

Medical Officer Review

Everolimus Safety Information from Renal Transplantation Studies

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

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Note: This review is abstracted from the original NDA review for everolimus. Sections of the original document relevant only to the safety of everolimus when studied for the prophylaxis of organ rejection in renal transplantation are included.

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1. Background

Safety information on the use of everolimus with cyclosporine and corticosteroids at doses similar to those used in Study B253 is also available from two Phase 3 studies in renal transplantation. 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,” Have been completed. Both studies compared two fixed dose regimens of everolimus, 1.5 mg/day (0.75 mg BID) and 3 mg/day (1.5 mg/day), to the approved dose of CellCept[®] (mycophenolate mofetil/MMF), 1gram bid, and used standard cyclosporine plus corticosteroid regimens. A total of 193 and 194 subjects were randomly assigned to the 1.5 mg/day total dose of everolimus (RAD 1.5), while an additional 194 and 198 subjects were assigned to a fixed 3.0 mg/day total dose of everolimus (RAD 3), in studies B201 and B251, respectively. The safety of these two treatment regimens was compared to that seen observed in the 196 subjects randomized to the mycophenolate mofetil (MMF) arm of both studies B201 and B251 (i.e., 196 MMF subjects in each study).

The two double blind studies were intended to last 12 months but each was continued for an additional 24 months as an open-label extension. However, after the last subject had completed 12 months on study, an increased rate of renal impairment was found in the everolimus arms compared to the MMF control: this led to a protocol amendment providing for lower cyclosporine exposure and adjustment of the everolimus dose to meet minimum whole blood concentrations in the everolimus arms. At the time of this amendment, a substantial proportion of subjects had already discontinued study drug, with discontinuations greater in the 3 mg/day everolimus treatment group compared to the other 2 study arms. Safety information continued to be collected on all subjects remaining on study drug up to 36 months.

The following is a bulleted summary of safety information extracted from the Medical Officer’s Clinical Review of renal transplantation studies B201 and B251 as the information pertains to the doses of everolimus used with cyclosporine and corticosteroids in heart transplantation study B253. In particular, renal function impairment, lipid abnormalities, wound complications, and hematologic abnormalities similar to those observed in heart transplantation recipients in Study B253 were observed in renal transplantation recipients receiving everolimus with cyclosporine and corticosteroids.

2. Safety summary and conclusions from studies B251 and B201

2.1. Discontinuation from Study Medication

- Patient discontinuation from study medication was greater 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 studies.
- Adverse events and unsatisfactory therapeutic effect were the most common reasons for discontinuation from study medication in both key renal studies.
- In general, dose related differences in the incidence of adverse events (AE), serious adverse events (SAE), and Adverse Events Leading to Discontinuation from Study Medication (DAE) were observed between the RAD arms, with RAD 3 arms > RAD 1.5. The RAD 3 arm presented the highest incidence of 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 at 12 months; because of this, 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.

Table 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, 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).

2.2. Adverse Events Leading To Discontinuation from Study Medication

- The incidence of adverse events leading to discontinuation from study medication¹ (DAE) was higher in the RAD arms compared with the MMF arm.
- 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 DAEs 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.
- In study B201, six (6) patients were discontinued from study medication for reason of pneumonia in the in the RAD 3 versus one patient the MMF arm.
- Thrombotic microangiopathy (TMA)² as a DAE was reported in 2%, 2%, and 1% (B251) and 1%, 4%, and 0% (B201) of subjects in the RAD1.5, RAD 3 and MMF arms, respectively. The number of cases was small but numerically higher in the RAD arms compared with the MMF and consistent

¹ Safety Population - 36 Month Analysis,

² Thrombotic microangiopathy (TMA) includes hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP)

across both key renal studies. Since TMA has been related to the toxic effect of CsA, this finding is relevant given the known interaction of RAD and CsA.

Table 2: Incidence Rates of Adverse Events Leading to Discontinuation of study Medication by Body System and Preferred Term (Safety Population - 36 Month Analyses) Studies B251 and B201.

