medical reviewers, recommend that this hypothesis be tested prospectively for various reasons including:

- The patients were not studied for TDM during the first 12 months after transplantation
- Pharmacodynamic parameters were not measured prospectively (patients were on fixed doses, and not randomized to target drug concentrations)
- Cyclosporine levels were not adjusted (reduced or eliminated) during the first 12 months of study, therefore, the impact on either efficacy or safety has not been assessed – this is important because of the drug interaction between these two products

Therefore, the expected efficacy and safety outcome cannot be extrapolated from the current trial. So, while it is reasonable for the company to explore whether results of B253 could support TDM, there is inadequate data to grant this approach. To date, immunosuppresants that are labeled to be used under TDM have actually been studied in protocols where drug levels were monitored and adjusted to target levels. The same approach was discussed with the company during telecons on September 4 and 12, 2003. The company also

(b) (4)

(b) (4)

KIDNEY TRANSPLANTATION:

(complete reviews by Drs. Hernandez and Davi; tables courtesy of reviewers)

Two clinical trials (B201 and B251) were conducted to support this indication, testing two doses of everolimus (0.75 mg BID or 1.5 mg BID) compared to mycophenolate mofetil 1 mg. These drugs were added to a regimen of cyclosporine and steroids. The primary goal of the trial was to prevent acute rejection of the transplanted kidney, and the primary endpoint was a composite of the following:

- Biopsy proved acute rejection grade \geq 3A or greater
- Graft loss
- Death
- Lost to follow up

Patients were evaluated at 3, 6 and 12 months, by which time it was apparent that there was an increase in renal toxicity in the everolimus arms, leading to a protocol amendment and TDM. As was seen in the heart transplantation trial, premature discontinuation of treatment was more common in the everolimus arm, particularly the 3 mg/day arm and attributed mostly to adverse events and abnormal laboratory values. Also noted in the table are inconsistent results of unsatisfactory efficacy in the two everolimus arms compared to the MMF arm. Withdrawal of consent was more common in the 3 mg/day arm. [Table from Dr. Ruthie Davi]

Premature Treatment or Study Discontinuation (ITT Group)						
	Study B201			Study B251		
	1.5 RAD (N=194)	3.0 RAD (N=198)	MMF (N=196)	1.5 RAD (N=193)	3.0 RAD (N=194)	MMF (N=196)
Prematurely Discontinued Treatment	69 (36%)	85 (43%)*	55 (28%)	56 (29%)	82 (42%)^	50 (26%)
Adverse event(s)	37 (19%)	55 (28%)	39 (20%)	36 (19%)	36 (19%)	20 (10%)
Abnormal lab value(s)	5 (3%)	5 (3%)	1 (1%)	0 (0%)	6 (3%)	3 (2%)
Abnormal test result(s)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Unsatisfactory efficacy	17 (9%)	8 (4%)	7 (4%)	13 (7%)	21 (11%)	14 (7%)
Protocol violation	2 (1%)	5 (3%)	4 (2%)	2 (1%)	7 (4%)	4 (2%)
Withdrawal of consent	5 (3%)	9 (5%)	2 (1%)	4 (2%)	8 (4%)	6 (3%)
Lost to follow-up	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Administrative problems	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Death	2 (1%)	3 (2%)	1 (1%)	1 (1%)	3 (2%)	2 (1%)
Prematurely Discontinued Study	11 (6%)	11 (6%)	6 (3%)	10 (5%)	10 (5%)	5 (3%)
Death	10 (5%)	10 (5%)	5 (3%)	6 (3%)	8 (4%)	4 (2%)
Withdrawal of consent	0 (0%)	1 (1%)	1 (1%)	3 (2%)	1 (1%)	0 (0%)
Lost to follow-up	1 (1%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)	1 (1%)

*Statistically significantly differences, p=0.0023 for 3.0 RAD versus MMF

^Statistically significantly differences, p=0.0079 for 3.0 RAD versus 1.5 RAD and p=0.0012 for 3.0 RAD versus MMF

#With modifications in format, this table was provided in the sponsor's submission.

Efficacy Outcomes:

As seen in the tables below, the everolimus regimens were not inferior to MMF (95% and 97.5% C.I. crosses zero), however, not all subgroup analyses met the prespecified -10% delta for assessing noninferiority. There is also inconsistency in the two everolimus arm regarding rates of graft loss and deaths. At 6 months, graft loss is more common in the 1.5 mg arm in B201 and the 3 mg arm in B251, death is more common in both everolimus arms compared to MMF. At 12 months the two regimens are again not inferior (C.I. does cross zero), yet the 3 mg regimen has more graft loss, death or loss to follow-up in B201 and the 1.5 mg regimen has more graft loss, death or loss to follow-up in B251.

Primary Efficacy Analyses (ITT Group)						
	Study B201			Study B251		
	1.5 RAD (N=194)	3.0 RAD (N=198)	MMF (N=196)	1.5 RAD (N=193)	3.0 RAD (N=194)	MMF (N=196)
Efficacy Failure Within 6 Months	52 (26.8%)	52 (26.3%)	58 (29.6%)	42 (21.8%)	46 (23.7%)	51 (26.0%)
Biopsy-proven acute rejection	42 (21.6%)	36 (18.2%)	46 (23.5%)	33 (17.1%)	39 (20.1%)	46 (23.5%)
Graft loss	5 (2.6%)	12 (6.1%)	10 (5.1%)	7 (3.6%)	3 (1.5%)	4 (2.0%)
Death	5 (2.6%)	4 (2.0%)	2 (1.0%)	2 (1.0%)	4 (2.1%)	1 (0.5%)
Loss to follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
95% CI* (RAD – MMF)	(-11.7%, 6.1%) [#]	(-12.2%, 5.6%) [#]	NA	(-12.7%, 4.3%) [#]	(-10.9%, 6.3%) [#]	NA
97.5% CI* (RAD – MMF)	(-13.0%, 7.4%)	(-13.4%, 6.8%)	NA	(-13.9%, 5.5%)	(-12.1%, 7.5%)	NA
Graft Loss, Death, or Loss to Follow-up within 12 Months	21 (10.8%)	33 (16.7%)	23 (11.7%)	22 (11.4%)	15 (7.7%)	13 (6.6%)
Graft loss	9 (4.6%)	21 (10.6%)	18 (9.2%)	17 (8.8%)	8 (4.1%)	10 (5.1%)
Death	9 (4.6%)	8 (4.0%)	3 (1.5%)	4 (2.1%)	6 (3.1%)	2 (1.0%)
Lost to follow-up	3 (1.5%)	4 (2.0%)	2 (1.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
95% CI* (RAD – MMF)	(-7.2%, 5.4%)	(-1.9%, 11.9%)	NA	(-0.9%, 10.5%)	(-4.0%, 6.2%)	NA
97.5% CI* (RAD – MMF)	(-8.1%, 6.3%) [#]	(-2.9%, 12.9%)	NA	(-1.7%, 11.3%)	(-4.7%, 6.9%) [#]	NA

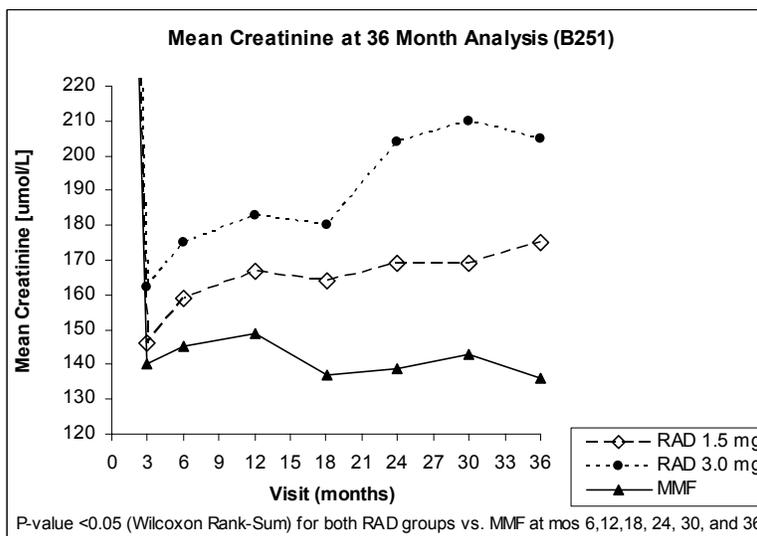
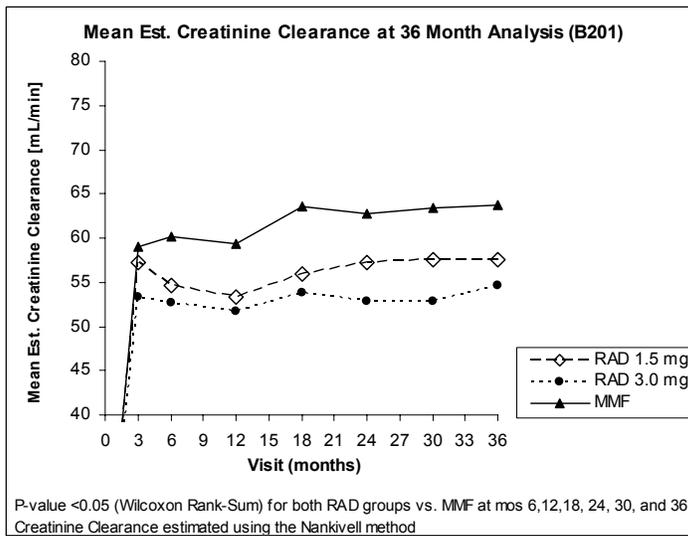
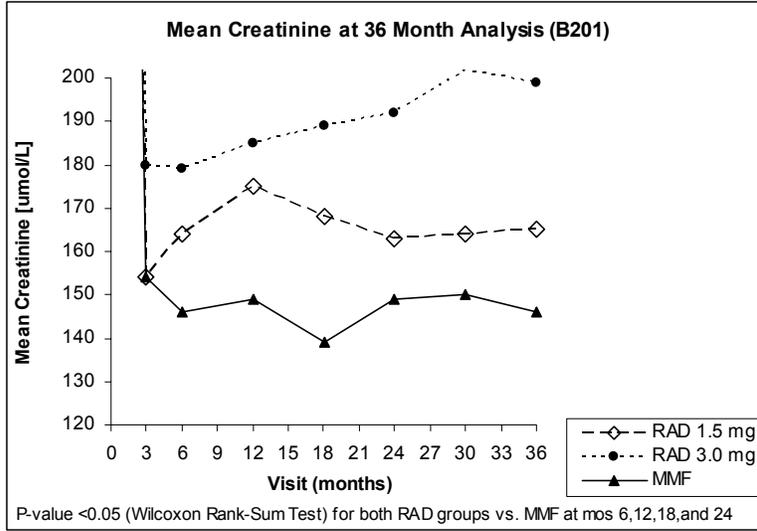
*Calculated using normal approximation methods.

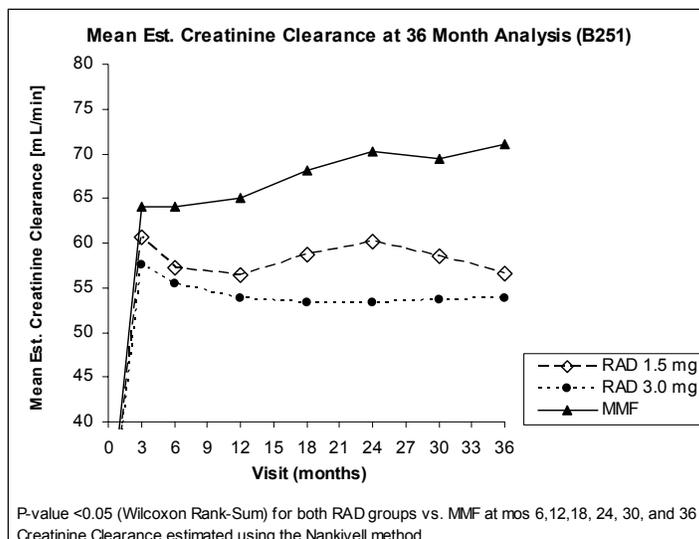
^Individual components of the efficacy endpoint are presented by first event and are mutually exclusive.

#Shaded areas indicate statistically noninferior results.

Renal Findings:

There is again a decrease in creatinine clearance and an increase in serum creatinine in the everolimus arms, with the effect being more pronounced in the 3 mg arm compared to the 1.5 mg arm and both having a greater adverse effect on the kidney than MMF. This finding led the company to amend the protocol at 12 months to provide the option for TDM and concentration controlled dosing and postpone submission of the NDAs until data were available through 36 months.





RELATED COMPOUND – Rapamune (sirolimus)

The findings in the heart and kidney studies, and the subsequent amendment were perhaps unanticipated at the time the trials were initiated in 1990's; however, the findings were not surprising as more became known about this drug class. The first product to be developed, sirolimus is the subject of NDA 21-083 (oral solution) and NDA 21-110 (tablets) by Wyeth Pharmeceutics. The company evaluated the drug for kidney transplantation in two trials and the drug was superior to the azathioprine control regimen in one study and to the placebo control in the second study. The reduction in renal function was noted and the product was approved, following discussion at an Advisory Committee meeting, in September 1999 with labeling reporting this finding. The company conducted further evaluation of rapamune in a "cyclosporine sparing" regimen where rapamune TDM levels were targeted and cyclosporine doses reduced or eliminated from the regimen after 2-4 months. The cyclosporine sparing regimen was approved in April, 2003, following an advisory committee meeting (1/24/02), approvable letter (2/8/02) and resubmission (10/11/02). The patients tested on this "cyclosporine sparing" regimen were generally considered low risk, and shown to have a good efficacy and safety outcome. The appropriate use of Rapamune in high risk transplant patients is under evaluation in Phase 4 trials. Careful evaluation of products in this class is prudent, given reports of disproportionate incidence of hepatic artery thrombosis in patients undergoing liver transplantation and wound dehiscence in patients undergoing lung transplantation.

SUMMARY:

The clinical trials of kidney transplantation and heart transplantation showed that everolimus was effective in the composite endpoint as defined above. However, the safety profile, particularly renal impairment, was judged not acceptable. The trials were amended at 12 months to allow TDM and patients renal function

appeared to stabilize. However, these results were not adequate to recommend TDM in the immediate post-transplantation period. In addition, the analysis reporting outcome in relation to drug concentrations in the first 12 months is informative but not valid because the patients were not randomized to target concentrations. However, the analysis does support that further evaluation of the appropriate dosage regimen for everolimus, in combination with cyclosporine, for patients undergoing kidney and heart transplantation should be pursued. The goal of the TDM regimen is to maintain efficacy and improve the safety profile of the regimen.

An approvable letter should be sent to the company, requesting prospectively collected data on TDM in patients undergoing kidney or heart transplantation. The recommended approach would be to conduct an adequate and well controlled trial, comparing the TDM regimen of everolimus and cyclosporine to a currently-approved regimen. Patients should be evaluated for the composite endpoint (and components thereof) used in previous trials, as well as safety, and the evaluation should be for approximately 6 months after transplantation for the purposes of resubmission. However, given that studies of other drug regimens of everolimus have been conducted, it is possible that other prospectively collected data may be used to address the question of an appropriate safe and effective dosing regimen. Final reports for studies A2306 and A2307 will be submitted to the Division [presumably as part of a resubmission] and will be reviewed to determine whether they provide adequate information to address a safe and effective concentration-controlled regimen.

The company should also develop (and ideally seek approval for) an assay to be used for TDM.

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this page is the manifestation of the electronic signature.**

/s/

Renata Albrecht
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NDA 21-560 and NDA 21-628

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10/17/03 06:28:21 PM
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MEDICAL OFFICER REVIEW

NDA 21-560 (adult tablets – Kidney transplantation)

NDA 21-628 (adult tablets – Heart transplantation)

NDA 21-561 (tablets for oral suspension – Kidney 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 Kidney and Heart Transplantation

Application submitted:

December 19, 2002 (NDAs 21-560 and 21-628) and 120-day safety update on May 2, 2003

January 31, 2003 (NDAs 21-561 and 21-631) and 120-day safety update on June 26, 2003

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

NDAs: 21-560, 21-561, 21-268, and 21-631

HFD-590/Original NDAs 21-560, 21-628, 21-561, and 21-631

HFD-590/Division File

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HFD-590/Chem/MSeggel

HFD-590/Pharm/SKunder

HFD-590/RRO/RAnderson

HFD-590/PMTL/EMolinaro

HFD-590/PM/MBacho

HFD-880/BphTL/Pcolangelo

HFD-880/Bph/JLee

HFD-725/StatTL/KHiggins

HFD-725/Stat/RDavi

HFD-725/Stat/LTracy

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2. 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
CInh	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™
RAD-1.5 group:	Certican™ 1.5 mg dose group (given as 0.75mg twice daily [bid])
RAD-3 group:	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

3. DEFINITIONS

Everolimus (40-O-[2-hydroxyethyl]-rapamycin), SDZ-RAD or RAD001: Is a Rapamycin derivative known also as Certican®. We will use all this synonyms when appropriate but we will use the term RAD primarily.

Acute Rejection Episodes: International Society of Heart and Lung Transplantation (ISHLT) classification.

Antibody treated acute rejection: Only *suspected* rejections (treated with antibodies) where *final clinical diagnosis* = **acute rejection** will be considered *antibody treated acute rejections*. *Antibody treated acute rejections* are thus a subset of *clinically confirmed acute rejections*.

Chronic Rejection: Also referred as allograft vasculopathy.

Clinically confirmed acute rejection episodes: include 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 = *rejections diagnosed as chronic on clinical grounds. Do not include biopsy-proven chronic rejection.*

DAE: Adverse Event Leading to Discontinuation

HDC (Hemodynamic compromise) was 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.

Efficacy failure in study B253 (Key Heart Study): 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])

Efficacy failure in studies B251 and B201 (Key Renal Studies):

Hemodynamic compromise: (HDC) is 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 inotropics.

Hypogonadism (Laboratory-defined): Low (age adjusted) testosterone level **and** LH >15 IU/L in an adult male.

Key Renal Studies: B251 (USA study) and B201 (EU study)

Non-significant, was not significant, etc.: This term is used to denote "not statistically significant"

Notable events include Deaths, NSAEs (Non-Fatal Serious AEs) and ADOs (Adverse dropouts). ADOs were patients with primary discontinuation reasons: AEs or abnormal laboratory values or abnormal test procedure result.

Novartis Pharmaceuticals Corporation: We may use Novartis or the applicant

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.

Subclinical rejections: acute rejection found on "protocol" [surveillance] biopsies performed [in the absence of clinical symptoms]. Protocol biopsies were required only at selected sites in study 251 at 6, and 36 months. In study 201 surveillance biopsies at 6, 12 and 36 were optional

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

Treatment failure

Treatment Endpoint (TEP) was used as a synonym of the last observation carried forward (LOCF)

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

4. EXECUTIVE SUMMARY

Everolimus (RAD) is a macrolide immunosuppressant derived from rapamycin that bind to FKBP¹. The RAD-FKBP complex binds and inhibits the action of mTOR² suppressing the 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 an original NDA for the prophylaxis of organ rejection in allogeneic kidney and heart transplant patients. The proposed regimen considers the use of Certican® concurrently with Neoral and corticosteroids.

To support this application, the applicant is presenting two key phase III *de novo* renal allograft trial (B201 and B251) for the kidney indication and one key *de novo* heart study (B253) for the heart indication.

Key Renal Studies: Two key phase III *de novo* renal allograft trials (Studies B201 and B251) were submitted to support the proposed regimen.

In these key studies, Certican (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 failure³ at 6 months.

During the first 12 month (Double blind phase), higher rates of renal allograft dysfunction were observed in both RAD arms (RAD1.5 and RAD 3) compared with MMF arm in both key renal studies. DSMB recognized a RAD/CsA interaction that was believed to enhance the nephrotoxic effects of CsA. DSMB did not recommended any changes in the protocol design at that point. However, Novartis' experts decided to amend both key renal studies.

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 years randomized, multicenter study, RAD 1.5 mg/day and RAD 3 mg/day, were compared versus Azathioprine (AZA), 1-3 mg/kg/d. The three arms received standard Neoral dose and corticosteroids. The efficacy was measured by the incidence of the composite endpoint⁴ in the first 6 months post-transplant.

(b) (4)

¹ FK binding protein

² Mammalian target of Rapamycin

³ Composite endpoint Key Renal Studies: Biopsy-proven acute rejection, graft loss, death or loss to follow-up

⁴ Composite endpoint Key Heart Study: Death, graft loss / re-transplant, biopsy-proven acute rejection episode (BPAR) ≥Grade 3A or any clinically suspected acute rejection episode associated with hemodynamic compromise (HDC)

The primary composite endpoint for RAD 1.5 and RAD 3 was superior to AZA. However, RAD fixed dose regimens 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. It provided for conversion from a double blind to an open label designs, from RAD fixed dose to 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 to reach conclusions based on fixed dose regimens.

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.

**Fixed dose RAD regimen and full dose Neoral® and
Concentration controlled regimen of RAD and reduced CsA exposure**

The originally proposed regimens for the prevention of allograft rejection in heart and kidney proved to be effective with respect to the primary endpoints⁵. However, RAD fixed dose regimens demonstrated to be unsafe due to marked nephrotoxicity. In an attempt to decrease nephrotoxicity while maintaining efficacy, the applicant implemented amendment # 3 at 12 month post-transplantations in both Key Heart and Key Renal studies. The studies were unblinded and the RAD fixed dose regimens were 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. In conclusion, dose adjustments implemented by amendment #3 at 12 months had a limited effect in improving renal function and fail to revert 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.

⁵ **Heart 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.

Kidney Primary endpoint: Composite of Biopsy-proven acute rejection, graft loss, death or loss to follow-up

5. STATEMENT OF CONCLUSIONS

In conclusion, the information provided in this NDA 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 regimens for the prevention of allograft rejection in heart and kidney proved to be effective with respect to the primary endpoints⁶. 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 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.

6. 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 further acceptable if it exceed the supposed benefits (Rejection free, patient and graft survival).

The information provided in these NDA's 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 endpoints⁷. However, RAD fixed dose regimens 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 amendments #3. By these amendments, patients with renal dysfunction in the RAD

⁶ **Heart 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.

Kidney Primary endpoint: Composite of Biopsy-proven acute rejection, graft loss, death or loss to follow-up

⁷ **Heart 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.

Kidney Primary endpoint: Composite of Biopsy-proven acute rejection, graft loss, death or loss to follow-up

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, suggest irreversible kidney damage.

In both RAD arms and across Key Heart and Renal Studies studies, common characteristic 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, TMA⁸, 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 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 in 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 it did not include any precautions to avoid bias for the collection of CMV related information.

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 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.

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

Hypertension and Diabetes Mellitus were common co-morbidities recognized among transplant patients and clinically relevant differences were not observed 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.

Hyperlipidaemia, proteinuria, hypertension and DM are conditions that are known to correlate with the progression of renal dysfunction. The concurrence of these co-morbidities was more frequently observed in both RAD arms across both key renal studies. This fact correlate 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 as well the most concerning issue. 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

⁸ TMA (Thrombotic microangiopathy) including HUS (Haemolytic uraemic syndrome) and TTP (Thrombotic thrombocytopenic purpura) are consumptive coagulopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia.

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 haemorrhage and new onset diabetes mellitus are 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 a 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 this patients at a greater risk for severe renal failure which has been associated to increased mortality.

7. 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 we 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 profile was observed in the original fixed dose regimen studied on the key heart and renal trials.

We believe that therapeutic drug monitoring is a promising approach. The use Everolimus plus CsA minimization strategy appears to 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.

RECOMMENDATIONS:

The provided information 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 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 with out compromising efficacy in both heart and kidney transplant patients.

Exposure-efficacy and exposure-safety analysis provided data to delineate a potential TDM range that in conjunction with CsA dose minimization appears to show a more acceptable safety profile. However, such concentration-controlled regimen 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, produces the desired improvement in renal function.

We recommend that this study defines prospectively target concentration ranges over time for both Certican and CsA and demonstrate 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 this indications, 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 FKBP⁹ that inhibits the action of mTOR¹⁰, suppressing the 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 (Novartis or applicant) submitted the original IND 52,003 application for everolimus Tablets on November 15, 1996¹¹. Novartis' rationale for developing a 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.

We have antecedents of three pre-NDA meeting 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 it 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 BB, DD design to open label at 12 months post randomization. These drastic changes resulted from the key renal studies 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 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 been already unblinded. (See teleconference minutes October 20, 2000).

⁹ FK binding protein

¹⁰ Mammalian target of Rapamycin

¹¹ 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".

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 worst renal function and a 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 a lower CsA though blood level (50 – 75 ng/mL) and Novartis' hope was that this change would help alleviate the nephrotoxicities associated with 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.

In summary:

- ***Key studies conversion 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***
(b)
(4) ***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. In this occasion, **Novartis** proposed NDAs for heart and renal transplantation. 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 filing NDA.

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 review¹². Furthermore, 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.

In December 19, 2002, Novartis Pharmaceuticals Corporation submitted NDA's 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 request 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, Pharmacotoxicology, medical, and statistical areas (**June 24, 2003**)

120-day safety updates were submitted to the respective NDA's on May 2, and June 26, 2003. The update 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:

- [REDACTED] (b) (4) [REDACTED]

¹² 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.

- [REDACTED] (b) (4)

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 through level of 12 ng/mL. However, no information was included on the relationship of the recommended upper limit of everolimus and the efficacy and safety.*

- [REDACTED] (b) (4)

On 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 teleconference 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**, in this response the Applicant provided information on:

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.

11. CLINICAL TRIALS

Key Renal, Key Heart, Supportive and Pediatric Studies

In December 19, 2002 Novartis Pharmaceuticals Corporation submitted NDA containing studies supporting the proposed indication of Certican® for the prophylaxis of organ rejection in allogeneic kidney and heart transplantation. Table 11.1 summarizes the key and supportive studies for the new proposed indications.

Table 11.1. Key and Supportive Studies.

Study no.	Design	Duration	No. of patients
B253 Key heart study	R, DB, DD, AC, MC, MD, E, S, PK, <i>de novo</i>	3 years (1-year DB /1 year OL by amendment) + 1-year OL extension	Total – 634 RAD 1.5 mg – 209 RAD 3 mg – 211 AZA 1-3 mg/kg/day – 214
B251 Key renal study	R, DB, DD, AC, MC, MD, E, S, PK, <i>de novo</i>	3 years (1 year DB / 2 years OL by amendment)	Total - 583 RAD 1.5 mg – 193 RAD 3 mg – 194 MMF 2 g – 196
B201 Key renal study	R, DB, DD, AC, MC, MD, E, S, PK, <i>de novo</i>	3 years (1 year DB/ 2 years OL)	Total - 588 RAD 1.5 mg – 194 RAD 3 mg – 198 MMF 2 g – 196
B156 Renal supportive study	R, OL, MC, MD, E, S, <i>de novo</i> , w/Simulect	3 years	RAD 3 mg – 111 (full dose Neoral – 53 & reduced dose Neoral – 58)
B157 Renal supportive study	R, DB, MC, MD, S, T, PK, <i>de novo</i>	3 years (1 year DB/ 2 years OL ext.)	Total - 103 RAD 1 mg – 34 RAD 2 mg – 34 RAD 4 mg – 35
B351 Renal pediatric study	OL, MC, MD, E, S, T, PK, <i>de novo</i>	1 year	Total -19 RAD 0.8 mg/m ² BSA bid (maximum of 1.5 mg independent of BSA)

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:

Key Renal studies were modified by four amendments and the heart study by three amendments. The original protocol and amendments for Renal Study B201 were not submitted to IND 52,003 because it was conducted outside the U.S. and we did not have the opportunity to discuss those amendments with the applicant.

Studies A2306 and A2307

Preliminary clinical reports on renal transplant studies A2306 and A2307 were submitted in NDA 21-560. These studies are ongoing at the completion of the prelim reports and, therefore, only included clinical data up to 6 months in half of the patients enrolled in these trials. The 120 days safety update included data on the rest of the missing patients at the original submission. (See studies A2306 and A2307 section)

Study B156

It was a three years open label study conducted in US, France, Germany, and Italy. Included 111 patient randomized to full dose Neoral – **53** or reduced dose Neoral – **58** that concomitantly received **RAD 3** mg and induction with Simulect.

Creatinine values were improved with reduced dose Neoral compared with high dose Neoral. Creatinine clearance at Month 12 was significantly higher in the reduced dose arm compared with the full dose regimen (62.4 mL/min vs. 51.5 mL/min respectively).

REVIEW PROCEDURES

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, endocrinology, and pregnancy test), and adverse events including incidence of infections.

- For 12-month analyses, the cut-off dates were 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. Patients were considered lost to follow-up if there was no patient contact after Day 154.
- In the efficacy analyses a lost to follow-up was considered 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 11-2. Number of patients in each analysis population - Key Renal Studies -

	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
ITT	193	194	194	198	196	196
Safety	193	194	194	198	196	196
Per protocol	185	191	178	195	191	186

Data obtained from Post-text Table 7.3-1 (B-251) and Post-text Table 7.3-1 (B-201) Analysis Populations by Treatment Group, (ITT Population - 12 Month Analysis)

Table 11-3. Number of patients in each analysis population - Key Heart Study -

	RAD 1.5 (209)	RAD 3 (211)	AZA (214)
ITT	209	211	214
Safety	209	211	214

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

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

A two-year randomized, multicenter study (One year DB and one year OL per 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.

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 8/19/98 and the last patient completed the study on June 26, 2002.

The Novartis' Heart Transplant Program was not discussed with the Agency. 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 this submissions. The agency new about 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 13-1. Study design.

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.

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 there after patients received or not steroids per local practice.

Rabbit Anti-human Thymocyte Globulin use was permitted only at selected sites as an induction therapy. Use of RATG for rejection treatment 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 analysis was carried out.

