CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-334

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	22-334
Submission Date:	27 June 2008
Brand Name:	Afinitor®
Generic Name:	everolimus
Formulation:	5 mg and 10 mg tablets
OCP Reviewer:	Julie M. Bullock, Pharm.D.
Pharmacometrics Reviewer:	Nitin Mehrotra, Ph.D.
OCP Team Leader:	Brian Booth, Ph.D.
Pharmacometrics Team Leader:	Christoffer Tornoe, Ph.D.
OCP Division:	Division of Clinical Pharmacology 5
ORM Division:	Division of Drug Oncology Products
Sponsor:	Novartis
Submission Type; Code:	Original NDA; 000
Dosing regimen:	10 mg once daily
Indication:	treatment of advanced renal cell carcinoma

OCP Briefing held on February 19, 2009 attended by: Amna Ibrahim, Pengfei Song, Ramana Uppoor, Phil Colangelo, Jun Yang, Aakanksha Khandelwal, Sarah Schrieber, Nam Atiqur Rahman, Gil Burckart, Rosane Charlab-Orbach, Gerlie Gieser, Qi Liu, Chris Tornoe, Ping Zhao, Lillian Zhang, Anthony Murgo, Ellen Maher, Qin Ryan, Partha Roy.

Table of contents

List of Tables

List of Figures

1 EXECUTIVE SUMMARY

Everolimus is an inhibitor of the human kinase mammalian target of rapamycin (mTOR). The current submission is the original NDA for everolimus for the treatment of advanced renal cell carcinoma (RCC). Everolimus has also been evaluated under two NDAs for transplant indications.

To support the efficacy in advanced renal cell carcinoma, the sponsor conducted one randomized, controlled phase 3 study. Patients in the phase 3 study were randomized to receive best supportive care plus placebo or 10 mg of everolimus daily. Progression free survival was the primary endpoint and the median PFS for the everolimus treatment arm ranged from 3.71 to 5.52 months compared to 1.87 months for patients receiving placebo.

Everolimus is a CYP3A4 substrate. Multiple drug-drug interaction studies were conducted under the NDAs for the transplant indications. Based on the results from the drug-drug interaction studies with ketoconazole, erythromycin and verapamil no dose adjustments will be provided in the label since the increases in everolimus exposures can not be adjusted by lowering the dose to 5 mg QD. For strong CYP3A4 inducers, a dose increase to 20 mg would compensate for the decrease in everolimus exposure. For strong CYP3A4 inhibitors because of the significant increase in exposure labeling instructions co-administration is not recommended. Currently, for moderate CYP3A4 inhibitors generic [redacted] tatements will be proposed until the sponsor can develop a 2.5 mg dose for market. b(4)

A study in patients with normal hepatic function and patients with moderate hepatic impairment supported the labeling recommendation of a 50% dose reduction for patients with moderate hepatic impairment. Patients with severe hepatic impairment have not been studied and that everolimus should not be used in this patient population.

The IRT review of the thorough QT study suggested that everolimus has a low potential to prolong the QT interval. IRT proposed labeling has been added to the package insert.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 22-334. This NDA is considered acceptable from a clinical pharmacology perspective.

Post Marketing Requirements

1. A study in patients with severe hepatic impairment.
2. Make available a 2.5 mg formulation.

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations

Reviewer: Julie M. Bullock, Pharm.D.	Deputy Director & Acting Team Leader: Brian Booth, Ph.D.

Cc: DDOP: CSO - C Cottrell; MTL - E Maher; MO - Q Ryan
DCP-5: Reviewers - J Bullock, N Mehrotra; PM TL - C Tornoe; Acting TL & DDD - B Booth; DD - A Rahman

1.2 CLINICAL PHARMACOLOGY SUMMARY

Everolimus is a derivative of rapamycin which acts as a signal transduction inhibitor. It targets mTOR (mammalian target of rapamycin), which regulates protein synthesis and cell growth, cell proliferation, angiogenesis and survival. Everolimus is being developed for oral use in the treatment of advanced renal cell carcinoma (RCC). Prior to it's development for RCC, everolimus has been under investigation as an immunosuppressant for transplantation under NDA [redacted] (allogeneic kidney transplant) and NDA 21-628 (allogeneic heart transplant). b(4)

The applicant has conducted several phase 1 studies in healthy volunteers, transplant patients, patients with solid tumors and patients with advanced renal cell carcinoma to evaluate the safety and pharmacokinetics of everolimus. The Tmax of everolimus typically occurs 1-2 hours following oral administration the concentrations of everolimus decreased over time with a half-life of approximately 39 hours after a single 10 mg oral dose. The AUC of everolimus is dose proportional over the dose range of 5 – 70 mg. Cmax rose in a roughly dose-proportional manner from 5 to 10 mg/week, but increased less than dose-proportionally at doses of 20 mg and higher. There are no significant differences between the pharmacokinetics in healthy volunteers and patients. A high-fat meal decreased AUC of everolimus by 16%.

After administration of radio-labeled everolimus in transplant patients, approximately 80% of the total radioactivity was eliminated in the feces. No parent drug was detectable in urine and feces, indicating metabolism was the main clearance mechanism of everolimus. Following oral administration, everolimus is the main circulating component in human blood. Six metabolites of everolimus have been detected in human blood, these metabolites were also identified in animal species used in toxicity studies. These metabolites and showed approximately 100-times less activity than everolimus itself. A hepatic impairment study in patients with moderate hepatic impairment showed that the average AUC was twice that found in patients with normal hepatic function. A 50% dose reduction for patients with moderate hepatic impairment is recommended.

Everolimus is a substrate of CYP3A4 and p-glycoprotein (p-gp). Drug-drug interaction studies indicate a 62% reduction in everolimus exposure (AUC), when administered with rifampin. Coadministration of everolimus with three different CYP3A4 inhibitors (ketoconazole, erythromycin, verapamil) increased the exposure (AUC) of everolimus over the range of 1371 to 124%. *In vitro* everolimus inhibited CYP3A and 2D6, however, based on Ki values a significant effect on the metabolism of CYP3A or 2D6 is not expected. Everolimus was not found to induce any cytochrome P-450 enzymes *in vitro.*

Results from two phase 1 studies in patients with advanced solid tumors were used to support dose selection and dose-response. These studies investigated the biochemical activity of everolimus based on a biomarker (p70 ribosomal S6 kinase 1 inhibition). A near complete inhibition of S6 phosphorylation in both skin and tumor samples at doses of 10 mg/day and 50 mg/week led to the recommendation that these doses should be explored further. The 10 mg/day dose was further evaluated in multiple phase 2 trials and was determined to have the desired anti tumor activity and safety profile for use in the phase 3 trial.

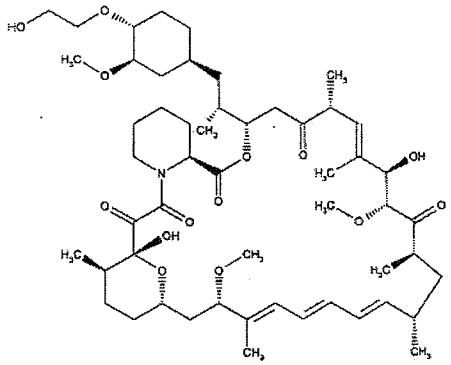
2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Physico-chemical properties

1. Structural formula:



2. Established name: everolimus
3. Molecular Weight: 958.25 g/mol
4. Molecular Formula: $C_{53}H_{83}NO_{14}$
5. Chemical Name: (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R),-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.0^{4,9}]-hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Everolimus is a signal transduction inhibitor targeting mammalian target of rapamycin (mTOR), an enzyme that regulates cell growth, proliferation, angiogenesis and survival. The proposed indication is for the treatment of advanced renal cell carcinoma.

2.1.3 What are the proposed dosage and route of administration?

The sponsors proposed dose of everolimus is 10 mg once daily at the same time every day b(4)

The labeling will recommend that everolimus should be taken at the same time every day

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Clinical Pharmacology Studies

Multiple clinical pharmacology studies conducted for the transplant indication were submitted to support part of the clinical pharmacology of everolimus for treatment of advanced renal cell

b(4)

carcinoma and all of these studies have been reviewed previously by Dr. Jang-Ik Lee under NDAs [redacted] & 21-628. Portions of theses trials listed in TABLE 1 will be used to support labeling for the oncology indications.

b(4)

TABLE 1. clinical pharmacology studies using the transplant tablets in healthy volunteers and transplant patients.

Study	Study population	Design
W107	renal transplant	ADME study. Single 3 mg radiolabeled dose of everolimus administered simultaneously with Neoral®
W303	healthy subjects	DDI study. atorvastatin (CYP3A4 substrate), pravastatin (non-CYP3A4 substrate)
A2302	healthy subjects	DDI study. Rifampin (CYP3A4 and p-gp inducer)
A2304	healthy subjects	DDI study. Cyclosporine (CYP3A4 substrate, Pgp inhibitor)
A2408	healthy subjects	DDI study. Erythromycin (moderate CYP3A4 inhibitor, Pgp inhibitor)
A2409	healthy subjects	DDI study. Ketoconazole (CYP3A4 inhibitor)
A2410	healthy subjects	DDI study. Verapamil (moderate CYP3A4 inhibitor, Pgp inhibitor)
W302	healthy subjects	Food effect study.
A2301	healthy subjects	Relative BA of transplant tablets.
B2303	healthy subjects	hepatic impairment study.

To support the clinical pharmacology and dose finding of everolimus in patients with advanced renal cell carcinoma the sponsor submitted multiple studies in cancer patients and healthy volunteers (TABLE 2).

TABLE 2. Clinical pharmacology studies using the oncology tablets in healthy volunteers and patients with cancer

Study	Study Population	Design
C2101 Part 1	solid tumors	Phase 1, dose finding, open label trial. Part 1: 8 cohorts receiving either weekly regimens (5, 10, 20, 30, 50, 70 mg) or daily regimens (5 and 10 mg) over a 4-week period.
C2102	solid tumors	Phase 1 dose finding study of monotherapy RAD001 given at 5, 10, 20, 30, 50, and 70 mg weekly or 5 and 10 mg QD.
C2107	solid tumors	Phase 1, non-randomized, open label. Daily (5 and 10 mg) and weekly (20, 50, 70 mg)
C1101	solid tumors	Phase 1, open-label, dose-escalation study of everolimus administered on a continuous once-daily schedule (2.5, 5, and 10 mg daily) in adult Japanese patients.
C2118	healthy subjects (females)	Phase 1 cardiac safety with everolimus 20 mg, 50 mg, moxifloxacin, and placebo.
C2119	healthy subjects	Phase 1 bioequivalence of a single 10 mg dose of RAD001 administered as either 5 mg market formulation (MF) tablet, 5 mg final market image (FMI) tablet or 10 mg FMI tablet

Additional phase 1 and 2 studies were conducted but do not pertain to the advanced renal cell carcinoma indication. These studies will mostly be used for intrinsic factor covariate analysis and safety.

TABLE 3. Phase 1 and 2 studies of everolimus for other cancer indications.

Study	Study Population	Design
C2101 Part 2	solid tumors	Part 2: Gemcitabine drug-drug interaction evaluation
C2106	prostate cancer	phase 1 optimal dose study for prostate cancer (weekly and daily doses).
C2104	solid tumors	Phase 1 everolimus (15 and 30 mg weekly) in combination with paclitaxel therapy.
C2108	breast cancer	Phase 1b in postmenopausal women with metastatic or loco regionally recurring breast cancer. Everolimus 5, 10 mg QD or 30 mg weekly + letrozole 2.5 mg QD.
C2207	Ph+ CML	Phase 1, everolimus (2.5 or 5 mg QD) in combination with imatinib at 600 or 800 mg/day.
C2222	breast cancer	Phase 2 double-blind, placebo-controlled, multi-center. Patients received daily administration of either everolimus 10 mg + letrozole 2.5 mg or placebo + letrozole 2.5 mg for 4 months prior to undergoing breast conserving surgery or mastectomy.
C2235	NSCLC	Phase 2, non-randomized, open label, multi-center study with 10 mg QD everolimus.
C2239	pancreatic neuroendocrine tumor	Phase 2 expanded two-stage, single-arm study. Patients received everolimus 10 mg QD or everolimus 10 mg QD + Sandostatin LAR® Depot.

Pivotal Study

Study C2240 was a randomized, double-blind, placebo controlled, phase 3 study in advanced renal cell carcinoma patients.

Eligible patients were enrolled in a 2:1 fashion to receive one of the following treatments:

- Everolimus 10 mg QD + best supportive care
- Placebo + best supportive care.

The primary efficacy endpoint was progression free survival (PFS). Of the 410 patients randomized, 272 were in the everolimus group and 138 were in the placebo group. At the time of the interim analysis the median progression-free survival (based on central radiological review) was 4.01 months in the everolimus group (95% CI, 3.71 to 5.52 months) and 1.87 months in the placebo group (95% CI, 1.81 to 1.94 months). On 25 February 2008 the independent data monitoring committee recommended stopping the study early due to the statistically significant efficacy results favoring everolimus treatment. All sites with patients receiving placebo were notified on 28 February 2008 to cross these patients over to open-label everolimus.

The most commonly occurring ($\geq$ 10%) adverse events related to everolimus treatment were: stomatitis, rash, fatigue, anemia, asthenia, diarrhea, anorexia, nausea, mucosal inflammation, hypercholesterolemia, cough, vomiting, and dry skin.

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Biomarkers

mTOR signaling is effected through phosphorylation of substrates p70 ribosomal S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E binding protein (4E-BP1). In a rat pancreatic tumor model, doses of everolimus that inhibited tumor growth also dramatically inhibited mTOR signaling in the tumor, skin, and peripheral blood mononuclear cells (PBMCs). In this model, decreases in p4E-BP1 were consistently observed in all three tissues. Striking reductions in pS6 were demonstrated only in tumor.

Results of an *in vitro* kinase assay using 40S ribosomal subunits as substrate, revealed a significant and consistent inhibition of S6K1 signaling in tumor, skin, and PBMCs. These factors were therefore thought to serve as biomarkers for monitoring mTOR inhibition and were

used in the dose finding trail C2107.

Clinical Endpoints

The clinical efficacy of everolimus in patients with advanced RCC has been demonstrated in the pivotal phase 3 study (C2240) and was supported by 3 dose-finding phase 1 pharmacokinetic studies in patients with advanced solid tumors. The design and endpoints from these studies are listed below in TABLE 4.

TABLE 4. Efficacy endpoints of the dose finding and efficacy trials for advanced RCC.

Study	Study design, objective, and population	Efficacy endpoints	No of patients	
			Everolimus 10 mg	Total
Pivotal, phase-III study				
[C2240]	Phase-III randomized, double-blind, placebo-controlled, efficacy and safety in patients with mRCC after failure of VEGFr-TKI therapy	Primary: PFS Secondary: ORR, OS, QoL	272	410
Dose selection trials				
[C2101 Part 1/ C2102]	Phase-I dose-escalation study in patients with advanced solid tumors	ORR	33	92
[C2107]	Phase-I investigation of safety, tolerability, and molecular pharmacodynamic effects in patients with advanced solid tumors	ORR	12	55
[C1101]	Phase-I dose-escalation study in Japanese patients with advanced solid tumors	ORR, PFS	3	9

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Please refer to Section 2.6 Analytical.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Preliminary PK-PD studies suggested that concentrations between 10-35 ng/ml are needed in order for everolimus to effect downstream effectors. The reviewer, divided the trough concentrations from the available patients into quartiles and performed a Kaplan Meier analysis (with four quartiles as different strata) to assess the exposure response for efficacy based on progression free survival. The survival curves of patients in different concentration-quartile groups were not significantly different (see FIGURE 1). However, the drug clearly seems to be effective as all the four survival curves for treatment were well differentiated from the placebo group.

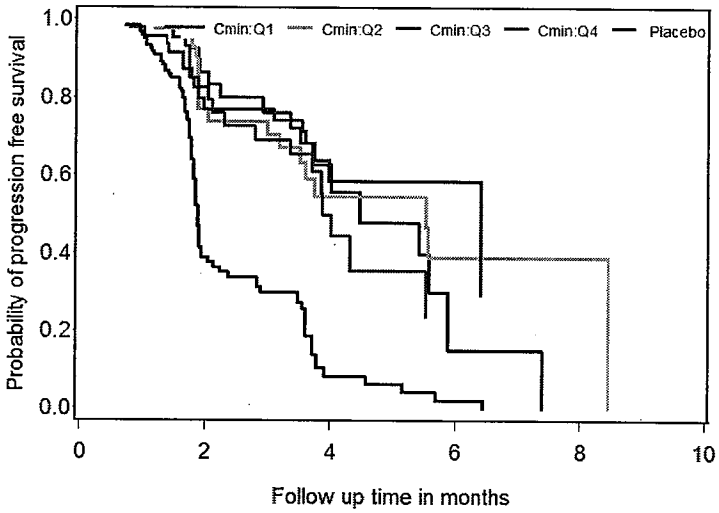


FIGURE 1. Kaplan Meier plots for progression free survival for placebo and treatment groups. Q1, Q2, Q3 and Q4 are quartiles based on steady state trough concentrations.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

To assess the exposure-safety relationship, the patients for whom the trough concentrations were available from the pivotal trial (C2240) were divided into quartiles and % subjects having adverse events were plotted against each quartile. Adverse events to be assessed were selected based on the clinical relevance and after discussion with the medical reviewer. GI disorders and, skin and subcutaneous infections were two of the most common adverse events observed. However, there was no trend observed in case of either of the adverse events (FIGURE 2).

