Interdisciplinary Review Team for QT Studies Consultation:

Thorough QT Study Review

NDA	22-334
Brand Name	AFINITOR
Generic Name	Everolimus, RAD001
Sponsor	Novartis
Indication	Treatment of advanced Renal Cell Carcinoma
Dosage Form	Tablets
Drug Class	mTOR inhibitor
Therapeutic Dosing Regimen	10 mg qd [redacted] b(4)
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not determined
Submission Number and Date	June 27, 2008
Clinical Division	DDOP / HFD 150
PDUFA GOAL DATE	March 30, 2009

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QT prolongation effect of RAD001 (20 mg and 50 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between RAD001 (20 mg and 50 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance. However, the exposures achieved with the 50-mg dose do not cover the increase in RAD001 exposures due to CYP3A4 and PgP inhibition. Higher exposure could not be achieved with administering higher doses because of the less than dose proportional increases in RAD001 exposure. There was no relationship between RAD001 concentrations and QTc changes within the current exposure range.

The TQT study (part 2) was a single-dose, randomized, blinded (RAD001 versus placebo), 4-period crossover study in 59 healthy volunteers. Overall findings are summarized in Table 1. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that the assay sensitivity of the study was established.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for RAD001 (20 mg and 50 mg) and the Largest Lower Bounds for Moxifloxacin (FDA Analysis)

Treatment	Time (h)	ΔΔQTcF	90% CI
RAD001 20 mg	12h	3.7	(1.6, 5.9)
RAD001 50 mg	12h	4.7	(2.5, 6.8)
Moxifloxacin 400 mg*	4h	12.8	(10.9, 14.6)

* Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment was 9.84 ms.

1.2 QT Interdisciplinary Review Team's Comments

RAD001 50 mg was selected as the supratherapeutic dose in part 1 of the study. This dose is not the maximum tolerated dose because there were no dose-limiting toxicities. Administering doses higher than 50 mg would not increase the exposure to RAD001 because it pharmacokinetics are less than dose proportional. The mean C_{max} achieved with RAD001 50 mg (160 ± 40 ng/ml, BSV = 25%) is approximately twice the mean C_{max} achieved after administering 10 mg qd to steady state (77 ± 39 ng/ml, BSV=51%).

The RAD001 doses evaluated (20 mg and 50 mg QD) in this study do not cover the expected increases in exposures due to metabolic inhibition with moderate and potent CYP3A4 and PgP inhibitors. Coadministration of moderate CYP3A4 and PgP inhibitors (erythromycin, verapamil) increased mean C_{max} by two-fold. Moreover, there was a 4- and 15-fold increase in C_{max} and AUC when RAD001 was coadministered with potent CYP3A4 and PgP inhibitors (ketoconazole). The use of strong inhibitors is not contraindicated in the proposed package insert; however, the sponsor does recommend that coadministration with strong inhibitors or inducers of CYP3A4 or PgP should be avoided where possible (see Drug Interactions).

In subjects with moderate hepatic impairment, the mean AUC value is doubled but there was no change in mean C_{max}. The sponsor recommends dose reduction to 5 mg daily in patients with Child-Pugh class B. RAD001 is not recommended in patients with Child-Pugh class C hepatic impairment.

2 PROPOSED LABEL

The sponsor did not include a description of study results in the proposed label. The following text is our suggestions for labeling. We defer all labeling decisions to the clinical review team.

12.2 Pharmacodynamics

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3 BACKGROUND

Everolimus is a derivative of rapamycin and acts as a signal transduction inhibitor. Its target is mTOR, a key regulatory serine-threonine kinase regulating metabolism, cell growth and proliferation, and angiogenesis. This submission by the sponsor is to obtain approval for everolimus 10 mg daily for the treatment of patients with advanced renal cell carcinoma.

3.1 MARKET APPROVAL STATUS

Everolimus (Certican®) is commercially available within the European Union and other markets for the prophylaxis of allograft rejection following renal or cardiac transplantation, in conjunction with cyclosporine and glucocorticoid therapy. The first marketing approval was received in June 2003 from the Swedish Health Authority. Overall, >3000 transplant patients have received treatment with everolimus in Novartis-sponsored studies; doses administered in this setting (where the initial dosage recommendation is 1.5 mg/day) are lower than those proposed for the oncology patient population (10 mg/day).

3.2 PRECLINICAL INFORMATION

Source: Pharrmacology Written Summary, 31-March 2008 (CTD 2.6.2)

> "RAD001 at a target concentration of 10 μM (9.6 μg/ml; corrected values: 3.4 μM and 3.3 μg/ml) and of 16 μM (15.3 μg/ml; corrected values: 9.7 μM and 9.3 μg/ml) inhibited hERG channel activity in stably transfected HEK293 cells by 2.6 and 17.5 %, respectively. [Report 0770800]
>
> "RAD001 had no influence on QT interval prolongation [TPCH_ 98-062_Expert]. Effects of RAD001 at concentrations of 100, 1000 or 10000 ng/ml, corresponding to 0.104, 1.04 or 10.4 μM, were assessed on intra-cellularly recorded action potential parameters in the sheep isolated cardiac Purkinje fibre preparation electrically paced at 1 Hz.
>
> RAD001 had no effect on the Purkinje fibre action potential duration, amplitude or maximum rate of depolarization. The diastolic membrane potential recorded in these fibres was also unaffected. These data indicate that plasma concentrations up to 10000 ng/mL are unlikely to have effects on ECG parameters.
>
> "The re-evaluation of electrocardiograms in the 2-week, 4-week and 26-week oral toxicity studies with RAD001 in cynomolgus monkeys did not indicate any test article-related changes. In a 4-week oral combination study with cyclosporin A, there were no changes attributable to a direct effect of the compounds. The increased QT interval in one animal treated with the cyclosporin A/RAD001 combination at 100/0.25 mg/kg, recorded before early necropsy, was associated with a decrease in heart rate. This was considered to be related to electrolyte disturbances secondary to dehydration and poor health status. The electrocardiographic recordings in minipigs after intravenous infusion of RAD001 showed no potential for QT interval prolongation."

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety, 22 May 2008, CTD -2.7.4

> "This safety evaluation of everolimus 10 mg daily, administered as monotherapy, is based upon data from 596 patients from the clinical development program. Data from a further 432 subjects (350 patients and 82 healthy volunteers) from completed studies also contribute to this evaluation
>
> "2.1.2.1 Deaths in double-blind phase of pivotal phase-III trial (Study C2240)
>
> Deaths 'on-treatment' (i.e., while receiving study medication or within the initial 28 days of discontinuing therapy) were recorded for 20 patients (5.0%) by the data cut-off date of 15-Oct-2007. Eighteen of these 20 deaths (90.0%) were attributed to the underlying malignancy (this includes the acute renal failure case [Patient 0758-00004]) while the remaining two were from solitary events. One patient ([Patient 609-00003]) treated with everolimus died from overwhelming candidal sepsis, complicated by acute respiratory failure, and which may have been attributable to the study drug. The second patient ([Patient 753-00002]), who was initially treated with placebo, died as the result of a myocardial infarct 3 days after commencing treatment with open-label everolimus.
>
> "2.1.2.2 Deaths in pooled dataset (monotherapy safety population)
>
> Across the broader development program reported in the pooled dataset, 6 patients (1.0%) have died where the primary cause of death was reported to be an AE within the 'respiratory, thoracic, and mediastinal disorders' system organ class. Review of the individual cases identified two deaths (reported as acute respiratory distress syndrome and respiratory failure, respectively) that were related to ARDS in the context of infection (*Pneumocystis carinii* pneumonia in one case and 'candidal pneumonia and sepsis' in the second. No common etiology was shared in the remaining four cases; these were due to progressive lung cancer (report of acute pulmonary edema), esophageal perforation (report of hydropneumothorax), aspiration of vomit (report of aspiration), and progressive renal cancer (report of respiratory failure).
>
> "ECGs were not routinely performed or analyzed in the phase-I, -II, or –III studies, although where these results were available, no significant mean changes from baseline QTc were evident. No patient receiving everolimus experienced a treatment-emergent QTc interval >500 ms or had ventricular tachycardia."