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. Pregnancy test and a medically approved birth control method for all females.

Exclusion criteria

Older donors >60 years and known CAD donors were excluded. Other usual a reasonable exclusion criteria were also applied. (HIV, Hepatitis C, HbsAg positivity, Hypercholesterolemia, hypertriglyceridemia, PRA ≥ 20%, WBC ≤ 5000 mm³, platelets ≤ 70,000 mm³ etc.)

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)

The efficacy was measured by the incidence of the composite endpoint (death, graft loss/retransplant, biopsy-proven acute rejection episode (BPAR) ≥ 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)

- Primary endpoint was also 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 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.

Patient Evaluation:

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

Efficacy:

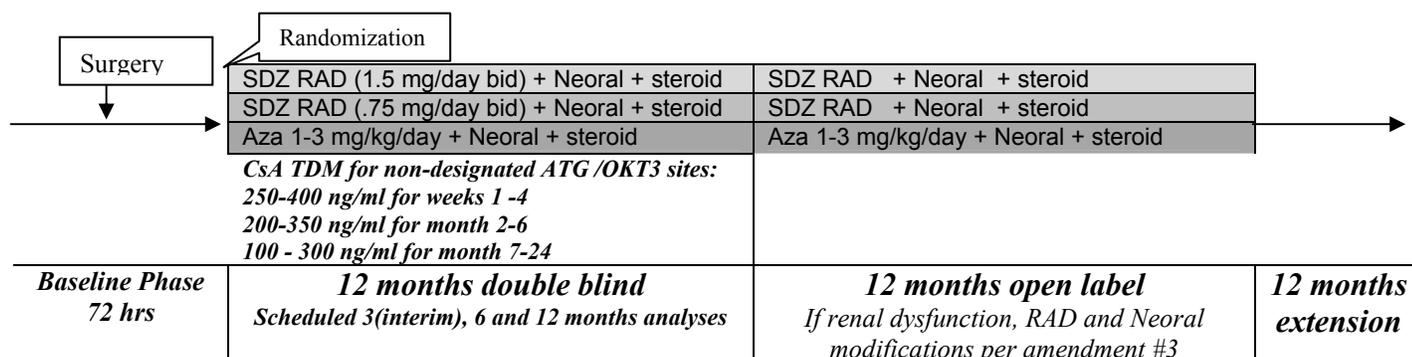
Acute rejections were assessed by endomyocardial biopsies on Days 7, 14, 21, and 28 and on months 2, 3, 4, 5, 6, 9, 12, 18, and 24. Any suspected rejection episode was to be biopsied at the investigators' discretion. In addition, echocardiograms were performed, to assess whether the acute rejection was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

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.

Fig 13-1. Protocol design



CONCOMITANT MEDICATIONS:

ATG or OKT3: Only sites using ATG or OKT3 were designated and allowed to use these antibodies as an induction therapy, other sites were not allowed to use them except for the treatment of AR.

Neoral: was used per local practice at designated ATG/OKT3 sites.

TDM ranges (250-400 ng/ml for week 1 -4 , 200-350 ng/ml for month 2-6 and 100 - 300 ng/ml for month 7-24) were used for not 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).

The 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.

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 Pharmaceuticals 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 test, 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)**).

PROTOCOL AMENDMENTS FOR STUDY CRAD001 B253

The protocol for study B-253 was finalized on May 8, 1998 and the study was modified by three amendments. We are listing the most relevant changes provided by these amendments. We use 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.

Amendment #1 (Released: 10-Sep -98) provided for:

- Patient safety guidelines for hyperlipidemia and neutropenia
 - HMG Co-A reductase are to be **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.

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).

Amendment #3 (Released: 29-Nov-01):

The applicant's rationale for this amendment was based on the 12-month analyses on 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 minimize 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 to 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 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 through concentration were decreased.***

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

During the pre NDA meeting, the Agency pointed the fact that the sponsor did not have as much experience with reduced-dose cyclosporine in heart transplant recipients. The sponsor agreed that they do 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 defined¹³.

Study Unblinding and Clinical Approach at 12 months: (See algorithm for Open-Label treatment for RAD Patients with signs of renal dysfunction Fig # 1.)

- **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.

¹³ 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.

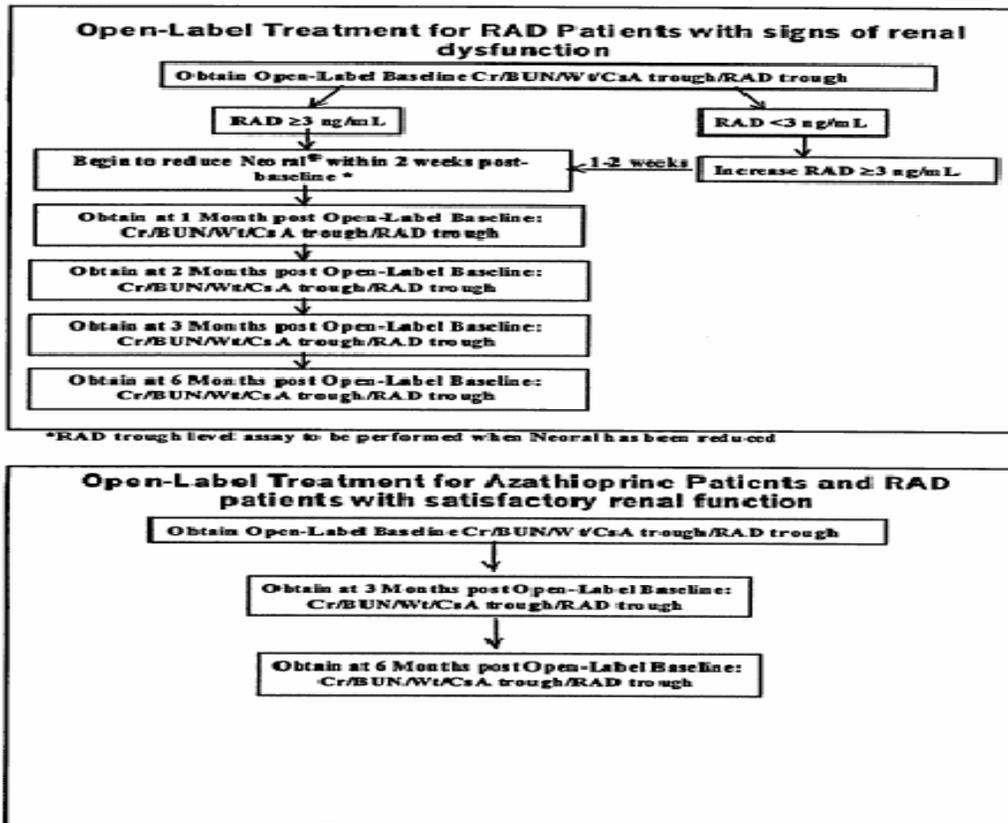
13.1.3. Drug concentration and pharmacokinetic evaluations after CsA and RAD dose modifications (Unblinded phase).

- 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 being this effect more important using both drug in combination than when CsA is used 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 13- 2. 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.*

13.2. RECIPIENT DEMOGRAPHIC 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) and the most common primary causes of end stage heart disease were idiopathic cardiomyopathy (46% to 54%) and coronary artery disease (32% to 40%).

Tables 13-2, 13-3, and 13-4 summarize baseline demographic characteristics, age groups and leading caused to ESHD. (Obtained from the original application Table 7-3, Clinical Study Report).

Table 13-2. 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 13-3. 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 13-4. 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. In all groups, the majority of patients were male and Caucasian. African American and other minorities were underrepresented in this study.

- *Demographic characteristics were comparable between treatment groups*
- *African American and other minorities were underrepresented in this study*

ORGAN DONOR AND RECIPIENT BASELINE CHARACTERISTICS.

Transplant-related background characteristics¹⁴ 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

Characteristics	Category summary statistics	RAD 1.5 mg (N=209)	RAD 3 mg (N=211)	AZA (N=214)
Donor age (years)	Mean (±SD)	32.5 (±12.5)	34.1 (±12.9)	33.6 (±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 (± SD)	2.9 (± 1.1)	3.2 (± 1.1) ^a	3.0 (± 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: The 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.

HBsA, hepatitis C or HIV tests were positive or not performed 2.2%, 1.3% and 0.5%, respectively. We do not believe that these results can influence the overall study results.

High risk for CMV (CMV-positive donors / CMV-negative recipient) was 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

¹⁴ 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.

- *Transplant-related characteristics in donors (sex, age and race) and recipients (ESH, 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. Anaemia nos, Leukopenia nos, Thrombocytopenia, Alanine aminotransferase, Aspartate aminotransferase and hyperlipidemias were similar across treatment arms.*

14. EFFICACY REVIEW - HEART STUDY B253 -

Table 14-1. Patient disposition - Premature Discontinuation from study medication (ITT population - 12 and 24 Month Analyses)

Discontinued from study medication # (%)	RAD 1.5 209	RAD 3 211	AZA 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, in all groups was mycophenolate mofetil (39% to 49%) 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:

- *Discontinuation rate was high across arms_at 24 months (39%, 49% and 39% in the RAD 1.5, RAD 3, and AZA groups, respectively).*
- *Regardless 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 month. 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 14-2. Antimetabolite Immunosuppressive Agents Administered After the Discontinuation of Randomized Study Medication (Safety Population - 24 Month Analysis)

	RAD 1.5 209	RAD 3 211	AZA 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 relative contribution of these agents after patient discontinuation to the final outcome in the ITT analyses.

Table 14- 3. Number (%) of patients with efficacy-related events (Months 6, 12 and 24) (ITT population)

	RAD 1.5 209	RAD 3 211	AZA 214	
Antibody-treated acute rejection episode of grade	12 (5.7%) 15 (7.2%)	6 (2.8%) 7 (3.3%)	14 (6.5) 15 (7.0%)	ns
Efficacy failure¹⁵ (Month 6)	76 (36.4%)	57 (27.0%)	100 (46.7%)	0.031 a <0.001 b 0.037 c
Acute rejection of ISHLT ≥ 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 ≥ 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 ≥ 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-days safety update reported 13 acute rejection episodes. Six, 5 and 2 in the RAD 1.5, RAD 3, and AZA groups, respectively.

Reviewer's comment:

- ***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 ≥ grade 3A were significant lower in the RAD arms at month 24 (35%, 23% and 48% in the RAD 1.5, RAD 3 and AZA arms , respectively.)***

¹⁵ Defined as the incidence of the composite efficacy endpoint (biopsy-proven acute rejection episode International Society of Heart and Lung Transplantation (ISHLT) ≥ grade 3A or any clinically suspected acute rejection episode associated with hemodynamic compromise [HDC], graft loss/re-transplant, death, and loss -to-follow-up.

- *Not significant differences were observed for graft loss, death, LOF, and acute rejection with HDC.*

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. 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 14-4. Number (%) of patients with efficacy failure related events (ITT population, with and without induction antibody therapy 12-month analysis)

<i>Induction Therapy</i>	RAD 1.5 N=209		RAD 3 N=211		AZA N=214	
	YES n=104	NO n=105	YES n=102	NO n=109	YES n=109	NO n=105
<i>Primary Efficacy Endpoint</i> ¹⁶	41 (39%)	46 (44%)	31 (30%)	37 (34%)	55 (50.5%)	58 (55%)
Acute rejection of grade ≥ 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)

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

¹⁶ **Primary efficacy endpoint:** Acute rejection of grade ≥ 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).

Reviewer's comment:

- *The number of patients who received and 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 incidences 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.*
- *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)*

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 14-5. Protocol Violations

	RAD 1.5 209	RAD 3 211	AZA 214
Any violation (12 months)	66%	71.0%	73.0%
Any violation (24 months)	65%	71%	71%
Study med. Related violations (12 months)	21%,	31%	24.0%,
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 presented higher rates in the RAD 3 arm at 12 and 24 months. The main contributor for 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).**

Biopsy Compliance:

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

Table 6 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 14-6. % 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 1.5 209	RAD 3 211	AZA 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 study medication at 6, 12 and 24 months were higher in the RAD3 arms compared with the RAD 1.5 and AZA groups which presented similar rates between them.*

At 24 months posttransplantation, the proportions of patient without biopsy 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 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. (See table 11. PATIENTS WHO DISCONTINUE STUDY MEDICATION, 24 MONTHS ITT POPULATION STUDY B253).

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. and blood creatinine increased) and pneumonia. While in the AZA arm Leukopenia nos. and Heart transplant rejection were the most common DAEs.

(See Table 2. Incidence Rates of DAE by System Organ Classification and Preferred Term (Safety Population - 24 Month Analysis) in the Adverse Event Leading to Discontinuation of Study Medication (DAE) section of the safety review)

In summary, missed biopsies were indirectly driven by specific drug related toxicities i.e. Renal dysfunction, leukopenia nos., pneumonia etc. and treatment failure i.e. rejection which has the potential to influence which patients are biopsied and therefore, have the opportunity 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 14-7. Dose reductions and dose interruptions from study medication (ITT Population 24 months analysis)

	RAD 1.5 209	RAD 3 211	AZA 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).***

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 re-defined the primary and secondary efficacy endpoints (See Amendments section). After this amendments the efficacy variables were defined as follows:

The 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.

Changes in IVUS Protocol after Amendments:

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 LCA 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.**

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

- **IVUS endpoints:** The incidence of chronic rejection was originally considered the primary efficacy variable. Amendment #2 re-defined 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.

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,
- Domestic and foreign data showed 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
Data Audit	B253 Site #11	Randall Starling

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 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 cause to not perform IVUS 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, (physicians who performed the studies at Hospital La Pitie) said 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"

Dr Robert Shibuya (FDA site investigator) quoted "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 for IVUS evaluation at baseline, 12 and 24 months. We received a response letter, dated August 7, 2003. After reviewing data submitted in the original application and additional requested data we observed that:

Table 14-8. Reasons for not performing IV US 24 month analysis - # of patients - (ITT population)

	RAD 1.5	RAD 3	AZA
	209	211	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)

- ***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 do not correlate with the site investigators' comments that noted technical problem as a major factor for not performing IVUS.*

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 1/3 of patients had baseline IVUS. At 12 months the evaluable patients dropped significantly and after 24 months 1/5 of the patients were eligible for evaluation and not equally distributed among arms.*
- *The imbalance in the proportion of subjects included at the 24th time point raises the 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 also 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.*

Conclusions: *The 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.

15. 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 safety population is the same as the ITT population.

The safety analyses include on-treatment assessments or on-treatment events. AE with an onset up to 7 days after the premature discontinuation of study drug will be 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.*

Patient Discontinuation:

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 (76/104) the 73% of the discontinued patients in this arm.

Table 15-1. PATIENTS WHO DISCONTINUE STUDY MEDICATION, 24 MONTHS 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 Discontinuation from study:

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. AE accounted for approximately 50% of the discontinuations from study medications in each arm.

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

15.3 Adverse Event Leading To Discontinuation of Study Medication (DAE):

Table 1 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 15-2. Incidence Rates of DAE by System Organ Classification and Preferred Term (Safety Population - 24 Month Analysis)

DAE System Organ Classification	RAD 1.5 209	RAD 3 211	AZA 214
Preferred Term			
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 TTP¹⁷	4 (2%)	3 (1.5%)	0
Infections / infestations	4 (2%)	11 (5%)	5 (2%)
Pneumonia	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 haemorrhage nos	0	3 (1%)	0
Heart transplant rejection	3 (1%)	0	4 (2%)

c. 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 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)***
- ***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.***

¹⁷ 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.

- *Anaemia, thrombocytopenia, pneumonia and gastrointestinal hemorrhage DAEs were higher in the RAD 3 arm compared to the AZA and RAD 1.5 arms.*
- *Heart rejection lead to DAE in 3 cases in the RAD1.5 and 4 cases in the AZA group.*

15.4. 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 analyses

Table 15-3. Frequent Adverse Events/Infections (Rates > 20%) by Preferred Term (Safety Population - 24 Month Analysis)

Preferred Term	RAD 1.5 209	RAD 3 211	AZA 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 the 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 15-4. Incidence of Adverse Events/Infections with Relevant Differences among Treatment Groups by Preferred Term (Safety Population - 24 Month Analysis)

Preferred Term	RAD 1.5 209	RAD 3 211	AZA 214
Anemia NOS	70 (33.5%)	93 (44%)	58 (27%)
Leukopenia NOS	43 (21%)	44 (21%)	63 (29%)
Neutropenia	1 (0.5%)	5 (2%)	10 (5%)
Thrombocytopenia	21 (10%)	37 (17.5%)	16 (7.5%)
TMA¹⁸ (Microangiopathic hemolytic anemia, HUS & TTP)	5 (2%)	6 (3%)	0%
Diarrhea NOS	43 (21%)	49 (23%)	31 (14.5%)
hypokalemia	23 (11%)	35 (17%)	27 (13%)
Pericardial effusion	48 (23%)	49 (23%)	36 (17%)
Cardiac tamponade	6 (3%)	10 (5%)	3 (1%)
Cytomegalovirus infection	15 (7%)	15 (7%)	45 (21%)
Herpes simplex	17 (8%)	12 (6%)	23 (11%)
Pneumonia nos	29 (14%)	20 (9.5%)	6 (3%)
Dyspnea NOS	36 (17%)	46 (22%)	29 (14%)
Nasopharyngitis	20 (10%)	21 (10%)	11 (5%)
Post procedural site wound infection	15 (7%)	11 (5%)	6 (3%)
Incisional hernia nos	9 (4%)	8 (4%)	3 (1%)
Renal impairment NOS	61 (29%)	65 (31%)	40 (19%)
Blood creatinine increased	24 (11.5%)	18 (8.5%)	10 (5%)
hyperlipidemia nos	38 (18%)	29 (14%)	13 (6%)
hypercholesterolemia ¹⁹	27 (13%)	25 (12%)	20 (9%)
hypertriglyceridemia ²⁰	13 (6%)	21 (10%)	11 (5%)
Total Lipid Abnormalities²¹	78(37%)	75(35.5%)	44(20.5%)
Edema peripheral	83 (40%)	80 (38%)	76 (35.5%)
Lymphocele	10 (5%)	9 (4%)	2 (1%)
Pyrexia	46 (22%)	57 (27%)	43 (20%)
Hypogonadism male	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:

¹⁸ TMA (Thrombotic Microangiopathy) including HUS (Hemolytic uremic syndrome) and TTP (Thrombotic thrombocytopenic purpura) are consumptive coagulopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia.

¹⁹ Includes blood cholesterol increased and Hypercholesterolemia aggravated

²⁰ Includes blood triglycerides increased and V Blood triglycerides abnormal

²¹ Includes hypertriglyceridemia, hypercholesterolemia and hyperlipidemia nos

- *Anemia NOS, Thrombocytopenia, TMA²², Diarrhea NOS, Cardiac tamponade, Renal impairment NOS, Edema, 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 Total Lipid Abnormalities²³, presented higher rates in both RAD arms compared to AZA. However, a dose related effect was not clearly defined.*
- *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 rated 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:
 12 Months Analysis -Safety Population- [18 (9%), 8 (4%), 4 (2%)] and
 24 Month Analysis -Safety Population- [9 (4%), 8 (4%), 3(1%)] for the RAD1.5, RAD3 and AZA groups, respectively.*

Edema:

Table 15-5 Incidence Rate of Edema by Preferred Term (Safety Population - 24 Month Analysis)

Preferred Term	RAD 1.5 209	RAD 3 211	AZA 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.

Gastrointestinal Haemorrhage:

²² TMA (Thrombotic Microangiopathy) including HUS (Hemolytic uremic syndrome) and TTP (Thrombotic thrombocytopenic purpura) are consumptive coagulopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia.

²³ Includes hypertriglyceridemia, hypercholesterolemia and hyperlipidemia nos

Table 15-6. Incidence Rate of GI hemorrhage by Preferred Term (Safety Population - 24 Month Analysis)

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

1. The dictionary used is the 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) 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. A dose related effect was observed in the incidence of GI haemorrhage between the RAD arms. Similarly, the incidence of AEs associated with bleedings in general were significantly higher in the RAD 3 group (30%) compared to AZA group (21%). These bleeding events were similar in the RAD 1.5 and 3 mg groups (26% and 30%, respectively)²⁴.

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

Infections:

Table 15-7. Incidence Rates of Infections by Type of Organism or preferred term (Safety Population - 24 Month Analysis)

	RAD 1.5 209	RAD 3 211	AZA 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 when compared to AZA (8.1 (95 CI: 0.1, 16.2)).***

²⁴ AEs associated with bleeding comprise epistaxis, haematemesis, hematoma, hemoptysis, melena, purpura, hemorrhage.

- *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.*

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 protocols, instead it uses the preferred term "cytomegalovirus infection" to include most of the reported terms.

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.

Table 8. compiles cytomegalovirus infections reported as Adverse **Events** and **Serious Adverse Events (SAE)**.

Cytomegalovirus infections reported as SAE are presented 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 one time, even though in two cases more than one episode of CMV infection was observed (*).

Table 15- 8. CMV infection reported as Adverse Events and Serious Adverse Events (SAE) (Safety Population - 24 Month Analysis)

Preferred Term	RAD 1.5 209	RAD 3 211	AZA 214
<i>CMV Infection</i> ²⁵ reported as AE	16 (7.7%)	16 (7.6%)	46 (21.5%)
Total # of CMV infections reported as SAE's.	3	3	7
Preferred term / Reported term			
Cytomegalovirus infection / <i>Cytomegalovirus</i>	1 moderate		1 mild
Cytomegalovirus infection / <i>CMV</i>			1 mild
Cytomegalovirus infection / <i>CMV Disease</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 / <i>CMV pneumonia or pneumonitis</i>	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).

(*) 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 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.

Cytomegalovirus Infections and Antibody Therapy.

Tables 15-9 and 15-10 summarize the relationship between the use of antibody therapy for induction and as a total use (Induction and AR treatment).

²⁵ 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)

Defined as symptomatic CMV infection and included both CMV syndrome and tissue invasive disease

Table 15- -9. Number (%) of patients with efficacy failure related events (ITT population, with and without induction antibody therapy at Month 12)

Induction Therapy	RAD 1.5 N=209		RAD 3 N=211		AZA N=214	
	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 15-10. 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 1.5 209	RAD 3 211	AZA 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 15-11. Contributing factors for the higher incidence of CMV infections observed in the AZA arm. (Protocol violations and antibody treated rejections)

<i>Protocol Violations -</i>	RAD 1.5 209	RAD 3 211	AZA 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 ≥ 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 higher in 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 ≥ 3A or associated to HDC), or both (ATG/OKT3 high dose).*
 - *The antibodies 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 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 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.

Pneumonia:

Table 15-12. Incidence Rate of Pneumonia by Preferred Term (Safety Population - 24 Month Analysis)

PNEUMONIA	RAD 1.5 209	RAD 3 211	AZA 214
Pneumonia NOS	29 (14%)	20 (9.5%)	6 (3%)
Bacterial pneumonia including: 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 comment:

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.

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 15-13. New Onset Post-transplant Diabetes Mellitus (PTDM) (24 month analyses -Safety Population):

New Onset Post-transplant DM	RAD 1.5 209	RAD 3 211	AZA 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 comment: 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 3 groups.

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

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 (CI: 9.9 (1.1, 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%).

Severe Adverse Events / Infections:

Table 15-14. 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 1.5 209	RAD 3 211	AZA 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 either 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 more frequently reported 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 group, 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 comment:

- ***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.***
- ***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 15-15. Primary Cause for Death Reported in ≥ 2 patients in any group (safety population)

	RAD 1.5 209	RAD 3 211	AZA 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 ¹	0	1 (0.5%)	2 (0.9%)
Heart transplant rejection ¹	2 (1.0%)	0	2 (0.9%)

¹ 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 and epithelioma in a RAD 1.5 mg).

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).

Malignancies:

The total incidence of malignancies was 8% in each group. Skin malignancies were the most commonly observed in 10(59%), 5(31%), and 6(33%) cases 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 15-16. 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 comment: *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.

**Table 15-17. Renal Function: (Safety Population - 24-Month Analysis)
 Estimated Mean Creatinine Clearance (Cockcroft-Gault) [mL/min] and**

	RAD 1.5mg			RAD 3mg			AZA		
	n	Mean ml/m in	Change from BL ml/min	n	Mean ml/m in	Change from BL ml/min	n	Mean ml/m in	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

Estimated Mean Creatinine Clearance Change from Baseline

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

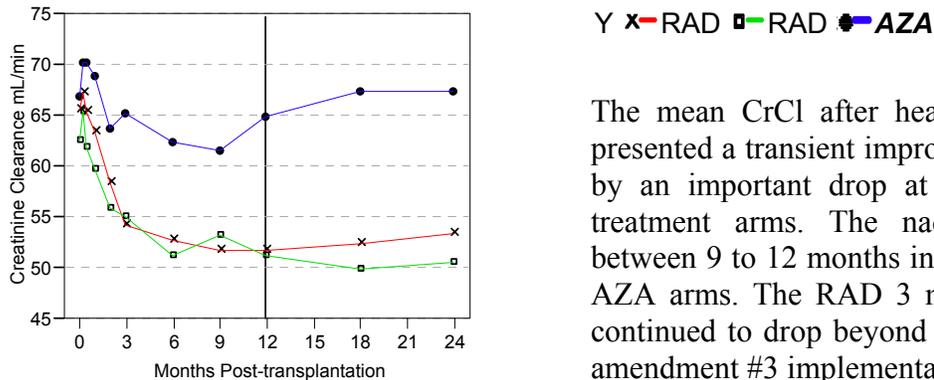
At 24 months post transplantation, the CrCl decreased by -14 ml/min, and -17.5 ml/min in the RAD 1.5 and RAD, respectively. In contrast, the CrCl in the AZA arm returned to baseline at 18 months post-transplantation and remained stable at 24 months analysis.

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 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.

The TEP (LOCF) analysis at 24 months showed the same trend.

Fig. 15-1 Mean Cockcroft-Gault calculated Creatinine Clearance Study B253
 (Safety Population - 24-Month Analysis)



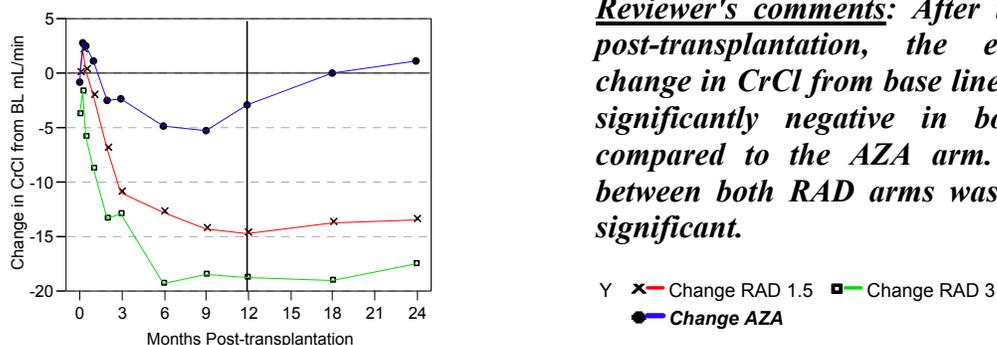
Data obtained from: Post-text Table 10.3-1a (Page 58 of 105)
 Page 610, Study B253 24 month analysis.

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 15-2. 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)

The mean CrCl after heart transplantation presented 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: *After the third month post-transplantation, the estimated mean change in CrCl from base line was statistically significantly negative in both RAD arms compared to the AZA arm. The difference between both RAD arms was not statistically significant.*

Table 15-18. 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	RAD 3	AZA	p-value
	209	211	214	
Month 6	53 (156)	51.8 (155)	62.7 (168)	a = 0.000 b = 0.000 c = 0.237
Month 12	52 (144)	53 (137)	64.8 (156)	a = 0.000 b = 0.000 c = 0.286
Month 24	54.5 (160)	53.9 (164)	67.4 (169)	a = 0.000 b = 0.000 c = 0.129
Month 24 SEP	51.0 (206)	50.5 (211)	65.7 (214)	a = 0.000 b = 0.000 c = 0.492

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

1. 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
2. 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
3. SEP = study endpoint

Reviewer's comments: ITT mean CrCl analysis showed the same trends as showed 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 3 vs. AZA group (73% and 79% vs. 57%)

Results on renal function after amendment #3 (120-days safety update)

Patients on the RAD plus full dose Neoral 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 group, 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 15-19. Mean creatinine values (µmol/L) in patients with amendment baseline and Month 6 creatinine values – Heart study B253 (amendment population)

# of patient included in this analysis / # of patients included in the amendments	RAD 1.5	RAD 3	AZA
Baseline at amendment entry	38/58 164	27/51 183	24/61 138
Month 6 post amendment	163	190	135

Data obtained from Post-text table 20.3-6.

