Clinical Pharmacology Review

NDA	22-088
Submission Date:	2 Dec., 2011
Brand Name:	Torisel™
Generic Name:	Temsirolimus injection
Formulation:	Torisel injection, 25 mg/mL supplied with Diluent for Torisel
OCP Reviewer:	Jeanne Fourie Zirkelbach, PhD
OCP Team Leader:	Qi Liu, PhD
OCP Division:	Division of Clinical Pharmacology V
PM Reviewer:	Jingyu Yu, PhD
PM Team Leader:	Christine Garnett, PharmD
ORM Division:	Division of Drug Oncology Products
Sponsor:	Wyeth
Submission Type; Code:	Supplement 014, SDN 353 - Efficacy Supplement, Pediatric Exclusivity
Approved Dosing regimen:	25 mg infused i.v. over a 30-60 minute period once per week.
Approved Indication:	Advanced renal cell carcinoma

Table of contents

1 EXECUTIVE SUMMARY

Temsirolimus (Torisel®) injection is a mammalian target of rapamycin (mTOR) inhibitor.

Temsirolimus injection (Torisel®) is currently approved in the United States for the treatment of advanced renal cell carcinoma. The current efficacy supplement was submitted to FDA for pediatric exclusivity determination. The applicant submitted proposed labeling and pediatric study results from a single clinical trial to address the Pediatric Written Request.

Protocol 3066K1-139-US was a phase 1/2 dose-escalation and efficacy trial of temsirolimus given as a 60-minute intravenous (IV) infusion once weekly in 3-week cycles to children and adolescents with recurrent or refractory solid tumors. The trial consisted of two parts. Part 1 determined the maximum tolerated dose (MTD), and Part 2 determined the preliminary efficacy of temsirolimus in pediatric patients with advanced solid tumors.

Part 1 of the trial was conducted in 19 pediatric patients with advanced cancer. Dose levels for Part 1 were 10, 25, 75 and 150 mg/m^2, and the maximum tolerated dose (MTD) was determined to be 150 mg/m^2. In Part 1, the single dose (Day 1, Cycle 1) and multiple dose (Day 1 Cycle 2) whole blood pharmacokinetics of temsirolimus and sirolimus were characterized in pediatric patients over the dose range of 10 to 150 mg/m^2.

Part 2 of the trial assessed the safety and antitumor activity of temsirolimus 75 mg/m^2 given as a 60-minute IV infusion once weekly in 3-week cycles to children and adolescents (n = 52) with refractory or relapsed neuroblastoma, rhabdomyosarcoma and high-grade gliomas. The multiple dose (Day 1, Cycle 2) whole blood pharmacokinetics of temsirolimus and sirolimus were characterized in 35 pediatric patients (25 male and 10 female) aged 28 days to 21 years (median age of 8 years) at the 75 mg/m^2 dose. In Part 2 of the trial, enrollment was halted due to insufficient antitumor activity for all three tested indications.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 22-088. From a Clinical Pharmacology perspective, the submitted results from the clinical trial are acceptable, and the study fairly responded to the Written Request.

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations.

1.2 PHASE IV COMMITMENTS

None.

1.3 REGULATORY BACKGROUND

The applicant submitted proposed labeling and pediatric study results from a single clinical trial to address the Pediatric Written Request first issued by the Division of Drug Oncology Products (DDOP) on January 12. 2001 with amendments on 30 September, 2004, September 28, 2007, September 29, 2010 and February 25, 2011.

1.4 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Temsirolimus (Torisel®) injection is a mammalian target of rapamycin (mTOR) inhibitor. It is approved in the United States for the treatment of advanced renal cell carcinoma.

The applicant submitted results from a clinical phase 1/2 dose-escalation and efficacy trial (3066K1-139-US) in pediatric patients with solid tumors for pediatric exclusivity determination. Temsirolimus given as a 60-minute IV infusion once weekly in 3-week cycles to pediatric patients with recurrent or refractory solid tumors. Pre-medication with IV diphenhydramine 1 mg/kg was given 30 minutes before the start of reach temsirolimus infusion.

The dose-escalation Part 1 of the trial was conducted in 19 pediatric patients with recurrent or refaractory solid tumors. The single dose (Day 1, Cycle 1) and multiple dose (Day 1 Cycle 2) whole blood pharmacokinetics of temsirolimus and sirolimus were characterized over the dose range of 10 to 150 mg/m^2. The the single dose (Day 1, Cycle 1) and multiple dose (Day1, Cycle 2) total systemic exposure (AUC) showed less than dose-proportional temsirolimus pharmacokinetics over the dose range studied (10 mg/kg to 150 mg/kg). The body surface adjusted clearance and mean terminal elimination half-life ($t1/2_\beta$) of temsirolimus and sirolimus appeared to increase over the dose range from 10 to 150 mg/m^2.

Part 2 of the trial assessed the safety and antitumor activity of the 75 mg/m^2 dose given as a 60-minute IV infusion once weekly in 3-week cycles to pediatric patients (n = 52) with refractory or relapsed neuroblastoma, rhabdomyosarcoma and high-grade gliomas. The 75 mg/m^2 dose was used in Part 2 based on investigator-based concerns regarding the tolerance of the 150 mg/m^2 dose and the adverse event profile of the 150 mg/m^2 dose.