DAE <i>System Organ Classification</i>	RAD 1.5 n = 209		RAD 3 n = 211		MMF n = 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%)
<i>Renal and urinary disorders</i>	12 (6%)	12 (6%)	9 (5%)	16 (8%)	8 (4%)	7 (4%)
<i>Renal impairment NOS</i>	1 (0.5%)	4 (2 %)	0	4 (2 %)	0	0
<i>Blood creatinine increased</i>	9 (5%)	4 (2%)	14 (7%)	4 (2 %)	3 (1.5%)	2(1%)
<i>TMA Including HUS & TTP</i>	4 (2 %)	2 (1 %)	4 (2%)	8 (4%)	2 (1%)	0
<i>Therapeutic Agent Poisoning</i>	4 (2 %)	2 (1 %)	2 (1 %)	2 (1 %)	0	0
<i>Infections / infestations</i>	9 (5 %)	8 (4 %)	9 (5 %)	16 (8 %)	0	10 (5 %)
<i>All Pneumonias^a</i>	2 (1%)	2 (1%)	1 (0.5%)	6 (3%)	0	1 (0.5%)
<i>Leukopenia nos</i>	0	2 (1.0%)	0	3 (1.5%)	1 (0.5%)	2 (1%)
<i>Thrombocytopenia / platelet count decreased</i>	1 (0.5%)	3 (1.5%)	5 (2.5%)	6 (3%)	0	2 (1%)
<i>DAE- lipid abnormalities^b</i>	3 (1.5%)	7 (4%)	6 (3%)	2 (1%)	4 (2%)	0

^aAll pneumonias includes bronchopneumonia and any DAE including pneumonia in the preferred term (e.g., PCP, CMV, etc.).

^bIncluded are 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, and Increased Low Density Lipoprotein Increased.*

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)

2.3. Overall Adverse Events

- Adverse Events/Infections were reported by System Organ Classification and Preferred Term in the Safety Population (36 Month Analysis).
- Both studies consistently showed higher rates of blood creatinine increased, hyperlipidemia, pneumonia, hemolytic uremic syndrome, lymphocele and peripheral edema in both RAD arms compared with MMF.

Table 3: 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^a</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 NOS^b</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 total^c</i>	4%	3%	2%	5%	1%	0.5%
<i>Proteinuria</i>	14 (7%)	18 (9 %)	18 (9 %)	18 (9 %)	10 (5 %)	5 (2 %)

^a 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.

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

^c TMA total Including TMA NOS, HUS and TTP

The dictionary used is the MedDRA; Adverse events/infections with onset date eight or more days after the discontinuation of randomized study medication are not included in this analysis.

Data obtained from 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.