Reviewer's comments:

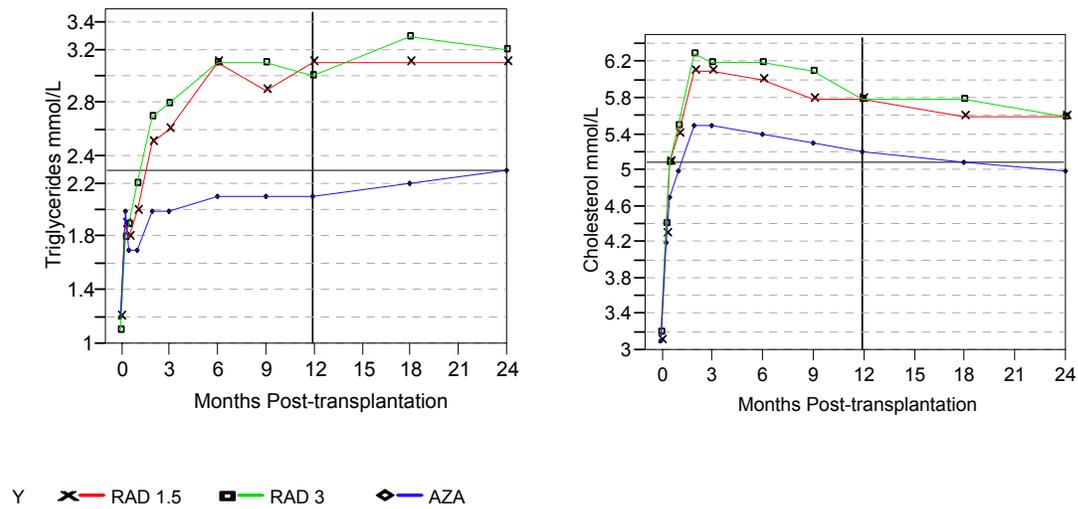
Only 50% of the patients that enter amendment # 3 was included in this analysis and an imbalance in the number of patients included per arm was evident.

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.

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 patient 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.

Fig 15-3. 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.

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 level²⁶ (≥ 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.

²⁶ NCEP high triglycerides : 4.5 -11.2 mmol/L

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 level²⁷ (≥ 6.2 mmol/L) in 67%, 70% and 47% in the RAD1.5, RAD 3 and AZA respectively.

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

Reviewer's comment:

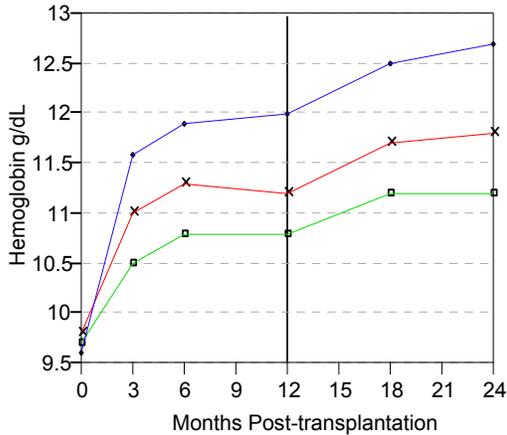
- *Serum cholesterol and triglycerides mean values rapidly increased in all groups after drug exposure to immunosuppressive drugs. The RAD groups presented significantly higher changes in mean values from baseline compared to the AZA group.*
- *Patients with normal baseline cholesterol and triglycerides at randomization presented higher rates of dyslipidemias in the RAD groups compared to the AZA group at 24-month analysis.*
- *Hypercholesterolemia / hypertriglyceridemia reported as an AE presented 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.*

²⁷ NCEP high total cholesterol : ≥ 6.2 mmol/L

ANEMIA

Fig 15-4. 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 comment: Hemoglobin mean values improved after transplant in all groups.

The improvement in the RAD arms was suboptimal compared to AZA group and the differences were statistically significant.

Lower hemoglobin mean values were observed in the RAD groups with a significant dose related effect.

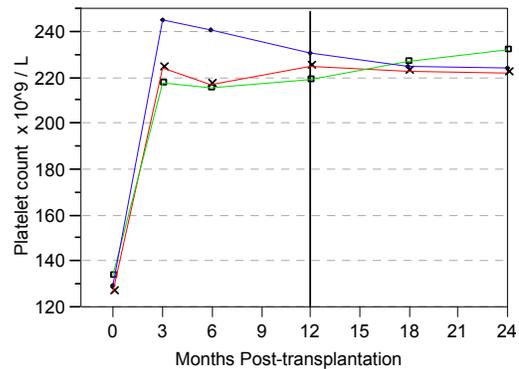
Y x—RAD 1, □—RAD 3 ♦—AZA

THROMBOCYTOPENIA:

Fig 15-5. Mean Platelet count [10⁹ /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.



Y x—RAD 1, □—RAD 3 ♦—AZA

S.

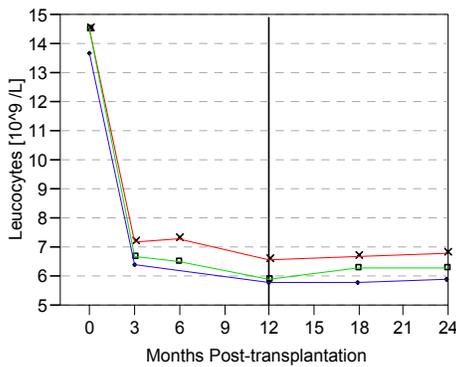
The incidence of thrombocytopenia reported as AE was significantly higher in the RAD 3 mg group (21%) compared with the RAD 1.5 mg and AZA groups (15% and 14%, respectively)

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).

Leucopenia:

Fig 15-6. Mean Leukocyte count [10⁹ /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



Y x—RAD ■—RAD ◆—AZA

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 leukopenia 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.

Liver Function tests:

SGOT (AST) mean values were within normal range²⁸ 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.

Alkaline Phosphatase mean values over time were within normal range across arms. 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%).

²⁸ SGOT (AST): 0-41 U/L, SGPT(ALT): 0-45 U/L

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

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 criteria²⁹, the incidence high diastolic blood pressure was similar in the RAD1.5 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.

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)

Endocrinology:

FSH, LH and Testosterone values in men:

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 range³⁰ 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.

SUMMARY AND CONCLUSIONS ON EFFICACY AND SAFETY KEY HEART STUDY

²⁹ 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)

³⁰ 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).

- *Both RAD 1.5 and 3 groups were superior with respect to the incidence of the composite endpoint³¹ “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 study medication was 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 through 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 Certican® plus CsA combination. It appears that the combination enhances the nephrotoxic effect of cyclosporine being this effect more important than when CsA is used alone.*
- *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), the mean CrCl did not improved.*

³¹ ISHLT grade \Rightarrow 3A acute rejection, acute rejection associated with HDC, graft loss, death or lost to follow-up.

- *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.*
- *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.*

Adverse Events:

- *Anemia NOS, Thrombocytopenia, TMA³², 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 abnormalities³³, presented higher rates in both 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 RAD3 and RAD 1.5 groups, respectively compared with 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) presented 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.*

³² TMA (Thrombotic microangiopathy) including HUS (Haemolytic uraemic syndrome) and TTP (Thrombotic thrombocytopenic purpura) are consumptive coagulopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia.

³³ Includes hypertriglyceridemia, hypercholesterolemia and hyperlipidaemia nos

- *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 artheriopathy 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)*

17. KEY RENAL STUDIES

EUROPEAN KEY RENAL STUDY B201

A 1-year double-blind, double-dummy and 2 year open-label, randomized, multicenter, parallel group study of the efficacy and safety of RAD001 (RAD) tablets versus mycophenolate mofetil as part of triple immunosuppressive therapy in *de novo* renal transplant recipients. (1 year DB and 2 years OL per amendment # 3)

Fifty four (54) centers participated in this study, Australia – 4 centers, Europe – 48 centers, South Africa – 2 Centers. 588 patients were enrolled (194, 199 and 195 in the RAD 1.5 mg, RAD 3 mg and MMF groups, respectively). All treatment groups received Neoral and steroids as part of a triple immunosuppressive therapy regimen in *de novo* renal transplant patients.

Table 17-1 summarizes the key and supportive studies for the new proposed indications.

Study no.	Design	Duration	No. of patients/study drug
B201	R, DB, DD, AC, MC, MD, E, S,	3 years	Total - 588
Key renal study	PK, <i>de novo</i>	(1 year DB/2 years OL by amendment # 3)	RAD 1.5 mg – 194 RAD 3 mg – 198 MMF 2 g – 196

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 comment: The original protocol and amendments for Study B201 were not submitted to IND 52,003 because it was conducted outside the U.S.

Main Study objectives:

The primary objective was to compare the efficacy of RAD 0.75 mg bid. or 1.5 mg bid. versus mycophenolate mofetil (MMF) 1 g bid, in *de novo* renal transplant recipients as measured by:

- 1) The incidence of efficacy failure (BPAR, graft loss, death or loss to follow-up during the first 6 months of treatment and by
- 2) Graft loss, death or lost to follow-up at 12 months.

Main Inclusion criteria:

Male or female patients, 18 to 68 years of age, who were *de novo* cadaveric, living unrelated or human leukocyte antigen, mismatched living related donor renal transplant recipients.

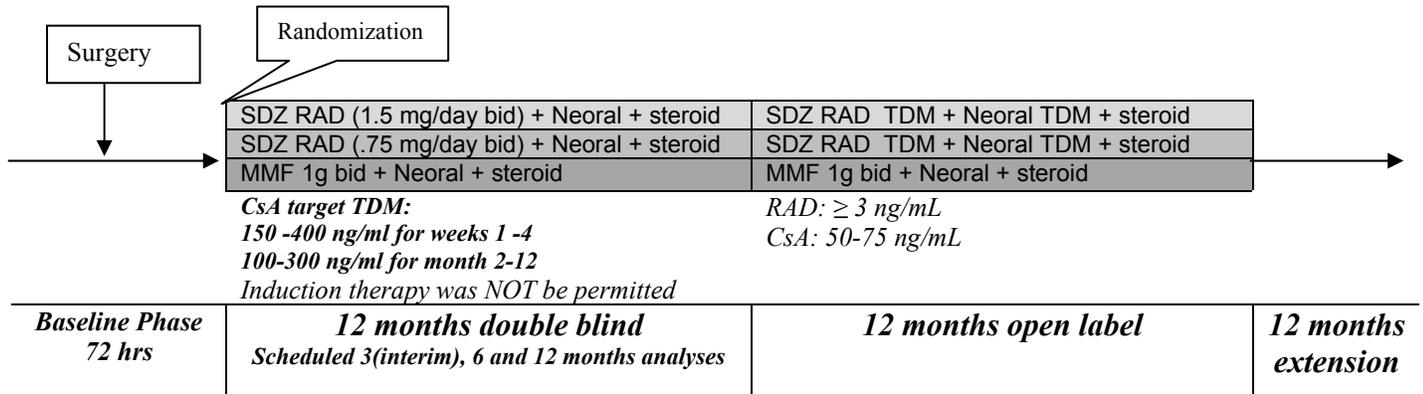
“High risk” patients were defined as recipients of a kidney from a cadaveric donor who also met at least one of the following criteria: Black, panel reactive antibody (PRA) >50%, CIT >24 hours, or total number of HLA mismatches ≥ 3 .

Exclusion criteria:

Relevant exclusion criteria were:

- Recipient's age ≥ 70 years, HLA-identical graft from a living related donor, CIT ≥ 40 hours and donor's age < 5 or > 65 years
- Induction therapy (i.e., ATGAM®, OKT3, Simulect® or Zenapax®)
- Evidence of liver injury,
- Human immunodeficiency virus (HIV)-positive status, or recipients of organs from donors who tested positive for HBsAg or hepatitis C. Presence of cardiac disease
- Severe uncontrolled hypercholesterolemia (≥ 350 mg/dL, 9.1 mmol/L) or hypertriglyceridemia (≥ 500 mg/dL, 5.6 mmol/L), white blood cell (WBC) count, $\geq 4500/\text{mm}^3$,

- Absolute neutrophil count (ANC) $\leq 2000/\text{mm}^3$ or platelet count $\leq 100,000/\text{mm}^3$.
- Pregnant or breast-feeding patients.
- Patients who had undergone any induction therapy prior to study entry.



Methylprednisolone IV perioperatively was permitted per local practice. Prednisone was given at po doses of no less than 20 mg per day and maintained for 6 months, thereafter, the prednisone taper was allowed per local practice to no less than 5 mg.

Concomitant Medications:

Lipid-lowering therapy was used as needed for the management of uncontrolled hyperlipidemia. Lovastatin and simvastatin were not allowed.

CMV prophylaxis:

Ganciclovir, CMV hyperimmune globulin, or acyclovir was indicated by local practice preferences in high risk for CMV allograft recipients. (CMV + Donor / CMV - Recipient). Prophylaxis was recommended for patients after acute rejection episodes treated with antibodies.

Therapy for acute rejection:

Acute grade III or vascular rejection was treated with **antithymocyte globulin, antilymphocyte antibodies (OKT3)** or other potent immunosuppressive agents. Steroid-resistant rejections or severe vascular rejection were to be treated with OKT3 at the appropriate dose for 7-14 days. Drugs with potential interactions with CsA, such as quinidine, fluoxetine and paroxetine, were prohibited.

Safety Assessment:

Safety Evaluation was performed at baseline , 1, 7, 14, and 28 days, and at 2, 3, 6, 9, 12, 18, 24, 30, and 36 months after surgery.

Safety assessment included Physical examination, Vital signs and Lab Tests.

Laboratory evaluations included Hemoglobin, WBC, differential count, and platelet count, sodium, potassium, chloride, calcium, magnesium, inorganic phosphorus, urea, creatinine, glucose, uric acid, bicarbonate, AST, ALT, alkaline phosphatase, total bilirubin, total cholesterol, HDL, LDL, triglycerides, CPK, lipase, amylase, protein in urine and glucose in urine.

CsA trough level and RAD trough level: At days: 1,7,14 and 28 and months: 2,3,6,9,12,18,24,30,and 36.

Renal biopsy and endocrinology tests: At baseline and at 3, 12 and 36 months. Biopsy material was also used in the surrogate marker for chronic rejection³⁴ analysis.

A biopsy-proven acute rejection was defined as a biopsy graded IA, IB, IIA, IIB or III using Banff '97 criteria.

Endocrinology test included follicle stimulating hormone, luteinizing hormone, and testosterone.

Discontinuations: For all patients prematurely discontinuing treatment, a follow-up contact will be made at 3, 6, 12, 24, and 36 months after the first dose of study medication. Information on rejection episodes, allograft and patient survival, malignancies and immunosuppressive medications will be collected. All patients will be contacted 90 days after the last dose of study medication regarding Serious Adverse Event information.

Adverse events and serious adverse events³⁵ were collected and recorded. Clinically notable laboratory abnormalities present at the time of discontinuation will be followed until the abnormality is no longer considered clinically significant. One should consider abnormal Serum creatinine a clinically notable lab abnormality.

Efficacy Assessment:

Efficacy analysis was performed on the **intent-to-treat (ITT) population** which should include all randomized patients.

Primary efficacy analysis: The main objective is to demonstrate that RAD 3 and RAD 1.5 are clinically equivalent to MMF in preventing biopsy-proven acute rejection episodes, graft loss or death. After accomplish this, there will be a further attempt to determine superiority of RAD versus MMF.

(See Statistical Review)

Renal Allograft Biopsies: (Acute and chronic rejection evaluation)

Renal biopsies were required at baseline and for suspected acute rejection at all sites.

Allograft biopsies at months 6, 12 and 36 (or at any time of discontinuation) were optional.

Drug concentration and pharmacokinetic evaluations:

Cyclosporine Whole Blood Trough Levels and RAD Whole Blood Trough Levels will be performed at all centers during all visits throughout the study

Pharmacokinetics of SDZ RAD:

RAD blood level measurements at 5 minutes before (time 0) and, 1, 2,5, and 8 hours after the study drug administration were required for an **abbreviated PK profile** at selected centers at Months 2, 3, and 6.

US KEY RENAL STUDY NO. RAD B251

³⁴ Multilayering of the peritubular capillary basement membrane as an ultrastructural marker at chronic renal allograft rejection was evaluated at designated centers.

³⁵ Defined as an event with one or more of the following characteristics: Fatal or life-threatening, required or prolonged hospitalization, was significantly or permanently disabling or incapacitating, constitutes cancer, a congenital anomaly or a birth defect, encompasses any other clinically significant event or is a result of an overdose

A three-year, randomized, multicenter, 1 year double-blind, double-dummy and 2-year open-label (amendment # 3), parallel group study of the efficacy and safety of SDZ RAD tablets vs. mycophenolate mofetil as part of triple immunosuppressive therapy in *de novo* renal transplant recipients. (Release date: April 13, 1998)

The original protocol was submitted to IND 52,003 on 7/9/98 (SN-023). The study was modified subsequently by four amendments. (See section: "Protocol amendments for Key Renal Studies B201 and B251")

Amendment #3 was submitted on March 19, 2001 (SN-211) and it provided for very drastic changes in the original protocol design. Table 17.2-1 summarizes the study design, duration and the number of patients enrolled per arm.

Table 17-2

Study no.	Design	Duration	No. of patients/study drug
B251	R, DB, DD, AC, MC, MD, E, S,	3 years	Total - 583
Key renal study	PK, <i>de novo</i>	(1 year DB and 2 years OL per amendment # 3)	RAD 1.5 mg – 193 RAD 3 mg – 194 MMF 2 g – 196

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.

44 centers participated in this study (33 US, 7 Canada, 2 Argentina, and 2 Brazil)
 The study scheduled 6, 12, 24, and 36 Months analyses.

Main Study objectives:

The original primary objective was to compare the efficacy of RAD, 1.5 mg/d and 3.0 mg/d, fixed doses with 2gm/d MMF as measured by the incidence of biopsy proven acute allograft rejection, graft loss, or death in the first six months of treatment in *de novo* renal transplant recipients.

The specific objectives analyzed in the 36-month interim report were:

- To compare the efficacy of 2 oral doses of RAD (0.75 or 1.5 mg twice daily [bid]) vs. mycophenolate mofetil (MMF) (1 g bid), as measured by the incidence of efficacy failure (defined as biopsy-proven acute rejection, graft loss, death or lost to follow-up [primary endpoint] and graft loss, death, or lost to follow-up [co-primary endpoint]) at 36 months.
- To compare the efficacy of both doses of RAD vs. MMF as measured by the incidence of each individual component of efficacy failure and biopsy-proven chronic allograft nephropathy at 36 months.
- To compare the safety of both doses of RAD vs. MMF at 36 months post-transplantation.

Main Inclusion criteria:

Male or female patients, 16 to 65 years of age, who had undergone primary cadaveric, living unrelated, or living related (HLA-mismatched) kidney transplant.

Donor age between 10 and 65 years, with CIT < 40 hours and adequate graft function on randomization (within 48 hours post transplantation). Pregnancy precaution and usual exclusion criteria were applied.

Relevant Exclusion criteria:

Concurrent or recent (within 4 weeks) use of other study drugs, liver abnormalities, and patients who were hepatitis C, hepatitis B surface antigen or HIV-positive. Recipients of Hepatitis C or B positive organs and multi transplant recipients are excluded.

Concomitant Medications:

Immunosuppressive regimens: The investigational and control immunosuppressive regimens are graphically described in figure 1. CsA target trough blood levels and RAD fixed doses are specified for the **Double Blind Phase** (first year). Similarly, target trough blood levels for both CsA and RAD are shown in Fig 1 for the open label phase.

Oral prednisone was tapered to achieve a dose of 20 mg per day, or 0.25 mg/kg/day, by Day 30 and no less than 5 mg per day for the first six months.

Therapy for acute rejection: IV Methylprednisolone and antilymphocyte antibody as anti-rejection therapy was permitted per local practices. ATG/OKT3 was allowed as first line treatment for grade III/vascular rejection or for steroid resistant rejection³⁶

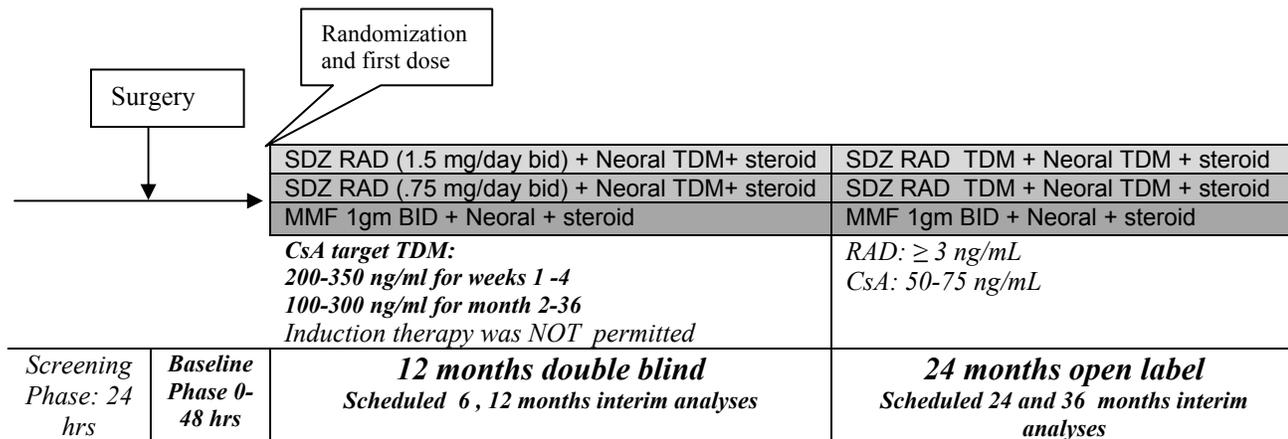
Cytomegalovirus (CMV) prophylaxis was mandatory for the CMV D+/R- mismatch.

Treatment with ganciclovir, cytomegalovirus hyperimmune globulin, or acyclovir was allowed per local practice. Low-risk patients for CMV disease were treated or received prophylaxis according to local practice. CMV prophylaxis was recommended following any antibody treatment for acute rejection episodes.

PCP prophylaxis was mandatory and according to local practices.

Lipid-lowering therapy:

Figure 17.2-1. Study B251 schematic



³⁶ Steroid resistant episode was defined as no improvement of creatinine level within 5 days after the initiation of methylprednisolone (after 4 boluses with a minimum dose of 250 mg/bolus or a total of 1.5 gm of methylprednisolone.)

Safety Assessment:

Safety analyses were performed on the **Safety population** which is defined as all randomized patients who received at least one dose of study medication and had at least one safety assessment.

Patient evaluation: Patients had baseline evaluation after screening phase (fig 1). During the Double-Blind Treatment period patients were evaluated at days: 1,7,14 and 28 and at months: 2, 3, and 6,9,12. During the Open label phase patients were evaluated at months 18, 24, 30 and 36. Physical examination, vital signs, ECG, hematology, biochemistry and urinalysis were evaluated. **Endocrine test** (FSH, LH, Testosterone) were scheduled at baseline, 6, 12 and 36 months.

Abbreviated PK profile of RAD was performed at selected centers (Blood draws 5 minutes before Time 0 at Months 2, 3 and 6 and, at 1, 2, 5 and 8 hours after the study drug administration were required) Cyclosporine and RAD trough levels were scheduled for measurement at all patient visits.

Discontinuation from study medication: Patients prematurely discontinued from study medication, a follow-up contact was planned at 3, 6, 12, 24 and 36 months after the first dose of study medication to obtain information on:

- **rejection episodes,**
- **allograft and patient survival,**
- **malignancies and**
- **immunosuppressive medication.**

Adverse events (AE's): will be collected and graded (mild, moderate and severe), abnormal lab values are considered AE's. Graft loss and death were considered SAE (serious adverse events).

Serious Adverse Events³⁷ (SAE): ALL patients will be followed up for 90 days after last dose of study medication. Graft loss, death and malignancies are considered SAEs.

Efficacy Assessment:

Efficacy analysis was performed on the **intent-to-treat (ITT) population, which** should include all randomized patients.

Primary efficacy analysis: The main objective is to demonstrate that RAD 3 and RAD 1.5 are clinically equivalent to MMF in preventing biopsy-proven acute rejection episodes, graft loss or death. After accomplish this, there will be a further attempt to determine superiority of RAD versus MMF.

(See Statistical Review)

Renal biopsies: (Acute and chronic rejection evaluation): Renal biopsies were required at baseline and for suspected acute rejection at all sites. They also were required at selected sites at 6, and 36 months, or at the time of premature discontinuation of medication. Biopsies at month 12 and at all other sites were optional.

³⁷ Defined as an event with one or more of the following characteristics: Fatal or life-threatening, required or prolonged hospitalization, was significantly or permanently disabling or incapacitating, constitutes cancer, a congenital anomaly or a birth defect, encompasses any other clinically significant event or is a result of an overdose

Recipient and Donors Characteristics in Studies B251 and B201

Transplant-related background characteristics³⁸ were reviewed to assess balance between treatment groups in both key renal studies. Tables 1 - 6 summarize demographic and other baseline donors and recipients characteristics.

Table 17-3. PATIENT DEMOGRAPHICS by treatment group (ITT population)

Demographic variable (OPTN data % of Tx) ³⁹	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
Male	110 (57.0%)	114 (58.8%) ^a	123 (63.4%)	127 (64.1%)	132 (67.3%)	139 (70.9%)
Caucasian (61%)	133 (68.9%)	181 (93.3%)	123 (63.4%)	181 (93.3%)	129 (65.8%)	171 (87.2%)
Black (23%)	29 (15.0%)	4 (2.1%)	36 (18.6%)	9 (4.5%)	33 (16.8%)	11 (5.6%)
Hispanic (11%)	20 (10.4%)	-	14 (7.2%)	-	24 (12.2%)	-
Oriental (4%)	3 (1.6%)	4 (2.1%)	6 (3.1%)	5 (2.5%)	2 (1.0%)	6 (3.1%)

Modified from post-text Table 7.4-1 (Page 1 of 3) Patient Demographics, Studies B251 and B201 (ITT Population - 12 Month Analysis)

a: RAD 1.5 mg vs. MMF; b: RAD 3 mg vs. MMF; and c: RAD 1.5 mg vs. RAD 3 mg (p<0.05, Fisher’s exact test).

Reviewer's comments:

In both key renal studies, the majority of patients were male (57% to 70%) and Caucasian (63 to 93 %). The EU study B201, enrolled Caucasians predominantly and the minorities were under-represented. The only statistically significant difference observed was the lower proportion of male patients in the RAD 1.5 mg group in S-B201 as compared to the MMF group (59% vs. 71%, respectively). This difference is not clinically relevant and we do not expect any drastic influence on the overall conclusions.

Table 17-4. PATIENT AGE by treatment group (ITT population)

Age Categories	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
<50 years	129 (66.8%)	115 (59.3%)	124 (63.9%)	121 (61.1%)	126 (64.3%)	112 (57.1%)
=>50 years	64 (33.2%)	79 (40.7%)	70 (36.1%)	77 (38.9)	70 (35.7%)	84 (42.9%)
Mean (± SD)	43.3 ± (12.44)	45.2 (11.4)	43.7 ± (12.09)	44.1 (11.9)	43.4 ± (12.12)	46.1 (12.3)
Range	16 – 71	19 - 67	19 - 70	19 - 67	16 - 68	18 - 71

Data obtained from post-text Table 7.4-1 (Page 1 of 3) Patient Demographics, Studies B251 and B201 (ITT Population - 12 Month Analysis)

³⁸ 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.

³⁹ Bases on OPTN data as July 6, 2001.

Reviewer's comments: The mean ages were 43 to 46 years (range: 16 to 71 years). The number of older donors (≥ 50 years) was balanced across arm in both key renal studies.

Table 17-5. DONOR SOURCE, n (%) by treatment group (ITT population)

Donor source, n (%)	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
Cadaveric heart beating	94 (48.7%)	162 (83.5%)	93 (47.9%)	169 (85.4%)	85 (43.4%)	155 (79.1%)
Cadaveric non-heart beating	5 (2.6%)	14 (7.2%)	7 (3.6%)	13 (6.6%)	5 (2.6%)	23 (11.7%)
Living related	62 (32.1%)	9 (4.6%)	67 (34.5%)	9 (4.5%)	79 (40.3%)	13 (6.6%)
Living unrelated	32 (16.6%)	9 (4.6%)	27 (13.9%)	7 (3.5%)	27 (13.8%)	5 (2.6%)

Data obtained from: Post-text tables 7.4-1, 7.4-3, and 7.4-12 Study B-251 12 months analysis.

Reviewer's comments: The proportions of cadaveric and living donors were adequately balanced across arms in both studies B-201 and B251.

The proportion of cadaveric and living donors was similar in the US study B251 (close to 50 and 50%). In contrast, EU study B201 included predominantly cadaveric donors (91 to 92% across arms). This population's characteristic determined a higher proportion of high-risk patients to be included in the European study (B-201).

“High risk” patients:

“High risk” patients were recipients of cadaveric grafts who also met at least one of the following criteria: Black, PRA >50%, cold ischemia time >24 hours, or total number of HLA mismatches ≥ 3. Characteristics of “high risk” patients are summarized in table 4.

Table 17-6 4. “High risk” patients by treatment group (ITT population)

High risk patients ⁴⁰	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
High risk total	83 (43.0%)	130 (67.0%)	80 (41.2%)	135 (68.2%)	73 (37.2%)	136 (69.4%)
Cadaveric donors and:						
Black	15 (7.8%)	4 (2.1%)	23 (11.9%)	8 (4.0%)	17 (8.7%)	11 (5.6%)
PRA >50%	1 (0.5%)	4 (2.1%)	4 (2.1%)	1 (0.5%)	1 (0.5%)	0
CIT >24 hours	24 (12.4%)	31 (16.0%)	17 (8.8%)	31 (15.7%)	17 (8.7%)	33 (16.8%)
HLA mismatches ≥ 3	73 (37.8%)	117 (60.3%)	67 (34.5%)	123 (62.1%)	61 (31.1%)	122 (62.2%)

Data obtained from Post-text Table 7.4-8 (Page 1 of 1), High Risk Patients Studies B-201 and b 251 (ITT Population - 12 Month Analyses)

1. Pairwise comparisons of treatment groups use Fisher’s exact test

⁴⁰ Recipients of a cadaveric donor with one of the following :

a) black, b) PRA >50%, c) cold ischemic time >24 hours, d) total number of HLA mismatches >=3

a = RAD 1.5mg vs. MMF, b = RAD 3mg vs. MMF, c= RAD 1.5 mg vs. 3mg DID NOT SHOWED ANY statistically significant difference among groups.