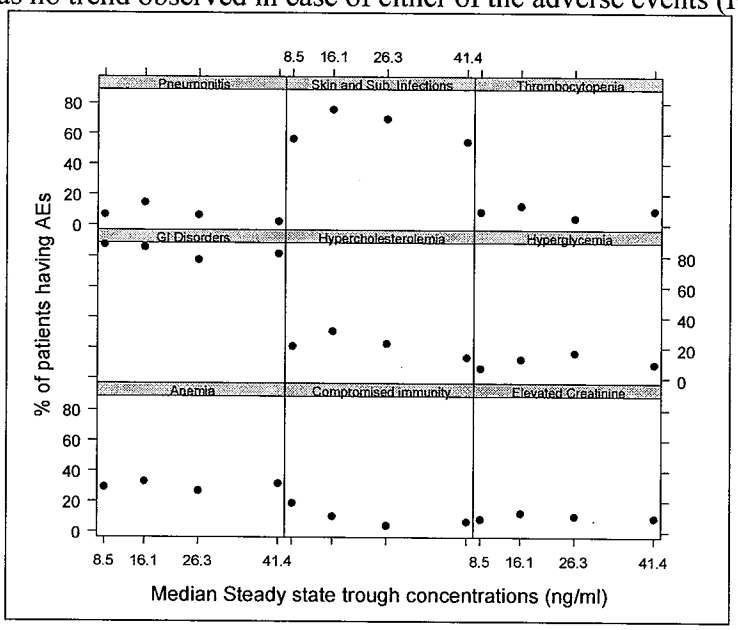


FIGURE 2. Percent adverse events in the four C_{trough} quartiles. The concentration ranges are 1.4-12.4, 12.5-19, 1.1-30.6 and 30.7 to 135 ng/ml for 1, 2, 3 and 4, respectively.

2.2.4.3 Does this drug prolong the QT or QTc interval?

A thorough QT (TQT) study was conducted and reviewed by the IRT. The TQT study was a single-dose, randomized, blinded (everolimus versus placebo), 4-period crossover study in 59 healthy volunteers. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, indicating that the assay sensitivity of the study was established. The results from the IRT analysis are below:

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.

The upper bound 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.

For more details please see the posted IRT review in DFS by Dr. Joanne Zhang. The IRT had labeling recommendations which can be found in Section 3 – Detailed labeling recommendations.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

An oral dose of 10 mg everolimus daily is proposed by the sponsor based on safety data from multiple trials and efficacy data from the phase 3 comparator trial. During the phase 1 trial (C2101) peripheral blood mononucleocyte (PBMC) derived p70 S6 kinase 1 (S6K1) activity was analyzed following 5 – 30 mg weekly doses. S6K1 is a primary downstream target of mTOR which functions in G1 of the cell-cycle, through phosphorylation of the 40S ribosomal protein S6, to increase the translation of mRNAs largely encoding ribosomal proteins and other elements of the translational machinery. Through inhibition of mTOR function, rapamycin blocks these essential translational events resulting in inhibition of G1 progression and contributes to the antiproliferative activity of everolimus.

Inhibition of the S6K1 in PBMCs was observed 24 hrs after everolimus administration and evidence of dose-dependent effects on the recovery of PBMC-derived S6K1 activity was observed by the sponsor. As S6K1 activity in PBMCs was found to be sufficiently inhibited for at least 7 days at a 20-mg weekly dose, this was considered to be a suitable starting dose for subsequent trials.

In study C2107, the pharmacodynamic effects of everolimus were determined in patients with

advanced tumors receiving weekly (20, 50, or 70 mg) or daily (5 or 10 mg) administration of everolimus. The downstream PD markers [total (T) and phosphorylated (P)] of 4E-BP1, S6, eIF-4G in tumor tissues and skin samples were assessed. The daily regimen was associated with a high inhibition of phosphorylation of S6 and eIF-4G at both 5 mg/day and 10 mg/day. In patients on the weekly schedule, inhibition of phosphorylation of S6 was complete and sustained at all dose levels while that of eIF-4G was completed and sustained at 50 mg/week but not at 20 mg/week.

The sponsor also performed PK-PD modeling using biomarker data (S6K1) to select the optimum dosing regimen. Model based simulations suggested that a 20-30 mg weekly dose would be associated with an anti-tumor effect and that daily administration (10 mg QD) would exert greater effect than doses of 50 or 70 mg given weekly.[1,2,3]

The molecular results from these two studies led to the recommendation to explore doses of 10 mg/day. The multiple phase 2 studies supported the safety and efficacy of this chosen dose.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose and multiple dose PK parameters?

Phase 1 – solid tumors

The sponsor combined the once-weekly (QW) and daily (QD) dosing data from 36 patients from two phase 1 trials in cancer patients (C2102 and C2101) to characterize the pharmacokinetic parameters of everolimus. In the first part of these phase 1 studies, everolimus was administered without chemotherapy in sequential cohorts at escalating doses of 5, 10, 20, and 30 mg/week (QW). Additional dose levels of 50 and 70 mg/week and 5 and 10 mg/day (QD) were added to the dose escalation in study C2101.

Pre-dose blood samples were obtained in Weeks 2, 3, 4 and 5 with a full concentration time profiles in Week 4. The full concentration time profiles obtained in Week 4 included sampling for up to 24 hours (daily administration) or 168 hours (weekly administration). There was no single dose PK obtained on Day 1 of Week 1 in either study.

Since there was no evaluation of single dose PK, the Week 4 concentration data from the QW groups was used to characterize the 'single dose' pharmacokinetic parameters. This assumes that minimal accumulation would be seen after once-weekly dosing. This assumption was confirmed from the pre-dose concentrations from the weekly cohorts in TABLE 5 (Cmin of daily administration > 5 ng/mL).

TABLE 5. Weeks 2-5 Pre-dose everolimus concentrations following 5 to 70 mg weekly doses.

	5 mg	10 mg	20 mg	30 mg	50 mg	70 mg
Number of patients	4	4	2	5	5	24
Mean ± SD	0	0.4 ± 0.4	0.4 ± 0.3	1.1 ± 1.1	0.6 ± 0.5	1.3 ± 1.3
CV%		105.5%	69.1%	99.0%	86.7%	97.3%
Median (range)	0 (0-0)	0.3 (0-0.8)	0.4 (0.2-0.6)	0.9 (0-2.9)	0.8 (0-1.2)	1.2 (0-6.5)

[1] Tabernero J, Rojo F, Calvo E, Burris, et. al. Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: a phase I tumor pharmacodynamic study in patients with advanced solid tumors. J Clin Oncol. 2008 Apr 1;26(10):1603-10.

[2] Laplanche R, Meno-Tetang GM, Kawai R. Physiologically based pharmacokinetic (PBPK) modeling of everolimus (RAD001) in rats involving non-linear tissue uptake. J Pharmacokinet Pharmacodyn. 2007 Jun;34(3):373-400.

[3] Tanaka C, O'Reilly T, Kovarik JM, et.al. Identifying optimal biologic doses of everolimus (RAD001) in patients with cancer based on the modeling of preclinical and clinical pharmacokinetic and pharmacodynamic data. J Clin Oncol. 2008 Apr 1;26(10):1596-602.

Following a single dose of everolimus, peak concentrations were seen by 1 to 4 hours post dose (FIGURE 3) and they slowly decreased over time with a half-life ranging from 25 to 39 hours. All four subjects at the 10 mg/week dose had evaluable concentrations at 264 hours (11-days) post-dose.

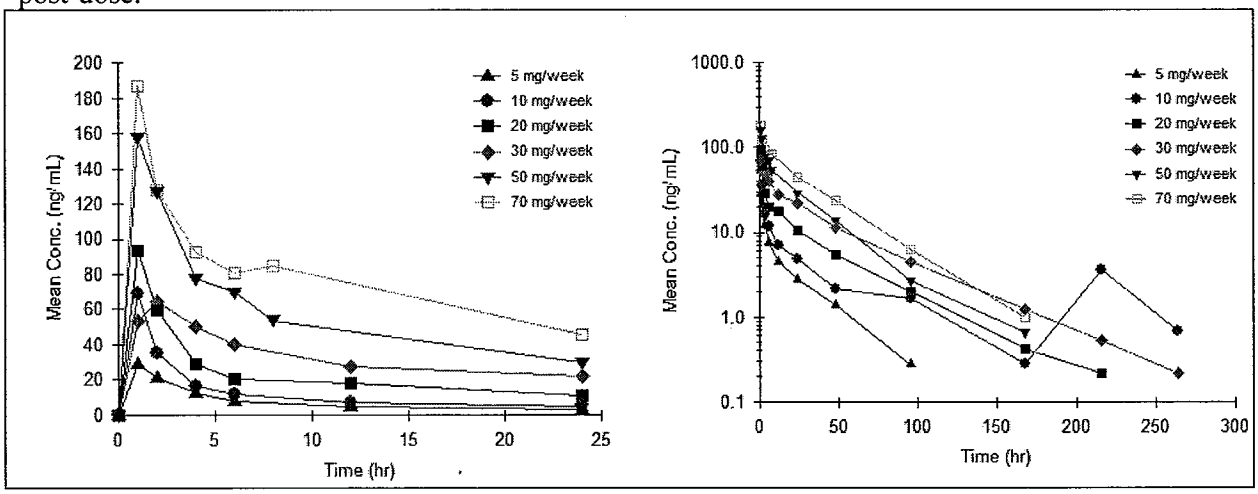


FIGURE 3. Mean week 4 everolimus vs. time concentrations (right: 24 hours; left 264 hours) for subjects with cancer who received once weekly doses.

The single and multiple dose PK parameters for 5 and 10 mg everolimus in patients with cancer are below in TABLE 6. For the single dose results, the Week 4 data from the QW schedule was analyzed by the reviewer using noncompartmental analysis (WinNonlin version 5.2) with data truncated at 24 hours (sampling in the study went to 168 hours post dose) in order to make an appropriate comparison to the multiple dose data. The multiple dose data results used the data from the 5 and 10 mg QD schedule at Week 4 (PK samples taken up to 24 hours post dose).

TABLE 6. Mean ± SD single- and multiple-dose pharmacokinetic parameters following a 5 or 10 mg oral everolimus dose in patients with cancer.

	Single-dose[a]	Multiple-dose[b]
5 mg	(N=4)	(N= 4)
Cmax (ng/mL)	32.4 ± 15.3	31.5 ± 9.4
AUC_{0-24} (ng·h/mL)	173 ± 26	255 ± 46[c]
CL/F (L/h)	21.4 ± 2.7	20.0 ± 3.5[c]
10 mg	(N=4)	(N = 7)
Cmax (ng/mL)	69.1 ± 8.1	59.7 ± 16.9
AUC_{0-24} (ng·h/mL)	296 ± 91.7	536 ± 77[d]
CL/F (L/h)	27.3 ± 13.5	19.05 ± 3.25[d]

a. Week 4 of once weekly dosing (data truncated at 24 hours)
b. Week 4 of once daily dosing
c. n = 3
d. n = 5

Comparing single and multiple dose parameters for AUC_{0-24} indicates accumulation (approx 1.5 fold) of everolimus following once-daily administration. This was expected as the mean terminal half life is 25.6 hours and 39.3 hours for the 5 mg and 10 mg QW dosing schedule, respectively.

Following daily doses of everolimus 5 or 10 mg, steady state is reached by Week 2 or earlier as the pre-dose trough concentrations collected on Weeks 2, 3, 4, and 5 were stable over time.

Average Cmin was 5.5 ± 1.6 ng/mL (CV = 29.7%) at the 5 mg daily dose and 13.7 ± 9.3 ng/mL (CV = 67.6%) at the 10 mg daily dose.

Phase 3 – Advanced Renal Cell Cancer

In the phase 3 trial (C2240), thirteen patients had full pharmacokinetic profiles obtained during Cycle 1 on Day 1 (single dose) and Day 15 (multiple dose) and the sponsor's results are listed in TABLE 7. Similar to what was seen above, accumulation is seen after multiple daily doses of everolimus. The values for AUC_{0-t} are not comparable to the values seen in solid tumor patients for both single and multiple dose everolimus. The reviewer believes the discrepancy and increased variability seen in these results is due to the lack of sampling between 5 and 24 hours in the phase 3 trial.

TABLE 7. Everolimus pharmacokinetic parameters on Cycle 1 Day 1 (single dose) and Cycle 1 Day 15 (multiple dose) in patients with advanced renal cell carcinoma receiving 10 mg QD.

	C_{max} (ng/mL)	T_{max} (h)	C_{min} (ng/mL)	AUC_{0-t} (ng.h/mL)	CL/F (L/h)	CL/F ($L/h/m^2$)
Day 1 (n = 13)	68.1 ± 29.8 (43.7%)	1 (1-2)	7.9 ± 3.4 (43.3%)	455.0 ± 168.5 (37.0%)	_	_
Day 15 (n =12)	76.7 ± 39.3 (51.2%)	1 (1-5)	19.6 ± 12.3 (61.8%)	729.1 ± 262.7 (36.0%)	15.4 ± 5.3 (34.3%)	7.5 ± 2.3 (30.1%)

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Two studies with the oncology tablet (C2118 and C2119) were conducted in healthy volunteers. Study C2118 was the QT study in healthy female subjects and Study C2119 was the relative bioavailability (BA) study.

The PK results from healthy volunteer BA study were used for comparison to pharmacokinetics in cancer patients because the sampling was long enough to characterize the elimination of everolimus. The QT study only enrolled females and PK sampling ended at 23.5 hours post-dose.

A cross study comparison was made between the single dose 10-mg data from the healthy volunteer BA study and the Week 4 QW dosing data ('single dose') from study C2101 in patients with solid tumors (see TABLE 8). There are no significant differences between pharmacokinetic parameters in healthy volunteers or patients. There is no data available at steady state in healthy volunteers.

TABLE 8. Mean ± SD single dose PK parameters of 10-mg everolimus in healthy volunteers (study C2119) and patients with cancer (C2101).

	Healthy Volunteers[a] (n = 40)	Patients[c] (n = 4)
Tmax[b] (hr)	1 (0.5 – 2.5)	1 (1)
Cmax (ng/mL)	64.4 ± 17.8	69.1 ± 8.1
AUC0-t (h ng/mL)	510.1 ± 165.8	573 ± 258
CL/F (L/hr)	20.6 ± 6.8	22.1 ± 14.1
Thalf (hr)	36.9 ± 9.5	39.3 ± 17.0

a – study C2119 2x5 mg MF arm only
b – median (range)
c – study C2101 Week 4 10 mg weekly

2.2.5.3 What are the characteristics of drug absorption?

Following administration of a single 5 to 70 mg dose the Cmax of everolimus was observed within 0.5-2 hours in patients with cancer.

2.2.5.4 What are the characteristics of drug distribution?

Ex-vivo Protein Binding

Ex-vivo protein binding of everolimus was investigated using predose serum samples and erythrocyte partitioning (Study A2303; Report DMPK(CH) R00-2228). Erythrocytes were mixed with the diluted serum and spiked with ^{3}H-everolimus to give a final concentration of 10 ng/mL ($Cmax_{ss}$ after 10 mg dose = 61.1 ng/mL). The mean percentage of ^{3}H-everolimus bound to proteins at concentrations of 10 ng/mL was 73% for patients with hepatic impairment and healthy subjects (see TABLE 9)

TABLE 9: Free fraction and bound fraction of [3H]-everolimus in serum (sponsors table)

Matched pair	Subject		Free fraction (%)		Bound fraction (%)	
	Hepatic	Healthy	Hepatic	Healthy	Hepatic	Healthy
1	5101	5109	31	23	69	77
2	5102	5110	23	25	77	75
3	5103	5111	26	30	74	70
4	5104	5112	30	27	70	73
5	5105	5113	30	26	70	74
6	5106	5114	22	24	78	76
7	5107	5115	25	28	75	72
8	5108	5116	23	29	77	71
N			8	8	8	8
Mean			26.3	26.5	73.8	73.5
SD			3.6	2.4	3.6	2.4
Median			25.5	26.5	74.5	73.5
Min			[redacted]			
Max						

Bound fraction is 100 - free fraction

b(4)

In-vitro plasma protein binding

The protein binding of everolimus was investigated *in-vitro* using serum samples from five volunteers (Study 303-044) and was reviewed previously by Dr. Jang-Ik Lee with the original 12-20-2002 transplant NDA submission (NDAs [redacted] & 21-628). He concluded that plasma protein binding is not an important factor in the disposition of everolimus and a change in the concentration of plasma proteins will not dramatically alter the free fraction.

b(4)

Blood distribution:

The blood distribution of everolimus was investigated in-vitro using serum samples from five volunteers (Study 303-044) and was reviewed previously by Dr. Jang-Ik Lee with the original 12-20-2002 transplant NDA submission (NDAs [redacted] & 21-628). Everolimus is strongly bound to human erythrocytes with an erythrocyte binding of approximately 85% at the blood concentration range of 5 - 100 ng/mL. At higher blood concentrations than 100 ng/mL, the blood cell uptake was concentration-dependent and saturable, and the ratios change rapidly with an increase in plasma concentration. b(4)

The sponsors figure below (FIGURE 4) visually depicts the concentration independence between 5-100 ng/mL and concentration dependence at concentrations > 100 ng/mL. As a consequence of the concentration dependent binding to blood cells, whole blood was used as the analytical matrix in all clinical pharmacokinetic studies.

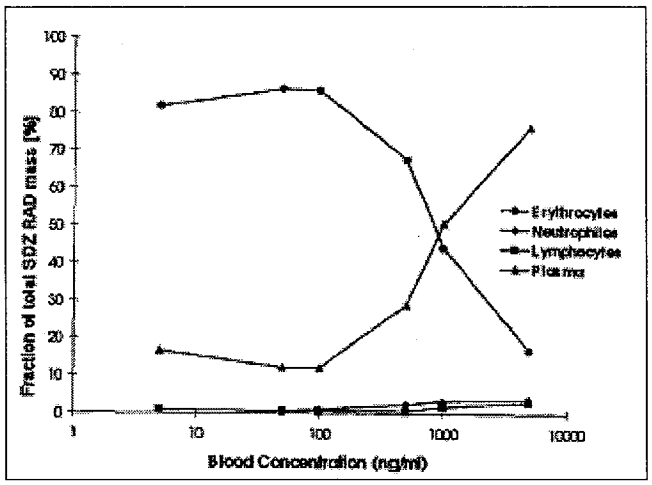


FIGURE 4: Distribution of [^{3}H]everolimus between human blood components (Sponsors figure)

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

An ADME study (Study W107) with a single dose of ^{14}C-everolimus was conducted in maintenance renal transplant patients whose immunosuppressive regimen included cyclosporine. This study included analysis of metabolites in blood urine and feces. This study was reviewed previously by Dr. Jang-Ik Lee with the original 12-20-2002 transplant NDA submission (NDAs [redacted] & 21-628). b(4)

Radioactivity was mainly excreted in feces during the collection interval of 0-240 hours: 79.5 ± 6.0 %, 5.1 ± 1.7 %, and 84.6 ± 7.3% of the administered radioactive dose were recovered in feces, urine, and total, respectively. Everolimus excretion was relatively slow: only about 30% of the radioactivity was excreted for three days after dosing. The excretion was still ongoing 10 days after dosing. No parent drug was detected in excreta, which suggests virtually complete metabolism of ^{14}C-everolimus administered.