Reviewer's Comments: There are no reports of AEs related to QT prolongation (i.e.) sudden cardiac death, syncope, seizure or significant ventricular arrhythmias.

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of RAD001's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor submitted the study report for CRAD001C2118, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A blinded, randomized, placebo and active controlled, single-dose crossover study to investigate the effect of RAD001 on cardiac intervals in healthy volunteers.

4.2.2 Protocol Number

CRAD001C2118

4.2.3 Study Dates

11 July 2007 to 19 November 2007

4.2.4 Objectives

The primary objective is to assess the effect of a single dose, on heart rate and cardiac conduction intervals (QT, QTc, QTcB, QTcI, QRS, RR, and PR) in adult healthy volunteers.

4.2.5 Study Description

4.2.5.1 Design

The study was carried out in two phases.

Part 1 was a dose finding pilot phase. The following doses were investigated to find the supra-therapeutic dose to be used in Part 2: RAD001 20 mg, RAD001 30 mg, and RAD001 50 mg.

Part 2 was the thorough QT/QTc study designed as a single-dose, randomized, blinded (RAD001 versus placebo), 4-period crossover study with active (moxifloxacin, open-label) and negative (placebo) control to assess the effect of RAD001 at a therapeutic (20 mg) and supratherapeutic dose (50 mg) on cardiac conduction and repolarization. A total of 60 subjects were planned for this part.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The administration of RAD001 and placebo was double-blinded. Moxifloxacin was administered open label.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms (Part 2)

Treatments	No. of RAD001 tablets or matching placebo tablets as single dose
20 mg	4 tablets of RAD001 5 mg and 6 matching placebo tablets
50 mg	10 tablets of RAD001 5 mg (supra-therapeutic dose)
Placebo	10 matching placebo tablets
Moxifloxacin	1 tablet of 400 mg moxifloxacin

All doses were administered under fasting conditions together with 200 mL of water and were to be swallowed within 3 minutes.

4.2.6.2 Sponsor's Justification for Doses

"Part 1 was a dose finding pilot phase. The following doses were investigated to find the supra-therapeutic dose to be used in Part 2: RAD001 20 mg, RAD001 30 mg, and RAD001 50 mg. The following procedure was performed, to determine the supra-therapeutic dose:

- If Dose Limiting Toxicity (DLT) / drug related AEs of Common Toxicity Criteria (CTC) equal or greater than grade 3 unexpectedly would occur in the 50 mg cohort the dose level was to be reduced to 30 mg and became the supra-therapeutic dose for the second part of the clinical study.
- If DLT / drug related AEs of CTC equal or greater than grade 3 unexpectedly would occur in the 30 mg cohort, Part 2 was to be conducted without a supra-therapeutic dose.
- If DLT / drug related AEs of CTC equal or greater than grade 3 unexpectedly would occur in the 20 mg cohort, Part 2 of the clinical study was not to be conducted.

"The duration of evaluation of DLT or drug related AEs was up to 14 days after dosing. According to the safety results of Part 1: no drug-related AEs of CTC grade 3 or greater in the 50 mg cohort, the supra-therapeutic dose was identified as 50 mg."

Reviewer's Comments: Sponsor's choice of therapeutic and supratherapeutic doses did not cover high exposures possible with coadministration of potent CYP3A4 and PgP inhibitors. There were no dose limiting toxicities observed in part 1 so 50 mg QD is not the MTD. However, since the increase in C_{max} beyond 10 mg single dose was less than dose proportional, increase in doses over 50 mg would not have helped increase the exposure.

Since RAD001 is primarily eliminated by liver, there are two possible worst case scenarios (hepatic impairment and coadministration of CYP3A4 inhibitors) that are likely to increase its exposure. Moderate hepatic impairment doubles the AUC while there is no change in C_{max}. Sponsor recommends reduction of dose to 5 mg daily in these

patients. RAD001 has not been studied in severe hepatic impaired subjects and thus its use is not recommended in this population.

Coadministration of moderate inhibitors of CYP3A4 increases the C_{max} by 2-fold, which is likely to be covered by the exposures achieved by supratherapeutic dose (50 mg). But, with coadministration of strong CYP3A4 inhibitors (Ketoconazole) the C_{max} and AUC is increased by 4 and 15-fold, respectively which is not covered by the supratherapeutic dose. However, concomitant use of strong CYP3A4 inhibitors is to be avoided (not contraindicated), as stated in the label. Even though there was a moderate accumulation (accumulation factor=1.7) for RAD001 after 10 mg daily dose, the C_{max} at first dose and at steady state were similar and exhibited high intersubject variability (40-50%).

4.2.6.3 Instructions with Regard to Meals

All doses were administered under fasting conditions together with 200 mL of water and were to be swallowed within 3 minutes.
Reviewer's Comments: It is acceptable as per the information provided in the label.

4.2.6.4 ECG and PK Assessments

Study Day	-1	1
Intervention	No treatment (Baseline)	20 or 50 mg single dose
12-Lead ECGs	Pre-dose (0 h) and 0.5, 1, 1.5, 2, 3,4, 8, 12 and 23.5 h	0.5, 1, 1.5, 2, 3,4, 8, 12 and 23.5 h
PK Samples for drug	None collected	Pre-dose (-5 min), 0.5, 1, 1.5, 2, 3,4, 8, 12 and 23.5 h

4.2.6.5 Baseline

Two kinds of baseline have been derived.

- Time average baseline: The baseline for post-dose measures at all time points is the mean of all time point measurements at Day –1.
- Time match baseline: The baseline for a post-dose measure is the measure at the same time point in Day –1.

Day –1 was the day immediately before first intake of study medication. The hypothesis tests used the time average baseline.

4.2.7 ECG Collection

In Part 2, continuous 12-lead ECGs were recorded using a 12-lead Digital Holter recorder. The subject was resting quietly in the supine position for at least 10 minutes before each triplicate scheduled ECG assessments on Day 1 for each period.

The ECG waveforms were recorded on the compact flash memory cards (flash cards) provided to the study site. Triplicate ECG (7.5 sec, 12 lead) assessments were extracted by the central lab —— at the time points specified in section 4.2.6.4. b(4)

Interval duration measurements were made from 3 waveforms, typically using Lead II. A standard digital 12-lead ECG was recorded during the treatment period if there were any safety concerns.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Healthy adult male (34) and female (30) subjects, 18-65 yrs of age with a normal baseline ECG and BMI 20-32 kg/m^2 were included.

In Part 1, 24 subjects were randomized. All 24 subjects completed the clinical study according to the protocol.

In Part 2, 64 subjects were randomized. Five subjects were withdrawn from the clinical study-3 because of AEs, Subject 20016 because of abnormal test procedure result, and Subject 20008 withdrew consent. In total, 59 subjects completed the clinical study as per protocol.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The change from baseline QTcF was analyzed using a linear mixed effects model fitting terms for sequence, treatment, period, time and treatment-by-time interaction, where subject-within-sequence was treated as a random effect. Baseline QTcF was included as a covariate in the model. Point estimates and 95% CIs (one-sided) were generated at each point for treatment difference (active-placebo). Results are provided in Table 2, Table 3 and Table 4 below.