2. Percentages are calculated using the ITT population as the denominator

Reviewer's comments:

Study B201, enrolled higher number of high-risk patients (67-69% across arms). However, the overall rates of “high risk patients” were comparable across the treatments groups in each key renal study individually. Since both studies were balanced across arms, we do not expect an effect from these differences on the overall conclusions.

Table 17-7. End Stage Renal Disease (ESRD) Leading to Transplantation

ESRD Leading to Transplantation	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
Glomerulonephritis/glomerular disease	50 (26%)	72 (37%)	40 (21%)	74 (37%)	43 (22%)	79 (40%)
Hypertension/nephrosclerosis	37 (19%)	9 (5%)	48 (25%)	16 (8%)	34 (17%)	25 (13%)
Diabetes Mellitus	27 (14%)	7 (4%)	37 (19%)	11 (6%)	43 (22%)	6 (3%)
Polycystic disease	25 (13%)	43 (22%)	13 (7%)	31 (16%)	30 (15%)	34 (17%)
Pyelonephritis/interstitial nephritis	9 (5%)	19 (10%)	8 (4%)	28 (14%)	6 (3%)	17 (9%)

Data obtained from Post-text Table 7.4-3 (Page 1 of 1), Studies B253 and B201 - Primary Disease Leading to Transplantation and Donor Source (ITT Population - 12 Month Analyses).

Reviewer's comments:

The most common primary cause of end stage renal disease was glomerulonephritis / glomerular disease in both key renal studies and the proportion of patients was balanced across arms in both renal studies.

Hypertension/nephrosclerosis was the second most important contributor in S-B251, while polycystic disease was the second most predominant cause for ESRD in the European S-B201. Diabetes Mellitus, as a cause of ESRD, was higher in the US B-251 (14 -22%) versus (3-6%) in EU B201. Study B-251 presented a higher proportion of DM leading to ESRD compared with the RAD arms.

Table 17-8. CMV Status: Recipient and Donor (ITT Population - 12-Month Analysis)

CMV-Matching	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
D + / R +	74 (38.3%)	73 (37.6%)	78 (40.2%)	84 (42.4%)	78 (39.8%)	74 (37.8%)
D + / R -	38 (19.7%)	43 (22.2%)	43 (22.2%)	38 (19.2%)	31 (15.8%)	39 (19.9%)
D - / R +	37 (19.2%)	28 (14.4%)	35 (18.0%)	40 (20.2%)	34 (17.3%)	46 (23.5%)
D - / R -	43 (22.3%)	41 (21.1%)	36 (18.6%)	29 (14.6%)	51 (26.0%)	30 (15.3%)

Data obtained from: Post-text Table 7.4-5b (Page 1 of 1), CMV Status: Recipient and Donor, (ITT Population - 12 Month Analysis)

Conclusions: Donor, Organ, and Recipient Baseline Characteristics.

- *In general, the characteristics on the donors and recipients were balanced across arms in both key renal studies.*
- *In both key renal studies, mean recipient ages were 43 to 46 years and the majority of patients were male and Caucasian. The minorities were markedly under-represented in the EU study B201.*
- *The proportions of cadaveric and living donors were adequately balanced across arms in both studies B-201 and B251. The EU study B201 included predominantly cadaveric donors (91 to 92% across arms). This population's characteristic determined the inclusion of a higher proportion of high-risk patients in the European study (B-201). However, the overall rates of "high risk patients" were comparable across the treatment arms in each key renal study individually.*
- *In both key renal studies, donors' and recipients' viral serology for hepatitis (Hepatitis B Surface and Antigen Hepatitis C Antibody) was negative in >97% across arms in both key renal studies.*
- *The donor characteristics of age, gender, type of renal transplant (cadaveric and living related and unrelated) and race, as well as the mean ischemia time for cadaveric or living related donors was similar across treatment groups. The number of HLA-mismatches and incidence of patients with no PRAs was also similar across groups.*
- *Past/coexistent medical conditions were typical for this patient population. The causes of ESRD leading to transplantation were glomerulonephritis / glomerular disease, hypertension / nephrosclerosis, polycystic disease and diabetes mellitus. Minor imbalances across arms in both renal studies are not considered clinically relevant.*

Protocol Amendments for Key Renal Studies B201 and B251

Background:

The original protocol and amendments for **B201** (European study) were not submitted to the agency because this study was conducted outside of the U.S.

For Study **B251**, the original protocol was submitted to IND 52,003 on 7/9/98 (SN-023). Both studies were modified subsequently by four amendments. We are listing the most relevant changes provided by each of these amendments.

Amendment #1 SN-050 (4/23/99). Release date: 1&2-Dec-98.

- Provided guidance in dose reduction for hyperlipidemia and neutropenia. The use of specific HMG Co-A reductase inhibitors was recommended [fluvastatin (Lescol) and pravastatin]. Lovastatin and simvastatin were not recommended because of the known interaction with Neoral and the newer statins, (atorvastatin and cerivastatin) were not recommended because the lack of data.

Amendment # 2. Release date: 30-Apr-99

Submission date and SN were not located in Novartis' records.

- This amendment provided for treatment recommendations for hyperlipidemia prior to reduction, interruption or discontinuation of study medication based on National Cholesterol Education Program Adult Treatment Panel II Report Guidelines (i.e., evaluations to determine LDL cholesterol whenever triglyceride levels are >400 mg/dL (>4.5 mmol/L).

Amendment #4 SN-242 (10/31/01). Release date: July 10 and 28-Jun-01.

This amendment provided for extending the treatment and observation period in order to collect additional long-term safety data until RAD001 (RAD) were commercially available. Additionally, monitoring of endocrine parameters was added to the protocol.

Amendment #3 SN-211 (3/19/01). Release date: January 16 &12, 2001:

Protocol amendment # 3 for Study B251 (Serial No. 211) was submitted on March 19, 2001 (**Release date: January 12, 2001**) and it provided for important changes in the original study design.

The rationale for this amendment was based on the 12-month data analyses from Phase III/IIIb de novo studies CRA001 B201, B251 and B156. The preliminary analyses of the key renal studies (CRAD001 B201 and B251) showed that RAD trough levels <3 ng/ml appear to be associated with an increased incidence of rejection. But most important, Novartis' concerns regarding renal dysfunction prompted the applicant to make drastic protocol changes.

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 this study indicated that both efficacy and safety were better in the low-dose Neoral treatment arm. Based on this analysis, **Novartis decided to unblind the key renal studies and alter the immunosuppressive regimen with the objective of minimize the risk of nephrotoxicity, while maintaining efficacy.**

The most relevant modifications provided by amendment #3 were:

- **The Key Renal studies were unblinded after 12-month double-blind phase.** (The blinding of the study was preserved at the sites until all patients had completed at least one year of double blind study medication).
- All patients were tested for Baseline **Drug concentration and pharmacokinetic evaluation** measurements (Cr/BUN/Wt/CsA trough/RAD trough) before starting the open label treatment.
- **Open Label Treatment:**
 - Corroboration or achievement of RAD trough level ≥ 3 ng/mL to minimize the risk of rejection (***Dose Regimen Modification***)
 - The CsA trough levels were progressively decreased to a therapeutic target range of 50 – 75 ng/mL in order to minimize nephrotoxicity.
 - The open-Label treatment for MMF patients **was not** modified; however, renal function and CsA levels were monitored.
- **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.
 - For patients who exhibited sub-optimal response in serum creatinine within 3 months after the initial Neoral dose reduction and with no satisfactory explanation for the creatinine elevation and no evidence of ongoing or recent acute rejection, further reduction or discontinuation of Neoral was considered.

Reviewer's comments:

- *It is well recognized that RAD has a clinically meaningful interaction with CsA. The applicant's 12-month analysis of the Key Renal Studies (B253 and B251) showed progressive renal function deterioration in the RAD arms when compared with the MMF arm. It was observed that CsA nephrotoxicity was enhanced in the proposed Fixed Dose Regimen (FDR), and even though it proved to be efficacious for the primary endpoint, the FDR was considered unacceptable due to safety issues and therefore, modified by amendment 3.*
- *Protocol Amendment #3 unblinded the Key Renal studies after 12 months, and modified the fixed dose therapeutic regimen. RAD trough level was targeted ≥ 3 ng/mL and the CsA through target level was drastically reduced to 50 - 75 ng/mL.*
- *The original main objective of the Key Renal Studies were to test two fixed RAD doses versus MMF, and as result of the protocol amendments, the study main objective cannot be adequately evaluated beyond the first 12-months of the study.*
- *In summary, the original fixed dose regimen in a double blind study was changes to TDM regimen in an open label study. Furthermore, patients with renal dysfunction in the RAD arms were identified, and every necessary treatment adjustment was made to improve renal function. Patients in the MMF arm continued on their originally*

established therapeutic regimen unmodified. Given this specific therapeutic intervention, we would expect an important improvement in renal function in the RAD arms if the chronic nephrotoxic insult sustained in these groups were reversible.

These amendments brought important implications and concerns to our review:

- *The sub-optimal response to Neoral dose reduction with no satisfactory explanation for the creatinine elevation persistence i.e. ongoing or recent acute rejection, may suggest irreversible kidney damage*
- *Since decreasing CsA levels increases the risk for rejection, the concomitant approach was to insure through RAD levels ≥ 3 ng/mL in order to maintain efficacy. One wonders if this approach would be successful during the first months after transplantation.*
- *Another concern is the identification of the RAD upper limit for the TDM regimen and the most appropriate time for CsA minimization after transplantation. This is particularly important, since chronic nephrotoxicity will lead to irreversible damage.*

REVIEW PROCEDURES

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, endocrinology, pregnancy test), and adverse events including incidence of infections.

- For 12-month analyses, the cut-off dates were 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. Patients were considered lost to follow-up if there was no patient contact after Day 154.
- In the efficacy analyses a lost to follow-up was considered 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.

AE with an onset up to 7 days after the premature discontinuation of study drug will be included. Any event occurring ≥ 8 days after drug discontinuation are omitted from the analysis.

Table 17-9 Number of patients in each analysis population - Key Renal Studies -

	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
ITT	193	194	194	198	196	196
Safety	193	194	194	198	196	196
Per protocol	185	191	178	195	191	186

Data obtained from Post-text Table 7.3-1 (B-251) and Post-text Table 7.3-1 (B-201) Analysis Populations by Treatment Group, (ITT Population - 12 Month Analysis)

Table 17-10 Number of patients in each analysis population - Key Heart Study -

	RAD 1.5 (209)	RAD 3 (211)	AZA (214)
ITT	209	211	214
Safety	209	211	214

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

18. EFFICACY REVIEW - KEY RENAL STUDIES B251 AND B201 -

Patient discontinuation from study medication:

Table 18-1. Patient disposition - Premature Discontinuation from Study Medication (ITT population - 12 and 36 Month Analyses) Studies B251 and B201.

Discontinued from study medication # (%)	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
12-month analysis. (Before 450 days)	56 (29%)	69 (36%)	82 (42%) ^{e, f}	85 (43%) ^d	50 (25.5%)	55 (28%)
36-month analysis. (Days 1 to 1170)	109 (56.5%) ^a	98 (50.5%)	126 (65%) ^b	113 (57%) ^c	89 (45%)	81 (41%)
Adverse event(s) (36 month analysis)	56 (29%)	49 (25%)	52 (27%)	70 (35%)	29 (15%)	49 (25%)
Unsatisfactory therapeutic effect (36 month analysis)	21 (11%)	23 (12%)	28 (14%)	14 (7%)	19 (10%)	9 (5%)

B-251 Source: Post-text table 7.1-1 and Post-text table 7.1-2, B201 Source: Post-text table 7.1-1 and Post-text table 7.1-2 (Clinical Study Reports) a: RAD 1.5 mg vs. MMF, p = 0.033 (Fisher's exact test), b: RAD 3 mg vs. MMF, p < 0.0001 (Fisher's exact test), c: RAD 3 mg vs. MMF, p = 0.002 (Fisher's exact test), d: RAD 3 mg vs. MMF; (p<0.05 Fisher's exact test), e: RAD 3 mg vs. MMF; and f: RAD 1.5 mg vs. RAD 3 mg (p<0.05 Fisher's exact test).

Reviewer's comments:

- *In both studies B251 and B201, patient discontinuation from study medication was numerically or significantly higher in both RAD groups compared with the MMF groups. RAD 3 versus MMF showed a statistically significant difference in both key renal studies.*
- *The disproportionate rate of discontinuation from study medication across arms is a major concern. More patients discontinued from the RAD arms, which means fewer*

opportunities in these arms for reporting safety events. On the other hand, discontinued patients from study medication received an alternative immunosuppressive regimen that influenced the efficacy outcome. (See table 2 below)

- *(See Safety Results - Key Renal Studies, Patient Discontinuations section)*
- *Time to event analysis of treatment discontinuation indicates that events occurs statistically significantly early and more often in the RAD3 group compared with MMF group in both key renal studies (See statistical review)*

Table 18-2. Immunosuppressive Agents Administered After the Discontinuation of Randomized Study Medication (Safety Population - 24-Month Analysis)

	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
Discontinued from study medication # (%) 36-month analysis. (Days 1 to 1170)	109 (56.5%) <i>a</i>	98 (50.5%)	126 (65%) <i>b</i>	113 (57%) <i>c</i>	89 (45%)	81 (41%)
Azathioprine	3 (3%)	18 (18%)	4 (3%)	14 (12%)	5 (6%)	10 (12%)
Mycophenolate Mofetil	54 (50 %%)	51 (52%)	69 (55%)	48 (43%)	44(49%)	29 (36%)
Tacrolimus	33 (30%)	34(35%)	35 (28%)	32 (28%)	28(32%)	14(17%)
Rapamycin	14 (13%)	3 (3%)	14(11%)	2 (2%)	12(14%)	2 (3%)

Data obtained from: Post-text Table 8.2-3 (Page 1 of 1) Immunosuppressive Agents Other than Neoral and Corticosteroids Administered after the Discontinuation of Randomized Study Medication by WHO Preferred Drug Name (Safety Population - 36 Month Analysis)

1. Medications summarized are medications that were administered one or more days after the discontinuation of randomized study medication
2. This table includes only patients of the safety population prematurely discontinued from randomized study medication
3. Patient may receive more than one agent after discontinuation of antilymphocyte therapy/monoclonal antibodies. They were not included since the number was small.

Reviewer's comment:

After discontinuation of study medication, Mycophenolate Mofetil and Tacrolimus were the most commonly used immunosuppressive agent in both RAD and MMF arms. Discontinued patients from the RAD1.5 and RAD3 arms received MMF (comparator) in approximately 50% of the cases after discontinuing RAD. There is concern about the relative contribution of these agents to the final outcome in these groups in the final analyses.

EFFICACY REVIEW - STUDIES B251 AND B201

Table 18-3. Table 2 Efficacy-related events (ITT Population - 6, 12 and 36 Month Analyses) Studies B251 and B201

Efficacy-related events	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
Primary efficacy failure⁴¹ 6 month analysis	42 (22%)	52 (27%)	46 (24%)	52 (26%)	51 (26%)	58 (30%)
Primary efficacy failure 12 month analysis	48 (25%)	58 (30%)	51 (26%)	60 (30%)	54 (28%)	61 (31%)
BPAR	37 (19%)	45 (23%)	43 (22%)	39 (20%)	47 (24%)	47 (24%)
Co-primary efficacy failure⁴² 12 month analysis	22 (11.4%)*	21 (10.8%)**	15 (7.7%)*	33 (16.7%)**	13 (6.6%)*	23 (11.7%)**
Primary efficacy failure 36 month analysis	65 (34%)	64 (33%)	66 (34%)	77 (39%)	61 (31%)	73 (37%)
BPAR	49 (25%)	47 (24%)	50 (26%)	49 (25%)	52 (26.5%)	52 (26.5%)
Graft loss / death	31 (16%)	27 (14%***)	27 (14%)	48 (24%***)	20 (10%)	32 (16%***)
Graft loss	23 (12%)	14 (7%)	15 (8%)	33 (17%)	14 (7%)	21 (11%)
Death	12 (6%)	15 (8%)	13 (7%)	18 (9%)	10 (5%)	16 (8%)
Loss to F/U 2	2 (1%)	0	1 (0.5%)	1 (0.5%)	1 (0.5%)	0
Late BPAR 12 to 36 months	12 (6%)	2 (1%)	7(4%)	10(5%)	5(2.5%)	5(2.5%)
Co-primary efficacy failure⁴³ 36 month analysis	33 (17%)	27 (14%)	28 (14%)	50 (25%)	22 (11%)	32 (16%)
§Clinically Confirmed AR Including Biopsy-Proven AR⁴⁴	58(31%)	65(33.5%)	60(32%)	70(35%)	59(30.5%)	67(34%)
§Antibody Treated Acute Rejection	19(10%)#	15(8%)	18(14%)	16(8%)	36(18%) #	14(7%)
§Biopsy-proven chronic allograft nephropathy	22 (11%)	26 (13%)	29 (15%)	22 (11%)	17 (9%)	20 (10%)
§Clinically Confirmed Chronic Rejection⁴⁵	31(16%) ^	23(12%)	40(21%) ^	29(15%)	13(7%) ^	18(9%)

Data obtained from Post-text Table 9.2-1 (Page 1 of 9), Comparing Simple Event Rates of an Event Using the Z-Test, (ITT Population - 36 Month Analysis), and 12 month analyses studies B201 and b251. § 36 month analyses.

* 95% CI (RAD1.5 - MMF) (-12.7%, 4.3%) and (RAD3 - MMF) (-10.9, 6.3)

**95% CI (RAD1.5 - MMF) (-11.7%, 6.1%) and (RAD3 - MMF) (-12.2, 5.6)

***95% CI (RAD3 - MMF) (0.0, 15.8) p-value 0.050 and 95% CI (RAD 1.5 - RAD 3mg) (-18.0,-2.6) p-value 0.009

#95% CI (RAD1.5 - MMF) (-15.5,-1.7) p-value 0.014

^ 95% CI (RAD1.5 - MMF) and (RAD3 - MMF), (3.3, 15.7) and (7.3, 20.7) p-value (0.003) and (<0.001), respectively.

⁴¹ Primary Efficacy Failure Endpoint : **Biopsy-proven acute rejection, graft loss, death or lost to follow-up**

⁴²Co-primary efficacy Failure Endpoint: **Graft loss, death, or loss to follow-up**

⁴³Co-primary efficacy Failure Endpoint: **Graft loss, death, or loss to follow-up**

⁴⁴ **Clinically confirmed acute rejection episodes** include 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 acute rejections* were not included.

⁴⁵ **Clinically Confirmed Chronic Rejection** includes rejections diagnosed as chronic in clinical grounds. Almost all of these rejections were biopsy proven.

The 120-day safety update reported:

Deaths:

In study B251, 4 deaths were reported, (RAD 1.5 [2], RAD 3 [1] and MMF [1]).

In study B201, 5 deaths were reported RAD 1.5[1], RAD 3 [2] and MMF [2]).

None of the deaths in both studies was considered drug related by the investigators.

Rejection:

Five cases in **study B251**, (RAD 1.5 [1], RAD 3 [1] and MMF [2]) and seven cases in **study B201** (RAD 1.5 [1], RAD 3 [5] and MMF [1])

Graft Loss:

In study B251, only one case in MMF group and in **study B201** three cases (RAD 3 [1], and MMF [2]).

Reviewers' comments:

- *Certican® 1.5 and 3 mg/day were non-inferior to MMF 2 g/day when both drugs were used in combination with Neoral® and corticosteroids with regard to the incidence of the primary efficacy failure⁴⁶ at 6 and 12 months post-transplantation in primary allograft recipients in both key renal studies.*
- *The co-primary efficacy failure endpoint⁴⁷ at 12 months presented discordant results between key renal studies. In study B201, only 1.5 RAD group showed to be non-inferior to the MMF group. In contrast, in study B251 only RAD3 group showed to be non-inferior to the MMF group.(See statistical review for details)*
- *At 36 months in study 201, the RAD 3 group was not non-inferior to the MMF group for the primary efficacy failure endpoint. However, this group (RAD3) was non-inferior at 6 and 12 months. The 1.5 RAD group was non-inferior to the MMF group for both co-primary efficacy endpoints at all time points in Study B201.*
- *At 36 months in study 251, the RAD3 and RAD 1.5 groups were not non-inferior to the MMF group for the primary efficacy failure endpoint. The RAD3 group was non-inferior to the MMF group for both the co-primary efficacy endpoints at 6 and 12 months. However, RAD 1.5 group was only non-inferior to MMF for the primary but not for the co-primary endpoint at 6 and 12 months.*
- *The inclusion of treatment discontinuation as a failure into the 12-month analysis, demonstrated that RAD 1.5 continued to be non-inferior to MMF in both key renal studies. However, RAD 3 arms presented statistically significant worst efficacy failure rates compares to MMF arms in both key renal studies. (See statistical review)*
- *BPAR was not statistically different across arms at 6, 12 and 36 in both key renal studies. Transplant rejection lead to discontinuation in two cases in S-B251, one in each RAD arm and only one case was reported in S-B201 in the RAD 3 arm.*

⁴⁶ Primary Efficacy Failure Endpoint : *Biopsy-proven acute rejection, graft loss, death or lost to follow-up*

⁴⁷ Co-primary efficacy Failure Endpoint: *Graft loss, death, or loss to follow-up*

- *Late biopsy-proven acute rejections from 12 to 36 months were present in small numbers in all groups in both key renal studies; however, In study B251 the number of late BPARs were higher in the RAD1.5 arms and double in RAD 3 arm compared with MMF arm. Even though these are small numbers this finding is relevant due to the fact that addresses the period in which CsA dose was reduced.*
- *The efficacy failure individual components did not show statistically significant differences across arms at 6, 12 or 36 months. However, graft losses were numerically higher in the RAD 1.5 (B251) and RAD 3 (B201) arms compared with the MMF arm in their respective studies.*
- *In study B201, the incidence of graft loss/death was significantly higher in the RAD 3 group compared with MMF or RAD 1.5. MMF and RAD1.5 presented similar rates. In study B251 the incidence of graft loss/death was numerically higher in both RAD arms compared with the MMF group.*
- *The incidence of clinically confirmed chronic rejection at 36 months was numerically or significantly higher in both RAD groups compared with the MMF group, in both key renal studies. This consistent trend in both key renal studies suggests a higher incidence of undetected sub clinical rejections in the RAD arms. (Surveillance biopsies were required at 6 and 36 months in study B251 at selected sites only and optional in study B201).*

Table 18-4. Banff Grades biopsy-proven acute rejection (ITT Population - 36 Month Analyses) Studies B251 and B201

Banff Grades BPAR	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
BPAR	49 (25%)	47 (24%)	50 (26%)	49 (25%)	52 (26.5%)	52 (26.5%)
Grades IA	23 (11.9%)	20 (10.3%)	16 (8.2%)	19 (9.6%)	14 (7.1%)	19 (9.7%)
Grades IB	11 (5.7%)	6 (3.1%)	13 (6.7%)	10 (5.1%)	17 (8.7%)	9 (4.6%)
Grades IIA	5 (2.6%)	15 (7.7%)	13 (6.7%)	9 (4.5%)	16 (8.2%)	13 (6.6%)
Grades IIB	2 (1.0%)	4 (2.1%)	3 (1.5%)	3 (1.5%)	2 (1.0%)	7 (3.6%)
Grade III	6 (3.1%)	0	5 (2.6%)	6 (3.0%)	3 (1.5%)	4 (2.0%)
Missing (1)	2 (1.0%)	2 (1.0%)	0	2 (1.0%)	0	0
Other (2)	16 (8.3%)	17 (8.8%)	16 (8.2%)	28 (14.1%)	9 (4.6%)	21 (10.7%)

Data obtained from: Post-text Table 9.2-1 (Page 1 of 9) Comparing Simple Event Rates of an Event Using the Z-Test (ITT Population - 36 Month Analysis studies B201 and B251) and Post-text Table 9.1-7b (Page 1 of 1) Frequency of Worst Biopsy-proven Acute Rejection Within 36 Months of the Initial Dose of Study Medication (ITT Population - 36 Month Analysis studies B201 and B251)

(1). Category 'Missing' includes patients who had biopsy-proven acute rejection but with missing grade

(2). Category 'Other' includes patients who have an outcome of death, graft loss or loss to follow-up

Not preceded by a BPAR.

Reviewers' comments:

- *The majority of cases of biopsy-proven acute rejection were mild or moderate⁴⁸ in severity in both key renal studies.*
- *Severe⁴⁹ acute rejection was reported in 10 cases of study B201 (6 and 4 in the RAD 3 mg and MMF groups, respectively). In study B251 severe acute rejection was reported in 6, 5, and 3 cases in the RAD2.5, RAD 3 and MMF arms, respectively.*
- *In study B251, the incidence of antibody-treated acute rejection episodes was significantly higher in the MMF group compared with RAD 1.5 mg group. This finding was not consistent with the severity of BPAR, since more cases of severe AR (Banff grade III) occurred in the RAD arms compared to MMF in this study. Study B201 presented similar rates of antibody-treated AR across arms.*

Table 18-5. The incidence of Late Biopsy-Proven Acute Rejection (ITT Population - 36 Month Analysis)

	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
Month 0 - 12	41 (21.2%)	46 (23.7%)	43 (22.2%)	40 (20.2%)	48 (24.5%)	49 (25.0%)
Month 12 - 36	11(6%)	2(1%)	11(6%)	10(5%)	6(3%)	4(2%)

Data obtained from: Post-text Table 9.3-13 and Table 9.2-1 assessment of Late Biopsy-Proven Acute Rejection ITT Population - 36-Month Analysis)

After Month 12, the incidence of biopsy-proven acute rejection was low in all groups the small numbers do not allow us to make any conclusions.

REVIEWER'S SUMMARY AND CONCLUSIONS ON EFFICACY S-B251 AND B201

- *There were inconsistent results for the efficacy endpoints across studies and at different time point of evaluation. The disproportionate rate of discontinuations from study medication across arm, may have contributed to these discordant results. Furthermore, the study unblinding and therapeutic drug adjustments after 12 month makes difficult to draw reliable conclusions.*
- *Certican® 1.5 and 3 mg/day were non-inferior to MMF 2 g/day when both drugs were used in combination with Neoral® and corticosteroids with regard to the incidence of the primary efficacy failure⁵⁰ at 6 and 12 months post-transplantation in primary allograft recipients in both key renal studies.*
- *The co-primary efficacy failure endpoint⁵¹ at 12 months presented discordant results between key renal studies. In study B201, only 1.5 RAD group showed to be non-inferior*

⁴⁸ Banff Grades I or II

⁴⁹ Banff Grade III

⁵⁰ Primary Efficacy Failure Endpoint : *Biopsy-proven acute rejection, graft loss, death or lost to follow-up*

⁵¹ Co-primary efficacy Failure Endpoint: *Graft loss, death, or loss to follow-up*

to the MMF group. In contrast, in study B251 only RAD3 group showed to be non-inferior to the MMF group. (See statistical review for details)

- *At 36 months in study 201, the RAD 3 group was not non-inferior to the MMF group for the primary efficacy failure endpoint. However, this group (RAD3) was non inferior at 6 and 12 months. The 1.5 RAD group was non-inferior to the MMF group for both co-primary efficacy endpoints at all time points in Study B201.*
- *At 36 months in study 251, the RAD3 and RAD 1.5 groups were not non-inferior to the MMF group for the primary efficacy failure endpoint. The RAD3 group was non-inferior to the MMF group for both the co-primary efficacy endpoints at 6 and 12 months. However, RAD 1.5 group was only non-inferior to MMF for the primary but not for the co-primary endpoint at 6 and 12 months.*
- *The efficacy failure individual components (including BPAR) did not show statistically significant differences across arms at 6, 12 or 36 months. However, graft losses were numerically higher in the RAD 1.5 (B251) and RAD 3 (B201) arms compared with the MMF arm in their respective studies.*
- *The inclusion of treatment discontinuation as a failure into the 12-month analysis, demonstrated that RAD 1.5 continued to be non-inferior to MMF in both key renal studies. However, RAD 3 arms presented statistically significant worst efficacy failure rates compared to MMF arms in both key renal studies. (See statistical review)*
- *The incidence of clinically-confirmed chronic rejection at 36 months was numerically or significantly higher in both RAD groups compared with the MMF group, in both key renal studies. This consistent trend in both key renal studies suggests a higher incidence of undetected sub clinical rejections in the RAD arms. (Surveillance biopsies were required at 6 and 36 months in study B251 at selected sites only and were optional in study B201).*
- *Patient discontinuation from study medication was numerically or significantly higher in both RAD1.5 and RAD 3 groups compared with the MMF group, in both studies B251 and B201. RAD 3 versus MMF showed a statistically significant difference in both key renal studies.*
- *The disproportionate rate of discontinuation from study medication across arms is a major concern. More patients discontinued from the RAD arms which means less opportunities in these arms for reporting safety events. On the other hand, discontinued patients from study medication received an alternative immunosuppressive regimen that influences the efficacy outcome. Discontinued patients from the RAD1.5 and RAD3 arms received MMF (comparator) in approximately 50% of the cases after discontinuing RAD.*
- *Three-year patient survival rates were comparable to national standards and similar across arms in both key renal studies.*
- *In study B201, the incidence of graft loss/death was significantly higher in the RAD 3 group compared with MMF and RAD 1.5. MMF and RAD1.5 presented similar rates. In study B251 the incidence of graft loss/death was numerically higher in both RAD arms compared with the MMF group.*

20. SAFETY REVIEW KEY RENAL STUDIES B251 AND B201

The safety evaluation was conducted reviewing data on physical examination including vital signs, adverse event reports, laboratory evaluation and ECG.

Patient discontinuation, adverse events, lipid abnormalities and renal functions were carefully examined.

For most of the safety analyses, we will include 36 months data. To evaluate the double blind phase of the studies, partial analyses at 12 months will be included when necessary. All 12 months analysis will be clearly specified other wise consider 36 month data.