2.2.5.6 What are the characteristics of drug metabolism?

Everolimus metabolism was investigated *in vitro* using liver microsomes of mouse, rat, money

and human (Report DMPK(CH) R00-2254) and was reviewed previously by Dr. Jang-Ik Lee with the original 12-20-2002 transplant NDA submission (NDAs [redacted] & 21-628). b(4)

Everolimus is mainly eliminated via metabolism with parent drug as the major circulating component in blood in all species. In human blood five major metabolite peaks plus parent drug were identified (see also FIGURE 5):

- PKF229-255 (P36): Ring-opened hydrolysis product of everolimus
- PKF226-320 (P40): Seco acid of everolimus
- 46-OH-RAD (P42): The 46-hydroxy metabolite of everolimus.
- 24-OH-RAD & 24-OH-RAD (P50): Two chromatographically inseparable 24- and 25-hydroxylated metabolites of everolimus.
- P57: A direct phosphatidylcholine conjugate of everolimus

These metabolites were also present in the blood of the mouse, rat, and monkey and were found to be approximately two orders of magnitude less active than everolimus itself. Hence, parent drug is considered to contribute the majority of the overall pharmacological activity of everolimus in patients.

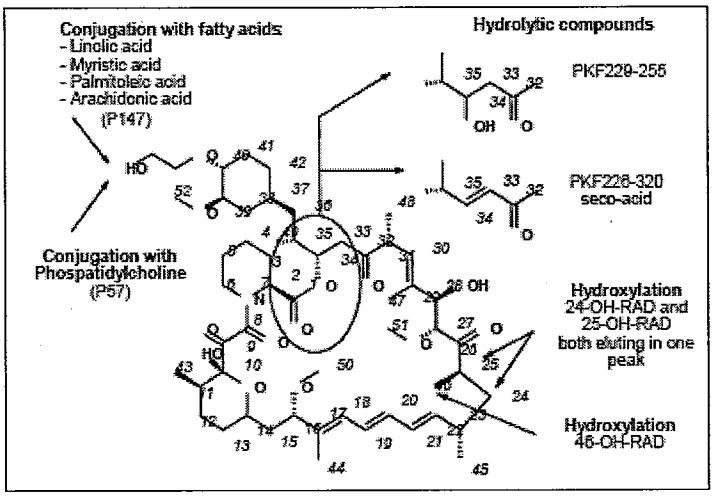


FIGURE 5: Proposed biotransformation pathways for everolimus (Sponsors figure)

An ADME study (Study W107) with a single dose of ^{14}C-everolimus was conducted in maintenance renal transplant patients whose immunosuppressive regimen included cyclosporine. This study included analysis of metabolites in blood urine and feces. This study was reviewed previously by Dr. Jang-Ik Lee with the original 12-20-2002 transplant NDA submission (NDAs [redacted] & 21-628). b(4)

Dr. Lee concluded that parent compound was the major component in blood accounting for 39.9% of the AUC of total radioactivity (TABLE 10). Mono-hydroxylated metabolites (p42 and p50) account for 25.0% of the AUC, while hydrolytic metabolites (p36 and p40) account for 10.6%. These metabolites were found to be at least two orders of magnitude less active than everolimus in a mixed lymphocyte reaction assay (see Pharmacology and Toxicology review). Rapamycin, the active metabolite, was present as a minor species accounting 1.2 % only. The parent compound and listed metabolites accounted for a total of 82.3% of the AUC.

TABLE 10. Mean ± SD and relative amounts for everolimus and metabolites in blood (taken from Dr. Lee's review)

Everolimus and Metabolites	Tmax (hr)	Cmax (pmol/mL)	AUC_{0-24} (pmol-hr/mL)	% of AUC_{0-24} of Radioactivity
PKF229-255 (p36, hydrolyzed)	2	4.5 ± 4.7	21.5 ± 12.6	4.1
PKF226-320 (p40, hydrolyzed)	2	6.3 ± 4.9	34.1 ± 8.7	6.5
46-OH-RAD (p42)	3	4.9 ± 0.6	65.7 ± 8.2	12.6
24-OH-RAD / 25-OH-RAD (p50)	3	6.8 ± 3.6	64.5 ± 13.3	12.4
Unknown (p57)	2	6.4 ± 1.7	29.3 ± 6.1	5.6
Rapamycin	2	0.8 ± 0.3	6.3 ± 0.8	1.2
Everolimus	2	33.1 ± 13.5	207.5 ± 26.3	39.9
others				17.7
Total radioactivity	2	69.3 ± 14.3	529.7 ± 54.1	100.0

According to Dr. Lee radioactivity was mainly excreted in feces during the collection interval of 0-240 hours. Approximately 79.5 ± 6.0 %, 5.1 ± 1.7 %, and 84.6 ± 7.3% of the administered radioactive dose were recovered in feces, urine, and total, respectively. Everolimus excretion was relatively slow with only about 30% of the radioactivity excreted for three days after dosing. The excretion was still ongoing 10 days after dosing. No parent drug was detected in excreta, which suggests virtually complete metabolism of 14C-everolimus administered. The metabolites in urine were hardly detectable.

In conclusion, everolimus is the main circulating component observed in human blood and is considered to contribute the majority of the overall pharmacological activity. Six main metabolites were identified in blood with only two (P42 and P50, mono-hydroxylated metabolites) compromising more than 12% of total radioactivity.

2.2.5.7 What are the characteristics of drug excretion?

Route of Elimination

Fecal excretion is the major route of elimination of everolimus. In the human ADME study the majority (79.5 ± 6.0%) of the total radioactivity was recovered in the feces during the collection interval of 0 to 240 hours. Only 5.1 ± 1.7% was recovered in the urine following the 3-mg [^{14}C]-everolimus dose.

Clearance

The mean (SD) clearance of everolimus following the daily oral doing of 10-mg was 26.2 (20.4) L/h in patients with advanced solid tumors and 20.5 (6.7) L/h in healthy subjects after a single 10-mg dose. In the of the 12 subjects with intensive PK profiles from the efficacy trial (C2240) the CL/F on Day 15 following QD 10-mg dosing was 15.4 (5.3).

Half-life

Everolimus half-life among healthy subjects and cancer patients was comparable with mean (SD) values of 36.9 (7.5) h in healthy subjects, and 30.7 (8.4) h in patients with advanced solid tumors.

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Weekly doses of 5 to 70 mg were given to patients with advanced solid tumors in study C2102. The results are below (see FIGURE 6) and indicate that Cmax rose in a roughly dose-proportional manner from 5 to 10 mg/week, but it increased less than dose-proportionally at

doses of 20 mg and higher. There were no major deviations from dose-proportionality for AUC_{0-t} in the dose range tested as evident by the regression slope of 0.97 (95% CI, 0.84-1.09) in the dose-proportionality model fitting log-AUC_{0-tau} on log-dose.

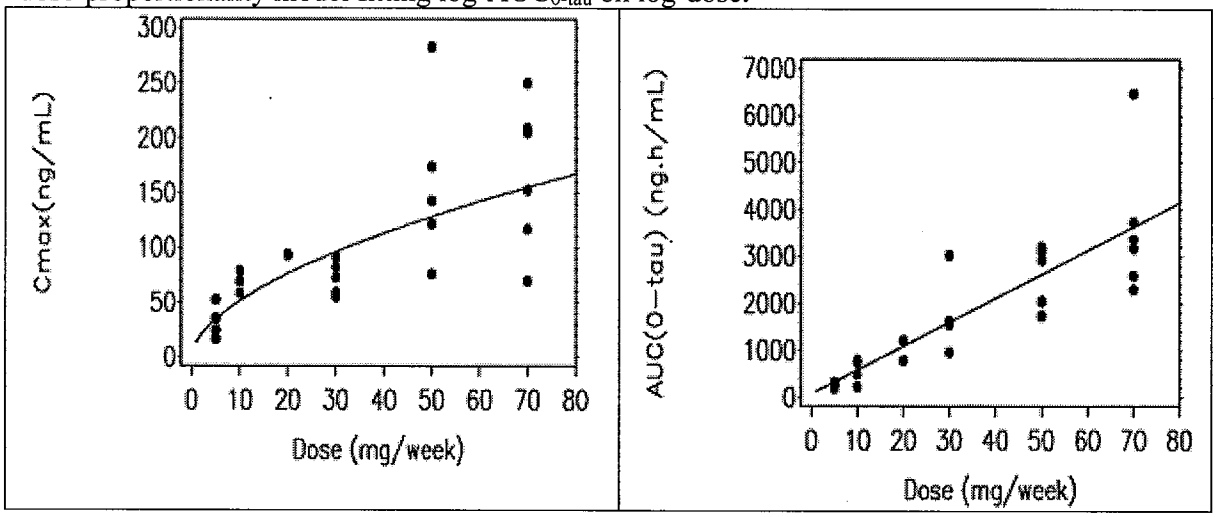


FIGURE 6: Dose proportionality of Cmax and AUC_{0-tau} for everolimus given once-weekly in patients with advanced solid tumors over the dose range of 5 to 70 mg.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

After multiple daily doses the AUC of everolimus increased and steady state was achieved before or at Week 2. Please see Section 2.2.5.1 for more information on the pharmacokinetics of everolimus following multiple doses.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Variability was similar between patients and healthy volunteers.

In healthy subjects the inter-subject variability (CV%) for Cmax ranged from 27.6% to 31.2% and for AUCs from 32.4% to 38.7%. The observed within-subject variability (CV%) of the primary PK parameters was 17% for AUC 19% for Cmax. In patients with renal cell carcinoma the inter-subject variability (CV%) was 51.2% for Cmax and 36.0% for AUC0-τ at steady-state.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Population PK analysis

The oral clearance of everolimus did not depend on age, weight or gender. Please see the population PK analysis in Section 4.2 for more details.

Race – Japanese Study

A phase 1 dose escalation study in adult Japanese patients with advanced solid tumors was conducted (C1101) in Japan. Everolimus was administered on a continuous once-daily dosing schedule with doses of 2.5, 5, and 10 mg/day. All nine enrolled patients participated in intensive 24-hour pharmacokinetic sampling on Days 1 and Day 15, and trough sampling on Days 8, 11 and 29. Following multiple daily doses accumulation was seen for both Cmax (R = 1.3-1.8) and AUC (R = 1.7-2.6). Following single doses over the dose range of 2.5 – 10 mg, exposure increased dose proportionally.

TABLE 11. Single and multiple dose pharmacokinetic parameters of everolimus in Japanese and multiple dose pharmacokinetics in Caucasian solid tumor patients.

	Japanese		Caucasian
	Single Dose	Multiple Dose	Multiple Dose
5 mg	(n = 3)	(n = 3)	(n = 4)
BSA (m^2)	-	1.6 ± 0.1	2.04 ± 0.3
AUCt (ng h/mL)	211 ± 50.0	543 ± 189	255 ± 46 [c]
Cmax (ng/mL)	31.5 ± 3.40	57.6 ± 17.6	31.5 ± 9.4
Cmin (ng/mL)	-	12.3 ± 2.8	5.48 ± 1.78
CL (L/hr)[a]	16.3 ± 3.5	9.9 ± 3.2	20.0 ± 3.5 [c]
CL (L/hr/m^2)[b]	10.6 ± 2.7	6.4 ± 2.1	10.7 ± 2.7 [c]
10 mg	(n = 3)	(n = 3)	(n = 6)
BSA (m^2)	-	1.7 ± 0.2	2.1 ± 0.2
AUCt (ng h/mL)	401 ± 51.6	711 ± 112.5	536 ± 77 [d]
Cmax (ng/mL)	49.4 ± 14.8	65.9 ± 1.4	59.7 ± 16.9
Cmin (ng/mL)	-	18.1 ± 3.9	15.6 ± 12.2
CL (L/hr)[a]	17.9 ± 3.4	14.3 ± 2.2	19.0 ± 3.2 5 [d]
CL (L/hr/m^2)[b]	10.8 ± 3.4	8.8 ± 2.6	9.1 ± 1.1 5 [d]

a – CL (L/hr) = Dose (mg) ÷ AUCt (ng hr/mL)
b – CL (L/hr/m^2) = CL (L/hr) ÷ BSA (m^2)
c. n = 3
d. n = 6

The multiple dose data from study C2101 (5 and 10 mg QD) in Caucasian solid tumor patients was used to compare PK differences between Caucasians and Japanese subjects. Similar to Caucasian subjects, everolimus in Japanese subjects was rapidly absorbed with a time to maximum blood concentration of 1-2 hours post dose. However, overall exposure was higher in the Japanese subjects compared to Caucasians (see FIGURE 7).

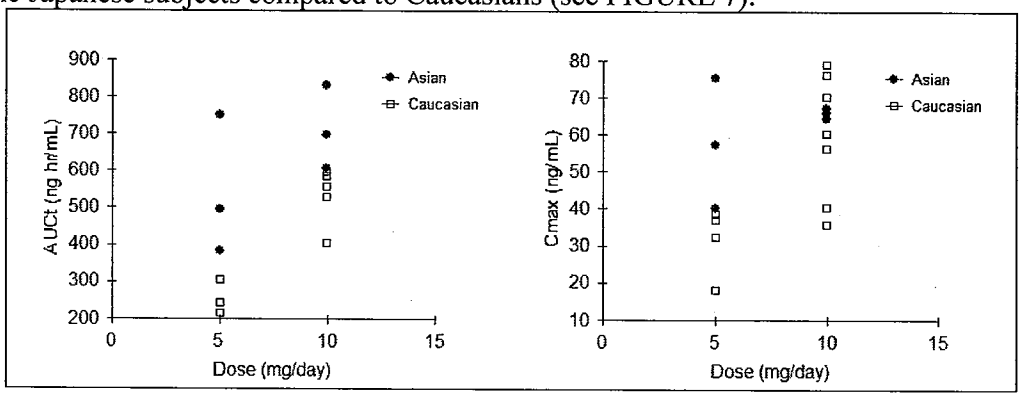


FIGURE 7. Everolimus AUCt and Cmax versus dose for Asian (Japanese) and Caucasian subjects with solid tumors.

Slower clearance values (9-14 L/hr) were seen for Japanese compared to Caucasian patients who

had clearance values ranging from 17-24 L/hr across the dose range. When normalized for BSA clearance was still higher in Caucasians for the 5 and 10 mg daily doses were 10.7 and 9.1 L/hr/m^2 compared to 6.4 and 8.8 L/hr/m^2 in Japanese subjects, respectively.

The sponsor concluded that the difference in clearance between Japanese and Caucasian patients could be explained by the different liver functions between the two groups. However, upon further graphical analysis the reviewer could not discern any trends with CL/F and various laboratory function tests (see FIGURE 8) that would explain that the difference in exposure between the patient groups would be due to liver function.

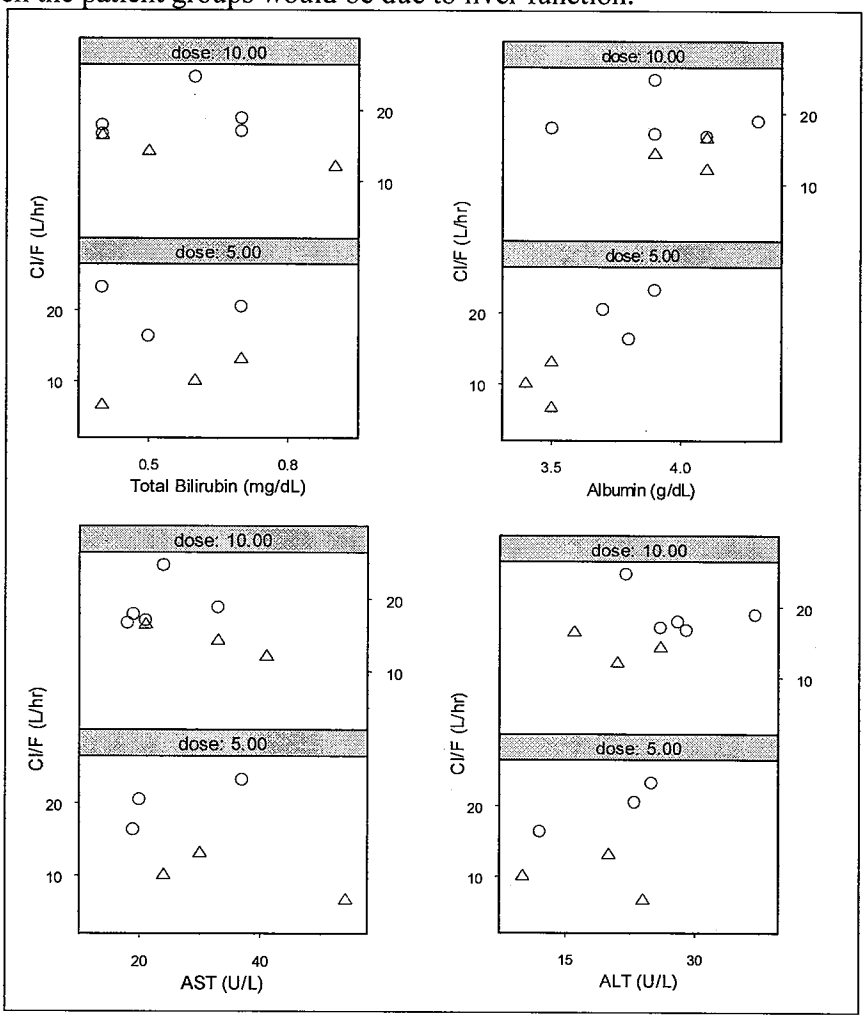


FIGURE 8. Multiple dose CL/F versus various liver function parameters for 5 and 10 mg everolimus in Caucasian (blue circles) and Japanese (red triangles) patients with solid tumors.