Table 2: Sponsor's ΔQTcF Analysis: RAD001 20mg vs. Placebo

Day	Time	Treatment Difference: ddQTcF		
		Estimate	S.E.	90% Confidence Interval
1	0.5h post-dose	–0.58	1.10	(–2.39, 1.23)
	1h post-dose	–0.16	1.10	(–1.97, 1.65)
	1.5h post-dose	0.72	1.10	(–1.09, 2.53)
	2h post-dose	1.60	1.10	(–0.21, 3.41)
	3h post-dose	0.56	1.10	(–1.26, 2.37)
	4h post-dose	1.60	1.10	(–0.21, 3.41)
	8h post-dose	2.26	1.10	(0.45, 4.08)
	12h post-dose	4.15	1.11	(2.33, 5.97)
	23.5h post-dose	3.36	1.11	(1.55, 5.18)

Source: Table 16.1-9.1.1b (page 1429) and Table 16.1-9.11b (page 1430)

Table 3: Sponsor's ΔQTcF Analysis: RAD001 50mg vs. Placebo

Day	Time	Treatment Difference: ddQTcF		
		Estimate	S.E.	90% Confidence Interval
1	0.5h post-dose	–1.32	1.10	(–3.14, 0.49)
	1h post-dose	–0.48	1.10	(–2.29, 1.34)
	1.5h post-dose	–0.40	1.10	(–2.21, 1.42)
	2h post-dose	0.35	1.10	(–1.47, 2.16)
	3h post-dose	0.90	1.10	(–0.91, 2.71)
	4h post-dose	0.84	1.10	(–0.97, 2.66)
	8h post-dose	3.09	1.10	(1.27, 4.90)
	12h post-dose	4.26	1.10	(2.45, 6.07)
	23.5h post-dose	3.46	1.11	(1.63, 5.29)

Source: Table 16.1-9.1.1b (page 1429) and Table 16.1-9.11b (page 1430)

Table 4: Sponsor's ΔQTcF Analysis: Moxifloxacin vs. Placebo

Day	Time	Treatment Difference: ddQTcF		
		Estimate	S.E.	90% Confidence Interval
1	0.5h post-dose	9.22	1.11	(7.41, 11.03)
	1h post-dose	10.95	1.11	(9.13, 12.77)
	1.5h post-dose	11.12	1.11	(9.31, 12.93)
	2h post-dose	13.01	1.11	(11.20, 14.82)
	3h post-dose	12.55	1.11	(10.74, 14.36)
	4h post-dose	13.08	1.11	(11.27, 14.90)
	8h post-dose	9.92	1.11	(8.10, 11.74)
	12h post-dose	9.93	1.11	(8.11, 11.74)
	23.5h post-dose	4.77	1.11	(2.96, 6.59)

Source: Table 16.1-9.1.1b (page 1429) and Table 16.1-9.11b (page 1430)

4.2.8.2.2 Categorical Analysis

The Sponsor reported that none of the subjects had their change from baseline QTcF over 30 ms. The Sponsor reported that 3 out of 59 (5%) subjects had their QT over 450 ms. However, none of the subjects had their QTcF over 450 ms.

4.2.8.3 Safety Analysis

There were no deaths or SAEs in this study.

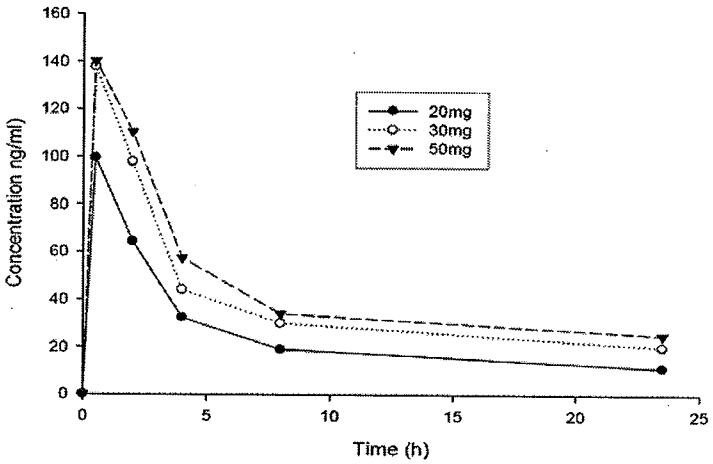
Three subjects discontinued due to AEs. Subject 20027 discontinued due to nausea and vomiting after receiving 50mg RAD001. Subject 20029 discontinued after developing a maculopapular rash and pruritis after receiving moxifloxacin. Subject 20120 developed stomatitis after receiving moxifloxacin and 50 mg RAD001.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

A summary of the main PK parameters of RAD001 are presented in **Table 5**. Mean concentration-time profile plots after 20, 30 and 50 mg of RAD001 from Part 1 are shown in **Figure 1**.

Figure 1: Mean blood concentrations of RAD001 after single oral doses of 20, 30 and 50 mg –Part 1



Source: c2118 report, Figure 11-5

Table 5: Main pharmacokinetic parameters of RAD001 in blood after single oral doses of 20 mg or 50 mg in healthy volunteers-Part 2.

Dose (mg)	T_{max} [h]	C_{max} [ng/mL]	$AUC_{0\text{-tlast}}$ [h.ng/mL]
20 (N = 61)	0.5 (0.5 - 2.0)	109.43 (25.31)	542.1 (149.2)
50 (N = 61)	0.5 (0.5 - 1.5)	159.71 (39.51)	1022.8 275.4)

Values are mean (SD) except for T_{max}, which is median (range).
AUC = Area under the curve; SD = Standard deviation

Source: c2118 report, Table 11-13

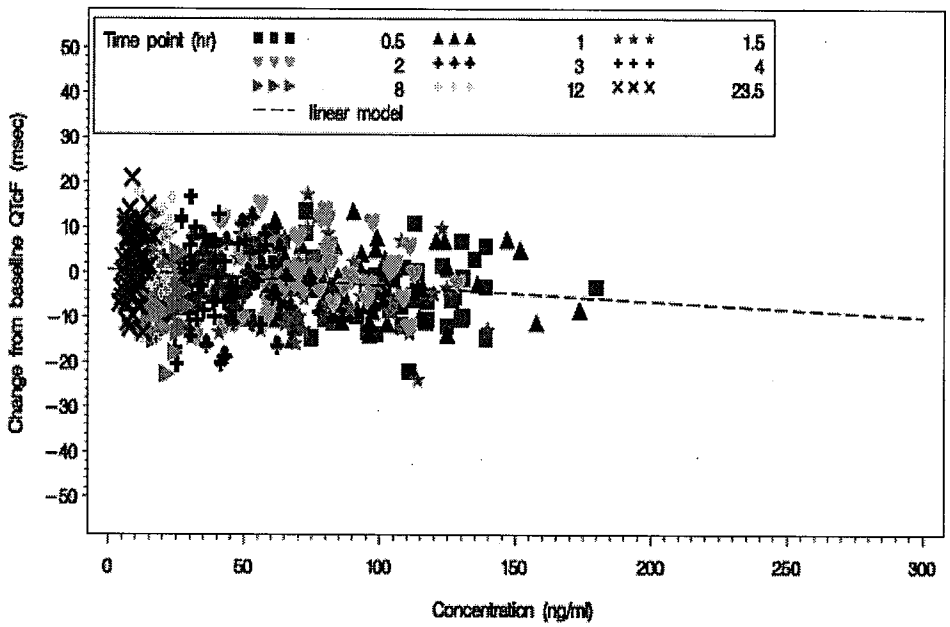
Reviewer's Comments: The C_{max} and AUC of RAD001 50 mg was 1.5 and 1.9-fold of the therapeutic dose (20 mg). However, the proposed dosing regimen for RAD001 is 10 mg daily and the C_{max} achieved with the 50-mg single dose is about twice the C_{max} (76.7±39.3 ng/ml, BSV=51%) achieved at steady state with 10 mg daily regimen (Summary Clin Pharm, Appendix 6.1). The increase in C_{max} was less than dose proportional after 10 mg single dose.