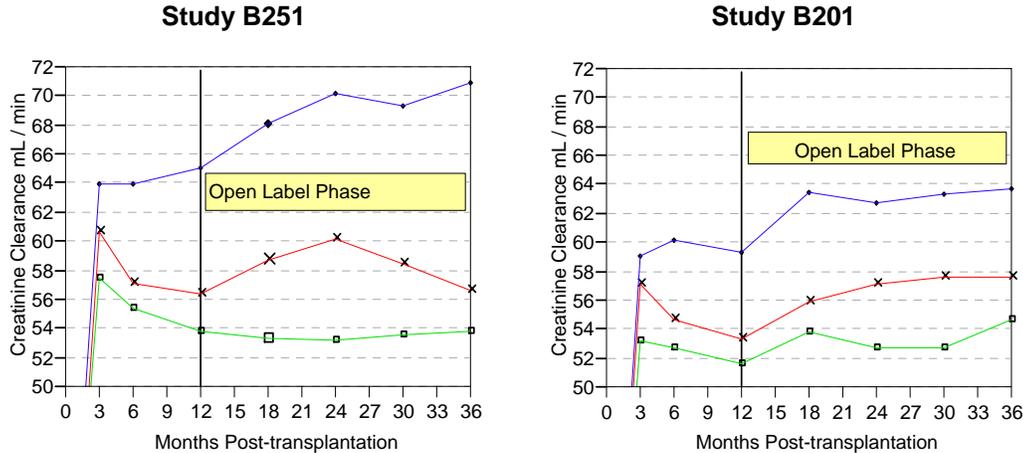
2.4. Renal Related Adverse Events

- Renal function disorders (e.g., 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.
- HUS rates were higher in both RAD arms compared to the MMF in both studies. The number of cases was small but consistent across both studies. Since TMA has been related to a potential toxic effect of CsA, this finding may be 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.

2.4.1. Renal Function

Figures 1 and 2: Renal function in Studies B251 AND B201 - Estimated Creatinine Clearance (Nankivell) [ml/min] by visit (Safety Population - 36 month analyses)



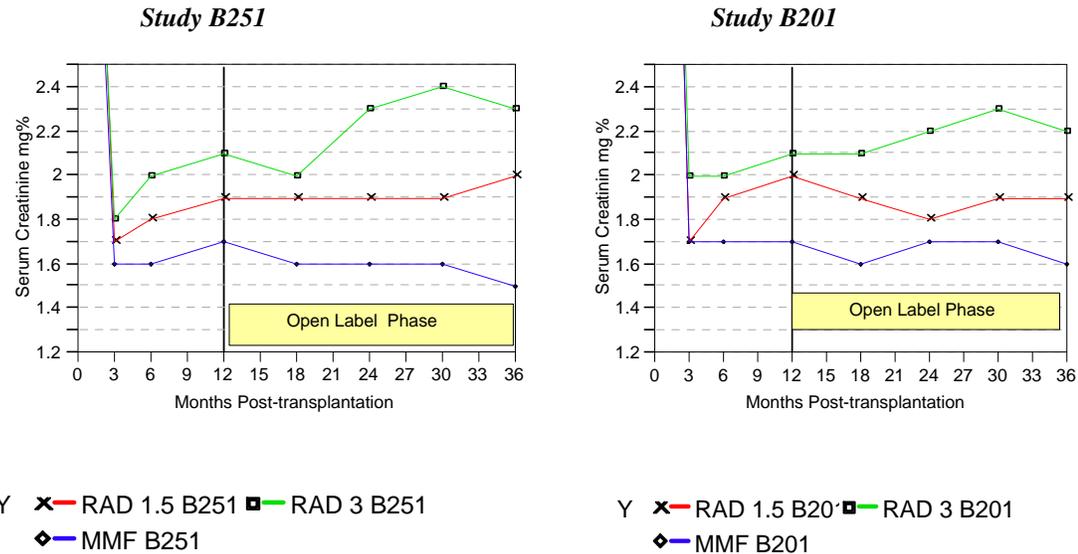
Y x—RAD 1.5 B251 □—RAD 3 B251
 ◆—MMF B251

Y x—RAD 1.5 B201 □—RAD 3 B201
 ◆—MMF B201

Data obtained from: NDA 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.

- Baseline creatinine clearance (CrCl) was similar across arms in both studies. After transplantation, mean calculated creatinine clearance reached its zenith approximately at three months post transplantation in all arms in both studies. Zenith values were lower and dose related in the RAD arms compared to MMF arms in both studies.
- The mean calculated CrCl values decreased significantly over time in both RAD arms up to 12 months. Caution must be taken in interpreting trends after the study was unblinded, dosing regimens were adjusted, and a number of subjects had discontinued study drug. The differences between RAD 1.5 and RAD 3mg versus MMF were statistically significant in both studies at 6, 12, 24, and 36 months.

Figures 3 and 4: Serum Creatinine (mg %) by Visit. (Safety Population - 36 Month Analysis)



Data obtained from: NDA Post-text Tables 10.3-1b Summary Statistics by Visit Renal Function: Creatinine mg% (Safety Population - 36 Month Analysis) Studies B251 and B201, respectively.