Patient Discontinuation:

Patient discontinuation from study at 36 months was similar across arms in both key renal studies. In study B251, the reported rates were 19%, 22%, and 20% and in study B201, 11%, 14% and 11% in the RAD 1.5, RAD 3 and MMF arms, respectively.

Patient death was the most common cause of patient discontinuation from study in both key renal studies.

Patient discontinuation from study medication: Table 1 summarizes the specific causes for patient discontinuation from study medication.

Table 20-1. Patient disposition - Premature Discontinuation from study medication (ITT population - 12 and 36 Month Analyses) Studies B251 and B201.

Discontinued from study medication # (%)	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
12 month analysis. (Before 450 days)	56 (29%)	69 (36%)	82 (42%) ^{e, f}	85 (43%) ^d	50 (25.5%)	55 (28%)
36 month analysis. (Days 1 to 1170)	109 (56.5%) ^a	98 (50.5%)	126 (65%) ^b	113 (57%) ^c	89 (45%)	81 (41%)
Adverse event(s)	56 (29%)	49 (25%)	52 (27%)	70 (35%)	29 (15%)	49 (25%)
Unsatisfactory therapeutic effect	21 (11%)	23 (12%)	28 (14%)	14 (7%)	19 (10%)	9 (5%)
Abnormal laboratory value(s)	3 (2%)	7 (4%)	13 (7%)	7 (3.5%)	5 (3%)	1 (0.5%)
Protocol violation	4 (2%)	3 (1.5%)	11 (6%)	6 (3%)	7 (4%)	4 (2%)
Withdrawn consent	11 (6%)	9 (5%)	13 (7%)	10 (5%)	12 (6%)	6 (3%)
Death, Lost to follow-up and Administrative problems	13(7%)	7(4%)	9 (3.5%)	6(3%)	15 (6%)	12(6%)

B-251 Source: Post-text table 7.1-1 and Post-text table 7.1-2, B201Source: Post-text table 7.1-1 and Post-text table 7.1-2 (Clinical Study Reports) a: RAD 1.5 mg vs. MMF, p = 0.033 (Fisher's exact test), b: RAD 3 mg vs. MMF, p < 0.0001 (Fisher's exact test), c: RAD 3 mg vs. MMF, p = 0.002 (Fisher's exact test), d: RAD 3 mg vs. MMF; (p<0.05 Fisher's exact test), e: RAD 3 mg vs. MMF; and f: RAD 1.5 mg vs. RAD 3 mg (p<0.05 Fisher's exact test).

Reviewer's comments:

- *In both studies B251 and B201, patient discontinuation from study medication was numerically or significantly higher in both RAD groups compared with the MMF groups. RAD 3 versus MMF showed a statistically significant difference in both key renal studies (Table 1).*

- *Adverse events and unsatisfactory therapeutic effect were the most common reasons for discontinuation from study medication in both key renal studies.*
- *From the total of discontinuations from study medication at 36 month, 50 to 75% occurred within the first 12 months in both key renal studies. From 12 to 36 month the rate of discontinuation from study medication continue to increase in 15 to 20% more across arms in both key renal studies.*
- *Time to event analysis of treatment discontinuation indicates that events occurs statistically significantly early and more often in the RAD3 group compared with MMF group in both key renal studies (See statistical review)*
- *Patient discontinuation rates from study were similar across arms in both S-B251 and S-B201. Patient death was the main contributor, and the rates were similar across arms in both S-B251 and S-B201.*

Adverse Event Leading to Discontinuation of Study Medication (DAE)

Due to inconsistencies in the preferred terms used to report DAE more than one term may indicate the same entity e.g. Thrombocytopenia and platelet count decreased. The terms used were mutually exclusive and the severity was similar since both led to discontinuation. We used the same "**Preferred Term**" as reported; however, we analyzed terms that refers to the same entity all together to overcome inconsistencies and reflect the most accurate data summary in our review. When two or more preferred terms are put together, we will clearly specify this with a footnote or a description prior to the table.

Table 2 summarizes the most frequent and relevant adverse events that led to discontinuation from study medication.

DAE-lipid abnormalities: We have included all lipid abnormalities that denoted an increment that lead to discontinuation from study medication i.e. hyperlipidemia NOS, Lipids Increased NOS hypercholesterolemia, Blood cholesterol increased, hypertriglyceridemia, Blood Triglycerides Increased, and Low Density Lipoprotein Increased.

DAE- All Pneumonias: We have included bronchopneumonia and any type of pneumonia reported as preferred term.

DAE - Thrombocytopenia /platelet count decreased: We have included both preferred terms in this category since platelet count decreased was low enough to lead to discontinuation.

Thrombotic Microangiopathy (TMA) including Hemolytic Aramaic syndrome (HUS) and Thrombotic thrombocytopenic purpura (TTP) are consumptive coagulopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia. All preferred terms such as Thrombotic Microangiopathy, Hemolytic Uremic Syndrome, and thrombocytopenic Thrombotic Purpura are presented together.

Table 20-2. Incidence Rates of DAE by Body System and Preferred Term (Safety Population - 36 Month Analyses) Studies B251 and B201.

DEA <i>System Organ Classification</i>	RAD 1.5 209		RAD 3 211		MMF 214	
<i>Preferred Term</i>	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
Any DAE 12 month analyses (Double blind phase)	40 (21 %)	43 (22 %)	43 (22 %)	60 (30 %)	24 (12 %)	42 (21 %)
Any DAE 36 month analyses	63 (33%)	61 (31%)	69 (36%)	77 (39%)	37 (19%)	55 (28%)
Renal and urinary disorders	12 (6%)	12 (6%)	9 (5%)	16 (8%)	8 (4%)	7 (4%)
Renal impairment NOS	1 (0.5%)	4 (2 %)	0	4 (2 %)	0	0
Blood creatinine increased	9 (5%)	4 (2%)	14 (7%)	4 (2 %)	3 (1.5%)	2 (1%)
TMA Including HUS & TTP	4 (2 %)	2 (1 %)	4 (2%)	8 (4%)	2 (1%)	0
Therapeutic Agent Poisoning	4 (2 %)	2 (1 %)	2 (1 %)	2 (1 %)	0	0
Infections / infestations	9 (5 %)	8 (4 %)	9 (5 %)	16 (8 %)	0	10 (5 %)
All Pneumonias⁵²	2 (1%)	2 (1%)	1 (0.5%)	6 (3%)	0	1 (0.5%)
Leukopenia nos	0	2 (1.0%)	0	3 (1.5%)	1 (0.5%)	2 (1%)
Thrombocytopenia / platelet count decreased	1 (0.5%)	3 (1.5%)	5 (2.5%)	6 (3%)	0	2 (1%)
DAE- lipid abnormalities⁵³	3 (1.5%)	7 (4%)	6 (3%)	2 (1%)	4 (2%)	0

Data obtained from: Post-text Table 10.2-1c (Page 1 of 10) and Post-text Table 10.2-1c (Page 1 of 11) S-B201 and B251 reports, respectively. Incidence Rates of DAE by Body System and Preferred Term DAE: Adverse Event Leading to Discontinuation of Study Medication (Safety Population - 36-Month Analysis)

Renal / urinary disorders and Infections / infestations were the most important contributors of the System Organ Classification for the incidence rates of DEA observed in both key renal studies. More detailed information by preferred term is analyzed below.

Reviewer's comments:

- ***The incidence of adverse events leading to discontinuation from study medication (DAE) were reported in 33%, 36%, and 19% (S-B251) and 31%, 39%, and 28% (S-B201) in the RAD1.5, RAD 3 and MMF, respectively. These rates were significantly higher in the RAD arms compared with the MMF arm and a dose-related effect was observed between the RAD arms.***

⁵² All pneumonias includes, bronchopneumonia, and any DAE including pneumonia in the preferred term (PCP, CMV etc)

⁵³ We include all lipid abnormalities that denoted an increment that lead to discontinuation from study medication including *Hyperlipidemia NOS . Lipids Increased NOS Hypercholesterolemia Blood cholesterol increased Hypertriglyceridemia Blood Triglycerides Increased Low Density Lipoprotein Increased*

- *From 12 month to 36 month the number of DAEs continue to increase at a higher rates in the RAD arms versus MMF arms (See table 1)*
- *Blood creatinine increased (BCI) and renal impairment denotes "abnormal kidney function" that lead to discontinuation from study medication. BCI or BCI plus Renal impairment were the most common DAEs⁵⁴ in the RAD arms while gastrointestinal disorders were the more common DAEs in the MMF arm. The preferred terms used to denote gastrointestinal disorders were diverse and no predominance was observed.*
- *BCI plus Renal impairment as DAEs were reported in 6%, 7% and 2% (S-B251) and 4%, 4%, and 1% (S-B201) in the RAD1.5, RAD3, and MMF arms, respectively.*
- *Blood Creatinine Increased (BCI) was the single most common AE that led to discontinuation from study medication (DAE) in the RAD arms in both key renal studies. In S-B251, this single adverse event accounted for 5% 7% and 2% of DAEs in the RAD 1.5, RAD 3 and MMF arms, respectively.*
- *TMA⁵⁵ (including HUS and TTP) as DAE was reported 2%, 2%, and 1% (S-B251) and 1%, 4%, and 0% S-B201) in the RAD1.5, RAD 3 and MMF, respectively. The number of cases was small but numerically higher in the RAD arms compared with the MMF and consistent across both key renal studies. Since TMA has been related to the toxic effect of CsA, this finding is relevant given the known interaction in the RAD / CsA combination.*
- *Pneumonia was the single most important infection-DAE. In study B201, six (6) patients were discontinued from study medication in the in the RAD 3 versus one patient the MMF arm, (see table 2).*
- *Lipid abnormality rates that led to DAE in S-B251 were low and similar across arms. In S-B201 the RAD 1.5 (4%) and RAD 3 (1%) presented discontinuations from study medication in low numbers while no patient was discontinued in the MMF arm.*

Most Frequent and Selected Adverse Events / Infections by System Organ Classification and Preferred Term.

The dictionary used is the MedDRA and the AE was reported by "preferred term" and included in the group by "Organ Classification". Adverse events/infections with onset date eight or more days after the discontinuation of randomized study medication were not included in the applicant's analysis.

Due to inconsistencies in the preferred terms used to report AE more that one term may indicate the same condition e.g. Leukopenia and WBC decreased. The terms used were mutually exclusive and the severity is considered similar since both led to the report as an adverse event. We used the same "**Preferred Term**" as reported; however, we analyzed terms that refers to the same entity all together to overcome inconsistencies and reflect the most accurate data summary in our review. When two or more preferred terms are presented together, we will clearly specify this with a footnote or a description prior to the table in which these terms are summarized.

⁵⁴ DAE: Adverse Event Leading to Discontinuation of Study Medication

⁵⁵ **Thrombotic Microangiopathy** (TMA) including Hemolytic uremic syndrome (HUS) and Thrombotic thrombocytopenic purpura (TTP)

Table 20-3. Incidence Rate of Most Frequent and Selected Adverse Events/Infections by System Organ Classification and Preferred Term (Safety Population - 36 Month Analyses S-B251 and B201)

Preferred Term	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
<i>Any AE/Infection</i>	191 (99.0%)	193 (99.5%)	194 (100%)	197 (99.5%)	196 (100%)	192 (98.0%)
<i>Anemia NOS*</i>	62 (32 %)	54 (28 %)	76 (39 %)	71 (36%)	42 (21%)	59 (30 %)
<i>Hb or Hto Decreased</i>	12(6 %)	2 (1 %)	8(4 %)	3 (1.5%)	5 (2.5%)	4 (2 %)
Total	38%	29%	43%	37%	24%	33%
<i>Thrombocytopenia*</i>	12 (6%)	20 (10%)	16 (8%)	23 (12%)	13 (7%)	11 (6%)
<i>Platelet Count Decreased</i>	6 (3%)	5 (3%)	6 (3%)	3 (1.5%)	1 (0.5%)	1 (0.5%)
Total	9%	13%	11%	13%	7%	6%
<i>Leukopenia NOS*</i>	12 (6 %)	20 (10 %)	20 (10 %)	24 (12 %)	19 (10 %)	30 (15 %)
<i>WBC decreased</i>	2 (1 %)	2 (1 %)	4 (2 %)	3 (1.5%)	4 (2 %)	3 (1.5%)
Total	7%	11%	12%	14%	12%	17%
<i>Diabetes Mellitus NOS</i>	13 (7%)	13 (7%)	18 (9%)	25 (13%)	9 (5%)	11 (6%)
<i>Diarrhea NOS*</i>	61 (32%)	18 (9%)	69 (36%)	16 (8%)	60 (31%)	11 (6%)
<i>Hypokalemia*</i>	35 (18%)	27 (14%)	48 (25%)	34 (17%)	34 (17%)	27 (14%)
<i>Hyperkalemia</i>	33 (17%)	19 (10%)	35 (18%)	13 (7%)	52(26.5%)	21 (11%)
<i>Pyrexia / Hyperpyrexia</i>	62 (32%)	27 (14%)	62 (31.5%)	34 (17%)	44 (22.5%)	22 (11%)
<i>Edema NOS</i>	65 (34%)	38 (20%)	59 (30%)	44 (22%)	62 (32%)	34 (17%)
<i>Edema peripheral</i>	101 (52%)	43 (22%)	92 (47%)	37 (19%)	82 (42%)	26 (13%)
<i>Hypertension NOS</i>	47 (24%)	64 (33%)	46 (24%)	70 (35%)	39 (20%)	66 (34%)
<i>Headache nos</i>	56 (29%)	19 (10%)	61 (31%)	17 (9%)	55 (28%)	32 (16%)
<i>Therapeutic Agent Poisoning</i>	15 (8%)	16 (8%)	25 (13%)	19 (10%)	13 (7%)	14 (7%)
<i>Nausea</i>	72 (37%)	31 (16%)	87 (45%)	24 (12%)	70 (36%)	27 (14%)
<i>Dyspnea NOS</i>	35 (18%)	8(4%)	50 (26%)	2 (1%)	39 (20%)	9(5%)
<i>Deep Venous Thrombosis NOS</i>	2 (1%)	2 (1%)	7 (4%)	6 (3%)	1 (0.5%)	1 (0.5%)

Data obtained from: Incidence Rate of Adverse Events/Infections by Body System and Preferred Term (Safety Population - 36-Month Analysis). Post-text Table 10.1-1a (Page 2 of 82) and Post-text Table 10.1-1a (Page 1 of 58) Studies B251 and B201, respectively.

Reviewer's comments:

The total of AE/Infection rates reported in S- B251 and B201 were similar across arms. Specific AE/Infections by preferred term showed the following differences between RAD arms and MMF arms. (For comprehensive summary of AE per study and treatment arms see table 18.)

- *The highest incidence of Anemia NOS⁵⁶ was observed in the RAD 3 arms across studies. A dose related effect between the RAD1.5 and RAD3 arms was observed, and these observations were consistent across both key renal studies. In S-B251, RAD1.5 and RAD3 arms presented higher anemia rates compared to MMF arm. In S-B201 anemia rates were similar between RAD 1.5 and MMF*
- *Leukopenia⁵⁷ rates were higher in the MMF arms compared with RAD 1.5 arms in both key renal studies. RAD3 arms and MMF arms were similar. A dose related effect was observed between RAD arms in both key renal studies.*
- *Thrombocytopenia⁵⁸ rates were higher in both RAD arms compared to MMF in both key renal studies. The dose related differences in the RAD arms were only observed in S-251.*
- *DM NOS rates were higher in the RAD3 arms compared with MMF in both key renal studies. The RAD 1.5 and MMF presented similar rates.*
- *Hypertension NOS rates were higher in both RAD arms compared with MMF in study B251. S-B201 presented similar rates across arms.*
- *Peripheral edema was more frequently observed in the RAD arms compared with the MMF arms in both S-B251 and B201.*
- *Three cases of Blood Testosterone decreased were reported as AE two in the RAD 3 arms S- B201 and B351 respectively and one case in the MMF arm S-B251. Only one case in the RAD 3 arm S-B201 was suspected to be drug related and there was no discontinuation from study medication due to blood testosterone decreased.*
- *Therapeutic agent poisoning as DAE was reported in 1-2% in the RAD arms and 0% in the MMF arms in both key renal studies.*
- *DVT NOS as an AE was reported at higher rates in the RAD 3 arms compared with RAD 1.5 and MMF (RAD 1.5 and MMF arms presented similar rates). Even though the numbers are small, the consistency of this finding in the two key renal studies and the clinical implications deserves further exploration to rule out a true finding.*

⁵⁶ *Anemia NOS or Anemia NOS + Hb decreased + Hto decreased*

⁵⁷ *Leukopenia NOS or Leukopenia NOS plus WBC count decreased.*

⁵⁸ *Thrombocytopenia NOS or Thrombocytopenia NOS + platelet count decreased*

Table 20-4. RENAL RELATED ADVERSE EVENTS
Incidence Rate of Renal Related AE by System Organ Classification and Preferred Term (Safety Population - 36 Month Analysis Studies B251 and B201)

<i>Preferred Term</i>	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
<i>Blood creatinine increased</i>	60 (31%)	30 (15.5%)	68 (35%)	37 (19%)	42 (21%)	25 (13%)
<i>Renal impairment NOS</i>	7 (4 %)	13 (7 %)	4 (2 %)	13 (7 %)	4 (2 %)	6 (3 %)
<i>Primary Graft Dysfunction</i>	10 (5 %)	21 (11 %)	11 (6 %)	29 (15 %)	3 (1.5%)	17 (9 %)
<i>Renal Tubular Necrosis</i>	16 (8 %)	7 (4 %)	22 (11 %)	14 (7 %)	8 (4 %)	5 (3 %)
<i>Renal failure acute</i>	8 (4 %)	4 (2 %)	6 (3 %)	3 (1.5%)	4 (2 %)	2 (1 %)
<i>Renal failure NOS</i>	3 (2 %)	5 (3 %)	1 (0.5%)	6 (3 %)	0	3 (1.5%)
<i>HUS</i>	5 (3%)	6 (3%)	3 (1.5%)	9 (4.5%)	1 (0.5%)	1 (0.5%)
<i>TMA NOS⁵⁹</i>	2 (1.0%)	0	0	1 (0.5%)	1 (0.5%)	0
<i>TTP</i>	0	0	1 (0.5%)	0	0	0
<i>TMA total⁶⁰</i>	4%	3%	2%	5%	1%	0.5%
<i>Proteinuria</i>	14 (7%)	18 (9 %)	18 (9 %)	18 (9 %)	10 (5 %)	5 (2 %)

1. The dictionary used is the 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
3. Data obtained from Incidence Rate of Adverse Events/Infections by Body System and Preferred Term (Safety Population - 36-Month Analysis). Post-text Table 10.1-1a (Page 2 of 82) and Post-text Table 10.1-1a (Page 1 of 58) Studies B251 and B201, respectively.

Blood creatinine increased (BCI) and Renal impairment are preferred terms that denote "abnormal kidney function" that was severe enough to be considered and adverse events. However, most of the cases were reported as BCI.

TMA (Thrombotic Microangiopathy) including HUS (Hemolytic uremic syndrome) and TTP (Thrombotic thrombocytopenic purpura) are consumptive coagulopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia we review the related AE as a group. HUS accounted for most of the cases.

Reviewer's comments:

- ***Blood creatinine increased / Renal impairment NOS, Primary graft dysfunction, and Renal tubular necrosis reported as AE presented higher rates in both RAD arms when compared to MMF. A dose related effect was observed between the low and high dose RAD arms.***

⁵⁹ TMA (Thrombotic Microangiopathy) including HUS (Hemolytic uremic syndrome) and TTP (Thrombotic thrombocytopenic purpura) are consumptive coagulopathies characterized by microangiopathic hemolytic anemia and thrombocytopenia.

⁶⁰ TMA total Including TMA NOS, HUS and TTP

- *Primary graft dysfunction and renal tubular necrosis rates reported as AE were higher in both RAD arms compared to MMF in both key renal studies. This consistent finding appears to present a dose related effect between the RAD arms. The fact that these AE are predominantly observed in the RAD arms suggests that these events may be related to the nephrotoxic effects of the RAD / CsA combination.*
- *HUS as AE was reported in 3%, 2%, and 1% (S-B251) and 3%, 5%, and 1% S-B201) in the RAD1.5, RAD 3 and MMF, respectively. These numbers of cases were small but numerically higher in the RAD arms compared with the MMF and consistent across both key renal studies. Since TMA has been related to the toxic effect of CsA, this finding is relevant given the known interaction in the RAD / CsA combination.*
- *HUS rates reported as AE were higher in both RAD arms compared to the MMF in both key renal studies. The number of cases was small but consistent across both key renal studies. Since TMA has been related to the toxic effect of CsA, this finding is relevant given the known interaction in the RAD / CsA combination.*
- *Proteinuria reported as AE presented higher rates in both RAD arms compared with MMF and consistent in both key renal studies (Table 4). A dose related effect was not observed between the RAD arms. This observation is in concordance with the rates of Clinically Confirmed Chronic Rejection which were numerically or significantly higher in the RAD arms compared with MMF in both key renal studies (See table 3 efficacy evaluation section). Furthermore, Proteinuria is not an uncommon feature in calcineurin inhibitor nephrotoxicity.*

Table 20-5. LIPID RELATED ADVERSE EVENTS

Incidence Rate of hyperlipidemia Related AE by System Organ Classification and Preferred Term (Safety Population - 36 Month Analysis Studies B251 and B201)

There was an inconsistency in coding, and more than one term may describe a same condition. These terms were mutually exclusive, and each patient was included under one term only.

<i>Preferred Term</i>	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
<i>Hyperlipidemia nos</i>	53 (27.5%)	54 (28%)	59 (30%)	50 (25%)	44 (22%)	29 (15%)
<i>Hypercholesterolemia</i>	59 (31%)	59 (30%)	53 (27%)	64 (32%)	44 (22%)	43 (22%)
<i>Blood Cholesterol Increased</i>	17 (9%)	3 (1.5%)	18 (9%)	3 (1.5%)	6 (3%)	1 (0.5%)
<i>Hypertriglyceridemia</i>	9 (5%)	22 (11%)	13 (7%)	26 (13%)	9 (5%)	14 (7%)
<i>Blood Triglycerides Increased</i>	10 (5%)	2 (1%)	9 (5%)	2 (1%)	7 (4%)	0
<i>Hyperlipidemia Total</i>	77%	72%	78%	73%	56%	44%

Reviewer's comment: *Hyperlipidemia Total⁶¹ presented higher incidence rates in both RAD 1.5 and RAD 3 arms compared to MMF arms in both key renal studies. Individual rates per preferred term reflected the same trend. (See table 5). RAD 1.5 and RAD 3 arms presented similar rates across both studies suggesting that a dose dependency do not exist. However, due to the individualized therapeutic efforts to maintain blood lipid levels within a target range, it is difficult to observe a dose related effect between the low and the high dose RAD arms. Drug dose regimen modification after amendment #3 is an additional confounding factor that impedes to identify a dose-related effect.*

Table 20-6. Administration of Lipid-Lowering Drugs in Studies B201 and B251 (Safety Population - 36 Month Analysis)

	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
Any Lipid-Lowering Drug	140 (72.5%)	126 (64.9%)	134 (69.1%)	114 (57.6%)	120 (61.2%)	86 (43.9%)
HMG CoA Reductase Inhibitors	137 (71.0%)	122 (62.9%)	131 (67.5%)	110 (55.6%)	115 (58.7%)	80 (40.8%)

Data obtained from: Post-text Table 8.2-6 (Page 1 of 2) Concomitant Administration of Lipid-Lowering Drugs by WHO Preferred Drug Name (Safety Population - 36 Month Analysis)

Reviewer's comment: *The requirements for lipid lowering agents were higher in both RAD arms compared with the MMF arm requirements. This observation was consistent across both key renal studies. Despite this therapeutic efforts the mean cholesterol and triglycerides values were significantly higher in both RAD arms compared with MMF in both key renal studies. (See Fig)*

INFECTIONS

Table 20-7. Incidence Rate of Infections by Type of Organism (Safety Population - 36 Month Analysis Studies B251 and B201)

<i>Preferred Term</i>	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
Any Infection	149 (77%)	155 (80%)	144 (74%)	149 (75%)	149 (76%)	144 (73.5%)
Bacterial	62 (32%)	96 (49.5%)	74 (38%)	89 (45%)	60 (31%)	80 (41%)
Fungal	22 (11%)	18 (9%)	16 (8%)	25 (13%)	12 (6%)	15 (8%)
Viral	18 (9%)	26 (13%)	18 (9%)	38 (19 %)	19 (10%)	57 (29%)

Post-text Table 10.1-7a (Page 1 of 2) and Post-text Table 10.1-7a (Page 1 of 2) Summary Statistics for the Number of Infections by Type of Organism (Safety Population - 36 Month Analysis) studies B-201 and B251.

⁶¹ Hyperlipidemia including: Hyperlipidaemia nos, Hypercholesterolemia, Blood Cholesterol Increased, Hypertriglyceridemia, Blood Triglycerides Increased. Individual analyses per preferred term reflect the same trend. (see table 5)

Reviewer's comments:

- ***Bacterial infection rates reported as AE were higher in both RAD arms versus MMF arm in study 201. In both key renal studies RAD 3 rates were higher than MMF. In study 251, a dose related effect between the RAD arms was observed and RAD1.5 and MMF rates were similar.***
- ***In general fungal infections were higher in both RAD arms compared with MMF. Either RAD 1.5 or RAD3 rates were higher than MMF in any of the key renal studies.***
- ***In S-B251 Viral infections rates were similar across arms. In contrast, in S-B201, Viral Infections presented higher rates in the MMF arm compared to the RAD arms. CMV infection was the main contributor for this higher incidence in the MMF arm in this specific study.***

CYTOMEGALOVIRUS INFECTIONS.

The key renal studies were not designed to demonstrate rate differences in CMV infection, CMV syndrome, or tissue invasive CMV.

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. In these studies, such definitions were not discussed prospectively.

"Cytomegalovirus infection" was the preferred term used to include the following reported terms: Cytomegalovirus, CMV, CMV disease, CMV infection, CMV primo infection, CMV reactivation, and Suspected CMV infection.

Other preferred terms were used to describe tissue invasive disease i.e. CMV Gastritis, Pneumonia Cytomegaloviral.

Table 20-8. Incidence Rate of Cytomegalovirus and Herpes Infections by Preferred Term (Safety Population - 36 Month Analysis Studies B251 and B201)

<i>Preferred Term</i>	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
<i>Cytomegalovirus Infection</i>	14 (7 %)	12 (6 %)	9 (5 %)	13 (7 %)	10 (5 %)	39 (20 %)
<i>CMV Gastritis</i>	2 (1.0%)	-	0	-	2 (1.0%)	-
<i>CMV Syndrome</i>	0	0	1 (0.5%)	1 (0.5%)	0	0
<i>CMV UTI</i>	0	-	0	-	1 (0.5%)	-
<i>Pneumonia Cytomegaloviral</i>	0	0	1 (0.5%)	1 (0.5%)	0	0
<i>CMV total⁶²</i>	8%	6%	6%	7.5%	7%	20%
<i>Herpes Simplex</i>	11(6%)	18 (9%)	15 (8%)	14 (7%)	11 (6%)	16 (8%)
<i>Herpes Zoster</i>	4 (2%)	7 (4%)	13 (7%)	11 (6%)	8 (4%)	11 (6%)

⁶² Includes all CMV reported as: *CMV Infection, CMV Gastritis, CMV Syndrome, CMV UTI, Pneumonia Cytomegaloviral.*

1. The dictionary used is the 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
3. Data obtained from: Incidence Rate of Adverse Events/Infections by Body System and Preferred Term (Safety Population - 36-Month Analysis). Post-text Table 10.1-1a (Page 2 of 82) and Post-text Table 10.1-1a (Page 1 of 58) Studies B251 and B201, respectively.

Reviewer's comments:

In S-B201, the incidence of CMV infection presented a higher incidence rate in the MMF arm; 6%, 7% and 20% in the RAD 1.5, RAD 3 and MMF, respectively. This results are not consistent with the results in the American study B251, in which the incidence of CMV infection was similar across arms 7%, 5% and 5% in the RAD 1.5, RAD 3 and MMF, respectively.

The 20% CMV incidence rate in the MMF2g/day group, study B201, is excessively higher compared to historical data⁶³. The MMF 3g/day arms in the European and Tricontinental MMF trials reported 15% and 13% rates, respectively. We cannot exclude that the differences observed in CMV rates are the result of differences in clinical practices regarding CMV prophylaxis, treatment and use of antibody therapy.

Herpes Simplex and Herpes Zoster infection rates were low and the differences across arms were not clinically relevant.

Table 20-9. Concomitant Administration of Immunosuppressive Agents Other than Randomized Study Medication and Neoral by WHO preferred drug name Study B201 (Safety Population - 36 Month Analysis)

Selective Immunosuppressive Agents	RAD 1.5 194	RAD 3 198	MMF 196
Methylprednisolone Sodium Succinate	82 (42.3%)	80 (40.4%)	80 (40.8%)
Methylprednisolone	74 (38.1%)	81 (40.9%)	78 (39.8%)
<i>Methylprednisolone Total</i>	80%	81%	81%
Antilymphocyte Immunoglobulin (Horse)	8 (4.1%)	9 (4.5%)	7 (3.6%)
Antithymocyte Immunoglobulin	4 (2.1%)	4 (2.0%)	4 (2.0%)
Muromonab-Cd3	5 (2.6%)	0	2 (1.0%)
<i>Antibody therapy total</i>	9%	6.5%	7%
Antibody Treated Acute Rejection	15(8%)	16(8%)	14(7%)

Data obtained from Post-text Table 8.2-2 (Page 1 of 2), page 197 Study B-201, 36-month analysis

Reviewer's comment: *The European study B201 presented significantly higher rate of cytomegalovirus infections in the MMF arm compared with the RAD arms. This finding was not consistent with the findings in USA study B251.*

It has been recognized that antibody therapy is a predisposing factor for CMV infection and CMV prophylaxis is recommended for all high-risk patients. In S-B201 there were no significant differences in the use of antibody therapy across arms that could explain the

⁶³ Ther Drug Monit, Vol 24; No1, 2002.

higher CMV infection rates observed in the MMF arm. However, dose and days of treatment were not taken into consideration in this analysis.