In Part 2, the multiple dose (Cycle 2, Day 1) whole blood pharmacokinetics of temsirolimus and sirolimus were characterized in 35 pediatric patients (25 male and 10 female) aged 28 days to 21 years (median age of 8 years) at the 75 mg/m^2 dose. Following multiple doses of temsirolimus 75 mg/m^2 as a 60 minute IV infusion (Part 2, Cycle 2, Day1) in pediatric patients with advanced solid tumors, the mean (± SD) temsirolimus AUC and C_{max} were 13900 ± 24100 ng.hr/mL and 6280 ± 21000 ng/mL, respectively. Following multiple doses of temsirolimus 75 mg/m^2 as once-per week 60 minute IV infusion (Part 2, Cycle 2, Day1) in pediatric patients with advanced solid tumors, the geometric mean body surface adjusted clearance of temsirolimus was 9.45 L/h/m^2 (67.7% CV (coefficient of variation), and the mean elimination half-life (t1/2β) was 30.7 hours.

In Part 2, following multiple doses of temsirolimus 75 mg/m^2 as a 60 minute IV infusion (Cycle 2, Day 1) in pediatric patients with advanced solid tumors, the mean (± SD) sirolimus AUC and

C_{max} were 9582 ± 7472 ng.hr/mL and 163 ± 71 ng/mL, respectively. Following multiple doses of temsirolimus 75 mg/m^2 as a 60 minute IV infusion (Part 2, Cycle 2, Day 1) in pediatric patients with advanced solid tumors, the geometric mean body surface adjusted clearance of sirolimus was 9.26 L/h/m^2 (45.5% CV (coefficient of variation), and the mean elimination half-life (t1/2β) was 44 hours.

Based on the population pharmacokinetic (PK) analysis, the total clearance of temsirolimus and sirolimus increases with increasing dose, which is possibly due to the saturation of specific binding in the blood. The dose-dependent PK of temsirolimus and sirolimus in pediatric subjects is consistent with that observed in adults.

Total clearance of temsirolimus increases with the body weight (WT) in pediatric patients. After accounting for body weight in the model, there was no additional effect of age, gender or other factors on clearance. The exposure (AUC_{ss}) to 75-mg/m^2 temsirolimus in pediatric patients is similar for subjects of different sizes as measured by BSA. Therefore, the BSA-based dosing regimen is reasonable. For sirolimus, however, there was no additional effect of WT on apparent clearance (CL/fm). The exposure (AUC_{ss}) to sirolimus in pediatric patients increases with increasing BSA.

The mean exposure to temsirolimus and sirolimus in pediatric patients at the 75-mg/m^2 dose, given as a 60-minute IV infusion, is approximately 6-fold and 2-fold higher, respectively, than the mean exposure in adult patients at a 25-mg dose administered as an intravenous infusion.

Signatures:

Reviewer: Jeanne Fourie Zirkelbach, PhD
Division of Clinical Pharmacology 5

Team Leader: Qi Liu, PhD
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - Y Adkins; MTL - E Maher; MO - P Kleutz,
DCP-5: Reviewers - J Fourie Zirkelbach, J Yu.
DDD - B Booth
PM TL - C Garnett
PG TL - R Charlab-Orbach
DD - A Rahman

2 QUESTION BASED REVIEW

Note: Only relevant sections were completed.

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

Study Design:

The applicant conducted an open-label, 2-part phase-1/2 dose-escalation and efficacy trial (3066K1-139-US) in pediatric patients with advanced solid tumors. Temsirolimus was given as a 60-minute IV infusion once weekly in 3-week cycles to pediatric patients with recurrent or refractory solid tumors. Pre-medication with IV diphenhydramine 1 mg/kg was given 30 minutes before the start of each temsirolimus infusion. Inclusion criteria included adequate renal function (creatinine clearance ≥ lower limit for age) and hepatic function (total bilirubin ≤ 1.5 x the upper limit of normal (ULN) for age, serum ALT ≤ 3 x ULN for age).

Four predefined dose levels were selected for Part 1 of this study (10, 25, 75, and 150 mg/m^2). The choice of the 4 dose levels was based first on results of study 3066K1-100-US, a phase 1 study in adult subjects with refractory solid tumors, in which the MTD for IV temsirolimus administered on a weekly schedule was determined to be 220 mg/m^2. In addition, the recommended dose approved in adults for the indication of renal cell carcinoma is 25 mg administered as a weekly IV infusion.

In part 2 of the trial patients were treated at the 75 mg/m^2 dose (as determined in Part 1) given as a 60-mintute IV infusion once weekly in 3-week cycles. The primary efficacy variable was the objective response rate (ORR), i.e., the proportion of subjects with complete response [CR] or partial response [PR] within 12 weeks of treatment.

Primary Objective for Part 1 of the Study:

- To evaluate the safety of IV temsirolimus given once weekly to children with solid tumors with disease that was recurrent or refractory to standard therapy or for whom standard therapy was not available.

Secondary Objectives for Part 1 of the Study:

- To identify the maximum tolerated dose (MTD) or a biologically effective dose of IV temsirolimus when administered once weekly.
- To obtain preliminary information on the antitumor activity of IV temsirolimus.
- To determine the single- and multiple-dose pharmacokinetics (PK) of temsirolimus in children with once-weekly IV treatment.

- To determine the effects of IV temsirolimus on changes in the mTOR signaling pathway in the peripheral blood mononuclear cells (PBMCs).