2.4.2. Renal Function Change from 12 to 36 months (amendment # 3 evaluation)

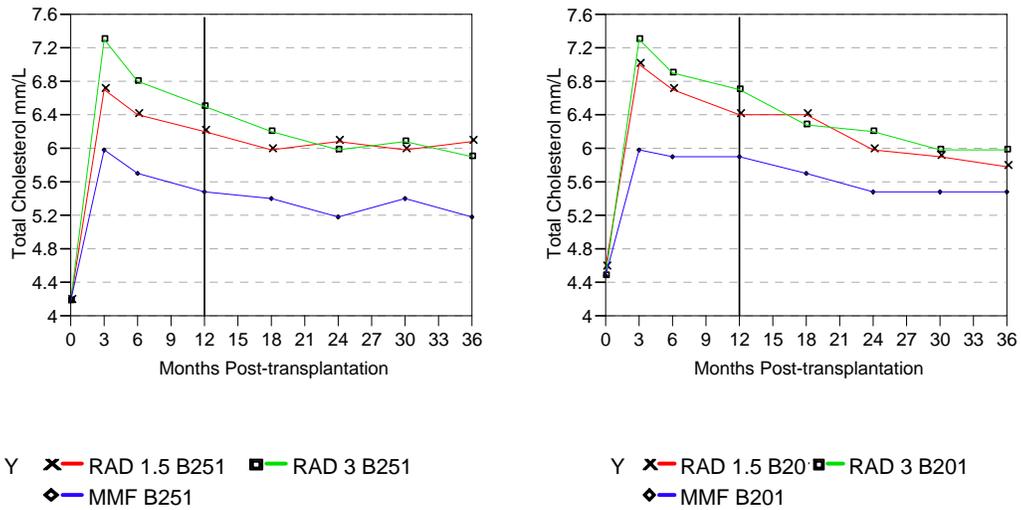
- After unblinding and dose adjustments at 12 months, any potential dose related effect should be interpreted with caution. However, a greater renal deterioration was observed in the RAD 3 arm compared with RAD 1.5.

2.5. Hyperlipidemia Assessment

- Hyperlipidemia reported as adverse events³ presented higher incidence rates in both RAD 1.5 and RAD 3 arms compared to MMF arms in both studies. Individual rates per preferred term reflected the same trend. RAD 1.5 and RAD 3 arms presented similar rates across both studies suggesting that a dose dependency may not exist. However, due to the individualized therapeutic efforts to maintain blood lipid levels within a target range, it may be 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.
- Hyperlipidemia appeared to be a dose related toxicity in the RAD plus CsA arms. Statistically significant differences were observed in cholesterol and triglyceride mean values from 3 to 36 months in the RAD 1.5 and RAD3 arms compared with MMF arm in both studies.

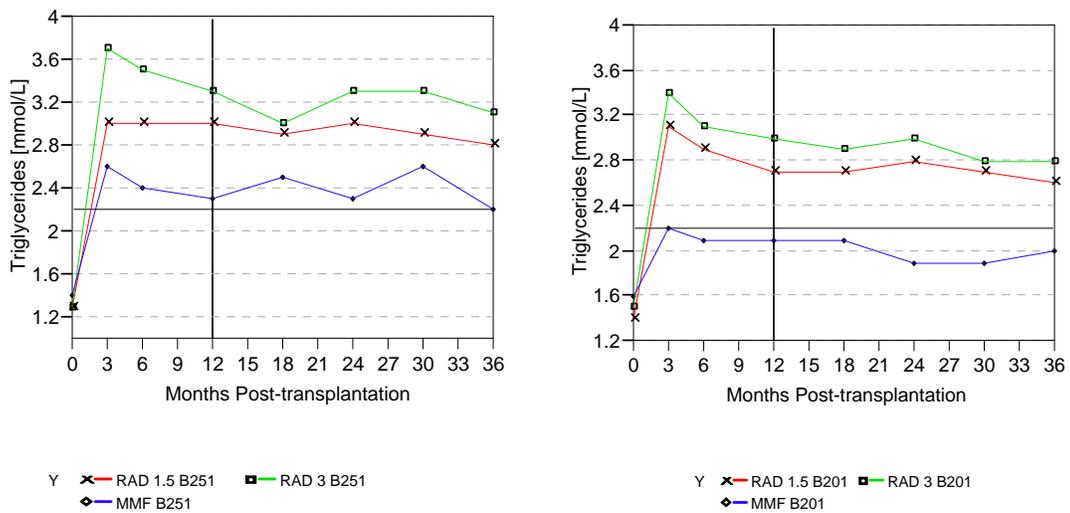
³ Hyperlipidemia including: Hyperlipidemia nos, Hypercholesterolemia, Blood Cholesterol Increased, Hypertriglyceridemia, Blood Triglycerides Increased. Individual analyses per preferred term reflect the same trend.