In conclusion, there was a trend for Japanese patients to have higher exposures compared to their Caucasian counterparts. Due to the small patient numbers for both groups, the clinical relevance of this trend is not known. Based on the population PK study, clearance of everolimus did not appear to be different between Asians and Caucasians. However, since only 11 of 398 patients in the POP PK dataset were of Asian origin, the power to affirm an absence of effect of race (Caucasian/Asian) on clearance is low. In addition it is not possible to discern from the available

data if exposure would be different in Japanese Americans all Asian Americans.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Pediatric patients

Pediatric studies were conducted with an oral solution using the transplant tablets in pediatric transplant patients. Since a pediatric indication is not being sought at this time, the studies were not reviewed.

2.3.2.2 Renal impairment

There was no effect of renal function on the clearance of everolimus (see FIGURE 9). Given that 5% of a dose of everolimus is eliminated renally, adjustments for renal impairment do not appear necessary.

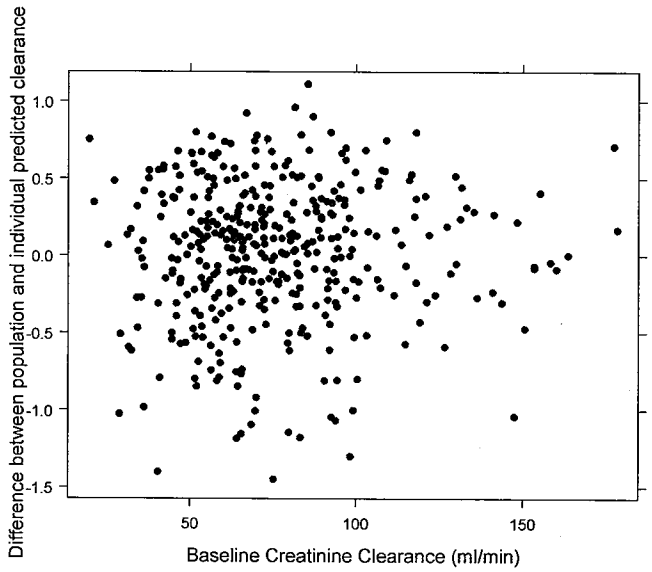


FIGURE 9. No effect of baseline creatinine clearance on oral clearance of everolimus.

2.3.2.3 Hepatic impairment

Dedicated study

A study was conducted under the transplant NDA in healthy patients and patients with moderate hepatic impairment (A2303). The patients in this study with hepatic impairment were classified using the Child-Pugh system (score between 7 and 9). All subjects received a single 2 mg dose of everolimus using the transplant formulation. This study was reviewed previously by Dr. Jang-Ik Lee with the original 12-20-2002 transplant NDA submission (NDAs [redacted] & 21-628). b(4)

Dr. Lee concluded patients with moderate hepatic impairment (Child-Pugh score between 7 and 9) had significantly lower everolimus elimination compared with the healthy subjects that were

matched for sex, age (± 5 years), weight (± 10%), and height (± 5 cm, Study A2303). The hepatically impaired patients had higher mean AUC, lower mean CL/F, and longer mean t1/2 by 115% (245 ± 91 versus 114 ± 45 ng-hr/mL), 47% (9.1 ± 3.1 versus 19.4 ± 5.8 L/hr), and 36 hr (43 versus 79 hours, Table 12). The differences in mean Cmax (11.7 ± 4.3 versus 15.4 ± 8.6, p = 0.32) and Vz,b/F (936 ± 301 versus 1219 ± 593, p = 0.19) were not statistically significant. The median Tmax was not different.

TABLE 12. Effect of moderate hepatic impairment on everolimus pharmacokinetic parameters following a single dose of 2 mg (taken from Jang-Ike's review)

Everolimus PK Parameter	Matched Healthy Controls (n = 8)	Patients with Hepatic Impairment (n = 8)	Difference	p-value
Tmax (hr)*	0.5 (0.5-2.0)	0.5 (0.5-1.1)		
Cmax,b (ng/mL)	15.4 ± 8.6	11.7 ± 4.3	-24%	0.32
AUCb (ng-hr/mL)	114 ± 45	245 ± 91	+115%	0.01
CLb/F (L/hr)	19.4 ± 5.8	9.1 ± 3.1	-47%	0.01
Vz,b/F (L)	1219 ± 593	936 ± 301	-23%	0.19
$t_{1/2}$ (hr)	43 ± 18	79 ± 42	+36 hr	0.04

* mean (median)

In addition, according to Dr. Lee's review the everolimus AUCb was positively correlated with total bilirubin levels (r = 0.857, p = 0.0001), negatively correlated with albumin levels (r = 0.717, p = 0.002), and positively correlated with prothrombin time with borderline significance (r = 0.492, p = 0.053). The fractions of ^{3}H-everolimus bound to plasma proteins were comparable (73.8 ± 3.6 % *versus* 73.5 ± 2.4 %) between the hepatic patients and matched controls.

In the transplant NDA review a 50% dose reduction was suggested by Dr. Lee for patients with moderate hepatic impairment. In the current proposed label for RCC the sponsor proposed a 5 mg/day dose for patients with moderate hepatic impairment (Child Pugh class B). In addition it is stated that patients with severe hepatic impairment have not been studied and that everolimus should not be used in this patient population. The reviewer agrees with the sponsors proposed labeling recommendations.

Population PK analysis

Since the hepatic impairment study did not include mild hepatically impaired individuals, an attempt was made to see if something informative could be obtained using population modeling. However, since most of the patients enrolled in the studies had normal hepatic function with levels of biomarkers (total bilirubin or serum albumin) in the normal range, not much could be gathered about mild hepatic impairment. As evident from FIGURE 10 given the narrow range of total bilirubin and serum albumin in the dataset, there was no effect of hepatic impairment observed on clearance of everolimus.

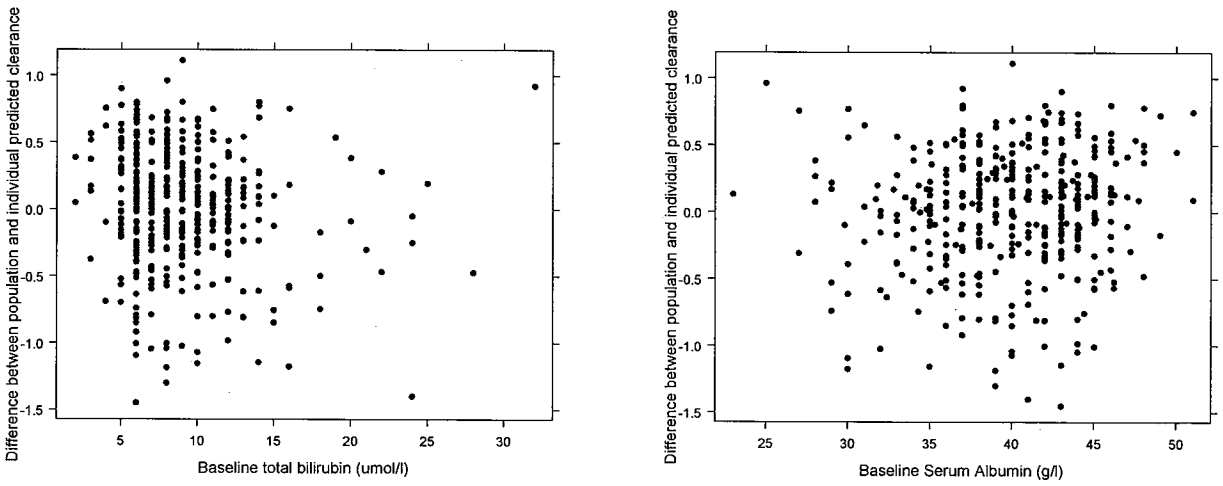


FIGURE 10. No effect of hepatic function ((Left) total bilirubin and (Right) serum albumin) on oral clearance of everolimus.

2.3.2.4 What pregnancy and lactation use information is there in the application?

No data regarding the excretion of everolimus in the milk of humans or animals was provided.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

There were no specific studies or analyses designed to evaluate the effects of factors such as herbal products, diet, smoking or alcohol use on the PK or PD of everolimus.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. Everolimus is a substrate of CYP3A4 and p-glycoprotein. It is also an inhibitor of p-glycoprotein.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

The in-vitro metabolism studies for everolimus in human liver microsomes (Report DMPK(US)1998/005; Report DMPK(CH)R99-2448) were reviewed previously by Dr. Jang-Ik Lee with the original 12-20-2002 transplant NDA submission (NDAs [redacted] & 21-628). b(4)

Conclusions from his review are as follows:

- Compounds known to inhibit CYP3A metabolism also inhibited everolimus metabolism.
- CYP3A substrates inhibited everolimus metabolism at concentrations at which they are known to inhibit competitively. Most relevant were cyclosporine, tacrolimus, rapamycin, ketoconazole, and lovastatin.

- Itraconazole strongly inhibited everolimus metabolism with IC50 of 0.18 ± 0.11 μM. However, fluconazole up to 2 μM did not significantly inhibit everolimus metabolism. Therefore, comedication of everolimus with fluconazole rather than ketoconazole or itraconazole may be considered appropriate.
- Metabolic profiles were comparable when everolimus was incubated with microsomes from cells expressing specifically CYP3A4.
- Everolimus metabolism was not detectable when everolimus was incubated with microsomes from cells expressing CYPs other than CYP3A4 including 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A5.

In conclusion, everolimus is a substrate of CYP3A4. Drugs which are inhibitors or inducers of 3A4 may alter everolimus exposure.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

***In vitro* inhibition**

The *in vitro* inhibition studies for everolimus in human liver microsomes (Report DMPK(US)1998/005) were reviewed previously by Dr. Jang-Ik Lee with the original 12-20-2002 transplant NDA submission (NDAs ——— & 21-628). b(4)

Dr. Lee concluded that everolimus competitively inhibited cyclosporine (CYP3A) metabolism and was a mixed inhibitor of dextromethorphan O-demethylation (CYP2D6). At concentrations up to 200 μM (192 μg/mL), everolimus had no effect on CYP1A2 and CYP2E1 as indicated by the lack of effect on phenacetin and chlorzoxazone metabolism. Using paclitaxel, tolbutamide and S-mephenytoin as probes, everolimus had little or no effect on CYP2C8, CYP2C9, and CYP2C19, respectively.

In conclusion, *in vitro* everolimus inhibited CYP3A and 2D6 with Ki values of 2.3 μM (2200 ng/mL) and 1.7 μM (1600 ng/mL), respectively. Since the everolimus Cmax measured following an oral dose of 10 mg was approximately 61 ng/mL (0.063 μM), a significant effect on the metabolism of CYP3A or 2D6 is not expected based on I/K_i values of 0.02 and 0.03, respectively. In addition there was no significant inhibition of 1A2, 2EI, 2C8, 2C9 or 2C19.

***In vitro* induction**

There was no evaluation *in vitro* in hepatocytes of the induction capability of everolimus.

In a 26-week oral toxicity study in rats at doses of 0.15, 0.5 and 1.5 mg/kg/day, minor changes were noted for rat CYP2B1/2 level (20% reduction compared to control) and for the rate of total metabolite formation (38%-50% increase). There were no significant alterations in the total liver cytochrome P450 content and in the CYP1A1, CYP3A and CYP4A levels.

In clinical studies, pre-dose blood concentrations of everolimus collected on Weeks 2, 3, 4, and 5 during daily administration of 5 or 10 mg everolimus were stable over time. This provides an indication of the absence of relevant induction on human drug metabolizing liver enzyme by everolimus on its own metabolism (CYP3A4).

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

The effect of p-glycoprotein (p-gp) and *in vitro* permeability was determined using human intestinal Caco-2 cell monolayers (Report DMPK(CH)1997/417) and were reviewed previously

by Dr. Jang-Ik Lee with the original 12-20-2002 transplant NDA submission (NDAs [redacted] & 21-628). b(4)

These incubations were performed for 2 hours at 37°C with everolimus administered in the apical (A→B) or basolateral (B→A) compartment and results and are listed below in TABLE 13. Verapamil (100 μM) a P-gp inhibitor, significantly increased the amount of everolimus that permeated across the monolayers in the A→B and decreased the amount that permeated across the monolayers in the B→A . The net flux ratio of everolimus in the presence of verapamil approximately 1.2 which is significantly reduced compared to the net flux ratio of everolimus alone (20-22). This suggests that everolimus is a P-gp substrate.

TABLE 13: Permeability Coefficient (P_{eff}) of everolimus in Caco-2 monolayers.

everolimus (uM)	P_{eff} (A to B), x 10^{-6} (cm/sec)	P_{eff} (B to A), x 10^{-6} (cm/sec)	(B to A) / (A to B) Ratio
0.2	1.63 ± 0.32	33.2 ± 1.72	20
1	2.03 ± 0.17	45.0 ± 0.08	22
+ 100 μM verapamil	≈ 23	≈ 18	1.2

Inhibition of P-glycoprotein activity by everolimus (up to 25 μM) was done with functional flow cytometry assays (Report DMPK R0700777) using fluorescent markers which are known p-gp substrates (Rho123). RAD001 inhibited Pgp with an IC50 value of 9.42 ± 0.49 μM. Cyclosporin A (CsA), a potent p-gp inhibitor was used as a control to ensure assay functionality. As seen below in FIGURE 11, 10 μM CsA was a more potent inhibitor (average cell florescence 225) than everolimus 25 μM (average cell florescence 143).

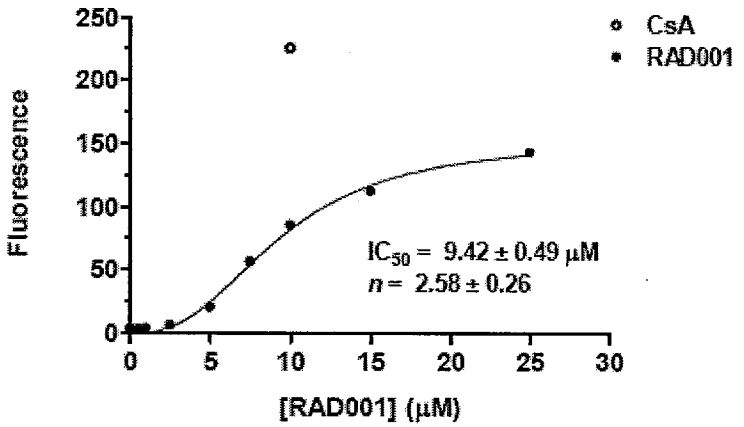


FIGURE 11: Inhibition of Rho123 efflux by RAD001

CsA has been found to inhibit p-gp mediated Rho123 efflux with an IC50 value of 1.5 μM, therefore everolimus is estimated to be a less potent p-gp inhibitor than CsA with respect to IC50 values.

In conclusion, everolimus is a p-glycoprotein substrate and a moderate p-gp inhibitor.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

None have been identified.

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

The label does not specify co-administration of another drug.

2.4.2.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Everolimus is a substrate of CYP3A4 and p-glycoprotein (p-gp). Absorption and elimination of everolimus may be influenced by drugs which inhibit or induce CYP3A4 and/or p-gp.

Everolimus is a moderate inhibitor of p-gp, a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6 *in vitro*. Everolimus was not found to induce any cytochrome P450 enzymes *in vitro*. Below in TABLE 14 is a outline of all the drug-drug interaction studies conducted under the everolimus transplant NDA and the oncology NDA.

TABLE 14: Drug-Drug interaction studies

Study	CYP450/P-gp classification	Tablets/Patient	Results
ketoconazole	3A4 strong inhibitor	1-mg transplant tablet healthy volunteers	everolimus: AUC ↑1371%; Cmax ↑ 288%
rifampin	3A4 strong inducer	1-mg transplant tablet healthy volunteers	everolimus: AUC ↓ 62%; Cmax ↓ 59%
erythromycin	3A4 moderate inhibitor	1-mg transplant tablet healthy volunteers	everolimus: AUC ↑ 351%; Cmax ↑ 102%
verapamil	p-gp inhibitor 3A4 moderate inhibitor	1-mg transplant tablet healthy volunteers	everolimus: AUC ↑ 240%; Cmax ↑ 124%
atorvastatin	3A4 substrate	1-mg transplant tablet healthy volunteers	atorvastatin: AUC ↔; ↑ Cmax 11%
cyclosporine	3A4 substrate, p-gp substrate *transplant co-med*	1-mg transplant tablet transplant patients	not reviewed.
sandostatin LAR	*oncology co-med in pancreatic NET*	5 mg oncology tablet pancreatic NET	combination for different indication. not reviewed
gemcitabine	*oncology co-med*	5 mg oncology tablet advanced solid tumors	combination not relevant to current NDA. not reviewed
paclitaxel	3A4 substrate; p-gp substrate *oncology co-med*	5 mg oncology tablet advanced solid tumors	combination not relevant to current NDA. not reviewed
letrozole	*oncology co-med*	5 mg oncology tablet advanced breast cancer	combination not relevant to current NDA. not reviewed
imatinib	*oncology co-med*	5 mg oncology tablet chronic myelogenous leukemia	combination not relevant to current NDA. not reviewed

CYP3A4 substrate – atorvastatin

A study with 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors "statins" was conducted under the transplant NDAs (W303). This study was conducted because

statins are commonly prescribed in transplant practice since elevations in blood cholesterol and triglycerides are common side effects of administration of rapamycin-class drugs and cyclosporine. An increased risk of myalgia as well as rhabdomyolysis has been reported after the concomitant use of some statins with drugs which are substrates and potent inhibitors of CYP3A4 and/or inhibitors of P-glycoprotein transport. Since everolimus was found to be an inhibitor of CYP3A4 and a moderate inhibitor of p-gp in vitro the sponsor conducted a study with the CYP3A4 substrate atorvastatin

The results from study W303 with atorvastatin and pravastatin was reviewed previously by Dr. Jang-Ik Lee with the original 12-20-2002 transplant NDA submission (NDAs [redacted] & 21-628). b(4)

From Dr. Lee's review the concomitant single oral dose of atorvastatin 20 mg or pravastatin 20 mg slightly decreased everolimus exposure following a single oral dose of 2 mg (TABLE 15). The respective mean Cmax of everolimus was reduced by 9% or 10% following atorvastatin or pravastatin coadministration. For everolimus AUC in both cases, the lower 90% confidence bounds were slightly outside the bioequivalence interval. There was no apparent change in the mean t1/2 or median Tmax.