Primary Objective for Part 2 of the Study:

- The primary objective of part 2 of the study was to obtain preliminary information on the antitumor activity of IV temsirolimus in children with relapsed/refractory neuroblastoma, high-grade gliomas, and rhabdomyosarcoma. Antitumor activity was assessed by determining the percentage of subjects exhibiting objective response (complete and partial responses) within 12 weeks.

Secondary Objective for Part 2 of the Study:

- To verify the safety of the selected dose.
- To evaluate the percentage of subjects exhibiting freedom from progression (ie, disease stabilization) at 3 months.
- To determine the multiple-dose PK of temsirolimus in children with once-weekly IV treatment.
- To determine the effects of IV temsirolimus on changes in the mTOR signaling pathway in the bone marrow.

Pharmacokinetic Data:

In Part 1, whole blood samples for the determination of blood levels of temsirolimus and sirolimus levels were collected at 0, 1, 2, 6, 24, and 168 hours during cycle 1 and at 0, 1, 2, 6, 24, 72, 96 and 168 hours during cycle 2. In part 2, whole blood samples for determination of temsirolimus and sirolimus concentrations were drawn at 0, 1, 6, 24, 48, 72, 96 and 168 hours during the first week of cycle 2. The single dose and multiple dose whole blood temsirolimus and sirolimus pharmacokinetics were characterized using non-compartmental analysis.

Part 1 Single Dose and Mutliple Dose Temsirolimus and Sirolimus Whole Blood Pharmacokinetic Results:

The single dose pharmacokinetics of temsirolimus and sirolimus were characterized in 19 pediatric patients (11 male and 8 female) aged 4 to 21 years (median age of 11 years) over the dose range of 10 to 150 mg/m^2 (See Table 1). The multiple dose pharmacokinetics of temsirolimus and sirolimus were characterized in 16 pediatric patients (9 male and 7 female) aged 4 to 20 years (median age of 12 years) over the dose range of 10 to 150 mg/m^2 (see Table 1).

The reviewer was able to replicate the results from the sponsor's non-compartmental analysis of the single dose and multiple dose pharmacokinetics of temsirolimus and sirolimus from Part 1 of the current trial. In pediatric patients with advanced malignancies, the single dose (Day 1, Cycle 1) and multiple dose (Day1, Cycle 2) total temsirolimus systemic exposure (AUC) showed less than dose-proportional pharmacokinetics over the dose range studied (10 mg/kg to 150 mg/kg) (see Figure 1).

The single dose (Part 1, Cycle 1, Day 1) temsirolimus AUC (mean ±SD) ranged from 2000 ± 959 ng.h/mL at the 10 mg/m^2 dose to 2810 ng.h/mL at the 75 mg/m^2 dose. The single dose temsirolimus Cmax (mean ± SD) ranged from 307 ± 91 ng/mL at the 10 mg/m^2 dose to 480 ±135

ng/mL at the 75 mg/m^2 dose, and occurred at the end of the infusion. The body surface adjusted temsirolimus clearance appeared to increase over the dose range studied from 10 to 150 mg/m^2 (see Figure 2, Table 2 and Table 3). The mean terminal elimination half-life ($t1/2_\beta$) of temsirolimus ranged from 14.4 to 24.2 hours and increased over the 10 to 150 mg dose range studied (see Table 3).

The single dose (Part 1, Cycle 1, Day 1) sirolimus AUC (mean ± SD) ranged from 2970 ± 1340 ng.h/mL at the 10 mg/m^2 dose to 7410 ± 3390 ng.h/mL at the 75 mg/m^2 dose. The single dose sirolimus Cmax (mean ± SD) ranged from 50 ± 15 ng/mL at the 10 mg/m^2 dose to 108 ± 42 ng/mL at the 75 mg/m^2 dose. The median Tmax values ranged from 2 to 6 hours. The body surface adjusted sirolimus clearance appeared to increase over the dose range studied from 10 to 150 mg/m^2 (see Figure 2, Table 2 and Table 3). The mean terminal elimination half-life ($t1/2_\beta$) of sirolimus ranged from 31 to 48 hours over the 10 to 150 mg dose range studied. (see Table 3).

Table 1. Demographics of patients for pharmacokinetic evaluation enrolled in Part 1.

Single Dose	**Age (Years)**	**BSA (m^2)**
N	19	19
Mean (standard deviation (SD))	12 (6)	1.26 (0.46)
Minimum	4	0.65
Maximum	21	2.00
Multiple Dose		
N	16	16
Mean (standard deviation (SD))	12 (6)	1.26 (0.44)
Minimum	4	0.68
Maximum	20	1.93

