2.1.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The total concentration of temsirolimus and sirolimus in whole blood was measured, and this was appropriate.

2.1.4 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation, http://www.fda.gov/cder/guidance/4252fnl.pdf)

In the current phase 1/2 trial (3066K1-139-US), whole blood concentrations of temsirolimus and its major metabolite (sirolimus) were determined simultaneously in human whole blood samples using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method. The bioanalytical method validation reports for this method were submitted in the initial NDA submission (NDA 22,088, SDN 000) under Module 5.3.1.4 in reports titled "RPT-39703" and RPT-39702". The reports were reviewed by the Clinical Pharmacology Reviewer for the original NDA submission, and were found acceptable.

In brief, temsirolimus and sirolimus were simultaneously measured in this study using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method with internal standard (RPT-60231). Two (2) separate assays were employed to cover the therapeutic exposure
ranges observed. For a low range of quantitation assay, concentrations of 0.25 to 25 ng/mL for temsirolimus and sirolimus were validated using 1 mL of whole blood (RPT-39702). For the high range of quantitation assay, concentrations of 2.5 to 2500 ng/mL for temsirolimus and 2.5 to
250 ng/mL for sirolimus were validated using 0.2 mL of whole blood (RPT-39703).
For the low range assay, the mean interday variability (coefficient of variation [CV]) of temsirolimus and sirolimus quality control samples was <9.6%, and intraday variability was <15.1%. Mean interday accuracy was within ± 6.7% and mean intraday accuracy was within ± 11.1%. Mean accuracy at the lower limit of quantitation of 0.25 ng/mL was acceptable (<16.8%), and mean bias was minimal (-4.4% for temsirolimus and 2.8% for sirolimus). No interference was observed in blank blood or blood spiked with internal standard.
For the high range assay, the mean interday variability (%CV) of temsirolimus and sirolimus quality control samples was <7.3%, and intraday variability was <10.1%. Mean interday accuracy was within ± 7.4% and mean intraday accuracy was within ± 9.1%. Mean accuracy at the lower limit of quantitation of 0.25 ng/mL was acceptable (<6.3%), and mean bias in minimal (9.2% for temsirolimus and 12.4% for sirolimus). No interference was observed in negative control blood or blood spiked with internal standard.

For further details, regarding the bioanalytical method used please refer to the Clinical Pharmacology Review of the original NDA 22,088 submision.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are shown in track change format below (FDA recommended language is underlined, and the sponsor's proposed changes to the current label

Table 7. PK Parameters of Sirolimus in Pediatric Patients with Relapsed/Refractory Solid Tumors and Adult Patients with RCC

Age (y)	Dose	n	Mean ± SD, CV%	
			AUC(ng*h/mL)	Cmax (ng/mL)
0-18	75-mg/m^2	30	7866±4959, 63%[b]	163±74, 45%[c]
Adult	25-mg[a]	11	3793±1466, 39%	34±19, 56%

[a] 25-mg flat dose is 14.4 mg/m^2 for BSA of 1.73 m^2
[b] Geometric mean (cv%) of AUC: 6944(47%)
[c] Geometric mean (cv%) of Cmax: 148(40%)

4.2 RECOMMENDATIONS

Division of Pharmacometrics recommends modifying the section 8.4 in label regarding the comparison of exposure levels between pediatric subjects and adult patients (See Section 1.3 and Section 3.1).

4.3 LABEL STATEMENTS

Please see section 3 of the clinical pharmacology review for full detailed labeling recommendations.

(b) (4)

5 PERTINENT REGULATORY BACKGROUND

Temsirolimus (Torisel, NDA022088) is approved for the treatment of advanced renal cell carcinoma for adults in United States in 2007. In addition, temsirolimus is also approved for the treatment of relapsed or refractory mantle cell lymphoma for adults in the European Union, Australia, and other countries.
The formal Written Request was issued on Sep 2004. Three amendments to Written Request were subsequently submitted on Sep 2007, Sep 2010 and Feb 2011. In Dec 2011 sponsor submitted a request for pediatric exclusivity determination and the pediatric study report as response to the Written Request. The study report indicated that the primary efficacy endpoint (objective response rate (ORR)) was not met

in pediatric population (1-21 y) given 75 mg/m^2 IV weekly dose. (b) (4) This review will focus on the PK aspects in this pediatric study report.

6 RESULTS OF SPONSOR'S ANALYSIS

Sponsor conducted population PK study to characterize the PK parameters of temsirolimus and sirolimus in pediatric patients with relapsed/refractory solid tumors and made comparison in PK exposure between adults and pediatric population.

6.1 COMPARISON OF PHARMACOKINETIC (PK) EXPOSURE BETWEEN ADULTS AND PEDIATRIC PATIENTS

Pediatric subjects in the analysis included 2 infants or toddlers (28 days to 23 months), 20 children (2 to 11 years), 8 adolescents (12 to 18 years), and 5 young adults (19 to 21 years). As shown in Table 8, the non-compartmental PK analysis indicated that mean exposures (AUC_{ss}) in whole blood for temsirolimus and sirolimus in pediatric subjects following the 75 mg/m^2 dose were approximately 10-fold and 2-fold higher, respectively, than adults receiving the 25-mg flat dose. In the pediatric patients with relapsed/refractory solid tumors, clearance of temsirolimus was lower.

Sponsor concluded: "Comparisons of exposure with adult subjects show that temsirolimus C_{max} and AUC_{sum} (sum of temsirolimus plus sirolimus AUCs) in the pediatric subjects were comparable to values in adult subjects for a given flat dose, while temsirolimus AUC was higher in the pediatric subjects. This greater exposure to parent drug in the pediatric population was balanced by the shorter half-lives of sirolimus metabolite and commensurate lower AUCs" (Figure 5). The exposures in pediatrics subjects appeared to exhibit significantly higher variability than the adult subjects. For AUC_{sum}, mean exposure following the 75 mg/m^2 dose was approximately 3-fold higher (15464/5141) than the respective mean AUC_{sum} value in adult patients following the multiple doses."