Interdisciplinary Review Team for QT Studies Consultation:

Thorough QT Study Review

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

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

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

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

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

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

1.2 QT Interdisciplinary Review Team's Comments

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

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

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

2 PROPOSED LABEL

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

12.2 Pharmacodynamics

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3 BACKGROUND

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

3.1 MARKET APPROVAL STATUS

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

3.2 PRECLINICAL INFORMATION

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

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

3.3 PREVIOUS CLINICAL EXPERIENCE

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

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

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

3.4 CLINICAL PHARMACOLOGY

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

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

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

4.2 TQT STUDY

4.2.1 Title

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

4.2.2 Protocol Number

CRAD001C2118

4.2.3 Study Dates

11 July 2007 to 19 November 2007

4.2.4 Objectives

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

4.2.5 Study Description

4.2.5.1 Design

The study was carried out in two phases.

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

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

4.2.5.2 Controls

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

4.2.5.3 Blinding

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

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