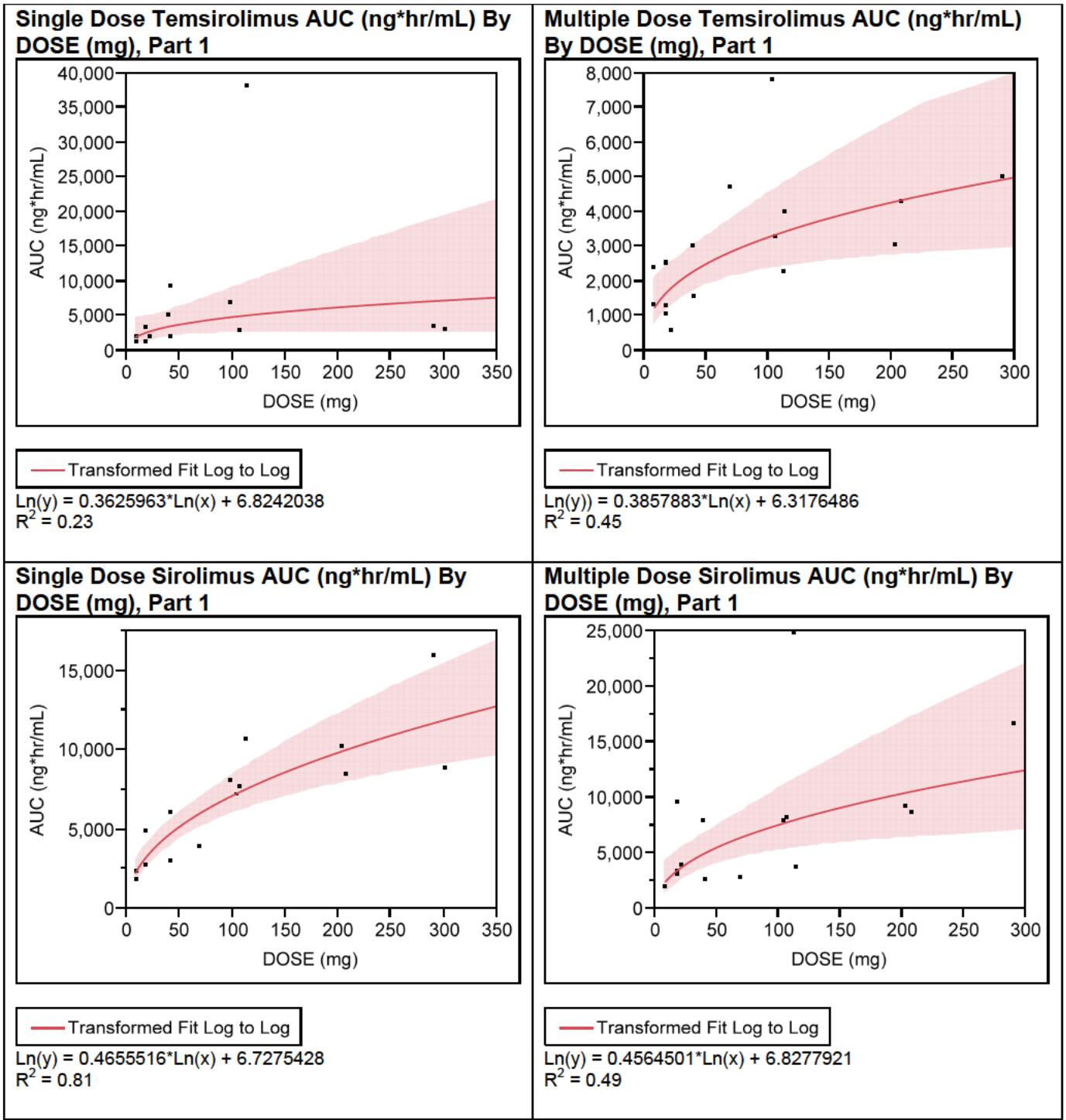


Figure 1. Transformed fit: Log AUC vs. Log of dose over the 10 to 150 mg/m^2 single (Cycle 1, Day 1) and multiple oral dose (Cycle 2, Day1) range in pediatric patients with metastatic cancer.