Exposure-Response Analysis

Sponsor conducted exposure response analysis to graphically explore QTcF change from baseline against RAD001 concentrations and found no noticeable trends.

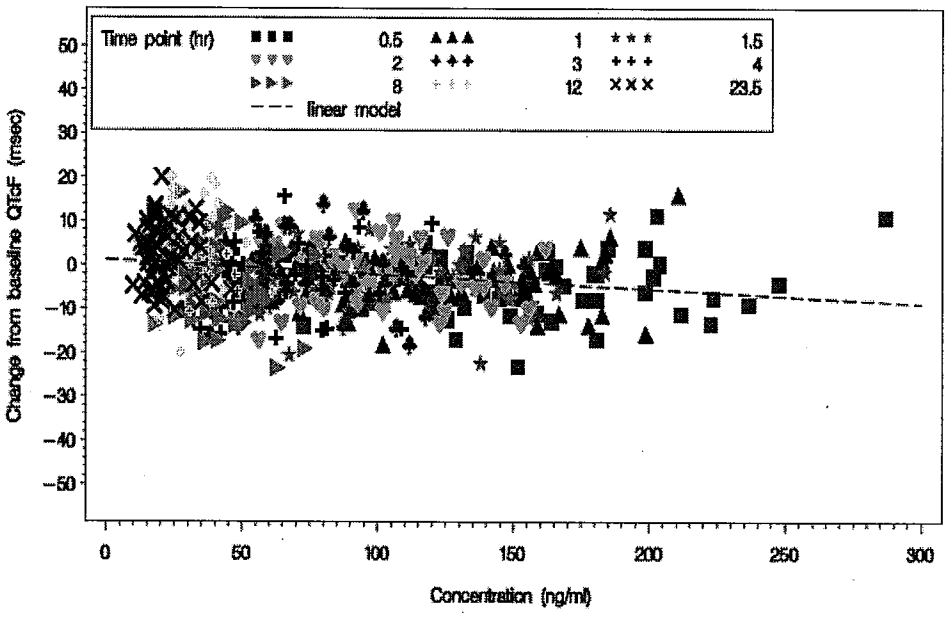
Figure 2: Concentration vs QTcF for (a) 20 and (b) 50 mg RAD001 showing lack of evidence of exposure-response.

(a)



Source: C2118 report, Pg 387

(b)



Source: C2118 report, Pg 388

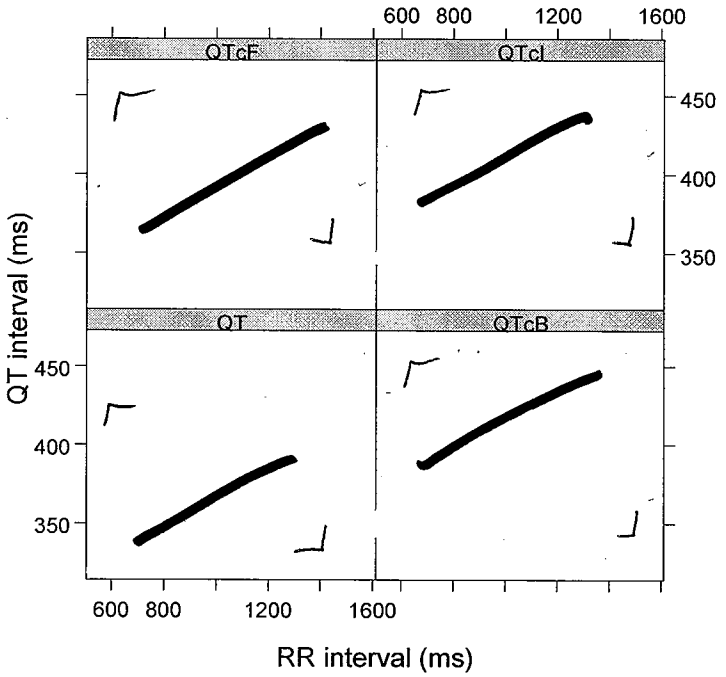
*Reviewer's Comments: The sponsor explored the correlation between concentration and Δ QTcF without adjusting for placebo. The reviewer performed the concentration-response analysis using ΔΔQTcF (*Figure 5*).*

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The observed QT-RR interval relationship is presented in together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI). QTcF was used for further analysis.

Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



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5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

The reviewer analyzed the Sponsor's SAS data provided in qtpk.xpt using a linear model.

The objective was to demonstrate no QT effect of RAD001 compared to placebo. Lack of QT effect was to be concluded if the upper bound of 95% one-sided CI for RAD100–placebo was less than 10 ms for all time points. The change from baseline in QTcF at each time point was the primary endpoint. The RAD001 (20 mg and 50 mg) was compared with placebo. The primary analysis was performed on all time points using analysis of covariance model, including sequence, treatment, period, and subject, where

subject-within-sequence was treated as a random effect. The moxifloxacin 400 mg was also compared with placebo using the same model. Point estimates and one-sided 95% CIs were generated at each time point for treatment differences (active –placebo).

As seen from Table 6 and Table 7, the upper bounds of the 90% confidence interval for the mean difference in QTcF change from baseline between RAD001 (20 mg and 50 mg) and placebo were below 10 ms at all time points, which demonstrates that this is a negative TQT study using the proposed dose.

As seen from Table 8, the largest lower 90% CI for the baseline adjusted mean difference of 400 mg moxifloxacin and placebo is 10.88 ms at hours 4 after dosing without multiple endpoint adjustment. If Bonferroni multiple endpoint correction method is applied (corrected for 9 time pints), the largest lower bound of ddQTcF between moxifloxacin and placebo is 9.83 ms. Since Bonferroni correction is the most conservative approach by assuming the independence of the data, we believe that assay sensitivity of the study has been established and this is further confirmed by the shape of moxifloxacin in Figure 4.

Table 6: Summary of ΔQTcF Analysis: RAD001 20 mg versus Placebo (C vs. B)

Day	Time-Hour*	Mean ΔQTcF		Treatment Difference: ΔΔQTcF		
		TRT: C	TRT: B	Estimate	S.E.	90% CI
1	0.5	–4.85	–3.67	–1.19	1.09	(–2.98, 0.61)
	1	–3.79	–2.98	–0.81	1.05	(–2.55, 0.93)
	1.5	–2.65	–2.68	0.04	1.09	(–1.77, 1.84)
	2	–1.55	–2.58	1.03	1.12	(–0.81, 2.88)
	3	–3.41	–3.41	0.00	1.04	(–1.72, 1.73)
	4	–2.23	–3.30	1.07	1.14	(–0.81, 2.95)
	8	–4.67	–6.46	1.79	1.17	(–0.14, 3.72)
	12	3.15	–0.58	3.73	1.30	(1.59, 5.87)
	23.5	1.69	–1.02	2.71	1.08	(0.93, 4.49)

* Post-dose

Table 7: Summary of ΔQTcF Analysis: RAD001 50 mg versus Placebo (D vs. B)

Day	Time-Hour*	Mean ΔQTcF		Treatment Difference: ΔΔQTcF		
		TRT: D	TRT: B	Estimate	S.E.	90% CI
1	0.5	–4.69	–3.67	–1.02	1.09	(–2.82, 0.77)
	1	–3.15	–2.98	–0.16	1.05	(–1.90, 1.58)
	1.5	–2.80	–2.68	–0.12	1.09	(–1.93, 1.69)
	2	–1.87	–2.58	0.71	1.12	(–1.14, 2.56)
	3	–2.18	–3.41	1.23	1.04	(–0.50, 2.95)
	4	–2.12	–3.30	1.18	1.14	(–0.70, 3.06)
	8	–2.93	–6.46	3.53	1.17	(1.60, 5.46)
	12	4.10	–0.58	4.68	1.29	(2.54, 6.81)
	23.5	2.78	–1.02	3.80	1.09	(2.00, 5.60)