TABLE 15. Effect of atorvastatin or pravastatin on everolimus PK (taken from Dr. Lee's Review)

Everolimus PK Parameter		Baseline	With Statin	Geometric Mean Ratio	90% CI
Atorvastatin	Tmax (hr)	0.5 (0.5 - 1.5)	0.5 (0.5 - 1.0)*		
	Cmax,b (ng/mL)	17.1 ± 4.0	16.4 ± 6.6	0.91	**0.75** - 1.10
	AUCb (ng-hr/mL)	120 ± 37	118 ± 46	0.95	**0.77** - 1.18
	$t_{1/2}$ (hr)	34 ± 13	34 ± 11		
Pravastatin	Tmax (hr)	0.5 (0.5 - 1.5)*	0.5 (0.5 - 1.0)*		
	Cmax,b (ng/mL)	16.7 ± 4.4	15.3 ± 4.4	0.90	**0.76** - 1.06
	AUCb (ng-hr/mL)	109 ± 43	98 ± 28	0.94	**0.79** - 1.12
	$t_{1/2}$ (hr)	34 ± 11	36 ± 17		

* median (range)

In the same study, Dr Lee reported that the concomitant everolimus dose increased the mean Cmax of atorvastatin by 11% (TABLE 16). The everolimus coadministration did not significantly influence the AUC, t1/2, and Tmax of atorvastatin. The concomitant everolimus dose decreased the mean Cmax and AUC of pravastatin by 10% and 5%, respectively.

TABLE 16. Effect of everolimus on the pharmacokinetics of atorvastatin and pravastatin (Taken from Dr. Lee's review).

	Statin PK Parameter	Baseline	With Everolimus	Geometric Mean Ratio	90% CI
Atorvastatin	Tmax (hr)*	0.5 (0.5 - 1.0)	0.5 (0.5 - 8.0)		
	Cmax (ng/mL)	11.1 ± 4.9	12.0 ± 5.4	1.11	**0.89 - 1.37**
	AUC (ng-hr/mL)	208 ± 62	209 ± 67	1.02	0.94 - 1.11
	$t_{1/2}$ (hr)	26 ± 5	26 ± 5		
	HMG Cmax (ng/ml)	11.9 ± 2.5	12.5 ± 3.5	1.06	0.93 - 1.21
	HMG AUC(0-tz) (ng-hr/mL)	212 ± 73	191 ± 71	0.93	**0.78** - 1.11
Pravastatin	Tmax (hr)*	1.0 (0.5 - 2.1)	1.0 (1.0 - 1.5)		
	Cmax (ng/mL)	24.4 ± 19.4	21.4 ± 11.6	0.90	**0.64 - 1.27**
	AUC (ng-hr/mL)	72 ± 40	68 ± 26	0.95	**0.74** - 1.23
	$t_{1/2}$ (hr)	3.7 ± 2.1	3.4 ± 1.5		
	HMG Cmax (ng/ml)	21.5 ± 13.9	17.9 ± 5.7	0.84	**0.65** - 1.10
	HMG AUC(0-tz) (ng-hr/mL)	54 ± 31	51 ± 17	0.98	**0.76 - 1.27**

* median (range)

The choice of pravastatin and atorvastatin was explained by the sponsor for being statins that are widely used in transplant medicine. Pravastatin served as a negative control because is not metabolized through CYP3A4. Atorvastatin is a known substrate of CYP3A4 (although not recommended by the FDA) and has shown in reports to cause rhabdomyolysis when administered in combination with cyclosporine. Since this study was done specifically because of concomitant administration concerns in transplant patients and no *in vivo* DDI interaction would be expected based on *in vitro* DDI data the use of these two agents is acceptable. The conclusion from Dr. Lee's review was that given the minimal effect (up to 16% decrease in Cmax) of everolimus on statin exposure and vice versa, no dose adjustments for everolimus or the two stains appear to be necessary for their coadministration.

In addition, in the efficacy trial 24 of 398 patients were administered the HMG-CoA reductase inhibitor simvastatin (CYP3A4 substrate). There was no effect on everolimus clearance with simvastatin co-administration. For more details please see the pharmacometric review in Section 4.2.

In conclusion, there is no significant change in everolimus exposure when administered with another CYP3A4 substrate, nor did everolimus significantly change the exposure of the co-administered CYP3A4 substrate.

CYP3A4 inducer – Rifampin

Since everolimus is a CYP3A4 substrate the effect of rifampin, a potent CYP3A4 inducer on everolimus PK was investigated in study A2302. This study was reviewed previously by Dr. Jang-Ik Lee with the original 12-20-2002 transplant NDA submission (NDAs [redacted] & 21-628). b(4)

TABLE 17. Effect of CYP3A induction by rifampin on everolimus pharmacokinetics (Taken from Dr. Lee's review)

Everolimus PK Parameter	Baseline	After Rifampin Induction	Geometric Mean Ratio	90% CI
Tmax (hr)*	0.5 (0.5-1.0)	0.5 (0.5-1.0)		
Cmax,b (ng/mL)	44.2 ± 13.3	18.3 ± 3.9	**0.42**	**0.36 – 0.50**
AUCb (ng-hr/mL)	219 ± 69	83 ± 37	**0.37**	**0.30 – 0.46**
CLb/F (L/hr)	19.7 ± 5.4	55.1 ± 19.0	**2.72**	**2.19 – 3.38**
$t_{1/2}$ (hr)	32.2 ± 6.1	23.9 ± 5.2		

* median (range)

According to the FDA drug-drug interaction guidance, the study design and choice of CYP3A4 inducer are appropriate. This study was completed using steady state administration (8 days) of rifampin 600 mg and single doses of the everolimus 4 mg transplant tablet.

Co-administration of everolimus with rifampin lowered the exposure of everolimus by 59% and 62% for Cmax and AUC respectively compared to when everolimus was administered alone. The 90% confidence intervals for both Cmax and AUC fell outside of the bounds of similarity (0.80 – 1.25) signifying a statistical impact on exposure. A dose increase to 20 mg QD would adjust the exposure in the presence of CYP3A4 inducers.

Although a 20 mg QD daily dose has not been studied, doses up to 70 mg weekly have been given to patients with advanced solid tumors. During everolimus development, eighty-seven subjects have been exposed to doses > 10 mg. These doses ranged from 20 to 70 mg weekly. Thirty-one of these subjects were exposed to the 70 mg weekly dose during the phase 1 dose escalation trial (C2101/02). Of these thirty-one subjects, 17 were exposed to the 70 mg weekly dose for > 2 months (6 were exposed for > 6 months). The mean AUC_{0-24} following a 70 mg weekly dose was is 1803 ng hr/mL which is almost double the steady state AUC_{0-24} seen after a 10 mg daily dose (536 ng hr/mL). The Cmax at steady state following 10 mg QD was 59.7 ng/mL which is about 50% lower than the Cmax values seen between 20 and 70 mg weekly doses (mean range 93.5 – 167 ng/mL).

In conclusion, the sponsor suggests avoiding coadministration with strong inducers of CYP3A4 and if they must be administered together the patient should be monitored for clinical response. A 50% increase in dose to compensate for the decrease in exposure caused by a strong CYP3A4 inducer would justify a dose of 20 mg QD. Based on the available data the reviewer will recommend a labeled dose increase for co-administration with strong CYP3A4 inducers.

CYP3A4 inhibitor – Ketoconazole

Since everolimus is a CYP3A4 substrate the effect of ketoconazole, a potent CYP3A4 inhibitor on everolimus PK was investigated in study A2409. This study was reviewed previously by Dr. Jang-Ik Lee with the 3-17-2005 transplant sNDA submission (NDA 21-628).

Everolimus pharmacokinetic parameters were determined following a single oral dose of everolimus 2 mg administered alone and in combination with oral ketoconazole 200 mg every 12 hours for 5 days in 12 healthy subjects. According to Dr. Lee, ketoconazole coadministration increased mean everolimus Cmax 4.1-fold (range: 2.6-fold to 7.0-fold) and AUC 15.3-fold (range: 11.2-fold to 22.5-fold) and prolonged median Tmax by 0.5 hr (see TABLE 18). The mean clearance was decreased by 93% from 23.8 L/hr to 1.6 L/hr. The mean Vz,b/F was also decreased by 88% from 1016 L to 126 L. The half-life was prolonged by approximately 26 hr

from 30 hr to 56 hr.

TABLE 18. Everolimus PK parameters following 5 days of ketoconazole administration (taken from Dr. Lee's review).

Pharmacokinetic Parameter	Everolimus Alone	Everolimus with Ketoconazole	Mean Ratio (Range)
Tmax (hr)*	1.0 (0.5 - 1.0)	0.5 (0.5 - 1.5)	0.5 (-0.5 to 1.0)^
Cmax,b (ng/mL)	15.3 ± 4.3	59.4 ± 13.4	4.14 (2.64- 6.97)
AUC∞,b (ng-hr/mL)	90 ± 23	1324 ± 232	15.3 (11.2 - 22.5)
CL,b/F (L/hr)	23.8 ± 7.4	1.6 ± 0.3	0.07 (0.04 - 0.09)
Vz,b/F (L)	1016 ± 294	126 ± 25	0.13 (0.09 - 0.19)
t½ (hr)	29.7 ± 4.0	56.0 ± 4.8	1.91 (1.49 - 2.44)

* median (range), ^ median difference

According to the FDA drug-drug interaction guidance, the study design and choice of CYP3A4 inhibitor are appropriate. This study was completed using steady state administration (5 days) of ketoconazole 200 mg BID and single doses of the everolimus 2 mg transplant tablet.

Co-administration of everolimus with ketoconazole increased the exposure of everolimus by 288% and 1371% for Cmax and AUC respectively compared to when everolimus was administered alone. Dr. Lee suggested that based on the degree of the increase in everolimus exposure, simultaneous use of ketoconazole or, other drugs that are strong CYP3A inhibitors such as itraconazole, voriconazole, clarithromycin, telithromycin, and ritonavir cannot be recommended.

In the proposed label the sponsor suggests avoiding coadministration with strong inhibitors of CYP3A4 and if they must be administered together the patient should be carefully monitored for undesirable effects. The reviewer agrees with this approach and the appropriate warnings will be added to the label.

Moderate CYP3A4 inhibitor – Erythromycin

Since everolimus is a CYP3A4 substrate the effect of erythromycin, a moderate CYP3A4 inhibitor on everolimus PK was investigated in study A2408. This study was reviewed previously by Dr. Jang-Ik Lee with the 3-17-2005 transplant sNDA submission (NDA 21-628).

Everolimus pharmacokinetic parameters were determined following a single oral dose of everolimus 2 mg administered alone and in combination with oral erythromycin 500 mg every 8 hours for 5 days in 16 healthy subjects (TABLE 19). According to Dr. Lee, erythromycin coadministration increased mean everolimus maximum blood concentration 2.1-fold and mean AUC 4.9-fold. There was no affect on Tmax. The mean apparent clearance of everolimus was decreased by 76% from 19.1 L/hr to 4.6 L/hr. The mean apparent volume of distribution was also decreased by 66% from 847 L to 287 L. The mean t½ was prolonged by approximately 12 hr from 32 hr to 44 hr.

TABLE 19. Everolimus pharmacokinetics in combination with erythromycin (taken from Dr. Lee's review)

Table 2: Comparison of everolimus pharmacokinetic parameters (mean ± SD) determined following a single oral dose of everolimus 2 mg alone and in combination with oral erythromycin 500 mg administered every 8 hours for 5 days to 16 healthy subjects (Study A2408).

Pharmacokinetic Parameter	Everolimus Alone	Everolimus with Erythromycin	Mean Ratio (Range)
Tmax (hr)*	0.5 (0.5 - 1.0)	0.5 (0.5 - 1.5)	0 (-0.5 to 0.5)^
Cmax,b (ng/mL)	19.9 ± 5.0	40.2 ± 10.4	2.10 (0.90 - 3.48)
AUC∞,b (ng-hr/mL)	116 ± 37	524 ± 225	4.94 (2.04 - 12.58)
CL,b/F (L/hr)	19.1 ± 6.4	4.6 ± 2.1	0.26 (0.08 - 0.49)
Vz,b/F (L)	847 ± 209	287 ± 128	0.35 (0.13 -0.59)
t½ (hr)	31.8 ± 6.0	43.7 ± 5.8	1.40 (1.09 - 1.72)

* median (range), ^ median difference

According to the FDA drug-drug interaction guidance, the study design and choice of CYP3A4 inhibitor are appropriate. This study was completed using steady state administration (5 days) of erythromycin 500 mg TID and single doses of the everolimus 2 mg transplant tablet.

Co-administration of everolimus with erythromycin increased the exposure of everolimus by 102% and 351% for Cmax and AUC respectively compared to when everolimus was administered alone. These increases were not as large as compared to when everolimus was administered with the potent CYP3A4 inhibitor ketoconazole.

The exposure seen following 2 mg everolimus + erythromycin (524 ± 225 ng hr/mL) is similar to the single dose AUCinf seen following a 10 mg dose (571 ± 261 ng hr/mL). This suggests that a 2 or 2.5 mg dose of everolimus in combination with CYP3A4 moderate inhibitors would adjust exposure seen when no inhibitor was present. There is no formulation available < 5 mg, therefore we will recommend that the sponsor develop a 2.5 mg tablet, [redacted] b(4)

[redacted]

P-glycoprotein inhibitor – Verapamil b(4)

Since everolimus is a p-glycoprotein inhibitor, the effect of verapamil, a p-glycoprotein and moderate CYP3A4 inhibitor on everolimus PK was investigated in study A2410. This study was reviewed previously by Dr. Jang-Ik Lee with the 3-17-2005 transplant sNDA submission (NDA 21-628).

Everolimus pharmacokinetic parameters determined following a single oral dose of everolimus 2 mg administered alone and in combination with oral verapamil 80 mg every 8 hours for 5 days in 12 healthy subjects. According to Dr. Lee's analysis, verapamil coadministration increased mean everolimus Cmax 2.4-fold and AUC 3.6-fold without affecting median Tmax. The mean clearance was decreased by 72% from 20.1 L/hr to 5.6 L/hr. The mean Vz,b/F was also decreased by 68% from 902 L to 291 L. The t½ was prolonged by approximately 5 hr from 32 hr to 37 hr.

TABLE 20. Everolimus pharmacokinetic parameters following co-administration with verapamil.

Pharmacokinetic Parameter	Everolimus Alone	Everolimus with Erythromycin	Mean Ratio (Range)
Tmax (hr)*	0.5 (0.5 - 1.5)	0.5 (0.5 - 1.5)	0 (-0.5 to 1.0)^
Cmax,b (ng/mL)	21.0 ± 8.1	47.1 ± 18.2	2.42 (1.32 - 3.84)
AUC∞,b (ng-hr/mL)	115 ± 45	392 ± 142	3.61 (2.21 - 6.30)
CL,b/F (L/hr)	20.1 ± 8.1	5.6 ± 1.5	0.30 (0.16 - 0.45)
Vz,b/F (L)	902 ± 388	291 ± 71	0.35 (02 - 0.57)
t½ (hr)	31.7 ± 6.4	36.9 ± 6.1	1.18 (0.95 - 1.52)

* median (range), ^ median difference

According to the FDA drug-drug interaction guidance, the study design and choice p-gp inhibitor are appropriate. This study was completed using steady state administration (5 days) of verapamil 80 mg TID and single doses of the everolimus 2 mg transplant tablet.

Co-administration of everolimus with verapamil increased the exposure of everolimus by 124% and 240% for Cmax and AUC respectively compared to when everolimus was administered alone. Dr. Lee recommended in the transplant submission that if verapamil use is necessary at the same time with everolimus administration, everolimus dosage reduction is recommended along with therapeutic drug monitoring (TDM) to prevent everolimus toxicity. The sponsor proposed label for how to administer concomitant moderate CYP3A4 inhibitors and p-gp inhibitors. b(4)

The exposure seen following 2 mg everolimus + verapamil (392 ± 142 ng hr/mL) is similar to the single dose AUCinf seen following a 10 mg dose (571 ± 261 ng hr/mL). This suggests that a 2 or 2.5 mg dose of everolimus in combination with p-gp inhibitors would adjust exposure seen when no inhibitor was present. There is no formulation available < 5 mg, therefore we will recommend that the sponsor develop a 2.5 mg tablet, b(4)

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Everolimus is a low permeability drug based on the in vitro permeability study using Caco-2 cell monolayers. The reported everolimus solubility is and, therefore, the highest dose strength of everolimus tablet (10 mg) would be soluble in Based on the permeability and solubility data, everolimus is a Class 3 drug (high solubility, low permeability) with respect to BCS. b(4)

2.5.2 What is the composition of the to-be-marketed formulation?

Oncology Tablet

The 5-mg everolimus oncology Market Formulation (MF) tablet was used in all the oncology clinical trials included in this submission. The oncology Final Market Image (FMI) tablets

intended for marketing have strengths of 5 and 10 mg. Except for the shape and embossing, the 5-mg oncology FMI tablet is identical to the 5-mg oncology MF tablet, and the 5-mg oncology FMI tablet and the 10-mg oncology FMI tablet are proportional in composition.

The sponsor conducted a randomized, three-way crossover study (C2119) to determine *in vivo* bioequivalence between MF tablets and the FMI tablets. Thirty-nine of the 42 enrolled subjects completed all three treatment periods and 40 subjects were included in the PK population for BE testing. Each subject was randomized into one of six sequences and all received the following three single doses of 10 mg everolimus:

- 2 x 5 mg MF tablet used in phase 2/3 clinical studies
- 2 x 5 mg FMI tablet intended for marketing (Batch No. X331JC)
- 1 x 10 mg FMI tablet intended for marketing (Batch No. X147CD)

Everolimus was administered with 240 mL of water after at least a 10 hour fast with a 14-day washout period between each dose. Since these were healthy subjects no medication other than study drug was allowed during the study. PK assessments occurred on each day of treatment for up to 144 hours post-dose. The mean pharmacokinetic parameters for everolimus from this study are in TABLE 21.