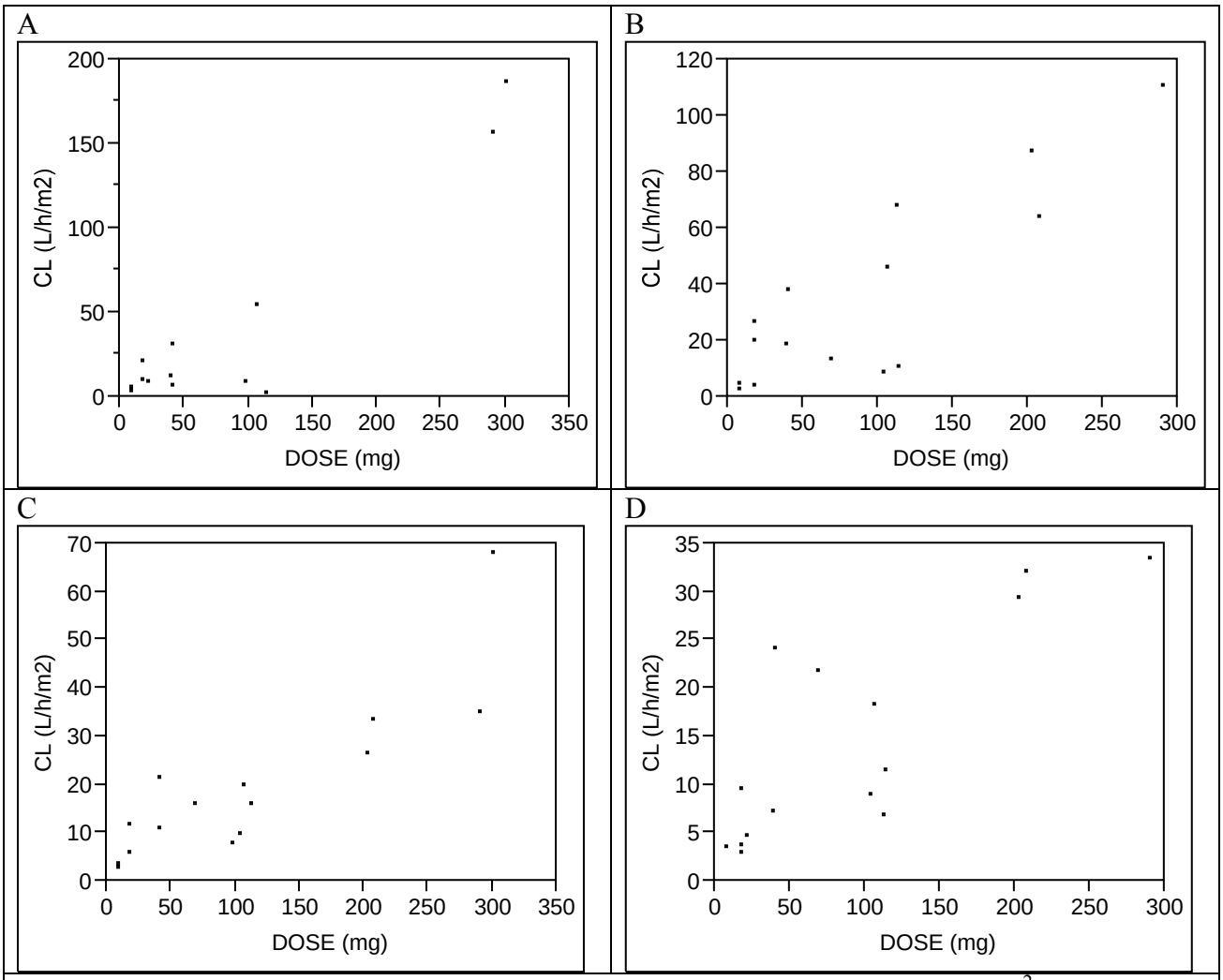


Figure 2. Plots of body surface adjusted clearance vs dose over the 10 to 150 mg/m^2 single (Cycle 1, Day 1) and multiple oral dose (Cycle 2, Day1) range in pediatric patients with metastatic cancer. Panel A- temsirolimus single dose; Panel B- temsirolimus multiple dose; Panel C- sirolimus single dose; Panel D- sirolimus multiple dose. Data are from Part 1 of the current study report.

Table 2. Summary of Temsirolimus and Sirolimus Whole Blood Single Dose Pharmacokinetics in Pediatric Patients after a single 60 min IV infusion (dose range 10 to 150 mg/m^2). Data are from Part 1 of trial 3066K1-139-US and are summarized from the sponsor non-compartmental pharmacokinetic analysis (Mean (SD)).

	Mean (SD)							
	Temsirolimus				**Sirolimus**			
	10 mg/m^2 (N=4)	**25 mg/m^2 (N=5)**	**75 mg/m^2 (N=3)**	**150 mg/m^2 (N=7)**	**10 mg/m^2 (N=4)**	**25 mg/m^2 (N=5)**	**75 mg/m^2 (N=3)**	**150 mg/m^2 (N=7)**
AUC ng.h/mL	2000 (959)	4640 (3430), n=4	2810, n=1	13000 (17000), n=4	2970 (1340)	4520 (2080), n=2	7410 (3390)	9800 (3150), n =6
Cmax ng/mL	307 (91)	487 (141)	480 (135)	9230 (18200)	50.2 (15.3)	63.9 (33.4)	108 (41.5)	261(121)
Tmax (h)[a]	1 (0.92-1.25)	1.08 (0.98-1.15)	1.42 (1.08-1.52)	1 .00 (0.98-1.58)	2 (1-2)	6 (1-25)	6 (5-6)	2 (1.-6)
T1/2 (h)[b]	10.6 (9-11.1)	16.4 (9.92-23.1), n=4	24 (24-24), n=1	19.3 (4.75-29.5), n=4	47.1 (40.6-60.2)	43.9 (38.1-49.7), n=2	41.9 (39.2-44.4)	39.5 (31.6-58.4), n =6
CL (L/h/m^2)	9. 7 (8)	14.7 (11), n=4	54.1, n=1	88.6 (96), n=4	6.0 (4)	16.0 (7), n=2	17.2 (2)	30.1 (24), n=6

Abbreviations: AUC = area under the curve (evaluated from 0-infinity for single dose); Cmax = maximal observed concentration; CL = systemic clearance; N = number of patients; t1/2 = half-life; tmax = time to maximal observed concentration.
a Median (range)
b Mean (range)

Table 3. Summary of Temsirolimus and Sirolimus Whole Blood Multiple Dose Pharmacokinetics in Pediatric Patients (Part 1, Cycle 2, Day 1; weekly 60 min IV infusion) over the dose range of 10 to 150 mg/m^2. Data are from Part 1 of trial 3066K1-139-US and are summarized from the sponsor non-compartmental pharmacokinetic analysis (Mean (SD)).