Table 20-10. CMV infection reported as Adverse Events and Serious Adverse Events EU Study B201 (Safety Population - 36 Month Analysis)

This table compiles cytomegalovirus infections reported as **Adverse Events** and **Serious Adverse Events**.

In the **Serious Adverse Events** section, we included the terms used by the investigator (reported term) to describe the event before it was coded in Medra (preferred term). The severity described by the investigator is also included.

Patients were counted only one time, even though one case could have presented more than one episode of CMV infection (*). The most severe form as reported by the investigator was counted.

Preferred Term	RAD 1.5 (N=194)	RAD 3 (N=198)	MMF (N=196)
CMV Infection⁶⁴ reported as AE	12 (6 %)	13 (7 %)	39 (20 %)
Total # of CMV infections reported as Serious Adverse Events. Preferred term / Reported term	3	9	18
Cytomegalovirus infection / Cytomegalovirus			2 Moderate
Cytomegalovirus infection / CMV	1 Severe*	1 mild	1 Mild 1 Moderate
Cytomegalovirus infection / CMVDisease		1 Mild 2 Moderate	2 Mild 3 Moderate
Cytomegalovirus infection / CMV Infection	1 severe	1 mod 2 severe 1 unknown	4 Mild 3 Moderate 1 Severe 1 mild
Cytomegalovirus infection / CMVprimo-infection			
Cytomegalovirus infection / CMV reactivation	1 mild		
Pneumonia Cytomegaloviral / CMV pneumonia or pneumonitis		1 Severe	

Data obtained from Post-Text Listing 10.2-2 (Page 1 of 118), Non-Fatal Serious Adverse Events (Including Infections) Occurring after Day 1(Safety Population - 36 Month Analysis) and Incidence Rate of Adverse Events/Infections by Body System and Preferred Term (Safety Population - 36 Month Analysis). Post-text Table 10.1-1a (Page 1 of 58) Study B201.

(*) One patient in the RAD 1.5 arms presented recurrence of CMV disease and it was reported as diarrhea (CMV) by the investigator.

Reviewer's comments:

Cytomegalovirus infections reported as serious adverse events in S-B201 were more frequent in the MMF arm. (3, 9 and 18 cases in the RAD 1.5, RAD 3 and MMF arms, respectively). Most of these cases were mild to moderate in severity as reported by the investigators. Severe cases of CMV were more frequently observed in the RAD arms (2, 3 and 1 cases in the RAD1.5, RAD 3 and MMF respectively).

Discontinuation from study medication due to CMV were reported in 4 mild to moderate cases in the MMF group and in two case of severe CMV infection in the RAD3 arms. There were no deaths attributed to any form of CMV infection or disease.

⁶⁴ 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)

Defined as symptomatic CMV infection and included both CMV syndrome and tissue invasive disease

In conclusion, the cytomegalovirus infections rate differences between RAD arms and MMF arm; it is based on mild to moderate cases and may not be clinically relevant. The fact that this is a retrospective finding in study B201 that is not consistent with study B251 diminishes the weight of this observation.

REVIEWER'S CONCLUSIONS ON CMV INFECTIONS

The definitions for CMV infection and CMV disease was not defined in this protocols, instead it uses the preferred term "cytomegalovirus infection" to include most of the reported terms.

CMV infection is a term generally used to describe an asymptomatic "CMV infection". On the other hand a symptomatic CMV infection is usually called "CMV disease".

Systematic viral monitoring is required diagnosed "asymptomatic CMV Infections". Since routine viral monitoring was not an integral part of the protocol, the exact incidence of CMV infection could not be assessed. One major problem is related to the techniques used for viral monitoring and how CMV infection is determined: the isolation of the virus⁶⁵, seroconversion⁶⁶, and four-fold rise in antibody titers⁶⁷ or IgM titers⁶⁸.

Furthermore, there is no consensus on the necessity and the efficacy of CMV prophylaxis⁶⁹ in the transplant community. Similarly, there is inconsistency in the duration of prophylaxis and antiviral agents used. In this studies CMV prophylaxis was "recommended" for high-risk patients and after antibody treated rejection, however, the final decision was left to local practice preferences.

The key 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 it did not included any precautions to avoid bias for the collection of CMV related information.

The cytomegalovirus infections rate differences between RAD arms and MMF arm, it is based on mild to moderate cases and may not be clinically relevant. Furthermore, discontinuation from study medication due to CMV were reported in 4 mild to moderate cases in the MMF group and in two case of severe CMV infection in the RAD3 arms and there were no deaths attributed to any form of CMV infection or disease.

In summary, the presence of many confounding factors does not allow us to draw valid conclusions base on a retrospective finding. The high incidence of cytomegalovirus infection in the European study B201 was not consistent with the findings in the US study 251, which diminish the weight of this observation.

The higher rates of CMV infection or disease in the MMF group was due to mild to moderate cases and there was no association with an increased incidence of opportunistic infections, or chronic rejection. On the contrary the incidence of Clinically Confirmed Chronic Rejection was numerically or significantly higher in both RAD arms compared with the MMF arms in both Key Renal Studies.

⁶⁵ Balfour 1989, Rondeau 1993, Saliba 1993, Singh 1994, Pouteil-Noble 1996, Kletzmayer 1996

⁶⁶ Rondeau 1993, Singh 1994, Pouteil-Noble 1996, Kletzmayer 1996, Cohen 1993

⁶⁷ Balfour 1989, Cohen 1993

⁶⁸ Cohen 1993, Saliba 1993, Pouteil-Noble 1996

⁶⁹ Glowacki 1994, Wittes 1996, Patel 1996

We recommend a prospective trial specifically design to demonstrate differences in CMV disease (Tissue invasive CMV disease and CMV syndrome) and CMV infection.

PNEUMONIA:

Table 20-11. Incidence Rate of Pneumonia by Preferred Term (Safety Population - 36 Month Analyses S-B251 and B201)

<i>Preferred Term</i>	RAD 1.5		RAD 3		MMF	
<i>PNEUMONIA</i>	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
<i>Pneumonia NOS</i>	14 (7 %)	12 (6 %)	13 (7 %)	11 (6 %)	11 (6 %)	8 (4 %)
<i>Bronchopneumonia NOS</i>	1 (0.5%)	4 (2.1%)	0	1 (0.5%)	1 (0.5%)	2 (1.0%)
<i>Lobar Pneumonia NOS</i>	3 (2%)	0	1 (0.5%)	1(0.5%)	0	0
<i>Bacterial pneumonia: Gram positive NOS, Pneumococcal, staphylococcal, streptococcal, gram-negative NOS, hemophilus, Legionella, Klebsiella, Enterobacter</i>	3(2 %)	1(0.5%)	3(1.5 %)	5(2.5%)	3(1.5%)	0
<i>Aspergillus/bronchopulmonary Aspergillosis</i>	0	0	3 (1.5%)	1(0.5%)	0	1(0.5%)
<i>Blastomyces P.</i>	1 (0.5%)	-	0	-	0	-
<i>PCP</i>	1(0.5%)	1(0.5%)	0	3(1.5%)	0	1(0.5%)
<i>Cytomegaloviral P.</i>	0	0	1(0.5%)	1(0.5%)	0	0
<i>Herpes viral P.</i>	1(0.5%)		0		0	
<i>Cryptogenic Organizing P.</i>	-	0	-	1(0.5%)	-	0
<i>TOTAL⁷⁰</i>	24 (12%)	18 (9%)	21 (11%)	24 (12%)	15 (8%)	12 (6%)

1. The dictionary used is the 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
3. Data obtained from: Incidence Rate of Adverse Events/Infections by Body System and Preferred Term (Safety Population - 36-Month Analysis). Post-text Table 10.1-1a (Page 2 of 82) and Post-text Table 10.1-1a (Page 1 of 58) Studies B251 and B201, respectively.

Reviewer's comments:

The incidence rate of pneumonic processes, regardless etiology, was higher in both RAD arms compared to MMF arm, in both key renal studies. A dose relation trend is observed in S-201 for the incidence of pneumonia reported as AE.

11 cases of pneumonia were discontinued from study medication in both RAD1.5 and RAD3 arms, in both Key renal studies while only one patient was discontinued from study medication due to pneumonia in the MMF arms.

⁷⁰ We included all the preferred terms that described the different types of pneumonia "pneumonia" we excluded a case in the RAD1.5 due to aspiration pneumonia and two case of pneumonitis one in the RAD3 and one in the MMF arm.

Table 20-12. Pneumonia as Primary Cause for Death (Safety Population - 36 Month Analysis Studies B251 and B201)

	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
Any Cause of death	12 (6%)	15 (8%)	13 (7%)	18 (9%)	10 (5%)	16 (8%)
Pneumonia NOS / Pneumonia	0	1	0	2	0	0
Pneumocystis Carinii Pneumonia	0	1	0	1	0	0
Pneumonia Fungal NOS / fungal pneumonia	0	0	1	0	0	0
Aspergillosis / Pulmonary Aspergillus	0	0	0	1	0	0
Total Pneumonia as cause of death	0	2	1	4	0	0

Data obtained from Post-Text Listing 10.2-1 Cases of Death Occurring after Day 1 (Safety Population - 36 Month Analysis) Studies B251 and B201.

Reviewer's comment: *Higher number of patients were discontinued from study medication or died due to pneumonia in the RAD1.5 and RAD 3 arms compared to the MMF arms in both key renal studies.*

Pneumonia reported as an adverse event presented higher rates in the RAD arms compared with the MMF arm in both key renal studies. This AE's were a potential cause for discontinuation and death and should be considered clinically relevant.

URINARY TRACT INFECTIONS

Table 20-13. Incidence Rate of Urinary Tract Infections (UTI) by Type of Organism and Preferred Term (Safety Population - 36 Month Analysis Studies B251 and B201)

	RAD 1.5		RAD 3		MMF	
<i>Preferred Term</i>	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
UTI NOS	43 (22%)	55 (28%)	36 (19%)	49 (25%)	48 (24.5%)	42 (21%)
Urosepsis	8 (4%)	2 (1%)	7 (4%)	4 (2%)	4 (2%)	1 (0.5%)
UTI Enterococcal	3 (2%)	22 (11%)	12 (6%)	15 (8%)	12 (6%)	9 (5%)
E coli UTI	17 (9%)	-	13 (7%)	-	16 (8%)	-
Any UTI⁷¹	37%	41%	35%	34%	41%	26.5%

1. Data obtained from: Incidence Rate of Adverse Events/Infections by Body System and Preferred Term (Safety Population - 36-Month Analysis). Post-text Table 10.1-1a (Page 2 of 82) and Post-text Table 10.1-1a (Page 1 of 58) Studies B251 and B201, respectively.

2. The dictionary used is the MedDRA

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

4. A fungal UTI in MMF arm S- B-251 and a CMV UTI in MMF arm S- B-251 are not included in this table.

⁷¹ Includes preferred terms which were described as UTIs

Reviewer's comments: UTI was a common adverse event. In S-B201, there was a higher UTI rates in both RAD arms compared with MMF. In contrast, in S-B251 MMF arm presented higher rates than RAD arms. We do not consider these differences to be clinically relevant.

Table 20-14. OTHER INFECTIONS AND WOUND COMPLICATIONS
Incidence Rate of Infections by Body System and Preferred Term
(Safety Population - 36 Month Analysis Studies B251 and B201)

<i>Preferred Term</i>	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
<i>Postoperative Wound Complication NOS</i>	20 (10%)	0	22 (11%)	4 (2%)	15 (8%)	4 (2%)
<i>Wound Dehiscence</i>	8 (4%)	3 (1.5%)	8 (4%)	3 (1.5%)	2 (1%)	2 (1%)
Post procedural site wound infection	8 (4%)	1 (0.5%)	3 (1.5%)	2 (1%)	1 (0.5%)	0
Wound Infection	11 (6%)	6 (3%)	14 (7%)	13 (7%)	11 (6%)	10 (5%)
Postoperative Wound Breakdown	-	0	-	0	-	1 (0.5%)
Wound Drainage	-	0	-	1 (0.5%)	-	0
Wound Hemorrhage	-	0	-	1 (0.5%)	-	1 (0.5%)
<i>Wound Complications Total⁷²</i>	24%	5%	24%	12%	15%	9%
<i>Lymphocele</i>	31 (16%)	24 (12%)	36 (19%)	35 (18%)	24 (12%)	16 (8%)

1. The dictionary used is the 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
3. Data obtained from: Incidence Rate of Adverse Events/Infections by Body System and Preferred Term (Safety Population - 36-Month Analysis). Post-text Table 10.1-1a (Page 2 of 82) and Post-text Table 10.1-1a (Page 1 of 58) Studies B251 and B201, respectively.

Wound Complications Total: We included in this category all preferred terms that included the word wound related to the surgical procedure as reported in CRF i.e. postoperative wound complication NOS. etc. Lymphocele was not included in this category.

Reviewer's comments: Wound complications as AEs were higher in the RAD3 arms compared with the MMF arms in both key renal studies. Wound dehiscence and wound infections are the major contributors for these differences.

Lymphocele rates were higher in both RAD1.5 and RAD3 compared with MMF arms in both key renal studies. A dose related incidence trend was observed between RAD1.5 and RAD3 in both renal studies.

One case of lymphocele in the RAD 3 that led to discontinuation in S-B201 and one in the RAD 1.5 in S- B251

Malignancies:

⁷² Includes all preferred terms in which the word wound was included

Table 20-15. Incidence Rate of Malignancies by Preferred Term (Safety Population - 36 Month Analysis Studies B251 and B201)

Preferred Term	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
Malignancies:						
PTLD	2 (1%)	4 (2%)	2 (1%)	0	0	0
Skin	5 (3%)	2 (1%)	4 (2%)	4 (2%)	5 (2.5%)	3 (1.5%)
Other	2 (1%)	4 (2%)	3 (2%)	5 (2.5%)	7 (3.5%)	6 (3%)
Any malignancy	9 (5%)	10 (5%)	10 (5%)	9 (4.5%)	12 (6%)	9 (5%)

Data obtained from Post-text Table 10.2-3 (Page 1 of 1), Incidence of Malignancies Safety Population - 36 Month Analysis) studies B201 and B251.

120- Safety update on Malignancies:

In study B251, 3 new malignancies were reported (ovarian neoplasm [RAD 1.5 mg group] and basal cell carcinomas [1 each in the RAD 3 mg and MMF groups]). In study B201, 4 malignancies were reported: Seminoma/abdominal neoplasm (suspected) in 1 RAD 1.5 mg patient Basal cell carcinomas (suspected) and Bowen’s disease in 1 RAD 3 mg patient each.

Reviewer’s comment: *The incidence of malignancies was equally distributed across arms in both key renal studies. Skin cancer was the most frequent malignancy observed and the differences observed across arms were not clinically relevant. Eight (8) PTLD cases were observed in the RAD arms. Six case in the lower dose and four cases in the higher dose arms. There were not PTLD cases observed in the MMF arms. The meaning of this trend is unclear due to the small numbers. Long tem follow up is recommended.*

Table 20-16. Primary Reason for Death Reported in ≥ 2 patients in any group (Safety Population - 36 Month Analysis Studies B251 and B201)

Cause of Death	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
Any death	12 (6%)	15 (8%)	13 (7%)	18 (9%)	10 (5%)	16 (8%)
Cardiac Disorders	1 (0.5%)	5 (3%)	2 (1%)	4 (2%)	4 (2%)	3 (1.5%)
Infections	3 (2%)	4 (2%)	3 (1.5%)	9 (4.5%)	2 (1%)	2 (1%)
CNS Disorders Cerebral Hemorrhage, CVA ,Intracranial Hemorrhage NOS	2(1%)	2 (1%)	0	2 (1%)	2(1%)	3 (1.5%)

Data obtained from: Post-text Table 10.2-1a (Page 1 of 3) Incidence Rates of Death (Primary Cause) by Body System and Preferred Term (Safety Population - 36-Month Analysis)

Reviewer’s comment: *Cardiovascular disease and infections were the leading causes of death. Incidence rates were similar across arms in both key renal studies.*

Notable Events⁷³ were higher in the RAD 1.5 (75% and 74%) and RAD 3 (83% and 81%) arms compared to MMF arm (62% and 66%) in S-B251 and B201, respectively.

120 safety update on Deaths:

In study B251, 4 deaths were reported, RAD 1.5(2), RAD 3 (1) and MMF (1) and none was considered drug related by the investigators.

In study B201, 5 deaths were reported RAD 1.5(1), RAD 3 (2) and MMF (2), and none was considered drug related by the investigators:

Adverse Events/Infections Suspected to be Drug Related:

The applicant also presented analyses on the incidence rates of AE/Infections **Suspected to be Drug related.** Table 17 summarizes these AE.

Table 20-17. Incidence Rates of Adverse Events/Infections Suspected to be Drug Related by Body System and Preferred Term (Safety Population - 36 Month Analysis Studies B251 and B201)

<i>Preferred Term</i>	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
<i>Any AE/Infection</i>	146 (76%)	37 (35%)	152 (78%)	33 (35%)	144 (74%)	47 (36%)
Anemia NOS	5 (3%)	6 (3%)	16 (8%)	13 (7%)	4 (2%)	8 (4%)
Pneumonia NOS	6 (3%)	7 (4%)	5 (3%)	7 (3.5%)	1 (0.5%)	5 (3%)
Pneumonia total ⁷⁴	10 (5%)	13 (7%)	8 (4%)	13 (6.5%)	4 (2%)	6 (3%)
Blood Cholesterol Increased	15 (8%)	2 (1%)	16 (8%)	1 (0.5%)	(3%)	0
Blood Creatinine Increased	14 (7%)	8 (4%)	19 (10%)	11 (6%)	8 (4%)	7 (4%)
Hypercholesterolemia	35 (18%)	41 (21%)	30 (15.5%)	52 (26%)	21 (11%)	32 (16%)
Hyperlipidaemia NOS	46 (24%)	48 (25%)	52 (27%)	42 (21%)	35 (18%)	25 (13%)
Hypertriglyceridemia	2	1 (11%)	-	24 (12%)	-	12 (6%)
Blood Triglycerides Increased	0	-	2 (1%)	-	0	-
Lymphocele	5 (3%)	5 (3%)	1 (0.5%)	3 (1.5%)	1 (0.5%)	4 (2%)
Thrombocytopenia	1 (1%)	16 (8%)	0	22 (11%)	1 (1%)	7 (4%)
Platelet Count Decreased	5 (3%)	5 (3%)	8 (4%)	3 (1.5%)	1 (0.5%)	1 (0.5%)
Leukopenia NOS	8 (4%)	19 (10%)	17 (9%)	21 (11%)	17 (9%)	28 (14%)
WBC Count Decreased	2 (1%)	2 (1%)	4 (2%)	3 (1.5%)	7 (4%)	3 (1.5%)

Data obtained from Post-text Table 10.1-1b (Page 1 of 43) Post-text Table 10.1-1b and Post-text Table 10.1-3a (Page 1 of 26) (Page 12 of 24)

⁷³ Notable events includes Deaths, NSAEs (Non-Fatal Serious AEs) and ADOs (Adverse dropouts) ADOs were patients with primary discontinuation reasons: AEs or abnormal laboratory values or abnormal test procedure result.

⁷⁴ Pneumonia total includes all types of pneumonias (Viral, bacterial and mycotic) plus Pneumonia NOS.

Reviewer's comment: The incidence Rates of Adverse Events/Infections Suspected to be Drug Related presented the same trends as AE or SAE.

Anemia, Pneumonia NOS, hypertriglyceridemia, hypercholesterolemia, presented higher rates in the RAD arms compared to MMF. These analyses should be interpreted with caution because the open-label design in the study after month 12.

AE/ Infections suspected to be drug related presented small numbers and do not allow us to draw definitive conclusions (See AE and SAE)

Diabetes Mellitus:

Table 20-18 Incidence rates of Diabetes Mellitus at base line and New onset Diabetes Mellitus (Studies B201 and B251 - 12 month Analyses)

	RAD 1.5		RAD 3		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
DM at baseline (ITT Population)	36 (19%)	8 (4%)	40 (21%)	17 (9%)	48 (25)%	12 (6%)
New Onset DM ⁷⁵ 12 months (Safety Population)	9/157 (6%)	4/186 (2%)	7/154 (4.5%)	7/181 (4%)	7/148 (5%)	2/184 (1%)

Data obtained from: Post-text Tables 7.4-12 and 7.4-12, studies B201 and B251, Pre-Study Diabetes (ITT Population - 12 Month Analysis) and Post-text Table 10.2-4 (Page 1 of 1) Incidence of Post-transplant Diabetes Mellitus (PTDM) in first 12 Months (Safety Population - 12 Month Analysis) S-b251 and S-B201

⁷⁵ Mayer's definition of PTDM : (1) had no history of insulin or non-insulin dependent diabetes before transplantation, and (2) required insulin after transplantation for 30 or more consecutive days, with fewer than 5 days interruption, to maintain a normal, fasting blood glucose level

Table 20-19. Summarizes AE/Infections by study and study arms higher rates. The AE/ Infections are organized according to the incidence rates summarized in tables 3, 4 and 5.

Table 20-19 Adverse Events/Infections Summarized by Consistently Higher Incidence Rates by Study Medication and Study

	<u>RAD 3 > MMF</u>	<u>RAD 3 and RAD1.5 > MMF</u>	<u>RAD 3 > MMF and RAD 1.5 similar to MMF</u>	<u>SIMILAR ACROSS ARMS</u>
B251 and B201	Anemia ⁷⁶			Constipation
	Bacterial Infections			
	Blood creatinine increased	Blood creatinine increased		
	Diabetes Mellitus NOS		Diabetes Mellitus	
	DVT		DVT	
	HUS			
	Hyperlipidemia Total ⁷⁷	HUS		
	Hypercholesterolemia ⁷⁸	Hyperlipidemia Total		
	Hypertriglyceridemia ⁷⁹	Hypercholesterolemia		
	Hypokalemia		Hypokalemia	
	Lymphocele			
	Edema peripheral	Lymphocele		
	Pyrexia /Hyperpyrexia	Edema peripheral		
	Pneumonia TOTAL ⁸⁰	Pyrexia /Hyperpyrexia		
	Proteinuria	Pneumonia TOTAL		
Therapeutic Agent Poisoning		Therapeutic Agent Poisoning NOS		
TMA total ⁸¹				
B251		Anemia NOS*	Bacterial Infections	Thrombocytopenia
	Diarrhea NOS*		Diarrhea NOS*	Viral Infections
	Dyspnea NOS		Dyspnea NOS	CMV infection
	Headache NOS	Hypertension NOS	Headache NOS	Wound Infection
	Hypertension NOS			
	Nausea	Wound Dehiscence	Nausea	
	Post-Op Wound Complication NOS		Proteinuria	
	Wound Dehiscence			
B201	Any UTI ⁸²	Any UTI ⁸⁴	Anemia NOS	Diarrhea NOS
		Bacterial Infections	Fungal Infections	Dyspnea NOS
	Edema NOS	Hypertriglyceridemia		Hypertension NOS
		Proteinuria		Nausea
	Renal impairment NOS			Post-Op Wound Complication NOS
Thrombocytopenia ⁸³	Thrombocytopenia		Wound Dehiscence	

⁷⁶ Anemia NOS or Anemia NOS plus Hemoglobin or Hematocrit decreased.

⁷⁷ Hyperlipidemia including: Hyperlipidemia nos, Hypercholesterolemia, Blood Cholesterol Increased, Hypertriglyceridemia, Blood Triglycerides Increased. Individual analyses per preferred term reflect the same trend. (see table 5)

⁷⁸ Also includes blood cholesterol increased

⁷⁹ Also includes blood triglycerides increased

⁸⁰ We included all preferred terms that describe different types of pneumonia

⁸¹ Includes TMA NOS, HUS and TTP

⁸² Including urosepsis.

⁸³ Thrombocytopenia or Thrombocytopenia plus Platelet count decreased.

⁸⁴ Including urosepsis.

Reviewer's comment:

Both Key Renal Studies consistently showed higher rates of Blood creatinine increased, Hyperlipidemia, Pneumonias, Hemolytic Uremic Syndrome, Lymphocele and Peripheral Edema in both RAD arms compared with MMF.

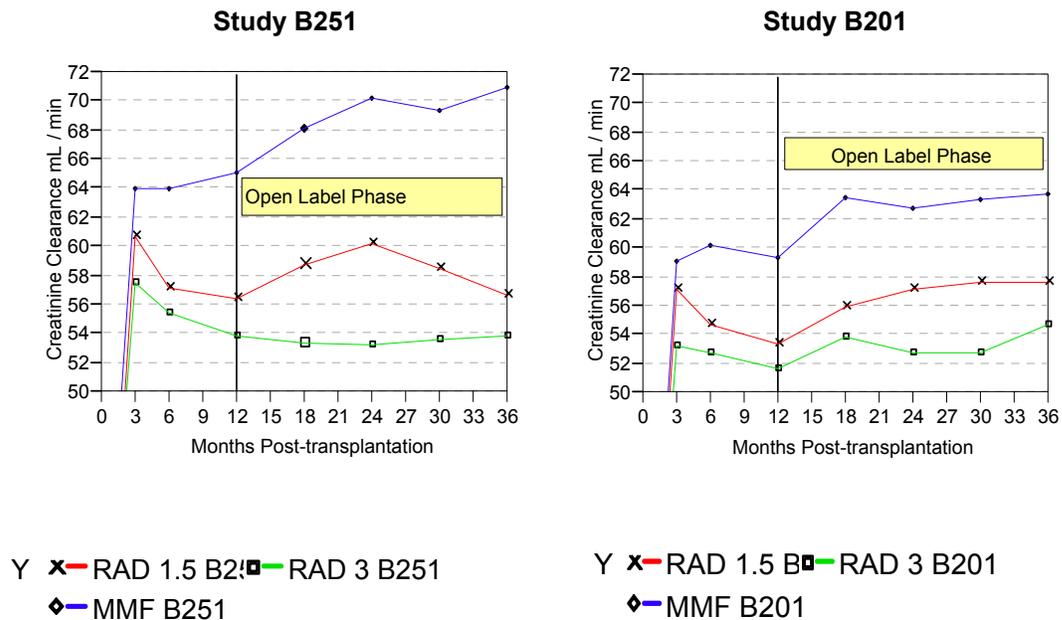
In study B201, both RAD arms showed higher rates of UTI, Bacterial infections, Hypertriglyceridemia, Thrombocytopenia and Proteinuria compared with MMF arm.

In study B251, both RAD arms presented higher rates of Anemia NOS, Hypertension NOS and Wound dehiscence compared with MMF arm.

Differences across studies and dose relationship are difficult to interpret in the 36 months analyses due to the open label characteristic after the initial 12 months.

RENAL FUNCTION STUDIES B251 AND B201

Figure 20-1. Estimated Creatinine Clearance (Nankivell) [ml/min] by visit (Safety Population -36 month analyses, S-B251 and B201)



Data obtained from: Post-text Tables 10.3-1b (Page 14 of 22) and (Page 13 of 22) Summary Statistics by Visit Renal Function: Estimated Creatinine Clearance (Nankivell) [mL/min] (Safety Population - 36 Month Analysis) Studies B251 and B201, respectively.

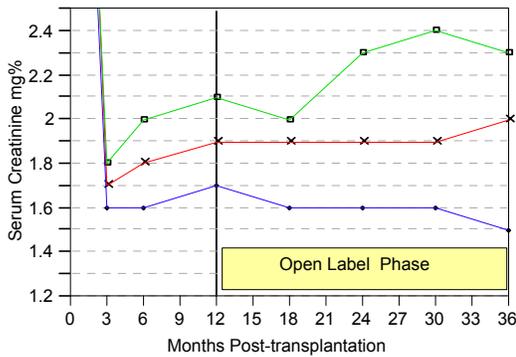
Reviewer's comment:

- ***Mean calculated creatinine clearance reached its zenith approximately at three months post transplantation in all arms in both key renal studies. Zenith values were lower and dose related in the RAD arms compared to MMF arms in both key renal studies. This observation indicates the RAD plus CsA combination has early post-transplant deleterious effects on renal function, identified by lower zenith mean CrCl values in both RAD arms in both key renal studies.***

- *The mean calculated CrCl values decreased significantly over time in both RAD arms. The differences between RAD 1.5 and RAD 3mg versus MMF were statistically significant in both key renal studies at 6, 12, 24, and 36 months.*
- *A dose related effect between the RAD groups was consistent in both key renal studies, RAD 3 arms presented numerically or significantly lower calculated CrCl compared with RAD1.5 arms in both key renal studies. These findings suggest a significant and sustained nephrotoxic effect that is markedly observed in the RAD plus CsA combination compared with CsA plus MMF.*

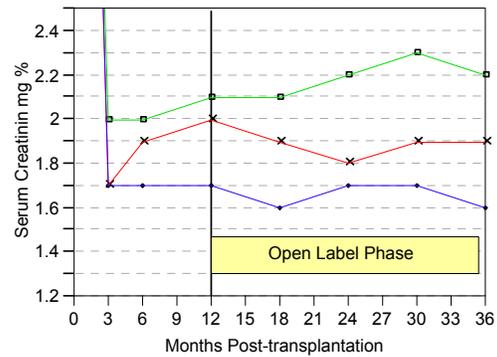
Fig 20-2. Serum Creatinine (mg %) by Visit. ITT Analysis (Safety Population - 36 Month Analysis)

Study B251



Y x— RAD 1.5 B251 ■— RAD 3 B251
 ◆— MMF B251

Study B201



Y x— RAD 1.5 B201 ■— RAD 3 B201
 ◆— MMF B201

Data obtained from: Post-text Tables 10.3-1b Summary Statistics by Visit Renal Function: Creatinine mg% (Safety Population - 36 Month Analysis) Studies B251 and B201, respectively.