TABLE 21. Mean ± SD pharmacokinetic parameters of everolimus in healthy subjects following single oral doses of 10 mg.

PK Parameter	2 x 5-mg MF tablets (N=40)	2 x 5-mg FMI tablets (N=40)	1 x 10-mg FMI tablet (N=39)
AUCinf (ng. h/mL)	536.7 ± 174.2	538.7 ± 185.5	537.8 ± 206.6
AUC(0-last) (ng. h/mL)	510.8 ± 167.9	512.3 ± 174.7	511.8 ± 198.1
Cmax (ng/mL)	64.4 ± 17.8	68.6 ± 20.0	61.2 ± 19.1
Tmax (h)[a]	1.0 (0.5-2.5)	1.0 (0.5-3.0)	1.0 (0.5-2.5)

a – median (range)

Geometric means of primary PK parameters (TABLE 22) after administration of the test formulations (2 x 5-mg FMI tablets or 1 x 10-mg FMI tablet) were similar to those seen after administration of the reference formulation (2 x 5-mg MF tablets). All 90% CIs for the ratios of the geometric means of the test formulations compared to the reference formulation were within the accepted interval (0.80-1.25) which indicate that the phase 2/3 formulations is bioequivalent to the formulation intended for marketing.

TABLE 22. Ratios of Geometric means (test/reference) and 90% confidence intervals for primary PK parameters.

PK parameter	Formulation	Adj. Geo. Mean	Comparison	ratio of Geo. Mean	90% CI Lower	90% CI Upper
$AUC_{0\text{-last}}$ (ng.h/mL)	A - 2 x 5 mg MF	487.3				
	B - 2 x 5 mg FMI	487.2	B:A	1.00	0.94	1.07
	C - 1 x 10 mg FMI	480.6	C:A	0.99	0.93	1.05
AUCinf (ng.h/mL)	A - 2 x 5 mg MF	512.9				
	B - 2 x 5 mg FMI	512.4	B:A	1.00	0.94	1.06
	C - 1 x 10 mg FMI	505.8	C:A	0.99	0.93	1.05
Cmax (ng/mL)	A - 2 x 5 mg MF	62.0				
	B - 2 x 5 mg FMI	66.0	B:A	1.06	0.99	1.14
	C - 1 x 10 mg FMI	58.3	C:A	0.94	0.88	1.01

Transplant Tablet

The 0.25-, 0.5- and 1-mg everolimus transplant MF tablets and the 1-mg everolimus transplant FMI tablet were used in the transplant clinical studies included in this oncology NDA submission. The 1-mg transplant MF tablet and the 1-mg transplant FMI tablet are identical in composition. In-vivo bioequivalence (study A2301) was demonstrated between the 0.25-mg transplant MF tablet, the 0.5-mg transplant MF tablet, the 0.25-mg transplant MFI tablet, and the 1-mg transplant FMI tablet. This BE study was reviewed previously by Dr. Jang-Ik Lee with the original 12-20-2002 transplant NDA submission (NDAs [redacted] & 21-628) and will not be discussed further. b(4)

Oncology Tablet vs. Transplant Tablet

Many of the clinical pharmacology studies submitted for the oncology NDA were conducted under the transplant NDA with the transplant tablet. There was no formal BA/BE comparison between the oncology tablet and the transplant tablet. In-vitro dissolution comparison was submitted.

The everolimus transplant tablets and the everolimus oncology tablets are qualitatively identical but differ quantitatively in strength of the drug substance and amounts of the excipients. The oncology tablets are manufactured with a [redacted] whereas the transplant tablets are manufactured with a [redacted] b(4)

The chemistry reviewer (Ravindra Kasliwal, Ph.D.) was consulted via email on July 22, 2008 regarding the necessity of an in-vivo BE study to bridge the studies using the transplant tablet to the oncology tablet. The CMC response to this inquiry is in Appendix 4.1. The CMC reviewer concluded that based on dissolution and the fact that similar components are used, the transplant tablets appear to be similar to the oncology tablet and no in-vivo BE study is necessary. The reviewer agrees with CMC's conclusions.

2.5.3 What moieties should be assessed in bioequivalence studies?

Everolimus should be measured in human whole blood.

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

A food effect study was completed (W302) and was reviewed previously by Dr. Jang-Ik Lee with the original 12-20-2002 transplant NDA submission (NDAs [redacted] & 21-628). b(4)

From Dr. Lee's review, when everolimus was administered after a high-fat meal defined in the Agency's guidance for food effect bioavailability studies, everolimus Tmax was delayed in 21 subjects; the median delay was 1.5 hr. Mean Cmax was notably decreased in all 24 subjects by 60% under the fed condition. The geometric mean ratio of fed/fasted AUC remained in the equivalence range of 80 – 125% for 10 subjects. The other 14 subjects had changes outside the range. The overall food effect on the extent of absorption was a reduction of 16%. The mean CLb/F, Vz,b/F, and t1/2 was comparable between fed and fasted conditions.

The overall conclusion from study W302 from Dr. Lee was that due to the significant effect on Cmax and moderate effect on AUC, it is recommended to administer everolimus tablets on a consistent basis; either with food or without food to avoid unnecessary fluctuations in

everolimus exposure over time. In the current label the sponsor suggests that everolimus tablets be administered once daily at the same time every day [redacted] This is the same dosing instruction that was given to the patients enrolled in the pivotal efficacy trail (C2240). b(4)

Because of the complications in defining a [redacted] the reviewer will recommend that everolimus be administered at least 1 hour before or 2 hours after a meal. b(4)

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

The original transplant NDAs (Certican®) included dissolution data for the transplant tablets and this data was reviewed by Dr. Seong Jang.

The sponsor proposed the following as the final dissolution method and specification for Certican® tablets.

[redacted] b(4)

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Parent drug accounted for the majority (approx. 40%) of the AUC following the administration of ^{13}C-everolimus. Most identifiable metabolites accounting for the 35% of the AUC were known to be much less active by two orders than the parent drug, and rapamycin accounting for only 1.2% was the only active metabolite identified. In conclusion, only everolimus concentrations in whole blood were measured in all CPB studies except the mass balance study (W107).

2.6.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

To assess systemic exposure of everolimus in human pharmacokinetic studies, HPLC methods coupled to mass spectrometry (LC-MS or LC-MS/MS) or enzyme-linked immunosorbent assay

(ELISA) were used. TABLE 23 provides a synoptic view of the different assay methods used to quantify everolimus in blood summarized by analytical technique.

TABLE 23. Analytical methods for determination of everolimus

Report number	Matrix	Technique	LLOQ (ng/mL)	Studies Used
DMPK(CH) 1996/227 DMPK(F)R99-2664	blood	LC/MS	0.3	Transplant: A1101, A2301, A2302, A2303, A2304, A2408, A2409, A2410, B157, B201, B251, B258, W105, W107, W302, W303 Oncology: C1101, C2104, C2106, C2107, C2108, C2206, C2207, C2222, C2235, C2239, C2240
DMPK(US)R99-2671	blood	LC/MS/MS	0.368	Transplant: B251, B351, Oncology: C2101, C2102, C2119, C2119, C2239, C2240
DMPK R0700750	blood	LC/MS/MS	0.300	Oncology: C2119, C2118, C2240, C2239
303-017	blood	ELISA	2	Transplant: B157

The ELISA method (303-017) was cross-checked with the LC-MS method, and both methods produced equivalent results over the concentration range of 3 to 32 ng/mL that covers the range of everolimus concentrations achieved in transplantation patients during BID administration of everolimus.

The original HPLC/MS (DMPK(CH) 1996/227, DMPK(F)R99-2664) method used for the analysis of most of the clinical studies conducted for the transplant submission and most of the studies to support the present oncology submission. This method consisted of a [redacted] was used as an internal standard. Detection was performed by using the single stage mass spectrometry. The method was validated in the range [redacted]. The mean inter-day accuracy for quality control samples was in the range of [redacted] The overall precision was in the range [redacted] The LLOQ corresponding to a precision of [redacted] was 0.300 ng/mL. b(4)

Alternatively, two HPLC/MS/MS methods were developed (DMPK(US)R99-2671). The first includes [redacted] .. Detection was performed by [redacted] mass spectrometry using [redacted] monitoring. The method was validated in the range of [redacted]. The method was specific for RAD001 (interference of blank samples below [redacted] of signal at LLOQ). The validated LLOQ was 0.368 ng/mL. The inter-day accuracy and precision were evaluated as the [redacted] s: at LLOQ, inter-day accuracy was [redacted] and overall precision was [redacted] Above LLOQ, inter-day accuracy was between [redacted] and overall precision between [redacted] b(4)

More recently another HPLC/MS/MS method (DMPK R0700750) was developed and validated according to FDA guidance " Bioanalytical Method validation". This method was used for the analysis of blood samples in for oncology studies C2119, C2118, C2240 and C2239 and consisted of the same extraction step as the original HPLC/MS method. The HPLC separation was improved to reduce run time. [redacted] mass spectrometry detection was performed in b(4)

multiple reaction monitoring. The method was validated with a LLOQ of 0.300 ng/mL. The method was specific for RAD001 (maximum interference of blank samples was [redacted] of signal at LLOQ). Linearity was validated in the range [redacted] ıL. The inter-day accuracy and precision were evaluated as the mean bias and precision of quality control samples analyzed during 3 validations days: at LLOQ, inter-day accuracy was [redacted] % and overall precision was [redacted] Above LLOQ, inter-day accuracies were between [redacted] and overall precision between [redacted] %. b(4)

Everolimus in human blood at concentrations between 2 and 100 ng/mL is stable at 4°C and at room temperature over 48 hours. Everolimus at concentrations between 1 and 30 ng/mL is stable in human blood stored below –20°C over 17 months, and after at least 3 freeze-thaw cycles in human blood. The determination of everolimus by the LC-MS, LC/MS/MS and ELISA methods was performed according to Good Laboratory Practices or in compliance with internal good laboratory practice standards.

The in-process performance for the analytical methods used for measurement of everolimus concentrations for the transplant NDA were reviewed previously by Dr. Ike Lee and will not be discussed. TABLE 24 lists the in-process assay performance of the assays used in each reviewed clinical pharmacology study conducted for the oncology indication. RAD001 is stable in human whole blood for at least 48 hours at room temperature, after 4 freeze/thaw cycles, and for at least 17 months after storage at ≤ -18°C or at ≤ -60°C.

TABLE 24. Summary of in-process performance of the analytical methods used for the measurement of everolimus blood concentrations in oncology studies.

Study	report no.	analyte	method	calibration range (ng/mL)	LOQ (ng/mL)	Within-study	
						Precision (%) RSE (US) or CV	Accuracy* (%) Recovery (US) or Bias
C2107	DMPK(CH) R00-1020	everolimus	LC/MS	0.2 - 100	0.2	5.1 to 7.2	98.5 to 104.0 a
C2102	DMPK RCRAD001C2102	everolimus	LC-MS/MS	0.378 – 98.0	0.378	3.7 to 12.9	-1.8 to 3.3
C1101	DMPK RCRAD001C1101	everolimus	LC-MS/MS	0.293 – 48.9	0.293	3.3 to 6.7	-5.4 to 4.2
C2101	DMPK RCRAD001C2101A	everolimus	LC-MS/MS	0.378 - 280	0.378	3.6 to 16.1[b]	-2.0 to 10.1
C2119	DMPK RCRAD001C2119	everolimus	LC/MS/MS	0.3 - 50	0.3	9.0 to 12.1	-6.9 to 2.5
C2106	DMPK RCRAD001C2106	everolimus	HPLC/MS	0.3 – 50	0.3	3.9 to 8.4	-8.1 to 4.2
C2104	BAPK (EU) R01-1073	everolimus	HPLC-MS	0.3 - 50	0.3	2.0 to 5.4	-7.5 to 7.8
	BAPK (EU) R01-1073B	paclitaxel	HPLC	10 – 5000	10	2.1 to 5.6	-3.7 to 4.0
C2108	BAPK(EU) R0301012A	everolimus	LC-MS	0.3 - 50	0.3	2.4 to 7.0	-6.0 to 8.8
	BAPK (EU) R0301012B	letrozole	HPLC	1.0 - 200[c]	1.0 [c]	2.1 to 9.7	-1.5 to 2.0
C2118	DMPK RCRAD001C2118A	everolimus	LC-MS/MS	0.3 - 50	0.3	7.0 to 10.5	-3.6 to 2.0
	DMPK RCRAD001C2118B	moxifloxacin	LC-MS	50- 10000	50.0	1 to 5.2	-3.2 to 2.0
C2222	DMPK RCRAD001C2222A	letrozole	HPLC	1.0 - 200[c]	1.0 [c]	1.7 to 6.6	-1.1 to 1.0

Study	report no.	analyte	method	calibration range (ng/mL)	LOQ (ng/mL)	Within-study	
						Precision (%) RSE (US) or CV	Accuracy* (%) Recovery (US) or Bias
	DMPK RCRAD001C2222B	everolimus	LC-MS/MS	0.3 - 50	0.3	3.5 to 8.1	-4.3 to 6.1
C2235	DMPK RCRAD001C2235	everolimus	LC-MS/MS	0.3 – 50	0.3	1.2 to 8.9	-7.5 to 5.4
C2239	DMPK RCRAD001C2239	everolimus	HPLC-MS/MS	0.3 – 50	0.3	3.9 to 10.5	-4.9 to 4.0
C2240	DMPK RCRAD001C2240	everolimus	LC-MS/MS	0.3 – 50	0.3	5.3 to 7.5	-6.5 to 12.0
a Accuracy = 100%-measured concentration/nominal concentration b 16.1% occurred at LLOQ c units are nmol/L							

3 DETAILED LABELING RECOMMENDATIONS

b(4)

5 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 5

4 APPENDICES

4.1 CMC RESPONSE

On July 21, 2008 the CMC reviewer was consulted regarding the need for a in-vivo BE study to bridge the clinical pharmacology studies using the transplant tablets to the oncology tablet. Below is the CMC reviewers emailed response and attached document (biopharm response.doc)

4.1.1 Email

From: Kasliwal, Ravindra K
Sent: Thursday, October 02, 2008 12:05 PM
To: Bullock, Julie
Cc: Pope, Sarah; Sarker, Haripada
Subject: RE: NDA 22-334: BE of onc vs. transplant tablet

Julie,

See attached descriptions of the compositions of the tablets. The tablets components are the same in all strengths, but the ratios differ slightly. The

b(4)

The company has also evaluated the bioequivalence of 5 mg and 10 mg tablets for which the data are presented in Section [5.3.1.2]. Assuming 5 mg and the 10 mg tablets are bioequivalent, I think based on dissolution (and the fact that similar components) are used, the lower strength tablets would appear to be similar.

Ravi Kasliwal << File: Biopharm response.doc >>

4.1.2 Biopharm response.doc

The drug product is an immediate-release compressed tablet containing everolimus. Previously, in NDA [redacted] 4 strengths, 0.25-, 0.50, 0.75-, and 1.0-mg were evaluated. In the current NDA 22-334, 5 mg and 10 mg strengths have been proposed.

b(4)

3 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 6

4.2 PHARMACOMETRIC REVIEW

Appears This Way
On Original

PHARMACOMETRICS REVIEW

Table of Contents

1 SUMMARY OF FINDINGS

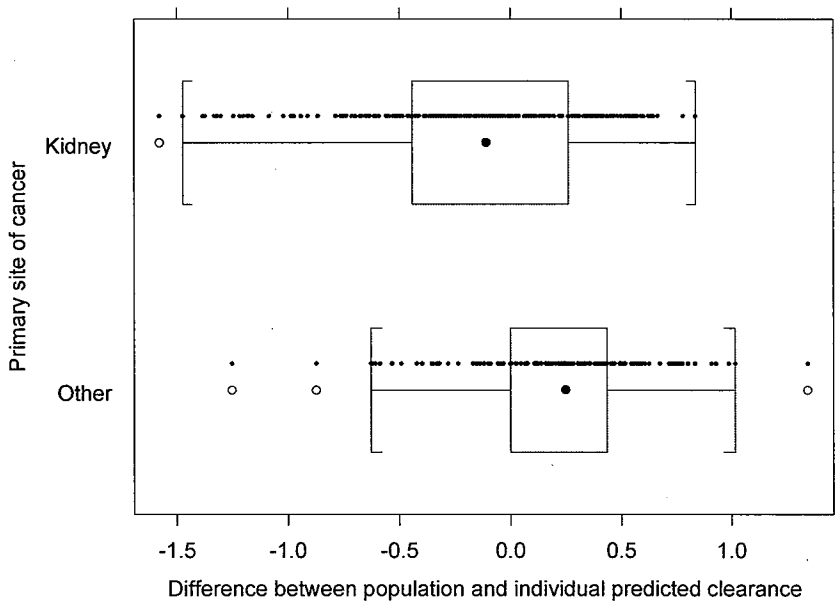
1.1 Key Review Questions

The following key questions were addressed in this pharmacometrics review.

1.1.1 Is there an effect of site of cancer on the pharmacokinetics of everolimus?

No, there does not seem to be an effect of site of cancer on clearance of everolimus. Primary site of cancer (kidney or other) was detected as a significant covariate (a decrease in objective function of 47 units), such that patients with renal cell carcinoma had clearance around 70% of the clearance in other patients (**Figure 1**). Even though, statistically it makes sense, it makes less biological sense as everolimus is primarily eliminated by liver (as argued by the sponsor). Moreover, even with a significant drop in objective function, the primary site of cancer only explained 4% of the inter-individual variability in clearance (reduced from 53 to 49%) which is not clinically relevant. It was also indicated by the sponsor that there were individuals in study C2240 with trough concentrations much higher than the peak concentrations of everolimus observed in other Phase 1 studies. Removing these individuals from the dataset did not result in primary site of cancer to be selected as a significant covariate during model building. Furthermore, study C2240 had patients only with renal cell carcinoma, therefore this effect may also be interpreted as study effect. Thus, it is reasonable to conclude that clearance of everolimus is not dependent on the site of cancer.