	Mean (SD)							
	Temsirolimus				**Sirolimus**			
	10 mg/m^2 (N=4)	**25 mg/m^2 (N=4)**	**75 mg/m^2 (N=3)**	**150 mg/m^2 (N=5)**	**10 mg/m^2 (N=4)**	**25 mg/m^2 (N=4)**	**75 mg/m^2 (N=3)**	**150 mg/m^2 (N=5)**
AUCtau ng.h/mL	1600 (540)	2580 (768), n=3	3500 (1140)	4960 (2000)	4190 (3660)	4380 (2380)	12000 (11500)	9240 (4710)
Cmax ng/mL	252 (98)	403 (128)	807 (279)	2570 (1110)	59.2 (38.1)	68.2 (22.4)	195(183)	276 (119)
Tmax (h)[a]	0.96 (0.92-1.42)	1.32 (1.00-3.15)	1.07 (1.00-1.38)	1.12 (0.97-1.52)	1.69 (0.98-2.03)	2.25 (1.22-7.17)	5.33 (2.15-6.18)	1.52 (0.97-5.33)
T1/2 (h)[b]	14.4 (8.5-18.2)	14.3 (7.89-26.3), n=3	24 (23.6-27.3)	24.2 (15.5-31.3),	46.0 (37.0-68.9)	39.0 (27.2-53.1)	48.0 (37.3-61.4)	31.1 (23.8-36.3)
CL (L/h/m^2)	13.5 (12)	20.3 (17), n=3	42.2 (28)	56.3 (46), n=5	4.9 (3)	9.9 (10), n=2	15.6 (8)	23 (9)

Abbreviations: AUC = area under the curve (dosing interval) for multiple dose; Cmax = maximal observed concentration; CL = systemic clearance; CV = coefficient of variation; N = number of patients; t1/2 = half-life; tmax = time to maximal observed concentration; Vss = volume of distribution at steady state.
a Median (range)
b Mean (range)

Part 2 Mutliple Dose Temsirolimus and Sirolimus Whole Blood Pharmacokinetic Results:
In part 1 of the protocol, the dose for further study in Part 2 of the protocol was determined to be 75 mg/m^2. In Part 2 of the protocol, 52 pediatric patients received 75 mg/m^2 temsirolimus given as a 60-mintute IV infusion once weekly in 3-week cycles.

Following a single 75 mg/m^2 dose of temsirolimus (Cycle 1, Day 1) in Part 2 of the protocol, the single dose pharmacokinetics were assessed in four patients. Due to the limited number of subjects from which samples were obtained, the single dose pharmacokinetic parameters were not determined in Part 2 of the protocol.

In Part 2 of the protocol, the multiple dose (Cycle 2, Day 1) pharmacokinetics of temsirolimus and sirolimus were characterized in 35 pediatric patients (25 male and 10 female) aged 28 Days to 21 years (median age of 8 years) at the 75 mg/m^2 dose. (see Table 4).

Table 4. Demographics of patients for multiple dose pharmacokinetic evaluation enrolled in Part 2.

Multiple dose	**Age (Years)**	**BSA (m^2)**
N	35	35
Mean (standard deviation (SD))	10 (6)	1.17 (0.52)
Minimum	1	0.54
Maximum	21	2.01

The reviewer was able to replicate the results from the sponsor's non-compartmental analysis of the multiple dose pharmacokinetics of temsirolimus and sirolimus from Part 2 of the current trial.

Following multiple doses of temsirolimus 75 mg/m^2 as a 60 minute IV infusion (Part 2, Cycle 2, Day1) in pediatric patients with advanced solid tumors, the mean (± SD) temsirolimus AUC and C_{max} were 13900 ± 24100 ng.hr/mL and 6280 ± 21000 ng/mL, respectively (see Table 5). Following multiple doses of temsirolimus 75 mg/m^2 as a 60 minute IV infusion (Part 2, Cycle 2, Day1) in pediatric patients with advanced solid tumors, the geometric mean body surface adjusted clearance of temsirolimus was 9.45 L/h/m^2 (67.7% CV (coefficient of variation), and the mean elimination half-life (t1/2β) was 30.7 hours (see Table 5).

Following multiple doses of temsirolimus 75 mg/m^2 as a 60 minute IV infusion (Part 2, Cycle 2, Day1) in pediatric patients with advanced solid tumors, the mean (± SD) sirolimus AUC and C_{max} were 9582 ± 7472 ng.hr/mL and 163 ± 71 ng/mL, respectively (see Table 5). Following multiple doses of temsirolimus 75 mg/m^2 as a 60 minute IV infusion (Part 2, Cycle 2, Day 1) in pediatric patients with advanced solid tumors, the geometric mean body surface adjusted clearance of sirolimus was 9.26 L/h/m^2 (45.5% CV (coefficient of variation), and the mean elimination half-life (t1/2β) was 44 hours (see Table 5).

Table 5. Summary of Temsirolimus and Sirolimus Whole Blood Multiple Dose Pharmacokinetics in Pediatric Patients (Part 2, Cycle 2, Day 1; weekly 60 min IV infusion) over the dose range of 10 to 150 mg/m^2. Data are from Part 2 of trial 3066K1-139-US and are summarized from the sponsor non-compartmental pharmacokinetic analysis.