* Post-dose

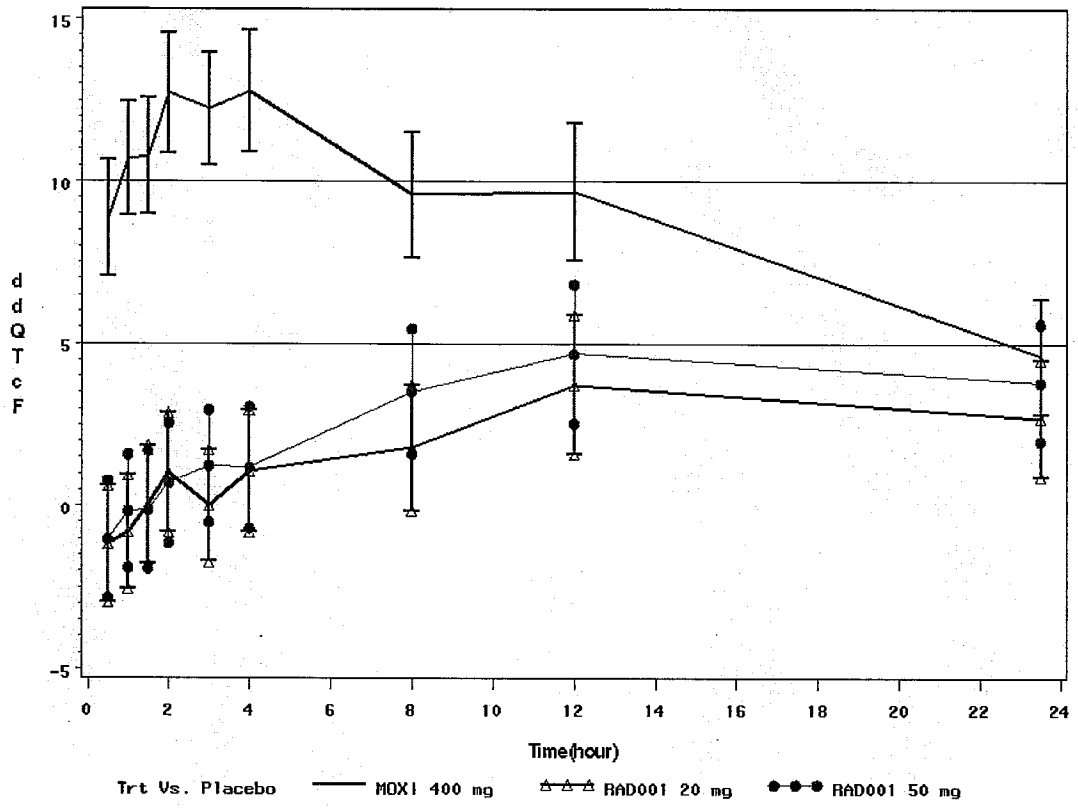
Table 8: Summary of ΔQTcF Analysis: Moxifloxacin versus Placebo (A vs. B)

Day	Time-Hour*	ΔQTcF		Treatment Difference: ΔΔQTcF		
		TRT: A	TRT: B	Estimate	S.E.	90% CI
1	0.5	5.20	–3.67	8.87	1.08	(7.08, 10.66)
	1	7.71	–2.98	10.69	1.06	(8.94, 12.43)
	1.5	8.09	–2.68	10.78	1.09	(8.97, 12.58)
	2	10.14	–2.58	12.71	1.12	(10.87, 14.56)
	3	8.81	–3.41	12.22	1.04	(10.50, 13.94)
	4	9.46	–3.30	12.76	1.14	(10.88, 14.64)
	8	3.12	–6.46	9.58	1.17	(7.65, 11.52)
	12	9.09	–0.58	9.67	1.29	(7.54, 11.80)
	23.5	3.58	–1.02	4.60	1.08	(2.81, 6.38)

* Post-dose

The time course of ΔΔQTcF for the study drug RAD001 and moxifloxacin is displayed in Figure 4.

Figure 4: ΔΔQTcF for RAD001 and Moxifloxacin



5.2.2 5.2.2 Categorical analysis

Two out of fifty-nine (<4%) subjects had their ΔQTcF over 30 ms. Details are provided in Table 9.

Table 9: Abnormal change from baseline QTcF

Subject ID	Treatment	Day	Time	ΔQTcF
0101_20022	Placebo	1	0.5h	b(4)
0101_20118	Moxifloxacin	1	2h	

All subjects had their QTcF below 450 ms.

5.2.3 PR Analysis

The change from baseline in PR at each time point was analyzed. The RAD001 (20 mg and 50 mg) was compared with placebo. The analysis was performed on all time points using analysis of covariance model, including sequence, treatment, period, and subject, where subject-within-sequence was treated as a random effect. The results are summarized in Table 10 and Table 11.

Table 10: Summary of ΔPR Analysis: RAD001 20 mg versus Placebo (C vs. B)

Day	Time-Hour*	Mean ΔPR		Treatment Difference: ΔΔPR		
		TRT: C	TRT: B	Estimate	S.E.	90% CI
1	0.5	0.67	0.07	0.60	0.89	(–0.86, 2.07)
	1	1.64	–0.11	1.75	0.89	(0.27, 3.22)
	1.5	0.75	1.15	–0.40	0.89	(–1.87, 1.08)
	2	0.72	0.05	0.66	0.88	(–0.79, 2.11)
	3	0.01	–1.59	1.60	0.95	(0.03, 3.17)
	4	0.50	–1.06	1.56	0.95	(–0.01, 3.12)
	8	–1.07	–2.12	1.06	0.91	(–0.45, 2.56)
	12	–0.10	–1.03	0.93	1.02	(–0.76, 2.61)
	23.5	0.86	1.98	–1.12	0.98	(–2.73, 0.50)

* Post-dose

Table 11: Summary of ΔPR Analysis: RAD001 50 mg versus Placebo (D vs. B)

Day	Time-Hour	Mean ΔPR		Treatment Difference: ΔΔPR		
		TRT: D	TRT: B	Estimate	S.E.	90% CI
1	0.5	0.85	0.07	0.78	0.89	(–0.68, 2.25)
	1	0.75	–0.11	0.86	0.89	(–0.61, 2.34)
	1.5	0.22	1.15	–0.93	0.89	(–2.41, 0.55)
	2	0.78	0.05	0.73	0.88	(–0.72, 2.18)
	3	–0.36	–1.59	1.23	0.95	(–0.34, 2.80)
	4	–0.47	–1.06	0.58	0.95	(–0.98, 2.15)
	8	–2.72	–2.12	–0.60	0.92	(–0.45, 2.56)
	12	–1.09	–1.03	–0.06	1.02	(–1.74, 1.62)
	23.5	0.93	1.98	–1.04	0.98	(–2.67, 0.58)

* Post-dose

5.2.4 QRS Analysis

The change from baseline in QRS at each time point was analyzed. The RAD001 (20 mg and 50 mg) was compared with placebo. The analysis was performed on all time points using analysis of covariance model, including sequence, treatment, period, and subject, where subject-within-sequence was treated as a random effect. The results are summarized in Table 12 and Table 13 below. Single oral doses of RAD001 20 and 50 mg had no clinically relevant effect on QRS.