Reviewer's comment:

Mean Serum Creatinine in the MMF arm was statistically significantly lower compared with RAD 1.5 and RAD 3 in both key renal studies. SCr reached its nadir at month 3 in all arms. In the RAD arms, SCr increased overtime until month 12. After implementation of CsA minimization strategy per amendment # 3, SCr transiently improved (RAD 3 arms) or prevented from further deterioration (RAD 1.5 arms). Therefore, we conclude that CsA minimization after month 12 was not a successful strategy in reversing the renal deterioration observed in the RAD arms during the double blind phase in both key renal studies.

Table 20-20. Estimated Creatinine Clearance (Nankivell) [mL/min] Summary Statistics by Visit. (Safety Population - 36 Month Analysis)

	RAD 1.5mg		RAD 3mg		MMF	
	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
Baseline	24	17.5	25	18	27	18
Month 3	61	57	58	53	64	59
Month 12	56	53	54	52	65	59
Month 36	57	58	54	55	71	64
Change from BL-36	+32	+40	+29	+37	+44	+46
Change from 3 mo to 36	- 4	+0.4	- 4	+1	+7	+5
Change from 12 mo to 36	+0.2	+4	0	+3	+6	+4

Data obtained from Post-text Tables 10.3-1b (Page 13 of 22) S-B251 page 2109 and B201 page 1958
 *All groups reached its zenith at 3 months, but MMF arm in S-B201, which reached its zenith at 6 months.

Reviewer's comments:

- *Baseline CrCl was similar across arms in both key renal studies. After transplantation CrCl reached its Zenith at three month in all treatment arms in both key renal studies. However the MMF arm in S-B201 continues to improve and reached its peak at 6 months. CrCl over time was statistically significantly lower in the RAD arms compared with MMF, at all comparison points in both key renal studies. CrCl in the RAD3 arms was lower than RAD 1.5 in both key renal studies. The differences between RAD arms, in both studies, did not reached statistical significance.*
- *After the 12 month CsA minimization intervention (amendment #3), the mean CrCl, showed no significant improvement in the RAD1.5 and RAD 3 arms in both key renal studies. In contrast, CrCl in the MMF arms continue to improve beyond 12 months with a positive change from baseline.*
- *These observations suggest that the renal function deterioration observed in the RAD arms is not reversible if the initially recommended therapeutic regimen is sustained up to 12 months. Dose adjustments implemented by amendment #3 at 12 months failed to reverse deterioration in CrCl in the RAD arms.*

**CHANGES IN CREATININE CLEARANCE AFTER AMENDMENT # 3
 KEY RENAL STUDIES**

The main objective of CsA minimization per amendment #3 was to improve renal function. Table 14 summarizes the changes in CrCl from 12 to 36 months.

Pairwise comparisons of treatment groups using Wilcoxon’s rank sum test: a = RAD 1.5mg vs. MMF, b = RAD 3mg vs. MMF, c= RAD 1.5 mg vs. 3mg. a and b comparisons showed p values ≤ 0.005 at 12, 24 and 36 month in both key renal studies.

Table 20-21. Estimated Creatinine Clearance (Nankivell) (unadjusted) [mL/min] by Visit. ITT Analysis (Safety Population - 36 Month Analysis)

	RAD 1.5mg		RAD 3mg		MMF 2g		CrCl difference MMF - RAD1.5 MMF - RAD 3 ml/min	
	B251 (193)	B201 (194)	B251 (194)	B201 (198)	B251 (196)	B201 (196)	B251	B201
Month 12 CrCl ml/min (# patients)	57 (143)	53 (131)	54 (120)	51 (125)	65 (143)	59 (143)	65 - 57= 8 65 -54=11	59 -53= 6 59 -51= 8
Month 24	60 (113)	56 (109)	54 (86)	52 (100)	70 (121)	63 (125)		
Month 36	57 (93)	56 (99)	53 (69)	54 (83)	70 (107)	63 (107)	70 -57= 13 70 -53=17	63 -56=7 63 -54=9
Change from 12 to 36 mo.	0	+3	-1	+3	+5	+4		

Data obtained from Post-text Tables 10.7-1a, Studies- B251 and B201, respectively Summary of Estimated Creatinine Clearance (Nankivell) (unadjusted) [mL/min] by Visit ITT Analysis (Safety Population - 36 Month Analyses)

- ITT analysis uses all values at each visit, including values obtained after discontinuing study medication
- Patients who are still on study medication or d/c study medication but still in study, patients who d/c study or had graft loss prior to study visit were not expected to have values.
- Values observed after Month 36 were used only for patients who did not have 36-month values but had later ones

Reviewer's comment:

CREATININE CLEARANCE CHANGE FROM 12 TO 36 MONTHS (Amendment # 3 evaluation)

- In B251 (USA study), amendment #3 did not improve renal function, no change in CrCl was observed in the RAD arms from 12 to 36 month follow up, in contrast the MMF arm CrCl further improve +5 ml per min. The difference in the mean calculated creatinine clearance between the RAD arms and MMF (MMF-RAD1.5 and MMF-RAD3) continue to increase from 12 to 36 months due to a CrCl improvement in the MMF arm (MMF-RAD1.5 = 8 and MMF-RAD3= 11) to 36 month (MMF-RAD1.5 = 13 and MMF-RAD3= 17) .(See table 14)***
- In B201 (European study), there was a mild improvement in CrCl in all treatment arms from 12 to 36 months (+3, +3 and +4 ml/min in the RAD1.5, RAD3 and MMF arms, respectively). Consequently, the differences in creatinine clearance between the RAD arms and MMF (MMF-RAD1.5 and MMF-RAD3) remained the same from 12***

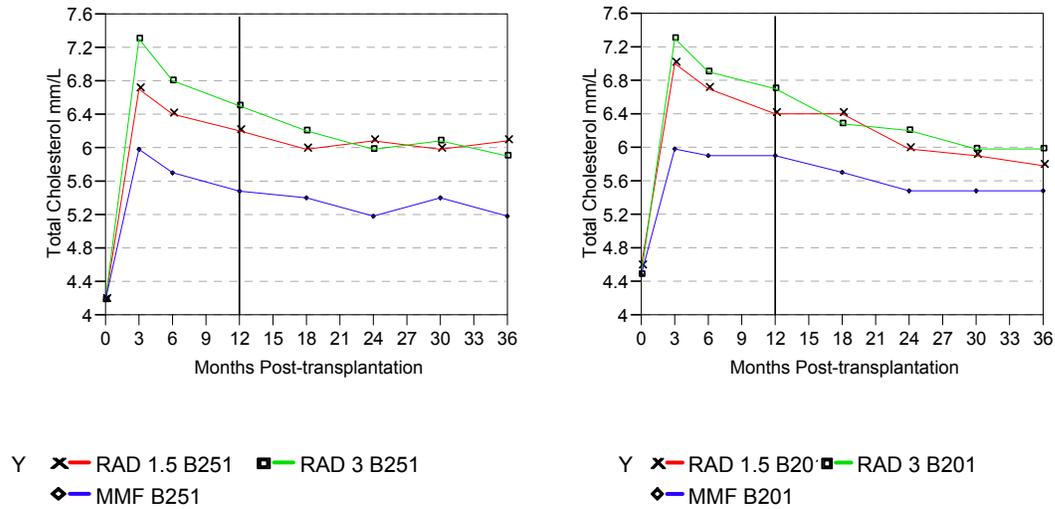
months (MMF-RAD1.5 = 6 and MMF-RAD3= 8) to 36 month (MMF-RAD1.5 = 7 and MMF-RAD3= 9). These observations suggest that the deleterious effect of the RAD plus CsA combination on renal function is significantly more important compared with the CsA plus MMF combination and that CsA minimization at 12 month prevents from further deterioration in renal function but do not reverse the nephrotoxic effects.

- *After unblinding and dose adjustments, any dose-related effect should be interpreted with caution. However, a most important renal deterioration was observed in the RAD 3 arm compared with RAD 1.5.*
- *Because important renal function deterioration was observed as early as 3 months post-transplantation in the RAD arms, CsA minimization at 12 months may be too late to prevent chronic irreversible changes. Even though the CrCl stabilized from 12 to 36 months in the RAD arms, the differences in CrCl between the RAD 1.5 vs. MMF, and RAD vs. MMF were statistically significant in both key renal studies at 12, 24, and 36 months. RAD 3 arms presented numerically lower calculated CrCl compared with RAD1.5, we observe a dose related effect between the RAD groups which is consistent in both key renal studies.*
- *These observations lead us to conclude that the amendment 3 was successful to prevent further deterioration in renal function in the RAD arms. However, it was unsuccessful in reversing renal function deterioration. These findings were consistent in both key renal studies and the differences in CrCl between the RAD and MMF groups were statistically significant at 6, 12 and 36 months. These findings also suggest the presence of irreversible changes that did not respond to decreasing exposure to CsA in combination with RAD ≥ 3 ng/ml TDM after 12 months of exposure to RAD and full dose CsA. An earlier intervention would be advisable.*

LABORATORY VALUES.

LIPIDS:

Fig 20-3. Lipids: Total Cholesterol [mmol/L] (Safety Population – 36-Month Analysis)



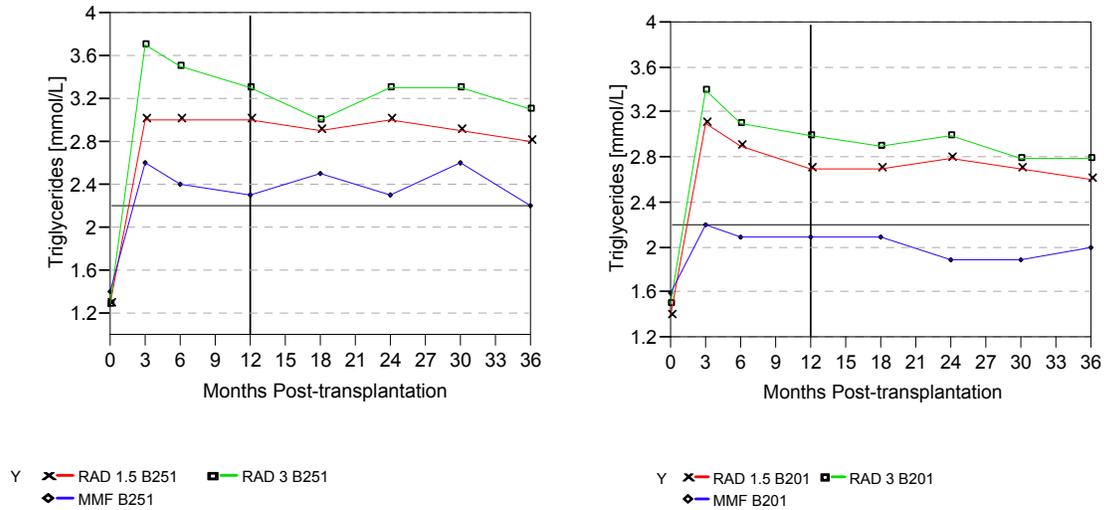
Data obtained from: Post-text Table 10.3-1b (Page 16 of 22) Summary Statistics by Visit

Reviewer's comment:

- *In both key renal studies, total cholesterol mean values were above the desirable values⁸⁵ (<200 mgmg/dL, <5.1 mmol/L) in all arms. However, RAD arms presented higher mean cholesterol levels at all measurement points compared to MMF arm (See fig 3.)*
- *Despite intensive therapeutic intervention to treat related dyslipidemias, the RAD arms mean cholesterol values remained ≥ 5.8 mmol/L at all measurement points, in both key renal studies. The long-term consequences on cardiovascular disease of these sustained higher lipid levels compared to MMF is unknown.*
- *During the first 12 months post-transplantation, a dose related effect between the RAD1.5 and RAD3 was observed. After RAD dose adjustments and CsA minimization (amendment #3), this dose effect is lost.*

Fig 20-4. Triglycerides (mmol/L) (Safety Population - 36 Month Analysis)

⁸⁵ NCEP-ATPIII National Cholesterol Education Program - Adult Treatment Panel III



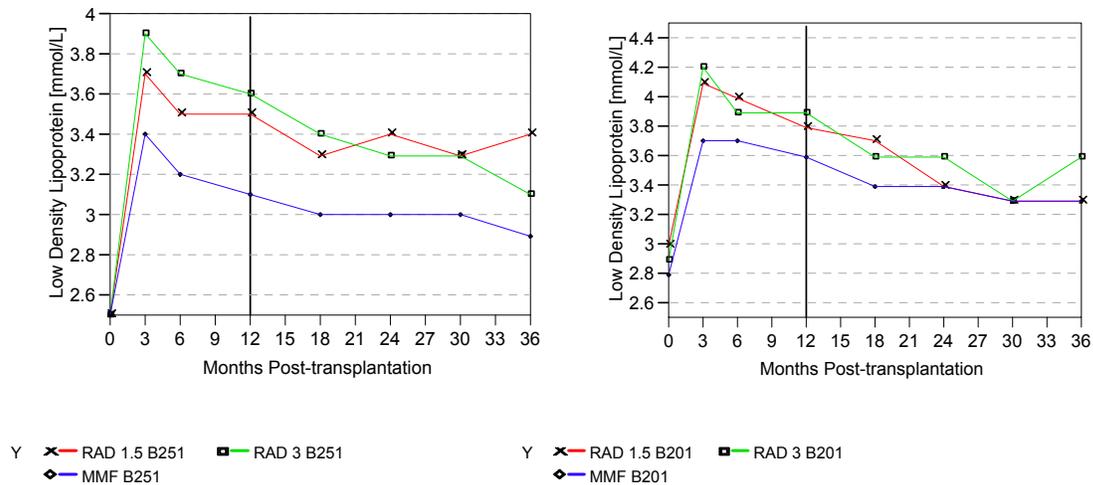
Data obtained from Post-text Table 10.3-1b (Page 21 of 22) Summary Statistics by Visit. The horizontal line indicates the lower limit for high triglyceride values⁸⁶ (200-449 mg/dL or 2.3 to 5.63 mmol/L).

Reviewer's comment:

Mean triglyceride values were significantly higher in both RAD arms compared with MMF arm in both key renal studies.

RAD arms presented higher mean triglyceride levels at all measurement points compared to MMF arm, in both key renal studies. This observation was dose dependent in the RAD arms. The mean triglyceride values in the MMF arm were in the high- borderline range or close to normal, while the all RAD arms were in the high range.

Fig 20-5. Low Density Lipoprotein [mmol/L] (Safety Population -36 Month Analysis)



Data obtained from Post-text Table 10.3-1b (Page 17 of 22) Summary Statistics by Visit. Lipids: Low Density Lipoprotein [mmol/L] (Safety Population - 36-Month Analysis)

⁸⁶ NCEP-ATPIII National Cholesterol Education Program - Adult Treatment Panel III

Reviewer's comments: Low-density lipoproteins mean values followed the same pattern as cholesterol and triglycerides especially during the double blind phase of the studies.

Table 20-22. Rise in Total Cholesterol and Triglyceride Levels and Related Events

	RAD 1.5mg		RAD 3mg		MMF 2g		Difference/95%CI for RAD 1.5mg-MMF RAD 3mg-MMF RAD 1.5mg-RAD 3mg	
	B251 (193)	B201 (194)	B251 (194)	B201 (198)	B251 (196)	B201 (196)	B251	B201
Cholesterol level \geq 6.2 mmol/L: no. pts/no. pts at risk (incidence rate)	151/193 (78.2%)	167/193 (86.5%)	163/191 (85.3%)	173/198 (87.4%)	136/193 (70.5%)	143/195 (73.3%)	7.8% (-0.9, 16.5) 14.9% (6.7, 23.0) -7.1%(-14.8, 0.6)	13.2%(5.3, 21.1) 14.0%(6.3, 21.8) -0.8%(-7.5, 5.8)
Triglyceride level \geq 4.5 mmol/L: no pts/no. pts at risk (incidence rate)	66/193 (34.2%)	71/193 (36.8%)	95/191 (49.7%)	90/198 (45.5%)	48/193 (24.9%)	39/195 (20.0%)	9.3% (0.3, 18.4) 24.9%(15.5, 34.2) -15.5%(-25.3, -5.8)	16.8%(8.0, 25.6) 25.5%(16.5, 34.4) -8.7%(-18.4, 1.0)
New onset of hypercholesterolemia/hyperlipidemia: No. pts/no. pts at risk (incidence rate)	131/156 (84.0%)	127/148 (85.8%)	139/161 (86.3%)	137/155 (88.4%)	117/154 (76.0%)	116/158 (73.4%)	8.0%(-0.9, 16.9) 10.4%(1.8, 18.9) -2.4%(-10.2, 5.5)	12.4%(3.5, 21.3) 15.0%(6.4, 23.5) -2.6%(-10.1, 5.0)
New onset of Hypertriglyceridemia/hyperlipidemia: no. pts/no. pts at risk (incidence rate)	119/164 (72.6%)	116/168 (69.0%)	133/174 (76.4%)	117/176 (66.5%)	97/160 (60.6%)	71/169 (42.0%)	11.9%(1.7, 22.1) 15.8%(6.0, 25.7) -3.9%(-13.2, 5.4)	27.0%(16.8, 37.2) 24.5%(14.3, 34.7) 2.6%(-7.3, 12.4)

(Safety Population - 36-Month Analysis) Studies B201 and B251.

Data obtained from Post-text Tables 10. 6-3, 10.6-4 10.6-5, (Safety Population - 36 Month Analysis)

Reviewer's comments:

- ***The incidence rate in high cholesterol (\geq 6.2 mmol/L) and high triglycerides levels (\geq 4.5 mmol/L) at 36 months were statistically significantly higher in both RAD arm compared to MMF and consistent in both key renal studies. (see Table 15)***
- ***New onset hypercholesterolemia was significantly higher in the RAD 3 arms and numerically or significantly higher in the RAD 1.5 compared with MMF arms in both key renal studies.***
- ***New onset hypertriglyceridemia was significantly higher in both RAD arms compared with MMF arms in both key renal studies.***

HYPERLIPIDEMIA ASSESMENT KEY RENAL STUDIES

Hyperlipidemia was a dose-related toxicity in the RAD plus CsA arms. Statistically significant differences were observed in hypertriglyceridemia and hypercholesterolemia mean values from 3 to 36 months in the RAD 1.5 and RAD3 arms compared with MMF arm in both key renal studies.

The incidence rate in high cholesterol (\geq 6.2 mmol/L) and high triglycerides levels (\geq 4.5 mmol/L) were statistically significantly higher in both RAD arm compared to MMF and consistent in both key renal studies. Similarly, new onset hyperlipidemias were significantly

higher in both RAD arms compared with MMF arms in study B201. In study B251 RAD1.5 was numerically higher and RAD 3 was significantly higher versus MMF arm.

In general population studies, it has been observed a marked stepwise increase in the cumulative incidence of CHD with increasing total-cholesterol levels⁸⁷. Since we do not have any large prospective study with this regard in the transplant population, it is believed that extrapolation of the general population results to the transplant population is reasonable.

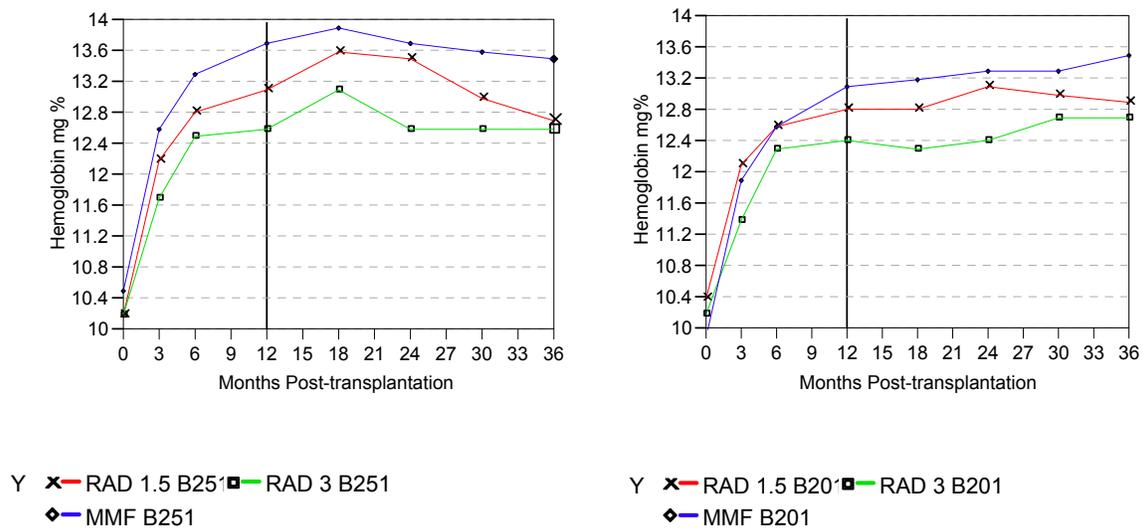
Cardiovascular disease causes deaths in more than 40% of kidney allograft recipients with functioning grafts and accelerates cardiac allograft vasculopathy. Since this is a preventable disease we should seriously consider the potential long term effects of higher lipid concentration in the proposed regimen than those produced by current immunosuppression regimens.

The fact that intensive therapy for hyperlipidemia did not succeed in decreasing RAD arms lipid levels to similar levels found in the MMF arm, raises the concern on the long term consequences of higher lipid level and higher incidence of new onset hyperlipidemias observed in the RAD regimen versus the control regimen.

The incidence of cardiovascular related deaths was low and comparable across arms. However, we cannot rule out a deleterious effect on long term patient or graft survival, since the incidence of clinically-confirmed chronic rejection at 36 months was numerically or significantly higher in both RAD groups compared with the MMF group, in both key renal studies.

**LABORATORY PARAMETERS:
 ANEMIA**

Fig 20-6. Mean Hemoglobin [g/dL] Values by Visit Studies B251 and B201 (Safety Population - 36 Month Analysis)



Data obtained from Post-text Table 10.3-1b (Page 2 of 22). Summary Statistics by Visit, Hemoglobin [g/dL]. Studies B201 and B251 (Safety Population - 36 Month Analysis)

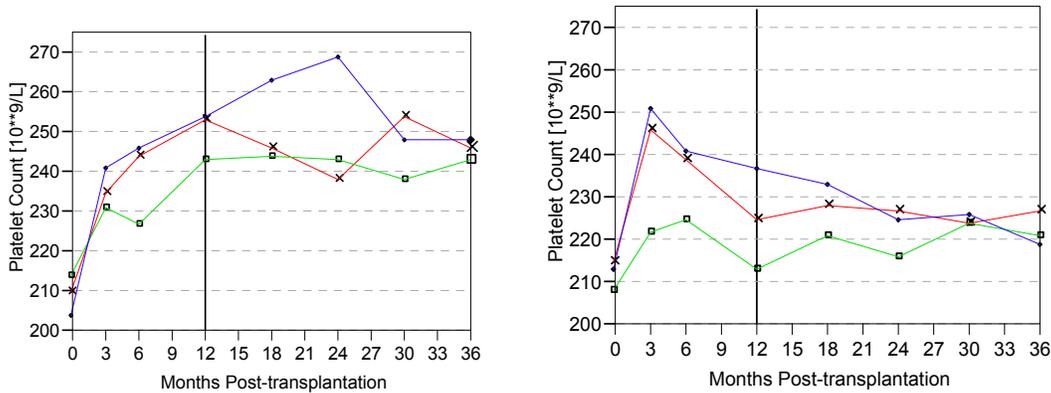
⁸⁷ Klag et al. *N Engl J Med.* 1993; 328:313-318.

Reviewer's comments:

Hemoglobin mean values improved after transplant in all treatment groups. The hemoglobin improvement in the MMF arm was numerically or significantly higher in the MMF arms compared with the RAD1.5 and RAD 3 arms in both key renal studies. Adequate hemoglobin levels were reached in all treatment arms.

THROMBOCYTOPENIA:

Fig 20-7. Mean Platelet Count [109/L] Values by Visit Studies B251 and B201 (Safety Population - 36 Month Analysis)**



Y X—RAD 1.5 B201 □—RAD 3 B201
 ◆—MMF B201

Data obtained from Post-text Table 10.3-1b (Page 8 of 22). Summary Statistics by Visit, Hemoglobin [g/dL]. Studies B201 and B251 (Safety Population - 36 Month Analysis)

Reviewer's comments:

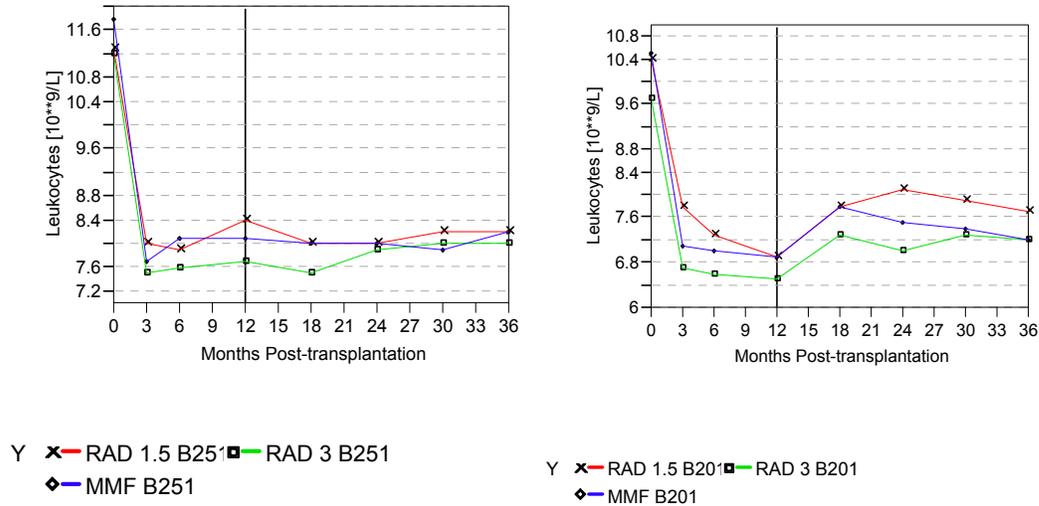
Mean platelet counts increased after transplantation in all treatment arms. During the double blind phase a similar pattern and mean values were observed between the RAD 1.5 and MMF arms in both key renal studies. In general the RAD 3 arm showed lower mean platelet count values compared with RAD 1.5 and MMF arms.

Thrombocytopenia⁸⁸ rates reported as adverse events at 36 months were higher in both RAD arms compared to MMF in both key renal studies. (See adverse event section Table 3.)

⁸⁸ Thrombocytopenia NOS or Thrombocytopenia NOS + platelet count decreased

LEUCOPENIA

Fig 20-8. Mean Leukocytes Count [109/L] Values by Visit Studies B251 and B201 (Safety Population - 36 Month Analysis)**



Data obtained from Post-text Table 10.3-1b (Page 4 of 22). Summary Statistics by Visit Leukocytes [10**9/L], Studies B201 and B251 (Safety Population - 36 Month Analysis)

Reviewer's comments:

Mean Leukocyte counts decreased significantly after drug exposure in the three treatment arms in both key renal studies. Mean values in the RAD 3 arms were numerically lower compared with RAD1.5 and MMF arms over time. These differences and a dose related effect between the RAD arms was observed during the double blind phase of the studies.

Leukopenia⁸⁹ reported as AE at 36 months presented lower rates in the RAD 1.5 arms compared to RAD3 and MMF arms, in both key renal studies. Similar rates in the MMF and RAD 3 arms were observed.

Vital Signs, Liver Function tests, Amylase, Lipase, Uric Acid, Ca, Mg, Glucose, and potassium: Based on notable criteria, all the referred parameters were reviewed from the 36-month analyses for the safety population.

Liver Function tests:

The incidence rates of patients with post-baseline liver function test based on notable criteria⁹⁰ were similar across arms and no significant differences were observed in both key renal studies. The incidence rates were below 6% for Alkaline Phosphatase, Total Bilirubin, and SGOT. SGPT rates observed at higher rates between 11 to 13 % in study B201 and between 13 and 18% in study 251 no significant differences were observed across arms in both key renal studies.

⁸⁹ Leukopenia NOS or Leukopenia NOS plus WBC count decreased.

⁹⁰ Alkaline Phosphatase [U/L] High: greater than 3*ULN
 Total Bilirubin [umol/L] High: greater than 34.2
 SGOT (AST) [U/L] High: greater than 3*ULN
 SGPT (ALT) [U/L] High: greater than 3*ULN

Amylase and Lipase:

Base on notable criteria⁹¹ amylase and lipase enzymes presented similar rates across arms in both key renal studies. Rates for amylase were from 12 to 17% and for lipase for 21-28% across arms and across key renal studies.

Uric Acid, Ca, Mg, Glucose, and potassium

Using the notable criteria⁹² Magnesium, Glucose, Calcium, and Uric Acid rates were similar across arms in both key renal studies

Significantly higher rates of low potassium were observed in the RAD3 arms compared with the MMF.