Temsirolimus

Dose (mg/m^2)	Summary Statistics	Cmax (ng/mL)[a]	Tmax (h)	T1/2β (h)	AUC_{tau} (ng.hr/mL)[a]	CL/F (L/hr/m^2)[b]
75	**N**	35	35	26	31	35
	Mean	6280	1.29	30.65	13900	12.83
	SD	21000	1.20	13.63	24100	8.69
	Minimum	117	0.00	12.03	2000	0.59
	Median	1180	1.00	28.35	5450	12.87
	Maximum	102000	6.00	66.74	106000	40.73
	% CV (Geometric mean)	335	94	44	173	67.7
	Geometric Mean	1370	NA	27.94	7400	9.45

Sirolimus

Dose (mg/m^2)	Summary Statistics	Cmax (ng/mL)[a]	Tmax (hr)	T1/2β (h)	AUC_{tau} (ng.hr/mL)[a]	CL/F (L/hr/m^2)[b]
	N	35	35	35	35	35
	Mean	163	5.51	44.00	9582	10.43
	SD	71	9.20	17.08	7472	4.75
	Minimum	77	1.00	25.15	3302	1.69
	Median	143	1.00	40.76	7166	10.49
	Maximum	396	48.00	124.36	44410	22.72
	% CV (Geometric mean)	44	166.9	38.8	78	45.5
	Geometric Mean	151	2.61	41.93	8100	9.26

[a] The calculated C_{max} and $AUC_{0-\infty}$ represent the estimated C_{max} and $AUC_{0-\infty}$ after a theoretical first-dose of the described dosing schedule.
[b] CL/F represents the estimated apparent clearance calculated from the estimated model parameters.

Population PK Analysis

The Applicant conducted a population PK analysis that included the PK data collected from Part 1 and Part 2 of the current pediatric study to characterize the PK parameters of temsirolimus and sirolimus in pediatric patients with relapsed/refractory solid tumors. The applicant also and made a comparison in PK exposure between the adults and pediatric patient population. This population PK analysis was reviewed by the Pharmacometrics reviewer (see Appendix for the pharmacometrics review).

Based on the population PK analysis, the total clearance of temsirolimus and sirolimus increases with increasing dose, which is possibly due to the saturation of specific binding in the blood. Dose-dependent PK of temsirolimus and sirolimus in pediatric subjects is consistent with that observed in adults.

The total clearance of temsirolimus increases with the body weight (WT) in pediatric patients. After accounting for body weight in the model, there was no additional effect of age, gender or other factors on clearance. The exposure (AUC_{ss}) to 75-mg/m^2 temsirolimus administered as a 60-minute IV infusion in pediatric patients is similar for subjects of different sizes as measured by BSA. Therefore, the BSA-based dosing regimen is reasonable. For sirolimus, however, there was no additional effect of WT on apparent clearance (CL/fm). The exposure (AUC_{ss}) to sirolimus in pediatric patients increase with increasing BSA.

The exposures (AUCss) to temsirolimus and sirolimus in pediatric subjects following the 75-mg/m^2 dose administered as a 60-minute IV infusion were approximately 6-fold and 2-fold higher, respectively compared to that in adults receiving the 25-mg flat dose administered as an IV infusion (see Appendix for the pharmacometrics review).

Determination of the maximum tolerated dose and efficacy in pediatric patients:

In the current phase 1/2 trial the maximum tolerated dose (MTD) was defined as the dose level at which ≥ 2 of 3 subjects or ≥ of 6 subjects if the dose level had been expanded, experience a dose limiting toxicity (DLT) by day 21 after the first dose of temsirolimus.

A total of 19 subjects were enrolled in Part 1. Subjects received 10 mg/m^2 (4 subjects), 25 mg/m^2 (5 subjects), 75 mg/m^2 (3 subjects), and 150 mg/m^2 (7 subjects). Dose escalation was halted at 150 mg/m^2 based on a DLT of grade 3 anorexia as well as a report of grade 4 thrombocytopenia lasting less than 7 days that occurred at this dose level. Based on the protocol, the 150 mg/m^2 dose did not meet the protocol-specified definition of MTD. However, the 150-mg/m^2 dose was not considered by the investigators and the sponsor to be well tolerated (based on the adverse event profile at this dose), and therefore the 75-mg/m^2 dose was selected as the dose for evaluation in Part 2.

Part 2 of the study was designed to assess the preliminary antitumor activity of temsirolimus in children with refractory or relapsed pediatric solid tumors. It was expected that 25 subjects would be enrolled in each of 3 cohorts for the indications of neuroblastoma, rhabdomyosarcoma, and high-grade gliomas. Fifty-two (52) subjects were enrolled: 17 had glioma, 19 had neuroblastoma, and 16 had rhabdomyosarcoma. However, enrollment in part 2 was halted because of insufficient antitumor activity in all 3 indications.

2.1 ANALYTICAL SECTION

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

In the current phase 1/2 trial (3066K1-139-US), whole blood concentrations of temsirolimus and its major metabolite (sirolimus) were determined in human whole blood samples.

2.1.2 Which metabolites have been selected for analysis and why?

Sirolimus is the major metabolite of temsirolimus and was measured in human whole blood.

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.