Figures 5 and 6: Lipids - Total Cholesterol [mmol/L] (Safety Population 36-Month Analysis)



Data obtained from: NDA Post-text Table 10.3-1b (Page 16 of 22) Summary Statistics by Visit

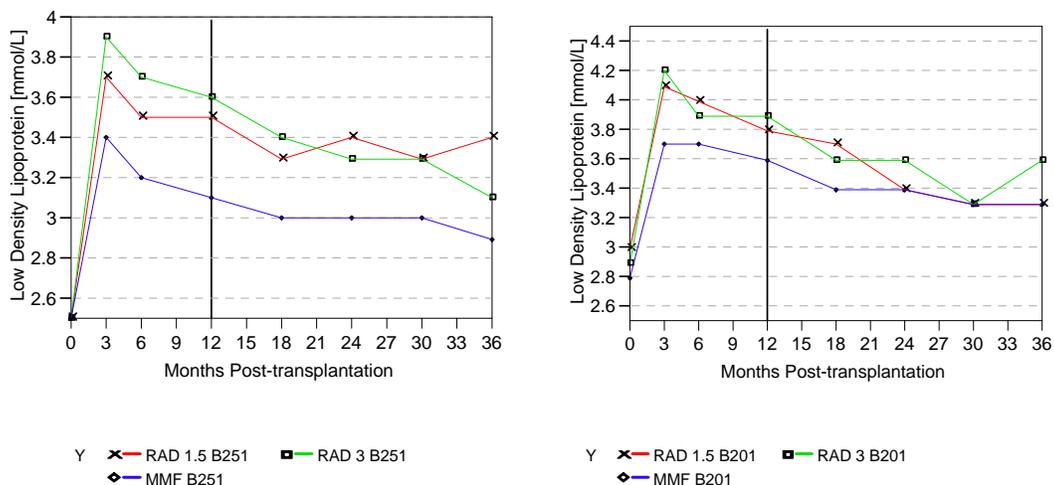
Figures 7 and 8: Lipids - Triglycerides (mmol/L) (Safety Population - 36 Month Analysis)



Data obtained from NDA Post-text Table 10.3-1b (Page 21 of 22) Summary Statistics by Visit.
 The horizontal line indicates the lower limit for high triglyceride values⁴ (200-449 mg/dL or 2.3 to 5.63 mmol/L).

⁴ NCEP-ATPIII National Cholesterol Education Program - Adult Treatment Panel III

Figures 9 and 10: Lipids - Low Density Lipoprotein [mmol/L] (Safety Population - 36 Month Analysis)



Data obtained from NDA 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)

Table 4: Rise in Total Cholesterol and Triglyceride Levels and Related Events (Safety Population - 36-Month Analysis) Studies B201 and B251