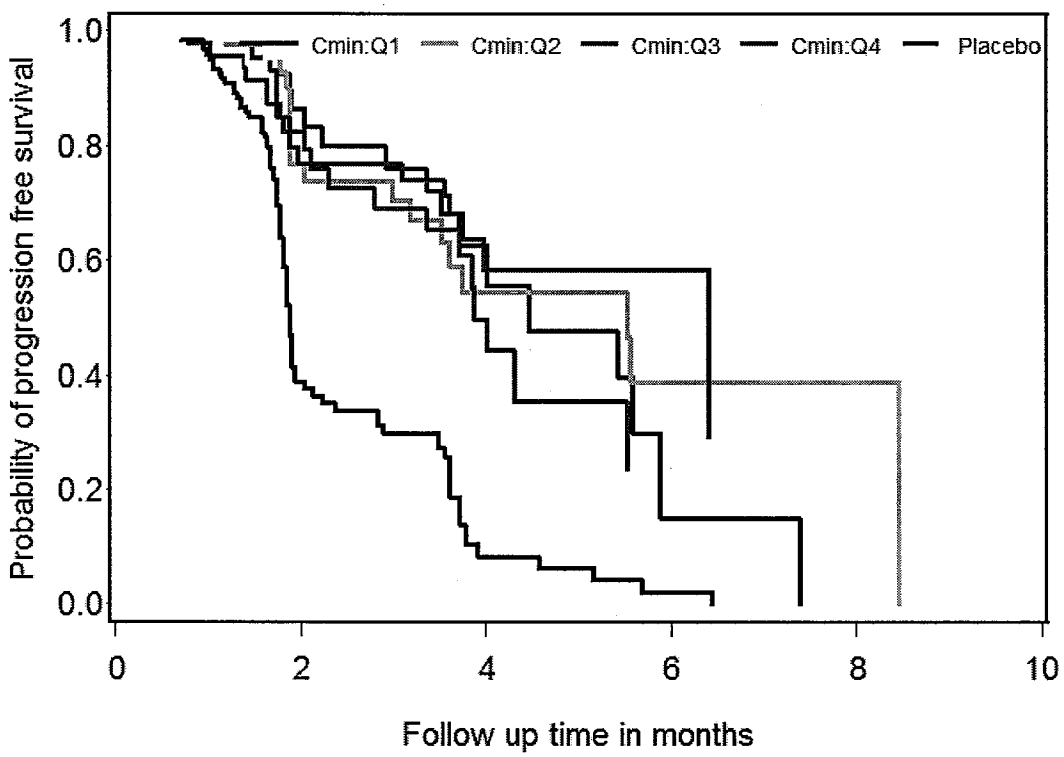
Figure 1: Steady state oral clearance in patients with kidney or other organs as primary site of cancer. Red dots are the inter-individual random variable (ETAs) for clearance.



1.1.2 Is there evidence of an exposure-response relationship for effectiveness and safety for everolimus?

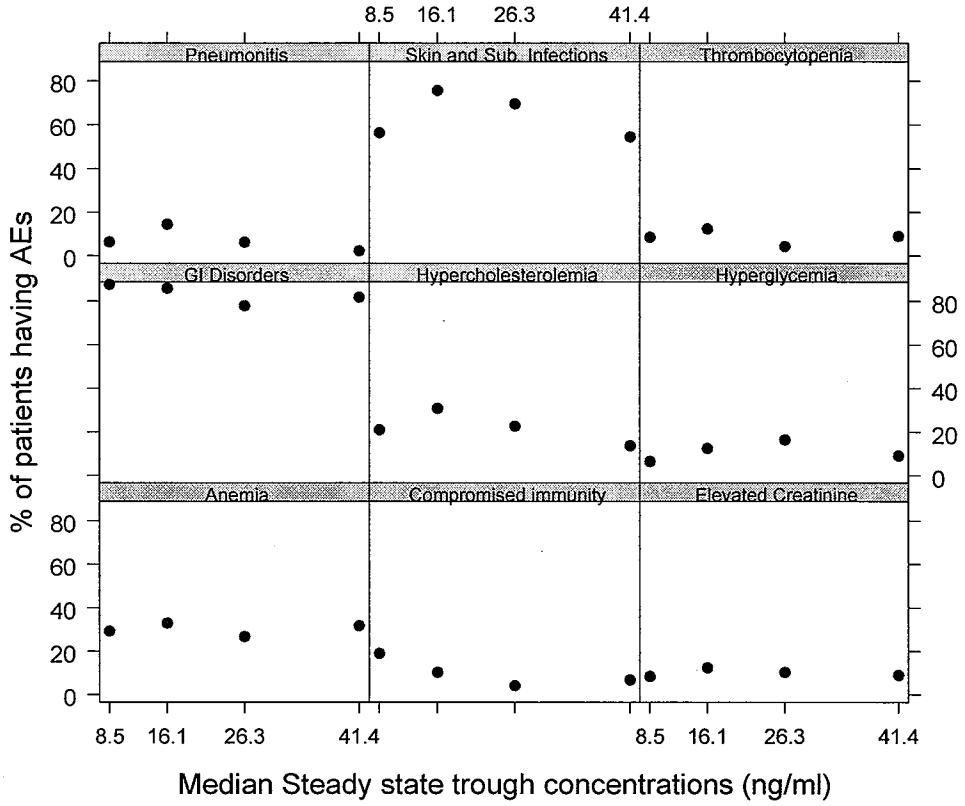
Kaplan Meier analysis was performed to assess the exposure response for efficacy based on progression free survival. As it is evident from **Figure 2** the survival curves of patients in different concentration-quartile groups were not significantly different. However, the drug clearly seems to be effective as all the four survival curves for treatment were well differentiated from the placebo group.

Figure 2: Kaplan Meier plots for progression free survival for placebo and treatment groups. Q1, Q2, Q3 and Q4 are quartiles based on trough concentrations.



To assess the exposure-safety relationship, the patients for whom the trough concentrations were available (C2240 trial) were divided into quartiles and % subjects having adverse events were plotted against each quartile. Adverse events to be assessed were selected based on the clinical relevance and after discussion with the medical reviewer. GI disorders and, skin and subcutaneous infections were two of the most common adverse events observed. However, there was no trend observed in case of either of the adverse events (see **Figure 3**).

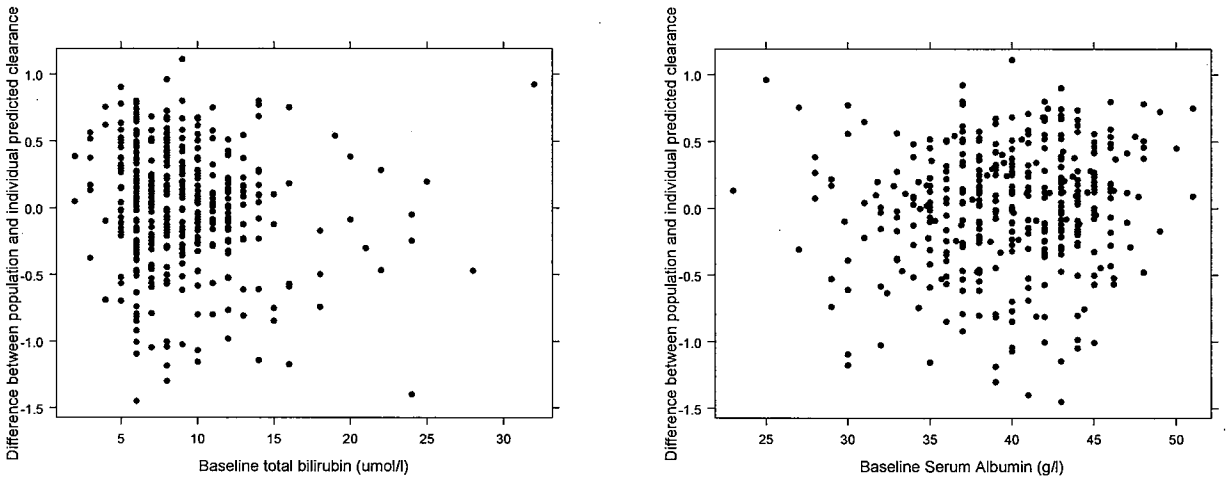
Figure 3: Percent adverse events in the four C_{trough} quartiles. The concentration ranges are 1.4-12.4, 12.5-19, 1.1-30.6 and 30.7 to 135 ng/ml for 1, 2, 3 and 4, respectively.



1.1.3 Is there an effect of hepatic function on the clearance of everolimus?

A dedicated hepatic impairment study has been conducted showing 114% exposure increase in moderately hepatic impaired compared to healthy individuals and thus the dose is proposed to be reduced by half. Everolimus is not studied in severe hepatic impaired subjects and thus is not recommended in this population. Since the hepatic impairment study did not include mild hepatic impaired individuals, an attempt was made to see if something informative could be obtained using population modeling. However, since most of the patients enrolled in the studies had normal hepatic function with levels of biomarkers (total bilirubin or serum albumin) in the normal range, not much could be gathered about mild hepatic impairment. As evident from **Figure 4**, given the narrow range of total bilirubin and serum albumin in the dataset, there was no effect of hepatic impairment observed on clearance of everolimus.

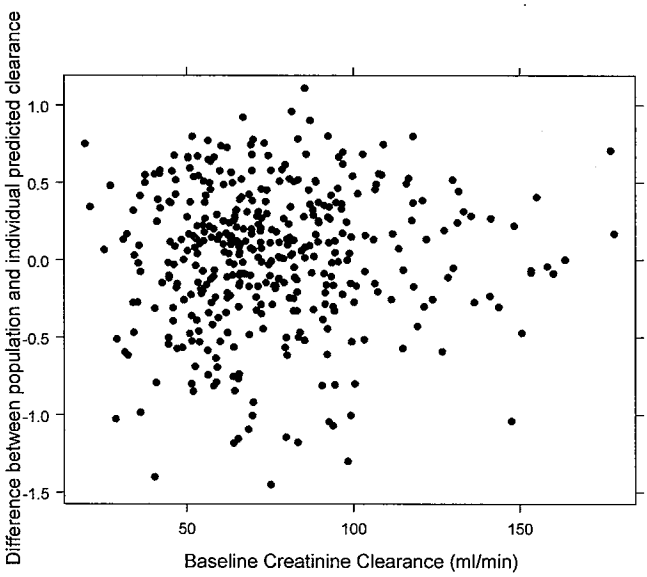
Figure 4: No effect of hepatic function ((Left) total bilirubin and (Right) serum albumin) on oral clearance of everolimus.



1.1.4 Is there an effect of renal function on the clearance of everolimus?

There was no effect of renal function on the clearance of everolimus (see **Figure 5**). It is expected as everolimus is mainly eliminated via hepatic route.

Figure 5: No effect of baseline creatinine clearance on oral clearance of everolimus.



1.1.5 Does pharmacokinetics of everolimus depends on age, weight or sex?

The oral clearance of everolimus dose not depend on age and weight within the range evaluated (Age range: 27-85 years; Weight range: 38-147 kg) (**Figure 6**). The clearance of everolimus also does not depend upon gender (**Figure 7**).

Figure 6: No effect of (Left) age and (Right) weight on oral clearance of everolimus.

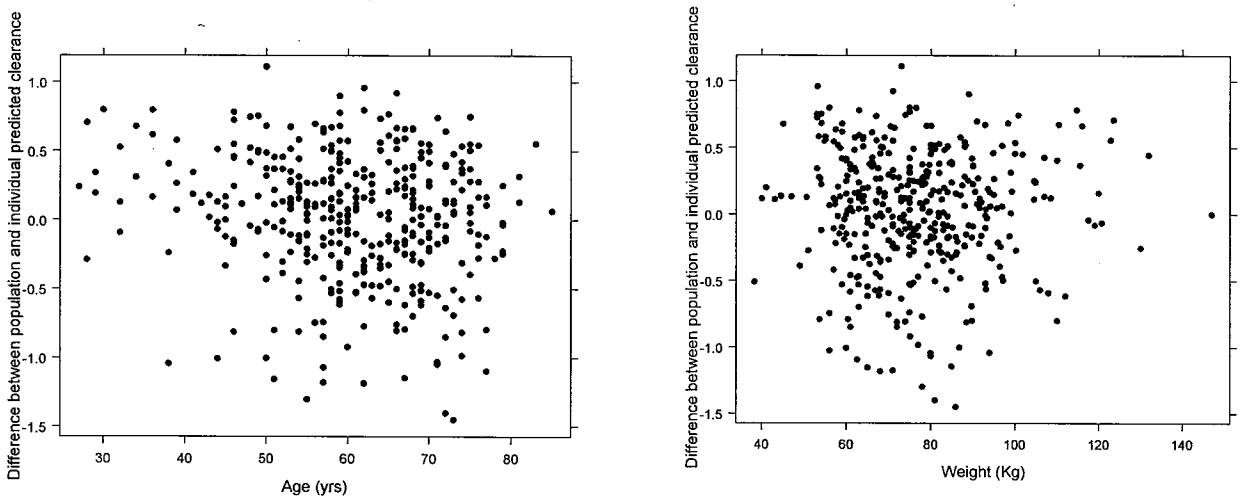
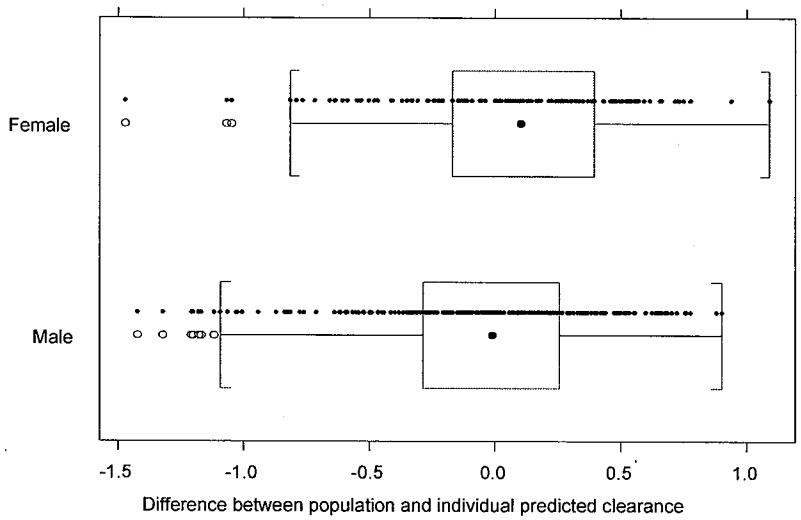


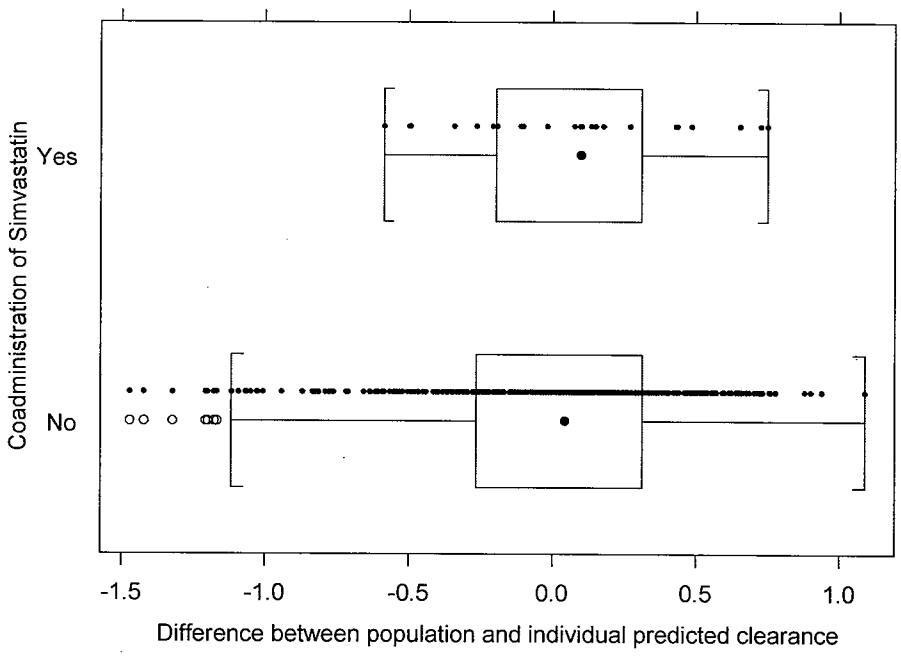
Figure 7: No effect of gender on oral clearance of everolimus. Red dots are the inter-individual random variable (ETAs) for clearance.



1.1.6 Is there an effect of coadministration of simvastatin on clearance of everolimus?

24 of 398 patients were coadministered simvastatin. There seems to be no effect of simvastatin co administration on clearance of everolimus (**Figure 8**). However, this should be interpreted with caution given the low number of patients on simvastatin which may be insufficient to affirm the absence of the effect of its co-administration on clearance of everolimus. Moreover, no drug interaction has been observed with other similar class of compounds (atrovastatin, pravastatin) in standalone drug interaction studies. Thus, it is reasonable to believe that simvastatin does not interact with everolimus pharmacokinetics.

Figure 8: No effect of coadministration of simvastatin on oral clearance of everolimus. Red dots are the inter-individual random variable (ETAs) for clearance.