Table 12: Summary of ΔQRS Analysis: RAD001 20 mg versus Placebo (C vs. B)

Day	Time-Hour	Mean ΔQRS		Treatment Difference: ΔΔQRS		
		TRT: C	TRT: B	Estimate	S.E.	90% CI
1	0.5	–0.66	0.17	–0.83	0.34	(–1.40, –0.26)
	1	–0.21	0.65	–0.86	0.37	(–1.47, –0.25)
	1.5	–0.48	–0.01	–0.47	0.35	(–1.05, 0.11)
	2	–0.37	0.00	–0.38	0.40	(–1.15, 0.03)
	3	–0.34	0.22	–0.56	0.36	(–0.43, 0.89)
	4	–0.27	–0.50	0.23	0.40	(–1.01, 0.36)
	8	–0.63	–0.30	–0.32	0.41	(–1.01, 0.36)
	12	0.37	–0.30	0.66	0.41	(–0.02, 1.34)
	23.5	–0.31	0.14	–0.45	0.44	(–1.17, 0.27)

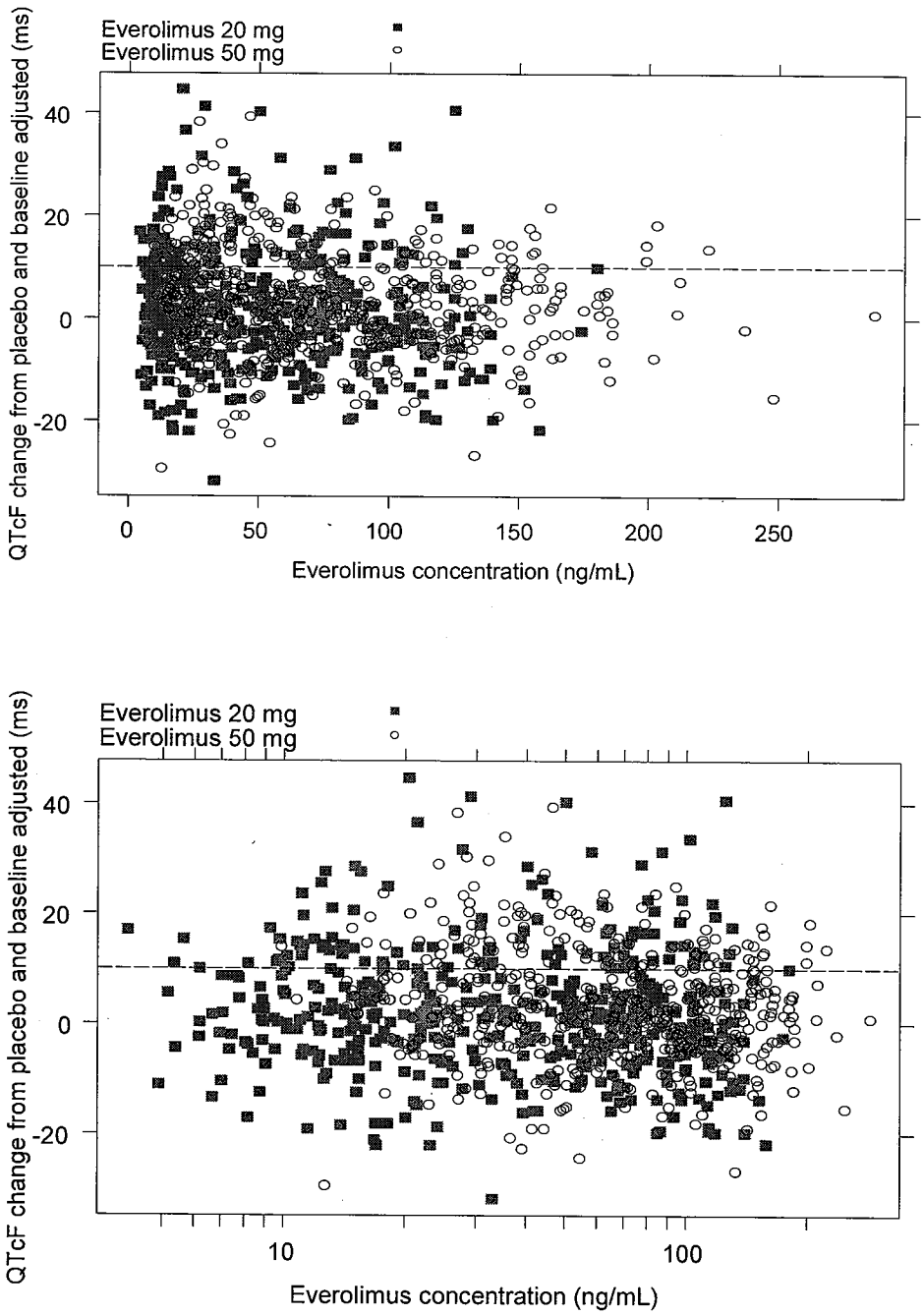
Table 13: Summary of ΔQRS Analysis: RAD001 50 mg versus Placebo (D vs. B)

Day	Time-Hour	Mean ΔQRS		Treatment Difference: ΔΔQRS		
		TRT: C	TRT: B	Estimate	S.E.	90% CI
1	0.5	0.33	0.17	0.15	0.34	(–0.41, 0.72)
	1	0.05	0.65	–0.59	0.37	(–1.21, 0.02)
	1.5	–0.04	–0.01	–0.03	0.35	(–0.61, 0.55)
	2	–0.04	0.00	–0.04	0.40	(–0.71, 0.63)
	3	0.22	0.22	0.00	0.36	(–0.58, 0.59)
	4	–0.17	–0.50	0.32	0.40	(–0.33, 0.99)
	8	0.30	–0.30	0.60	0.41	(–0.08, 1.28)
	12	0.50	–0.30	0.79	0.41	(0.12, 1.47)
	23.5	–0.14	0.14	–0.28	0.44	(–1.00, 0.45)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

QTcF at predose was used as baseline. The relationship between ΔΔQTcF and RAD001 concentrations is visualized in Figure 5 with no evident exposure-response relationship over a dose range of 20-50 mg QD.

Figure 5. ΔΔ QTcF vs. RAD001 concentration.



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics over 96% of the ECGs were annotated in the primary lead II, with none of the ECGs reported to have significant QT bias, according to the ECG warehouse automated algorithm. Overall, ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There were no clinically significant effects due to RAD001 on the PR and QRS intervals with the largest upper bound of the 90% CI of the difference compared to placebo being 3.3 ms and 1.5 ms for the PR and QRS intervals respectively.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	10 mg daily	
Maximum tolerated dose	The phase 1 program was not designed to determine the maximum tolerated dose. RAD001 was in general well tolerated at daily doses up to 10 mg and weekly doses up to 70 mg.	
Principal adverse events	The commonest dose limiting adverse event in Phase 1 monotherapy studies was Grade 3 mucositis. Other dose limiting adverse events in these studies were Grade 3 fatigue, hyperglycemia and neutropenia. The most common adverse events occurring in >10% of patients in the placebo controlled study C2240 (irrespective of relationship) were stomatitis, anemia, asthenia, fatigue, rash, diarrhea, cough, anorexia, nausea, dyspnea, edema peripheral, pyrexia, constipation, vomiting, mucosal inflammation, hypercholesterolemia, headache, epistaxis, dry skin, pruritus and hypertriglyceridemia [SCS-Table 2-6]. The frequencies of the most common AEs seen with everolimus were consistent between study C2240 and the pooled dataset [SCS-Table 2-8].	
Maximum dose tested	Single Dose	50 mg single oral dose in healthy subjects using the oncology tablet [Study C2118] 4 mg single oral dose in healthy subjects using the transplant tablet [Study W105]
	Multiple Dose	10 mg daily and 70 mg weekly oral dose in oncology patients using the oncology tablet [Study C2102 CP report]
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean ± SD (%CV) C_{max} and AUC [Study W105]: 4 mg single oral dose in healthy subjects (n=4) C_{max} = 43.1 ± 5.3 ng/mL (CV = 12.4%) $AUC_{0-\infty}$ = 373 ± 112 ng.h/mL (CV = 30%) [Study C2118]: single 50 mg oral dose in healthy subjects (n=61) C_{max} = 159.71 ± 39.51 ng/mL (CV = 24.7%)
	Multiple Dose	Mean ± SD (%CV) C_{max} and $AUC_{0-\tau}$ [Study C2102 CP report] 70 mg weekly oral dose in oncology patients (n=6) C_{max} = 174 ± 49 ng/mL (CV = 28.5%) $AUC_{0-\tau}$ = 3616 ± 1496 ng.h/mL (CV = 41.4%) 10 mg daily oral dose in oncology patients (n=6) C_{max} = 61.1 ± 17.5 ng/mL (CV = 28.6%) $AUC_{0-\tau}$ = 514 ± 231 ng.h/mL (CV = 45.0%)
Range of linear PK	Daily schedule: C_{max}: 5 to 10 mg; AUC: 5 to 10 mg Weekly schedule: C_{max} 5 to 10 mg, AUC: 5 to 70 mg	
Accumulation at steady state	Mean ± SD (%CV); specify dosing regimen [Study C2240] (10 mg daily, n =12): Day 15/Day 1 $AUC_{0-\tau}$ ratio = 1.65 ± 0.31 (CV = 18.8%)	