	RAD 1.5mg		RAD 3mg		MMF 2g		Difference/95%CI: (a) RAD 1.5mg - MMF (b) RAD 3mg - MMF (c) 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)	13.2% (5.3, 21.1)
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%)	14.9% (6.7, 23.0)	14.0% (6.3, 21.8)
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%)	-7.1% (-14.8, 0.6)	-0.8% (-7.5, 5.8)
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%)	9.3% (0.3, 18.4)	16.8% (8.0, 25.6)
							24.9% (15.5, 34.2)	25.5% (16.5, 34.4)
							-15.5% (-25.3, -5.8)	-8.7% (-18.4, 1.0)
							8.0% (-0.9, 16.9)	12.4% (3.5, 21.3)
							10.4% (1.8, 18.9)	15.0% (6.4, 23.5)
							-2.4% (-10.2, 5.5)	-2.6% (-10.1, 5.0)
							11.9% (1.7, 22.1)	27.0% (16.8, 37.2)
							15.8% (6.0, 25.7)	24.5% (14.3, 34.7)
							-3.9% (-13.2, 5.4)	2.6% (-7.3, 12.4)

Data obtained from NDA Post-text Tables 10. 6-3, 10.6-4 10.6-5, (Safety Population - 36 Month Analysis)

- The rates of 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 studies. Similarly, in both studies new onset hyperlipidemia was numerically or significantly higher in both RAD arms compared with MMF arms.

2.6. Wound Complications and Lymphocele

- Wound complications as AE were higher in the RAD3 arms compared with the MMF arms in both 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 studies. A dose related incidence trend was observed between the RAD arms in both studies.

**Table 5: Wound Complications
(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)
Postoperative Wound Complication NOS	20 (10%)	0	22 (11%)	4 (2%)	15 (8%)	4 (2%)
Wound Dehiscence	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 Total[†]</i>	24%	5%	24%	12%	15%	9%
Lymphocele	31 (16%)	24 (12%)	36 (19%)	35 (18%)	24 (12%)	16(8%)

The dictionary used is the MedDRA; Adverse events/infections with onset date eight or more days after the discontinuation of randomized study medication are not included in this analysis

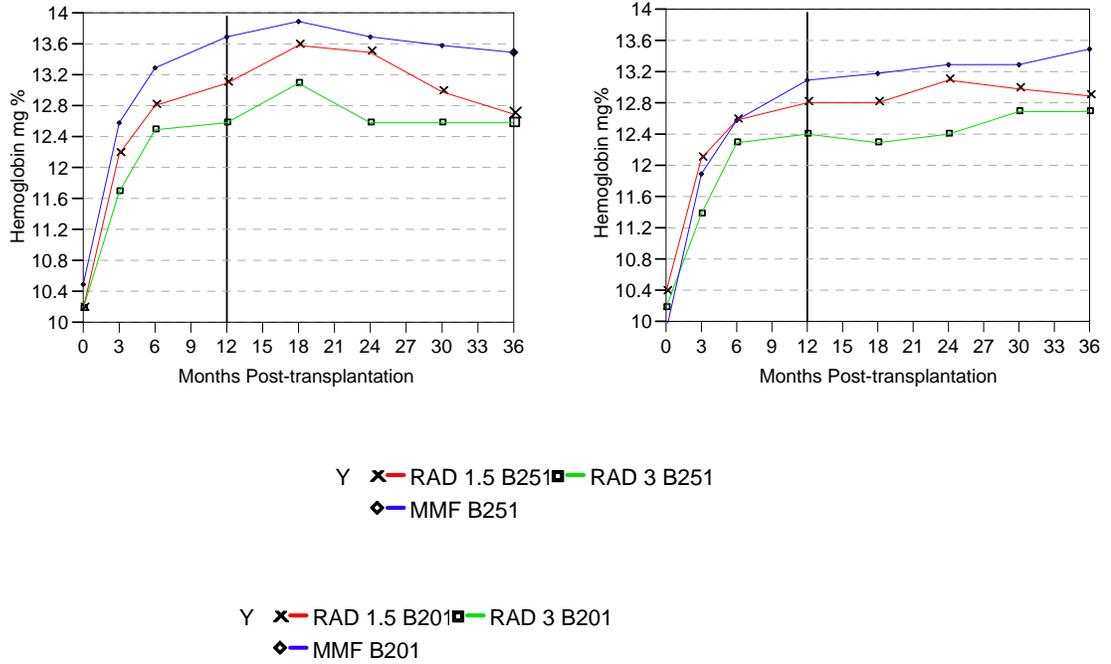
Data obtained from: Incidence Rate of Adverse Events/Infections by Body System and Preferred Term (Safety Population - 36-Month Analysis). NDA Post-text Table 10.1-1a (Page 2 of 82) and Post-text Table 10.1-1a (Page 1 of 58) Studies B251 and B201, respectively. Includes all preferred terms in which the word wound was included related to the surgical procedure as reported in CRF, i.e. postoperative wound complication NOS, etc. Lymphocele was not included in this category.