1.2 Recommendations

None

1.3 Label Statements

The following are the labeling recommendations relevant to clinical pharmacology for NDA 22334. The ~~red strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

b(4)

2 Pertinent Regulatory Background

Everolimus is a derivative of rapamycin and acts as a signal transduction inhibitor of mTOR (mammalian target of rapamycin) ultimately regulating cell growth, proliferation, angiogenesis and survival. Everolimus is approved in more then 60 countries in transplant setting. It was also submitted to FDA under NDA —— and NDA 21628 for the prophylaxis of organ rejection in allogenic kidney and heart transplantation. An approvable letter was issued by the FDA for these indications. Everolimus was again submitted in 2008 to FDA but for oncology indication (Advance renal cell carcinoma). Safety and efficacy was demonstrated as part of an international, multicenter, randomized, double-blind, placebo-controlled, trial (C2240) designed to evaluate the efficacy and safety of everolimus 10 mg in conjunction with best supportive care (BSC) *versus* placebo plus BSC in patients with mRCC whose disease had progressed despite prior therapy with VEGFr-TKI therapy. The trial was terminated early due to outstanding efficacy when assessed in terms of the primary end point, progression free survival. Please refer to C2240 study report for complete details of this registration trial.

b(4)

3 Results of Sponsor's Analysis

3.1 Population PK analysis

Sponsor performed population PK modeling utilizing data from various Phase 1, 1b trials and the main registration trial (C2240). 398 patients with 1667 concentrations which corresponded to 1-20 samples per subject constituted the PK population. The population pharmacokinetics of RAD001 was adequately described by a two-compartment model, and the associated inter-individual and intra-individual variabilities were characterized. Based on the complete dataset, the renal cell carcinoma population presented a typical clearance of about 68% of the overall population. No evidence for impact of the other covariates under consideration was detected. A sensitivity analysis was performed, on a reduced dataset without suspected outliers and removing C2240 patients with trough concentrations only (while keeping the profile data from study C2240). This analysis delivered much better 'goodness of fit' plots, but also confirmed the base model obtained with the complete dataset. However, the apparent difference of clearance in the renal cell carcinoma population could no longer be estimated as different from 0. Therefore, sensitivity analyses suggest that this result may be due to inconsistencies of trough measurements in the study concerned, rather than a true physiological effect. The details of the analysis can be found in population-pk-report submitted by the sponsor. The model was successfully evaluated using predictive check.

Table 1: Parameter values from sponsor's population pharmacokinetic model.

Parameters (n=15)	pgm03CLPR012runF52	
	Estimate	(std. error)
θ_{01} Nominal TVV2 (L) Central volume	191	(15.2)
θ_{02} Nominal TVV3 (L) Peripheral volume	517	(44)
θ_{03} Nominal TVCL (L/h) Clearance	18.8	(0.85)
PR01 on CL (θ_{10}) : TVCL* θ_{10}^{**PR01}	0.682	(0.04)
θ_{04} Nominal TVQ (L/h) Intercomp. clearance	46.2	(3.67)
θ_{05} Nominal TVk_a (h^{-1})	6.07 FIXED	NA
Ω_{11} Intersubject variance for V3/f	0.223	(0.073)
Ω_{22} Intersubject variance for V2/f	0.266	(0.059)
Ω_{32} Intersubject covariance for V2/f and CL/f	0.104	(0.053)
Ω_{33} Intersubject variance for CL/f	0.239	(0.021)
Ω_{44} Intersubject variance for CL_d/f	0.132	(0.050)
Ω_{55} Intersubject variance for k_a	0 FIXED	NA
Σ_1 Residual variance (multiplicative part) for profiles	0.283	(0.021)
Σ_2 Residual variance (additive part) for profiles	0.075	(0.033)
Σ_1 Residual variance (multiplicative part) for trough concentrations	0.380	(0.019)
Σ_2 Residual variance (additive part) for trough concentrations	0.096	(0.061)
NONMEM objective function	8314	

Note: θ represents fixed effect, Ω and Σ represents random effects.

(Source: Population PK of RAD001 in Phases I studies and Study C2240, Table 5-5, Pg 44*)*

Reviewer's comments: *Sponsor's analysis followed a reasonable and thorough approach in describing the pharmacokinetics of everolimus. The sensitivity analysis described above resulted in removal of more than half of patients from the dataset (n=217 with only trough concentrations in the study C2240 were removed while 13 patients with full PK profiles were retained). Following which primary site of cancer was not identified as a significant covariate. Sponsor provides an explanation saying that this could be due to the inconsistencies of trough concentrations and acknowledging the fact that these might not be true trough concentrations due to misreported time of sampling. The exposure-response and exposure safety analysis rely on these trough levels and may be interpreted incorrectly if the trough levels are not correct.*

3.2 Exposure Efficacy Analysis

Preliminary PK-PD studies suggested that 10-35 ng/ml concentration is needed for execution of complete effect of everolimus through its downstream effectors. Therefore sponsor divided the patients with concentrations available into three groups (<10 (low C_{min} subgroup), 10-35 (median C_{min} subgroup) and >35 ng/ml (high C_{min} subgroup)) and performed Kaplan Meier analysis on the three groups to estimate the median progression free survival time. Similar median progression free survival times for all C_{min} subgroups indicated lack of exposure-response.

Table 2: Analysis of PFS based on central radiology review using the Kaplan-Meier method by C_{min} subgroups

	C_{min} subgroup 0-10 ng/mL N = 32	C_{min} subgroup 10-35 ng/mL n = 130	C_{min} subgroup > 35 ng/mL n = 55
No. of PFS events	12 (37.5%)	44 (33.8%)	22 (40.0%)
No. of progression	9 (28.1%)	43 (33.1%)	17 (30.9%)
No. of death	3 (9.4%)	1 (0.8%)	5 (9.1%)
No. of censored	20 (62.5%)	86 (66.2%)	33 (60.0%)
Kaplan-Meier estimates [90% CI] at			
4 months	64.1 [44.6;83.7]	58.1 [46.7;69.6]	50.8 [32.8;68.8]
6 months	NA [NA;NA]	34.0 [16.5;51.4]	22.6 [2.1;43.0]
25th percentile for PFS [95% CI] (months)	1.87 [1.77;4.47]	3.19 [2.10;3.71]	1.84 [1.74;3.84]
Median PFS [95% CI] (months)	4.47 [3.35;NA]	5.55 [3.75;6.41]	4.30 [3.35;5.52]
75th percentile for PFS [95% CI] (months)	NA [4.01;NA]	7.39 [5.75;8.44]	5.52 [5.19;NA]

(Source: C2240 Clinical study report, Table 11-13, Pg 123)

3.3 Dose-Exposure-Safety analysis.

Sponsor compared the adverse events among various C_{min} subgroups as described above. No trend was observed for any of the adverse events.

Table 3: Clinically notable adverse events in various C_{min} subgroups in study C2240

	C_{min} subgroup 0-10 ng/mL (n = 32)	C_{min} subgroup 10-35 ng/mL (n = 130)	C_{min} subgroup > 35 ng/mL (n = 55)
Stomatitis/oral mucositis/ulcers	18 (56.3%)	54 (41.5%)	21 (38.2%)
Anemia	10 (31.3%)	33 (25.4%)	14 (25.5%)
Hypercholesterolemia	4 (12.5%)	27 (20.8%)	5 (9.1%)
Hyperglycemia	1 (3.1%)	13 (10.0%)	4 (7.3%)
Rash and similar events	6 (18.8%)	53 (40.8%)	10 (18.2%)

(Source: C2240 Clinical study report, Table 11-15, Pg 125)

Reviewer's comments: Some of the trough concentrations used in the exposure-efficacy and exposure-safety analysis were not actual trough concentrations. Reviewer used

actual dosing and sampling times to isolate true trough concentrations and used them for further analysis (see section 4.2 and 4.3).

4 Reviewer's Analysis

4.1 Population PK Analysis

4.1.1 Objectives

To re-estimate the model parameters after removal of primary site of cancer as a covariate on clearance in the sponsor's model.

4.1.2 Methods

FOCE estimation with interaction was used for parameter estimation.

4.1.3 Datasets

The complete dataset (nmpka.xpt) was utilized for running the model.

4.1.4 Software

NONMEM VI, which was also used by the sponsor for their analysis, was utilized for the present analysis.

4.1.5 Model

Similar model as that of sponsor was utilized with effect of primary site of cancer on clearance deleted.

4.1.6 Results

Table 4 compares the parameter estimates between sponsors and reviewers modified population pharmacokinetic model. The removal of the effect of primary site of cancer on clearance only increased the between subject variability in Cl by 4% (53% from 49%) although there was a significant increase (47 units) in objective function. Goodness of fit plots and other parameters, relative standard error (RSE) remained similar. Moreover, the clearance in patients with renal carcinoma is 68% of other patients which can be considered as a moderate decrease. Considering that everolimus is primarily excreted by hepatic route, and the fact that this effect could also be a study effect (rather than true physiological effect) since only metastatic kidney carcinoma patients were recruited in the C2240 trial, it may be reasonable to conclude that primary site of cancer does not effect everolimus clearance (see **Figure 1**).

Table 4: Comparison of parameter estimates between sponsor's and reviewer's population PK model.

Parameters	Estimates (%RSE)	
	Sponsor's model	**Reviewer's model**
Central volume (θ1) (L)	191 (8)	172 (8.2)
Peripheral volume (θ2) (L)	517 (8.7)	495 (7.6)
Clearance (θ3) (L/h)	18.8 (4.6)	14.8 (3)
Primary site of cancer on clearance(θ_{10}) : TVCL* $\theta 10^{**PR01}$	0.68 (5.9)	
Inter-compartmental clearance (θ4) (L/h)	46.2 (7.8)	48 (7.5)
K_a (θ5) (hr^{-1})	6.07	6.07
Inter-subject variability for V_3 (%)	51.5 (22.2)	54.2 (24.3)
Inter-subject variability for V_2 (%)	47.2 (32.6)	46.2 (32.5)
Correlation between V_2 and CL	0.4	0.63
Inter-subject variability for CL (%)	48.8 (8.7)	53.1 (8.1)
Inter-subject variability for intercompartmental clearance (%)	36.3 (37.7)	36.1 (38)
Inter-subject variability for K_a (%)	0	0
Residual variance (multiplicative) for profiles	0.283 (7.5)	0.283 (7.4)
Residual variance (additive) for profiles	0.075 (33.1)	0.076 (26.6)
Residual variance (multiplicative) for trough	0.38 (5)	0.383 (5)
Residual variance (additive) for trough	0.096 (42)	0.0939 (44.2)
Objective function	**8314**	**8361**

4.2 Exposure-Effectiveness Analysis

4.2.1 Objectives

To evaluate exposure response for efficacy with progression free survival as the response variable for the study C2240.

4.2.2 Methods

The main difference between the reviewer's analysis and the sponsor's analysis was that only true trough concentrations (identified based on the dosing and sampling times) were utilized for the reviewer's analysis. Other difference was, instead of grouping the concentrations as sponsor did, the reviewer tried to group them into quartiles, binary groups, three groups etc. to see if any exposure-response relationship could be established.

4.2.3 Datasets

Pkconc.xpt, a_cenpat.xpt, a_ident.xpt, trt.xpt of the C2240 study was utilized in the analysis.

4.2.4 Software

SAS 9.1 was utilized for data refinement and S-PLUS was used for graphical evaluations.

4.2.5 Model

Kaplan Meier analysis was performed to evaluate the progression free survival curves among various subgroups.

4.2.6 Results

As indicated in **Figure 2**, the progression free survival was similar among various concentration subgroups whichever way the data was grouped. There was high pharmacokinetic variability in trough concentrations ranging from 1.4 to 135 ng/ml. These trough concentrations are even higher than the peak concentrations of everolimus reported in other Phase 1 studies. Sponsor have acknowledged in the population PK report that several of these trough concentrations which are unusually high may not be actual trough concentrations because of the possibility of misreporting in sampling times. If this is true then the results cannot be interpreted with confidence. It might also be true that the dose selected (10 mg daily) for registration trial is at the higher end of the dose response curve, because if we notice in **Figure 2**, even though the survival curves of treatment group are merged together, they are well separated from the placebo and therefore assure towards the effectiveness of everolimus in this patient population.

4.3 Dose-Exposure-Safety Relationship

4.3.1 Objectives

To explore dose-exposure-safety relationship of everolimus.

4.3.2 Methods

Trough concentrations for C2240 study were divided into quartiles and % of subjects having adverse events in each quartile were plotted. Since only one dose (10 mg daily) was employed in this study and there were doubts regarding the validity of these trough concentrations, data from other controlled phase 1b study (C2107) was also explored for exposure-safety relationships. Both weekly (20, 50 and 70 mg) and daily (5 and 10 mg) dosing regimens were administered in this study and thus this study was expected to provide wider range of concentrations to explore exposure-safety relationships.

4.3.3 Datasets

Pkconc.xpt and a_aev.xpt of the C2240 study and, c2107cnc.xpt and a_aev.xpt of the C2107 study were utilized for the analysis.

4.3.4 Software

SAS 9.1 was utilized for data refinement and S-PLUS was used for graphical evaluations.

4.3.5 Model

No formal statistical analysis was conducted as the aim was to graphically evaluate if there was a trend for exposure-safety in various subgroups.

4.3.6 Results

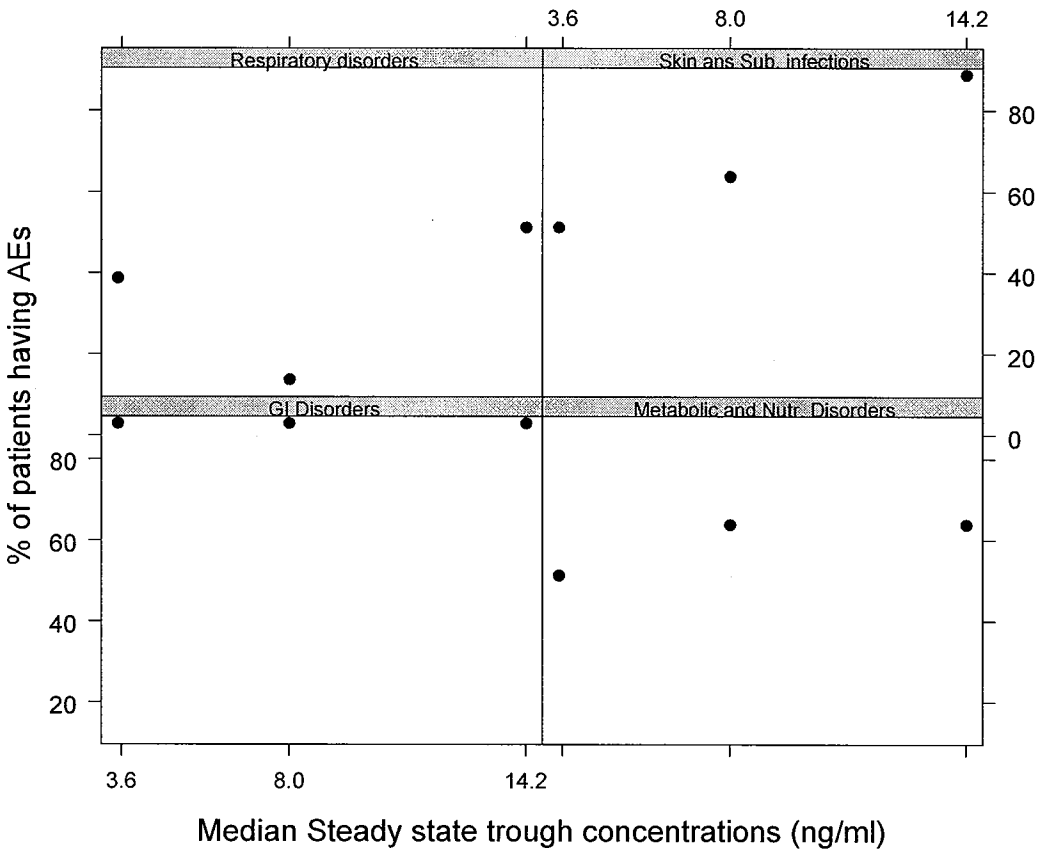
As evident from **Figure 3**, no trend was observed for any of the adverse events (C2240 study). This could be attributed to similar reasons as explained in section 4.2.6. **Table 5** shows adverse events by class for all dosage regimens in C2107 study. In general no trend was observed, however for skin and subcutaneous infections, the % adverse events increased with dose for either weekly or daily regimens. The trough concentrations for 24 subjects administered daily regimen (5 or 10 mg daily) were divided into three groups and % subjects having adverse events were plotted (

Figure 9). Skin and subcutaneous infections, metabolism and nutritional disorders increased with increase in concentrations.

Table 5: Patients with frequent AEs by system organ class (at least 10% of all patients, Safety population).

	Weekly			Daily		All
	20 mg	50 mg	70 mg	5 mg	10 mg	patients
	N=12	N=12	N=7	N=12	N=12	N=55
System organ class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with AEs	12 (100)	12 (100)	7 (100)	12 (100)	12 (100)	55 (100)
Gastrointestinal disorders	7 (58.3)	9 (75.0)	5 (71.4)	10 (83.3)	11 (91.7)	42 (76.4)
General disorders and admin. site conditions	7 (58.3)	7 (58.3)	6 (85.7)	9 (75.0)	8 (66.7)	37 (67.3)
Metabolism and nutrition disorders	5 (41.7)	7 (58.3)	4 (57.1)	7 (58.3)	7 (58.3)	30 (54.5)
Skin and subcutaneous tissue disorders	3 (25.0)	6 (50.0)	4 (57.1)	7 (58.3)	9 (75.0)	29 (52.7)
Nervous system disorders	6 (50.0)	3 (25.0)	4 (57.1)	9 (75.0)	5 (41.7)	27 (49.1)
Respiratory, thoracic and mediastinal disorders	3 (25.0)	4 (33.3)	5 (71.4)	3 (25.0)	5 (41.7)	20 (36.4)
Infections and infestations	3 (25.0)	2 (16.7)	3 (42.9)	2 (16.7)	3 (25.0)	13 (23.6)
Blood and lymphatic system disorders	3 (25.0)	2 (16.7)	4 (57.1)	1 (8.3)	2 (16.7)	12 (21.8)
Musculoskeletal and connective tissue disorders	2 (16.7)	4 (33.3)	1 (14.3)	2 (16.7)	2 (16.7)	11 (20.0)
Investigations	3 (25.0)	1 (8.3)	2 (28.6)	2 (16.7)	1 (8.3)	9 (16.4)
Psychiatric disorders	3 (25.0)	0	0	0	3 (25.0)	6 (10.9)

Figure 9: Percent adverse events in the three groups. The concentration ranges in these three groups were 2.3-6, 7-11 and 11.7-46.7, respectively.



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

/s/

Julie Bullock
3/5/2009 04:44:52 PM
BIOPHARMACEUTICS

Nitin Mehrotra
3/5/2009 06:38:44 PM
BIOPHARMACEUTICS

Christoffer Tornoe
3/5/2009 07:45:28 PM
BIOPHARMACEUTICS

Brian Booth
3/6/2009 08:27:17 AM
BIOPHARMACEUTICS

Atiqur Rahman
3/9/2009 02:16:21 PM
BIOPHARMACEUTICS