Vital Signs:

Vital sign including mean systolic and diastolic pressures were similar across arms over time and consistent in both key renal studies. Incidence Rate of Vital Sign Abnormalities Based on Notable Criteria did not show any significant difference across arms in both key renal studies

Endocrinology (Hypogonadism):

Endocrinology studies performed in the adult pivotal de novo renal trials revealed that male patients in all study groups (RAD and MMF) generally had low testosterone values at baseline, which is consistent with the effects of end-stage renal disease. Mean testosterone values increased in all groups, with the mean values at Months 6 and 12 within the normal range. Although mean testosterone levels did increase to within the normal range in the RAD-treated patients, they did not increase as much as in MMF-treated patients (p<0.05). This was also associated with statistically significant increases in mean levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH), although no clinical symptoms of hypogonadism were reported in association with these endocrine lab abnormalities in the RAD arms. Hypogonadism in males reported as an AE was observed in one case in study B251

SAFETY SUMMARY AND CONCLUSIONS -KEY RENAL STUDIES (B251 AND B201)-

- ***Patient discontinuation from study medication was numerically or significantly higher in both RAD groups compared with the MMF groups in both key renal studies. RAD 3 versus MMF showed a statistically significant difference in both key renal studies.***
- ***Adverse events and unsatisfactory therapeutic effect were the most common reasons for discontinuation from study medication in both key renal studies.***
- ***In general, a dose related differences in the incidence of AE⁹³, SAE⁹⁴ and DAE⁹⁵ was observed between the RAD arms⁹⁶. The RAD 3 arm presented the highest incidence of***

⁹¹ Amylase [U/L] High: > 2*ULN

Lipase [U/L] High: > 2*ULN

⁹² Potassium [mmol/L] Low : < 3 and High: > 6

Magnesium [mmol/L] Low : < 0.4 and High: > 1.5

Glucose [mmol/L] Low : < 2.5 and High: > 13.9

Calcium [mmol/L] Low : < 1.5 and High: > 3.2

Uric Acid [mmol/L] High: > 0.714 (Male)and >0.535 (Female)

⁹³ AE: Adverse Events.

⁹⁴ SAE: Serious Adverse Events

⁹⁵ DAE: Adverse Events Leading to Discontinuation from Study Medication.

⁹⁶ RAD3 incidence rates >RAD 1.5

SAEs and premature discontinuation from study medication among the groups. The dose related effect was less evident or lost in some instances after unblinding and dose adjustments. (Amendment #3). Due to these facts, the presence or absence of a dose related effect between the RAD 1.5 and RAD3 should be interpreted with caution in the 36 month analyses.

- *Time to event analysis of treatment discontinuation indicates that events occurs statistically significantly early and more often in the RAD3 group compared with MMF group in both key renal studies (See statistical review)*

Adverse Events Leading To Discontinuation from Study Medication:

- *The incidence of adverse events leading to discontinuation from study medication⁹⁷ (DAE) was significantly higher in the RAD arms compared with the MMF arm and a dose related effect was observed between the RAD arms.*
- *Blood creatinine increased (BCI) and Renal impairment denote "abnormal kidney function" that lead to discontinuation from study medication. BCI or BCI plus Renal impairment were the most common DAE's⁹⁸ in the RAD arms while gastrointestinal disorders were the more common DAE's in the MMF arm. The preferred terms used to denote gastrointestinal disorders were diverse and no predominance was observed.*
- *Pneumonia was the single most important infection-DAE. In study B201, six (6) patients were discontinued from study medication in the in the RAD 3 versus one patient the MMF arm, (see table 2).*
- *TMA⁹⁹ (including HUS and TTP) as DAE was reported 2%, 2%, and 1% (S-B251) and 1%, 4%, and 0% S-B201) in the RAD1.5, RAD 3 and MMF, respectively. The number of cases was small but numerically higher in the RAD arms compared with the MMF and consistent across both key renal studies. Since TMA has been related to the toxic effect of CsA, this finding is relevant given the known interaction in the RAD / CsA combination.*

Adverse Events / Infections:

- *Adverse Events / Infections were reported by System Organ Classification and Preferred Term in the Safety Population (36 Month Analysis). There were inconsistencies in the preferred terms used to report AE. The terms used were mutually exclusive and more that one term may indicate the same condition e.g. Leukopenia and WBC decreased.*
- *Both Key Renal Studies consistently showed higher rates of blood creatinine increased, hyperlipidaemia, pneumonias, haemolytic uremic syndrome, lymphocele and peripheral oedema in both RAD arms compared with MMF.*
- *In study B201, both RAD arms showed higher rates of UTI, Bacterial infections, hypertryglyceridema, thrombocytopenia and proteinuria compared with MMF arm.*
- *In study B251, both RAD arms presented higher rates o Anaemia NOS, Hypertension NOS and Wound dehiscence compared with MMF arm. Differences across studies and dose relationship are difficult to interpret in the 36 months analyses due to the open label*

⁹⁷ Adverse Event Leading to Discontinuation of Study Medication (DAE) (Safety Population - 36 Month Analysis):

⁹⁹ **Thrombotic microangiopathy** (TMA) including Haemolytic uraemic syndrome (HUS) and Thrombotic thrombocytopenic purpura (TTP)

characteristic after the initial 12 months. (See table 18 for a comprehensive summary of AE per study and treatment arms.)

- *Urinary tract infections occurred more frequently in both RAD groups than in the MMF group*

Renal Related Adverse Events:

- *Renal function disorders (Serum creatinine elevation) presented a meaningful association with RAD dose, and rates were generally higher in the RAD 3 mg groups.*
- *Blood creatinine increased / Renal impairment NOS, Primary graft dysfunction, and Renal tubular necrosis reported as AE presented higher rates in both RAD arms when compared to MMF. A dose related effect was observed between the low and high dose RAD arms. The fact that these AE are predominantly observed in the RAD arms suggests that these events may be related to the nephrotoxic effects of the RAD / CsA combination.*
- *HUS rates were higher in both RAD arms compared to the MMF in both key renal studies. The number of cases was small but consistent across both key renal studies. Since TMA has been related to the toxic effect of CsA, this finding is relevant given the known interaction in the RAD / CsA combination.*
- *Proteinuria reported as AE presented higher rates in both RAD arms compared with MMF and consistent in both key renal studies. This observation is in concordance with the Clinically Confirmed Chronic Rejection rates which were numerically or significantly higher in the RAD arms compared with MMF in both key renal studies (See table 3 efficacy evaluation section). Furthermore, proteinuria is not an uncommon feature in calcineurin inhibitors (CI) nephrotoxicity.*

Renal Function:

- *Baseline CrCl was similar across arms in both key renal studies. After transplantation, mean calculated creatinine clearance reached its zenith approximately at three months post transplantation in all arms in both key renal studies. Zenith values were lower and dose related in the RAD arms compared to MMF arms in both key renal studies. This observation indicates the RAD plus CsA combination has early post-transplant deleterious effects on renal function, identified by lower zenith mean CrCl values in both RAD arms in both key renal studies.*
- *The mean calculated CrCl values decreased significantly over time in both RAD arms. The differences between RAD 1.5 and RAD 3mg versus MMF were statistically significant in both key renal studies at 6, 12, 24, and 36 months*

Renal Function Change from 12 to 36 months (amendment # 3 evaluation)

- *After unblinding and dose adjustments, any dose related effect should be interpreted with caution. However, a most important renal deterioration was observed in the RAD 3 arm compared with RAD 1.5.*
- *In B251 (USA study), amendment #3 did not improve renal function, no change in CrCl was observed in the RAD arms from 12 to 36 month follow up. In contrast, CrCl in the MMF arm presented additional improvement.*
- *The difference in the mean calculated creatinine clearance between the RAD arms and MMF (MMF-RAD1.5 and MMF-RAD3) continue to increase from 12 months (MMF-*

RAD1.5 = 8 and MMF-RAD3= 11) to 36 month (MMF-RAD1.5 = 13 and MMF-RAD3= 17) .(See table 14)

- *In B201 (European study), there was a mild improvement in CrCl in all treatment arms from 12 to 36 months (+3, +3 and +4 ml/min in the RAD1.5, RAD3 and MMF arms, respectively). However, the differences in creatinine clearance between the RAD arms and MMF (MMF-RAD1.5 and MMF-RAD3) from 12 months (MMF-RAD1.5 = 6 and MMF-RAD3= 8) to 36 month (MMF-RAD1.5 = 7 and MMF-RAD3= 9) remained significant. These observations suggest that the deleterious effect of the RAD plus CsA combination on renal function is significantly more important compared with the CsA plus MMF combination and that CsA minimization at 12 month may prevents from further deterioration in renal function but do not reverse the nephrotoxic effects.*
- *A late reduction in the dose of CI appears to have a limited beneficial effect in improving renal function. This poor response is probably related to irreversible changes in the kidneys. In summary, we have observed that enhanced CsA nephrotoxicity in the RAD and CsA combination is not reversible when is chronically sustained, the drop in GFR is significant, and has been associated with increased mortality in other clinical trials¹⁰⁰*

Hyperlipidaemia Assessment Key Renal Studies:

- *Hyperlipidaemia reported as adverse events¹⁰¹ presented higher incidence rates in both RAD 1.5 and RAD 3 arms compared to MMF arms in both key renal studies. Individual rates per preferred term reflected the same trend. (See table 5). RAD 1.5 and RAD 3 arms presented similar rates across both studies suggesting that a dose dependency do not exist. However, due to the individualized therapeutic efforts to maintain blood lipid levels with in a target range, it is difficult to observe a dose related effect between the low and the high dose RAD arms. The requirements for lipid lowering agents were higher in both RAD arms compared with the MMF. Finally, immunosuppressive regimen modifications after amendment #3 are an additional confounding factor that impedes to identify a dose related effect.*
- *Hyperlipidaemia was dose related toxicity in the RAD plus CsA arms. Statistically significant differences were observed in hypertriglyceridemia and hypercholesterolemia mean values from 3 to 36 months in the RAD 1.5 and RAD3 arms compared with MMF arm in both key renal studies.*
- *The incidence rate in high cholesterol (≥ 6.2 mmol/L) and high triglycerides levels (≥ 4.5 mmol/L) at 36 months were statistically significantly higher in both RAD arms compared to MMF and consistent in both key renal studies. Similarly, new onset hyperlipidaemia were numerically or significantly higher in both RAD arms compared with MMF arms in both key renal studies.*
- *The fact that intensive therapy for hyperlipidaemia did not succeeded in decreasing RAD arms lipid levels to similar levels found in the MMF arm, raises the concern on the long term consequences of higher lipid level and higher incidence of new onset hyperlipidaemia observed in the RAD regimen versus the control regimen.*

¹⁰⁰ Akinlolu O. Ojo, et. al. N ENG J MED 349(10):931- , September 4, 2003.

¹⁰¹ Hyperlipidaemia including: Hyperlipidaemia nos, Hypercholesterolaemia, Blood Cholesterol Increased, Hypertriglyceridaemia, Blood Triglycerides Increased. Individual analyses per preferred term reflect the same trend. (see table 5)

- *The incidence of cardiovascular related deaths was low and comparable across arms. However, we cannot rule out a deleterious effect on long term patient or graft survival, since the incidence of clinically-confirmed chronic rejection at 36 months was numerically or significantly higher in both RAD groups compared with the MMF group, in both key renal studies. Furthermore, In general population studies, it has been observed a marked stepwise increase in the cumulative incidence of CHD with increasing total-cholesterol levels*

Cytomegalovirus Infections:

- *The European study B201 presented a higher the incidence rate of CMV infection in the MMF arm; 6%, 7% and 20% in the RAD 1.5, RAD 3 and MMF, respectively. These results were not consistent in the American study B251, in which the incidence of CMV infection was similar across arms 7%, 5% and 5% in the RAD 1.5, RAD 3 and MMF, respectively. This inconsistency definitely diminishes the weight of this observation.*
- *The key 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 it did not included any precautions to avoid bias for the collection of CMV related information.*
- *The presence of many confounding factors does not allow us to draw valid conclusions base on a retrospective finding. The high incidence of cytomegalovirus infection in the European study B201 was not consistent with the findings in the US study 251 which diminish the weight of this observation. The higher rates CMV infection or disease in the MMF group was due to mild to moderate cases (See table 9) and there was no association with an increased incidence of opportunistic infections, or chronic rejection. On the contrary the incidence of Clinically Confirmed Chronic Rejection was numerically or significantly higher in both RAD arms compared with the MMF arms in both Key Renal Studies.*
- *We recommend a prospective trial specifically design to demonstrate differences in CMV disease (Tissue invasive CMV disease and CMV syndrome) and CMV infection.*

Pneumonia:

- *The incidence rate of pneumonia, regardless etiology, was higher in both RAD arms compared to MMF arm, in both key renal studies. Higher number of patients were discontinued from study medication or died due to pneumonia in the RAD arms compared to the MMF arms in both key renal studies and a dose relation trend is observed in S-201 for the incidence of pneumonia reported as AE. These AE's were a cause for discontinuation and death and are considered clinically relevant.*

Wound Complications and Lymphocele:

- *Wound complications as AE were higher in the RAD3 arms compared with the MMF arms in both key renal studies. Wound dehiscence and wound infections are the major contributors for these differences.*
- *Lymphocele rates were higher in both RAD1.5 and RAD3 compared with MMF arms in both key renal studies. A dose related incidence trend was observed between the RAD arms in both renal studies.*

Malignancies and Deaths:

- *The incidence of malignancies was equally distributed across arms in both key renal studies. Skin cancer was the most frequent malignancy observed and the differences observed across arms were not clinically relevant.*
- *Cardiovascular disease and infections were de leading causes of death. Incidence rates were similar across arms in both key renal studies.*

Laboratory Parameters¹⁰²:

- *Hemoglobin mean values improved after transplant in all treatment groups. The hemoglobin improvement in the MMF arm was numerically or significantly higher in the MMF arms compared with the RAD1.5 and RAD 3 arms in both key renal studies.*
- *Mean platelets counts increased after transplantation in all treatment arms. During the double blind phase a similar pattern and mean values were observed between the RAD 1.5 and MMF arms in both key renal studies. In general the RAD 3 arm showed lower mean platelet count values compared with RAD 1.5 and MMF arms. Thrombocytopenia¹⁰³ rates reported as adverse events at 36 months were higher in both RAD arms compared to MMF in both key renal studies. (See adverse event section Table 3.)*
- *Mean leukocyte counts decreased significantly after drug exposure in the three treatment arms in both key renal studies. Mean values in the RAD 3 arms were numerically lower compared with RAD1.5 and MMF arms over time. Leukocyte counts were not statistically significantly or clinically relevantly different between the groups from months 1 to 12. Discontinuations of study medication due to leukopenia were seldom observed.*
- *Bases on notable criteria, Vital Signs, Liver Function tests, Amylase, Lipase, Uric Acid, Ca, Mg, and Glucose presented similar rates across arms in both key renal studies*
- *The incidence rates of patients with post-baseline liver function test based on notable criteria¹⁰⁴ were similar across arms and no significant differences were observed in both key renal studies.*
- *Significantly higher rates of low potassium were observed in the RAD3 arms compared with the MMF.*
- *Testosterone levels were low among all treatment groups at Baseline and rose to the normal range in all groups at Month 12. The rise in serum testosterone in male patients during the course of this study was not surprising, since patients become clinically improved after transplant surgery. The increase in testosterone in RAD-treated patients was less than that observed in the MMF-treated patients, and was associated with increases in FSH and LH. The reason for this is unknown.*

¹⁰² 36 month analyses for the safety population

¹⁰³ Thrombocytopenia NOS or Thrombocytopenia NOS + platelet count decreased

¹⁰⁴ Alkaline Phosphatase [U/L] High: greater than 3*ULN

Total Bilirubin [umol/L] High: greater than 34.2

SGOT (AST) [U/L] High: greater than 3*ULN

SGPT (ALT) [U/L] High: greater than 3*ULN

22. RENAL STUDIES CRAD001 A2306 AND CRAD001 A2307

Studies A2306 and A2307 are one year randomized studies, open-label using a historical controls. These studies address 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).

Background:

During the **last** Pre-NDA meeting held on March 25, 2002, applicant inform to the agency that the 12-month data for studies A2306 and A2307 would not be available until the 3rd quarter of 2003.

The agency stated that *"if the full reports for A2306 and A2307 were not included with the initial NDA submission, they would not be reviewed"*.

Renal studies A2306 and A2307 are randomized, open-label, which used the key renal studies as historical control. With this regard, the agency stated that *"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"*.

In the initial Submission on Dec 19, 2002 incomplete data (Preliminary report) on both studies was submitted. A 6 month analysis with approximately half of the patients' data was submitted for each study:

In **CRAD001A 2307** A total of 256 patients were enrolled (117 and 139 in the RAD 1.5 and 3 mg groups, respectively). In the initial NDA submission the applicant included data only on 65 patients in the RAD 1.5 mg arm and 68 patients in the RAD 3 mg.

In **CRAD001 A2306:** A total of 237 patients were enrolled (112 and 125 in the RAD 1.5 and 3 mg groups, respectively). In the initial NDA submission the applicant included data only on 62 patients in the RAD 1.5 mg and 60 patients in the RAD 3 mg arm.

The **120-day Safety update: (May 2, 2003)** provided for new data on studies A2306 and A2307 including all missing patients at the original submission. ("**Synoptic**" analysis including 6 months data.).

On September 19, 2003, additional information was received on studies A2306 and A2307 containing the "**First interpretable results of the 12 month data**"

Study design:

Studies A2306 and A2307 were designed as "**A 1 year multicenter, randomized, open label, parallel group study of the safety, tolerability and efficacy of two doses (1.5 and 3 mg/day) of Certican™ (RAD001) with steroids and optimized administration of Neoral in de novo renal transplant recipients (partial 6-month analysis)**" With the variant that S- A2307 additionally used Simulect® as induction therapy.

Primary Objective was similar in both studies : *"To compare renal function, as measured by serum creatinine, of 2 doses of RAD (1.5 and 3 mg/day), and to assess whether acceptable renal function (improved creatinine vs. historical data) can be achieved at 6 months post-transplantation in de novo renal transplant recipients"*.

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).

Table 22-1 summarizes the study design and enrolment for both studies

Table 22-1. Study design and enrolment

Study no.	Design	Duration	Target C ₂ BL (ng/mL)	Historical control	No. of patients
A2306 32 Centers ¹⁰⁵	MC, R, OL, PG, S, T and E. <i>de novo</i>	1 year (partial 6- month analysis)	Weeks 0 – 4 (1000 – 1400) Weeks 5 – 8 (700 – 900) Weeks 9 – 12 (550 – 650) Months 4 – 6 (350 – 450)	B201 B251	Total – 237 RAD 1.5 mg – 112 RAD 3 mg – 125
A2307 37 Centers ¹⁰⁶	MC, R, OL, PG, S, T and E. <i>de novo</i>	1 year (Partial 6- month analysis)	Weeks 0 – 8 (500 – 700) Months 3 – 6 (350 – 450) With Simulect®	B156 (RAD 3 FDN vs. RDN)	Total -256 RAD 1.5 mg – 117 RAD 3 mg – 139

MC = multicenter, R = randomized, OL = open label HC = Historical control, S = safety, and T = tolerability, E = efficacy. All Black transplant recipients were treated with Certican 3mg/day without randomization

Reviewers comment:

- *The Agency expressed their concern about the use of historical controls in studies A2306 and A2307 (Pre-NDA meeting held on March 25, 2002).*
- *The main limitations of studies 2306 and 2307 are the open label design and the lack of an approved comparator arm (Use of historical controls). The small study size does not allow a precise estimate of 12 month patient or graft survival.*
- *The complete reports were not submitted during the initial NDA filling application. Complete data on ongoing Phase IIIb studies A2306 and A2307 was not available for review at the original submission. The 120 day safety update included additional data for the 6-month analyses and therefore we were not able to draw reliable conclusion on partial data on these open label studies using historical controls.*
- *The pivotal trials were extensively amended midstream and were impacted by numerous other conditions that were present during that study, such as type of population, concomitant medications, and the timing of the study. These conditions would be different for A2306 and A2307, so that considering the pivotal trial data as a historical control arm for these studies would not be appropriate.*
- *The results from study A2306 and A2307 (reduced-dose cyclosporine) showed improved creatinine clearance compared with the key renal studies. However we*

¹⁰⁵ US (11), Italy (6), Brazil (4), Canada and Spain (3 each), Poland and Venezuela (2 each), and Belgium (1).

¹⁰⁶ Italy (8), US (7), Australia and France (5 each), Argentina, Germany, and The Czech Republic (3 each), and Columbia, Norway, and Switzerland (1 each)

cannot adequately evaluate comparisons across studies with different immunosuppressive regimens and different designs.

- *These studies relied C2 CsA blood concentrations and key renal studies used through CsA monitoring*
- *CsA minimization was started after one month in S-A2306 while in S-A2307 started immediately after transplantation including Simulect in its regimen.*
- *Different design characteristics in the historical controls etc.*
- *This studies evaluated only kidney transplant patients and cannot on their own be used to support a modified (TDM) regimen with low dose cyclosporine in heart transplantation.*
- *The use of Simulect® with Certican and CsA was explored in studies A2307 and B156 (historical control). The safety and efficacy on this new therapeutic regimen which included antibody induction therapy in study A2307 cannot be adequately evaluated without full study reports and long term follow up and may require further evaluation in a prospective, well controlled clinical trial.*
- *We cannot identify a safe and effective TDM regimen based on incomplete data reports of studies A2307 and A2306. Furthermore, the use of historical controls for these open label studies presents important difficulties due to differences in study design, regimens, CsA target concentration and method used for dose adjustments.*
- *We acknowledge that the revised proposed label submitted by Novartis with the 120 day safety update has modified the recommended dosage and administration, based on the "synoptic" information, and that we interpret this as an agreement that fixed dosing (without TDM) for RAD and with "full dose" cyclosporine may not be an acceptable regimen.*

23. PEDIATRIC STUDIES

On April 25, 2000 a written request for pediatric studies was issued from FDA to Novartis and the requested pediatric studies were also submitted (See Pediatric Exclusivity Report).

Study B351 (Study 3):

Multicenter, open-label, single-arm, safety, tolerability, efficacy and pharmacokinetic study of RAD001 in pediatric de novo renal transplant patients (12-month analysis)

Primary endpoint: To evaluate the safety and tolerability of RAD administered bid in combination with Neoral and corticosteroids in pediatric *de novo* renal transplant recipients. Sixteen of 19 patients (84%) completed 12 months of treatment with the study medication

Table 23-1 Demographics, Study B351 (Study 3).

	Group I < 10 yr. (N=10)	Group II 10 - 16 yr. (N=9)	Total (N=19)	UNOS 2002 U.S Kidney transplants <1 - 17 yr. (N=769)
Caucasian	7 (70.0%)	4 (44.4%)	11(57.8%)	429 (56%)
Black	1 (10.0)	1 (11.1)	2 (10.5)	140 (18)
Oriental	0	0	0	19 (2)
Other	2 (20.0)	4 (44.4)	6 (31.5)	
Hispanic				156 (20)

Multiple Dose: 1.5 mg/m2.

All minorities were underrepresented.

Study B257 (Study 1):

Multi-center, open-label single oral dose pharmacokinetic, safety and tolerability study of RAD001 in pediatric stable renal transplant patients.

Primary endpoint:

- To characterize the single-dose pharmacokinetics of RAD001 in combination with Neoral and corticosteroids, with or without azathioprine, in clinically stable pediatric renal transplant recipients.
- To characterize the steady-state PK of CsA during systemic exposure to RAD001.

Table 23-2 Demographics, Study B257 (Study 1).

	Group I < 8 yr. (N=7)	Group II 8 - 16 yr. (N=12)	Total (19)	UNOS U.S. Kidney transplants 2002 <1 - 17 yr. (N= 769)
Caucasian	6 (85.7%)	10 (83.3%)	16 (84%)	429 (56%)
Black	1 (14.3%)	1 (8.3%)	2(11%)	140 (18%)
Oriental	0	1 (8.3%)	1(5%)	19 (2%)
Hispanic				156 (20%)

Single Dose: 1.2 mg/m² surface area RAD001

Study B258 (Study 2):

Multi-center, open-label single oral dose pharmacokinetic, safety and tolerability study of RAD001 in pediatric stable liver transplant patients

Primary endpoint: To characterize the single-dose PK of RAD in combination with Neoral in pediatric stable liver transplant recipients.

Table 23-3 Demographics, Study B258 (Study 2).

	Group I ≤ 3 yr. (N=5)	Group II >3- ≤9 yr. (N=7)	Group III >9 - <16 yr. (N=12)	Total (24)	UNOS U.S Liver Transplants 2002 <1 - 17 yr. (N=554)
White	3 (60%)	4 (57%)	7(58%)	14(58%)	289 (52%)
Black	1 (20)	2 (29)	4 (33)	7(29)	101 (18%)
Other	1(20)	1 (14)	1 (8.3)	3 (13)	
Hispanic					116(21%)
Asian					18 (3%)

8 centers total (5 US, 1 Germany, 1 France, and 1 Canada)

Dose: single oral dose of 1.2 mg/m² body surface area of RAD

24. PEDIATRIC WRITTEN REQUEST AND PEDIATRIC EXCLUSIVITY

Background:

A Pediatric Written Request (PWR) was issued on April 25, 2000 for Certican® (everolimus) Tablets to Novartis Pharmaceuticals Corporation to obtain needed pediatric information on the active moiety, everolimus (RAD001), in pediatric transplant patients, for the prophylaxis of acute rejection in allogeneic kidney and liver transplantation.

Three studies were requested by FDA. These studies were intended to provide safety and basic pharmacokinetic information (such as AUC, Tmax, and Cmax) for selecting an adequate and dosing regimen in children. In addition, Study 3 was intended to collect information on longer term safety, incidence of biopsy-proven acute rejection, graft loss or death and chronic graft dysfunction at 6 and 12 months post-transplantation. (See CLINICAL TRIALS AND REVIEW PROCEDURES, Section Pediatric Studies)

On July 9, 2001 Novartis submitted Amendment # 3 to the ongoing Study **B351**, which provided for assessment of sexual hormones levels (FSH, LH and testosterone), sexual maturity (Tanner Staging) and testicular volume every 6 months. The rationale for this amendment was based on endocrine laboratory findings from adult phase III trials in de novo renal transplant recipients.

Reviewers Comment:

In these trials, male patients presented with low testosterone values at base line in both the everolimus and control groups. These findings are consistent with what is expected in all patients with End Stage Renal Disease (ESRD). As expected, following successful transplantation testosterone levels improved over time, as did renal function. However, mean testosterone values in the Certican group were significantly lower compared to the control group, while remaining within normal range. All groups reached normal values at 6 and 12 months. The clinical significance of these laboratory value differences among groups is uncertain. No clinical symptoms of hypogonadism were reported, nor did any patient discontinue everolimus because of low testosterone, or require hormonal replacement therapy.

On July 31, 2001 Novartis was granted a teleconference with the reviewing Division to discuss the endocrine findings from their Certican® Phase III program. Novartis' evaluation suggested that some male renal transplant patients on Certican® might be at risk for hypogonadism, which was based on the laboratory.

The FDA concurred with Novartis' conclusion that this endocrine finding was linked to everolimus and seemed dose-dependent. The Agency also agreed with Novartis' proposal to notify the investigators and Institutional Review Boards on this findings and the implementation of a modified Written Informed Consent.

On December 12, 2002, Novartis submitted a request to amend the PWR. This amendment (IND 52,003 SN 275, received December 16, 2002) stopped enrollment "for administrative purposes." Study 351 enrolled a total of 19 patients, instead of the expected 40.

Three pediatric study reports were submitted on December 19, 2002, (NDA **21-560**)

- Study B257: Multicenter, open-label, single oral dose, pharmacokinetic, safety and tolerability study of RAD001 in pediatric stable renal transplant patients.
- Study B258: Multicenter, open-label, single oral dose, pharmacokinetic, safety and tolerability study of RAD001 in pediatric stable liver transplant patients.
- Study B351: Multicenter, open-label, single-arm, safety, tolerability and pharmacokinetic study of RAD001 in pediatric *de novo* renal transplant patients.

A new NDA for Certican® (everolimus) Rapidly Dispersible Tablets was subsequently submitted on January 31, 2003 (NDA 21-561). This submission contained a Request for Determination of Pediatric Exclusivity.

Reviewer's Comments:

Studies B257 and B258 met the requirements stated in the PWR. Study B351, failed to meet the number of patients to be studied, specified in the PWR. The firm chose unilaterally to put a hold on enrollment and later terminate the study for administrative reasons.

In S-B351, Nineteen patients (9 boys and 10 girls) out of the targeted 40 subjects, completed the trial, and only 16 out of 19 patients completed 12 months of treatment with study drug. The number of subjects who completed 12 months of treatment was too small to allow a reliable estimate of renal graft function and other adverse events by age group, and evaluate the effect of RAD in combination with cyclosporine and corticosteroids on graft function across age's groups.

Reviewer's Comments:

The rationale for decreasing the enrollment size in study 3 was considered unconvincing and insufficient to support amending the PWR, to reduce the number of evaluable subjects requested in Study 3.

The lower mean testosterone levels in the RAD group, which were largely within normal range, may not be clinically significant. There were no clinical signs of hypogonadism in adult male transplant patients or in rat reproduction toxicity trials.

Amendment #3 was made in July 2001. The firm's very conservative approach, does not allow further evaluation of the potential significance of this finding in children. Patients who receive everolimus and cyclosporine have decreased renal function, which may also be responsible for decreased testosterone. We still believe that with the measures proposed in July 2001, the study would have been safe,

(b) (4)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Arturo Hernandez
10/20/03 05:25:07 PM
MEDICAL OFFICER

Marc Cavaille Coll
10/24/03 05:23:20 PM
MEDICAL OFFICER

A subsequent version of this MOR is being reformatted
and edited for clarity ,and will be submitted
to DFS when completed. I concur with the
conclusions and recommendations, that have been communicated to
the applicant in the action letter.

Renata Albrecht
10/27/03 11:30:44 AM
MEDICAL OFFICER