2.7. 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.

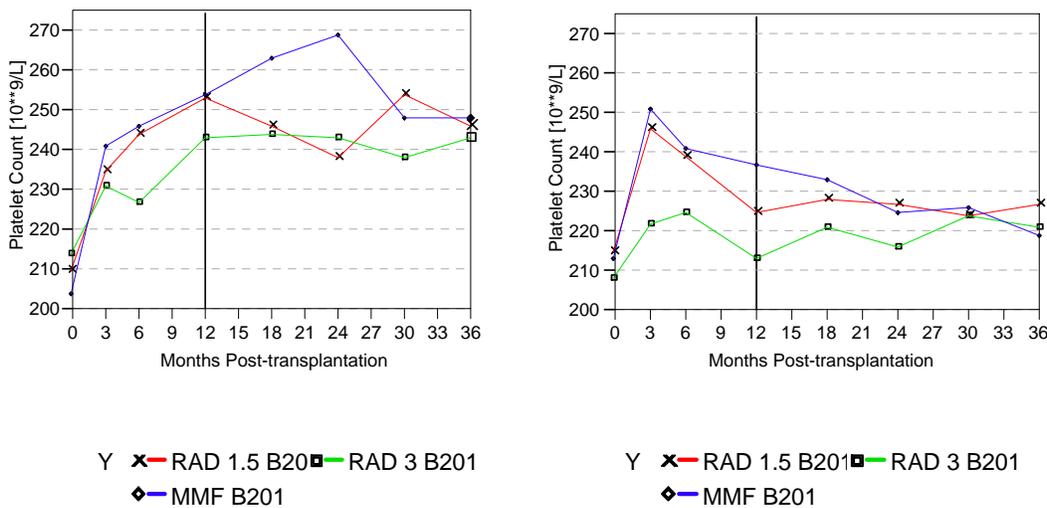
2.8. Hematology

Figures 11 and 12: Mean Hemoglobin [g/dL] Values by Visit, Studies B251 and B201 (Safety Population - 36 Month Analysis)



Data obtained from m NDA 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)

Figures 13 and 14: Mean Platelet Count [$10^9/L$] Values by Visit, Studies B251 and B201 (Safety Population - 36 Month Analysis)



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)

- Mean hemoglobin 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 studies.
- Mean platelet counts increased after transplantation in all treatment arms. During the double blind phase a similar pattern of 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. Thrombocytopenia⁵ rates reported as adverse events at 36 months were higher in both RAD arms compared to MMF in both key renal studies.

Table 6: Hematologic Abnormalities Reported as Adverse Events

	B251 (N=193)	B201 (N=194)	B251 (N=194)	B201 (N=198)	B251 (N=196)	B201 (N=196)
<i>Adverse Event</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>Hemoglobin or Hematocrit Decreased</i>	12(6 %)	2 (1 %)	8 (4 %)	3 (1.5%)	5 (2.5%)	4 (2 %)
<i>Total</i>	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%)
<i>Total</i>	9%	13%	11%	13%	7%	6%

⁵ *Thrombocytopenia NOS or Thrombocytopenia NOS + platelet count decreased*