<table>
<tr><td>Metabolites</td><td colspan="2">
<table>
<tr><th>Major peaks</th><th>Compound</th><th>Human, 3 mg a) AUC_{0-24h} (ng-eq•h/mL)</th><th>In vitro pharmaco-logical activity b) IC50 (nM)</th></tr>
<tr><td>P36</td><td>PKF229-255</td><td>21</td><td>213</td></tr>
<tr><td>P40</td><td>PKF226-320</td><td>33</td><td>98</td></tr>
<tr><td>P42</td><td>46-OH-RAD</td><td>63</td><td>369</td></tr>
<tr><td>P50</td><td>24-/25-OH-RAD</td><td>62</td><td>55</td></tr>
<tr><td>P57</td><td>ATG181 b</td><td>28</td><td>108</td></tr>
<tr><td>PD</td><td>RAD001 (ref.)</td><td>199</td><td>2.1</td></tr>
</table>
a): 3 mg 14C-radiolabeled everolimus per patient [Study W107]
b): in vitro T-cell immune response assay (mixed lymphocyte reaction (MLR) assay)
The concentrations of the main metabolite peaks declined roughly in parallel to RAD001 with the exception of metabolite peak P57. The half-life of P57 (determined from the time-interval of 8-24h) was approximately 3 times shorter than the corresponding half-lives of P42 and P50, respectively.
</td></tr>
<tr><td>Absorption</td><td>Absolute/Relative Bioavailability</td><td>Absolute bioavailability data are not available.
Absorption is approximately 11% or higher based on radioactivity data in the human ADME study [Study W107]</td></tr>
<tr><td></td><td>Tmax</td><td>• Median (range) for parent
Median (range) T_{max} in oncology patients [Study C2102 CP report]
Dose — T_{max} (h)
5 mg daily (n=4) — 1 (1-1)
10 mg daily (n=6) — 1 (1-6)
5 mg weekly (n=4) — 1 (1-2)
10 mg weekly (n=4) — 1(1-1)
20 mg weekly (n=2) — 1(1-1)
30 mg weekly (n=5) — 1 (1-2)
50 mg weekly (n=5) — 1 (1-2)
70 mg weekly (n=6) — 1 (1-1)
• Median (range) for main metabolites
data are provided in Attachment 1</td></tr>
<tr><td>Distribution</td><td>Vd/F or Vd</td><td>Mean ± SD (CV%) Vd/F in oncology patients (calculated from raw data in [Study C2102 CP report])
Weekly dose — Vd/F (L)
5 mg (n=4) — 678 ± 54 (CV = 8.0%)
10 mg (n=4) — 1031± 238 (CV = 23.0%)
20 mg (n=2) — 926 ± 30 (CV = 3.2%)
30 mg (n=5) — 989 ± 415 (CV = 42.0%)
50 mg (n=5) — 790 ± 296 (CV = 37.5%)
70 mg (n=6) — 820 ± 282 (CV = 34.4%)</td></tr>
<tr><td></td><td>% bound</td><td>Mean ± SD (%CV) protein binding in plasma [Study A2303]
74 ± 2% (CV = 3%)</td></tr>
<tr><td>Elimination</td><td>Route</td><td>• Primary route; percent dose eliminated
After a single dose of ^{14}C-everolimus in transplant patients, 85% of total radioactivity was excreted in feces (80%) and urine (5%) over a 10-day collection period. Parent drug was not detected in feces or urine [Study W107].
• Other routes</td></tr>
</table>

		None
	Terminal t½	• Mean ± SD (%CV) for parent drug Mean ± SD (%CV) T1/2 in oncology patients after weekly administration [Study C2102 CP report] Weekly dose T1/2 (h) 5 mg (n=4) 26.3 ± 2.9 (CV = 11.2%) 10 mg (n=4) 38.8 ± 14.7 (CV = 38.0%) 20 mg (n=2) 32.0 ± 8.6 (CV = 26.9%) 30 mg (n=5) 36.2 ± 5.0 (CV = 13.9%) 50 mg (n=5) 27.2 ± 6.5 (CV = 24.0%) 70 mg (n=6) 26.0 ± 2.8 (CV = 10.8%) • Mean (%CV) for metabolites data are provided in Attachment 1
	CL/F or CL	Mean ± SD (CV%) CL/F in oncology patients [Study C2102 CP report]: Dose CL/F (L/h) 5 mg daily (n=4) 23.6 ± 10.6 (44.8%) 10 mg daily (n=6) 26.2 ± 20.4 (77.8%) 10 mg daily (n=5)[a] 18.0 ± 4.6 (25.6%) 5 mg weekly (n=4) 18.1 ± 3.7 (20.3%) 10 mg weekly (n=4) 21.8 ± 13.5 (61.8%) 20 mg weekly (n=2) 20.9 ± 6.3 (30.0%) 30 mg weekly (n=5) 19.1 ± 7.8 (40.8%) 50 mg weekly (n=5) 20.1 ± 5.5 (27.4%) 70 mg weekly (n=6) 21.6 ± 7.1 (32.8%) [a] excluding one patient who had a very high CL/F value of 66.9 L/h [Study C2240] (10 mg daily dose, n=12) CL/F = 15.4 ± 5.3 L/h (CV = 34.3%)
Intrinsic Factors	Age	No significant influence of age (27-85 years) was detected on CL/F in a population PK analysis in patients with advanced cancer [RAD001 Modeling Report Population PK]. In the population PK analysis in transplant patients [CP Study B251 – Attachment 2] age was a statistically significant covariate on CL/F (0.33 % reduction in CL/F per year) in the age range of 16 to 70 years. However, the age effect on CL/F is not considered clinically significant.
	Sex	No significant influence of gender was detected on CL/F of RAD001 based on population PK analysis in patients with advanced cancer [RAD001 Modeling Report Population PK] and in transplant patients [CP Study B251-Attachment 2].
	Race	No significant difference in CL/F was detected in Asians in a population PK analysis in transplant patients, whereas Blacks had in average 20% higher CL/F than non-black. [CP Study B251-Attachment 2]. Japanese and Non-Japanese healthy subjects had similar AUC vs dose and Cmax vs dose relationships [meta-analysis report]. CL/F are similar in Japanese and Caucasian cancer patients with similar liver functions [Study C2102 CP report], [Study C1101].
	Hepatic & Renal	Hepatic impairment [Study A2303]

	Impairment	dose = 2 mg single oral dose Liver function Normal Moderate impaired n 8 8 C_{max} (ng/mL) 15.4 ± 8.6 11.7 ± 4.3 AUC (ng.h/mL) 114 ± 45 245 ± 91 No significant influence of creatinine clearance (25-178 mL/min) was detected on CL/F in a population PK analysis in patients with advanced cancer [RAD001 Modeling Report Population PK]. In a Phase 2 study in transplant patients [CP Study B157], CL/F was not significantly correlated with creatinine clearance (11-107 mL/min).
Extrinsic Factors	Drug interactions	Listing of studied DDI studies with mean changes in C_{max} and AUC provided in Attachment 2
	Food Effects	Effects of high-fat breakfast (44.5 g fat) on PK of RAD001 [Study W302] after single 2 mg dose using the transplant tablet Fasting Fed Ratio (90%CI) (Fed to Fasting) C_{max} (ng/mL) 17.9 ± 5.9 7.1 ± 2.0 0.40 (0.35-0.46) AUC (ng.h/mL) 122 ± 52 97 ± 19 0.84 (0.74-0.95)
Expected High Clinical Exposure Scenario	RAD001 has been demonstrated to be generally well tolerated at weekly doses up to 70 mg with a mean C_{max} of 174 ng/mL and a mean $AUC_{0-\tau}$ of 3616 ng.h/mL (range: 2163-6467 ng.h/mL). A potential worst case scenario is one in which the patient might accidentally take double the recommended dose by ingesting 10 mg tablets rather than 5 mg tablets. This would result in an exposure of 20 mg daily dose and should be covered by the C_{max} and AUC of the 70 mg weekly dose. Another worst case scenario is the administration of the 10 mg daily dose in patients with moderate hepatic impairment. The exposure of RAD001 in patients with moderate hepatic impairment is expected to be twice as much as in patients with normal liver function. The exposure of RAD001 in this case scenario should be covered by the 70 mg weekly dose. The recommended daily dose of RAD001 for patients with moderate liver dysfunction in the proposed label is 5 mg. Additional worst case scenarios include the concomitant administration of moderate or potent CYP3A4 and/or moderate or potent P-glycoprotein inhibitors. Moderate CYP3A4 and/or moderate P-glycoprotein inhibitors may increase C_{max} by 2 fold and AUC by up to 4.4 fold. This increase in exposure should be covered by the C_{max} and AUC of the 70 mg weekly dose. The concomitant administration of potent CYP3A4 and/or potent P-glycoprotein inhibitors may increase C_{max} and AUC of RAD001 by 4 fold and 15 fold, respectively. This increase in exposure may not be covered by the C_{max} and AUC of the 70 mg weekly dose. However, it is clearly stated in the label for RAD001 that concomitant administration of potent inhibitors of CYP3A4 and/or P-glycoprotein should be avoided.	

Attachment 1

Listing of all main metabolites and their T_{max}, $T_{1/2}$, and in vitro pharmacological activity

Major peaks	Compound	Human, 3 mg a) AUC_{0-24h} (ng-eq•h/mL)	T_{max} (h)	Estimated half-life of elimination (h)	In vitro pharmaco-logical activity b) IC50 (nM)

P36	PKF229-255	21	2	≤ 33	213
P40	PKF226-320	33	2	≤ 33	98
P42	46-OH-RAD	63	3	≤ 33	369
P50	24-/25-OH-RAD	62	3	≤ 33	55
P57	ATG181 b	28	2	~10	108
PD	RAD001 (ref.)	199	1.5	33	2.1

a): 3 mg ^{14}C-radiolabeled everolimus per patient [Study W107]

b): in vitro T-cell immune response assay (mixed lymphocyte reaction (MLR) assay)

Attachment 2:

Effects of CYP3A4 and P-glycoprotein inhibitors/inducers on the C_{max} and AUC of RAD001 in healthy subjects

Study	RAD dose	Tested drug	Tested drug properties	Change in C_{max} (ratio of comb. to RAD001 alone)	Change in AUC (ratio of comb. to RAD001 alone)
A2409	1 mg	ketoconazole	Potent CYP3A4 and PgP inhibitor	3.94 (3.35-4.64)	15.0 (13.6-16.6)
A2408	2 mg	erythromycin	Moderate CYP3A4 inhibitor and PgP inhibitor	2.01 (1.75-2.31)	4.35 (3.49-5.43)
A2410	2 mg	Verapamil		2.27 (1.93-2.68)	3.49 (3.11-3.91)
A2304	2 mg	Neoral 175 mg	CYP3A4 substrate and PgP inhibitor	1.82 (1.63-2.04)	2.68 (2.22-3.24)
A2304	2 mg	Sandimmun 300 mg		1.06 (0.88-1.27)	1.74 (1.49-2.04)
W303	2 mg	Atorvastatin 20 mg sd	CYP3A4 substrate	0.91 (0.75-1.1)	0.95 (0.77-1.18)
A2302	4 mg	Rifampin 600 mg qd	CYP3A4 inducer and PgP inducer	0.42 (0.36-0.50)	0.37 (0.30-0.46)
W303	2 mg	Pravastatin 20 mg sd	Non-CYP3A4 substrate	0.90 (0.76-1.06)	0.94 (0.79-1.12)

Effects of other anti-cancer drugs on the Cmax and AUC of RAD001 in cancer patients

Study	RAD001 dose	Tested drug	Tested drug properties	Change in RAD C_{max}	Change in RAD AUC
C2101	20 mg QW	Gemcitabine 600 mg/m^2 QW	Deaminated in plasma by cytidine deaminase	1.16 (0.97-1.39)	1.18 (0.83-1.67)
C2104	15 & 30 mg qw	Paclitaxel 80 mg/m^2/week	Substrate of CYP2C8 and CYP3A4	No apparent change	

6.2 TABLE OF STUDY ASSESSMENTS

Assessments	Screening	Period 1				Period 2				Period 3				Period 4			End of Study
Visit no.	1	2	3	4	Washout	5	6	7	Washout	8	9	10	Washout	11	12	13	16
Day	−28 to −2	−2	−1	1	2 – 15	13	14	15	16 – 29	27	28	29	30 – 43	41	42	43	44
Confinement		−12 h	BL 24 h	Dose +24 h		−12 h	BL 24 h	Dose +24 h		−12 h	BL 24 h	Dose +24 h		−12 h	BL 24 h	Dose +24 h	
Demography / informed consent	X																
Inclusion/exclusion criteria	X																
Relevant medical history & current medical conditions	X	X															
Vital signs, height, weight (height and weight only at screening)	X			X				X				X			X		X
Physical examination	X		X				X				X				X		X
Screening labs	X																X
Safety labs			X	X[1]			X	X[1]			X	X[1]			X		X
Hepatitis/HIV screen	X																
Alcohol test	X		X				X				X				X		
Drug screen	X		X				X				X				X		
Pregnancy test	X		X				X				X				X		X
Cardiac enzymes	X		X	X[1]				X[1]				X[1]					X
Drug administration record				X				X				X				X	
Safety ECG (standard 12-lead)	X		X	X			X	X			X	X			X	X	X
Holter monitoring			X	X			X	X			X	X			X	X	
PK/blood sampling				X				X				X				X	X
Prior/concomitant medications	X	X															X
Adverse events		X															X
Study completion information																	X

[1] Blood samples were drawn under fasting conditions 24 hours post-dose (on Days 2, 16, 30 and 44).
HIV = human immunodeficiency virus; BL = baseline; ECG = electrocardiogram; PK = pharmacokinetic

Source: Sponsors Table 9-5 from CSR, Visit evaluation Schedule-Part 2

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joanne Zhang
11/14/2008 01:02:47 PM
BIOMETRICS
Dr. Kallappa Koti was the primary statistical reviewer for the TQT study report.

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11/14/2008 01:06:33 PM
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