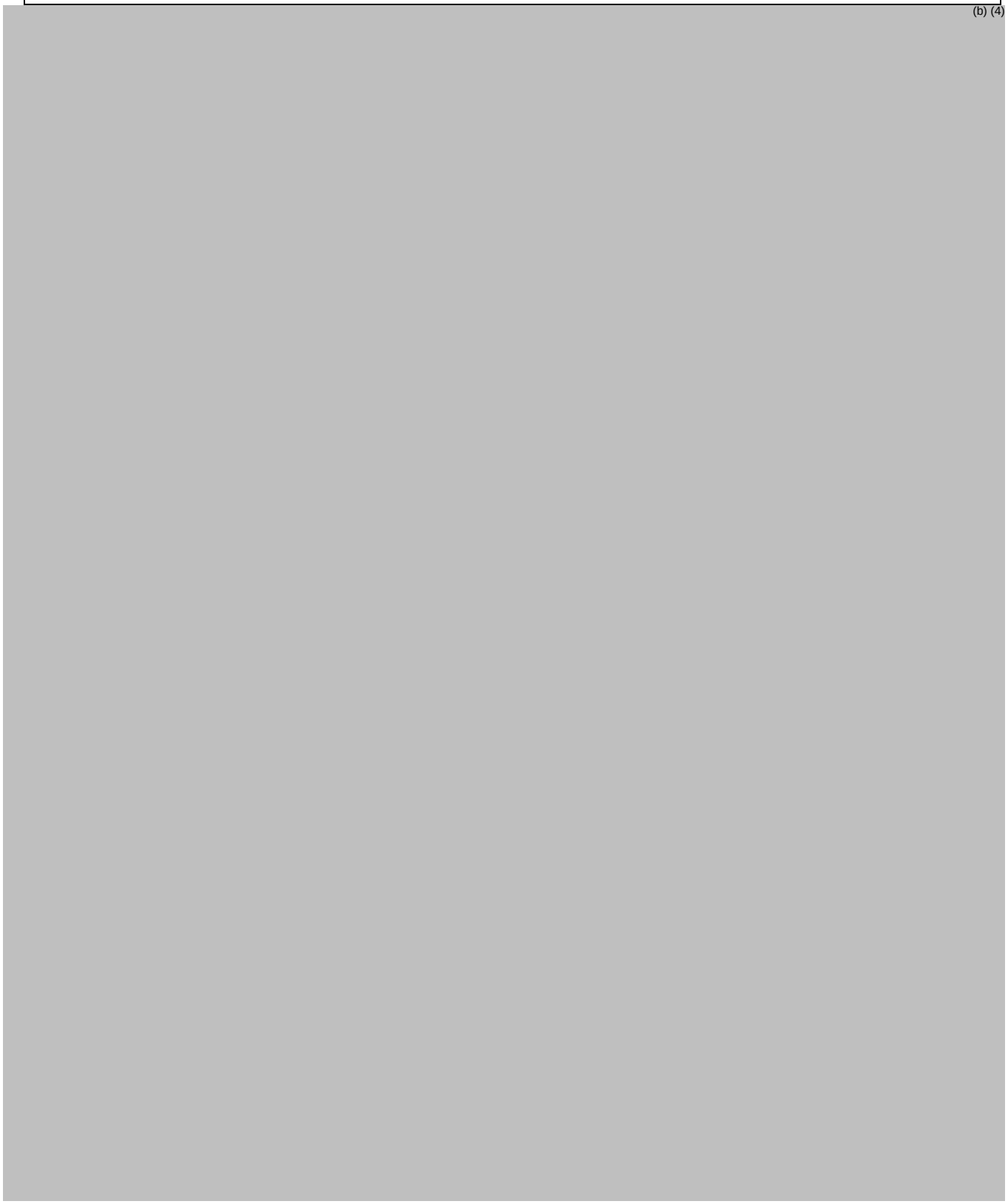
3 DETAILED LABELING RECOMMENDATIONS

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

are shown in **bold** font).

SPONSOR PROPOSED PACKAGE INSERT

(b) (4)



APPENDICES

4 OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRICS REVIEW

4.1 KEY REVIEW QUESTIONS

The purpose of this review is to address the following key questions.

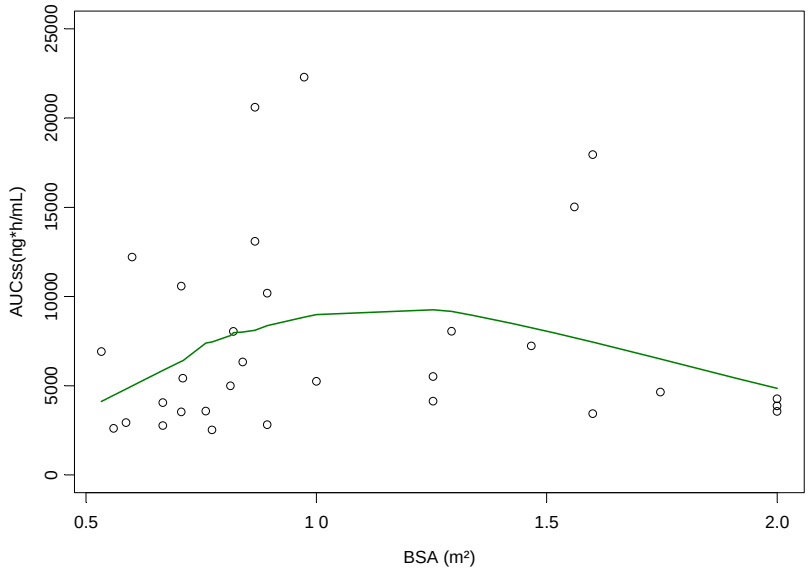
4.1.1 What are the pharmacokinetic characteristics of 75 mg/m^2 IV temsirolimus administered at weekly doses to pediatric patients with relapsed/refractory solid tumors?

Based on the population PK analysis, the total clearance of temsirolimus and sirolimus increases with increasing dose, which is possibly due to the saturation of specific binding in the blood. Dose-dependent PK of temsirolimus and sirolimus in pediatric subjects is consistent with that observed in adults.

Total clearance of temsirolimus increases with the body weight (WT) in pediatric patients. After accounting for body weight in the model, there was no additional effect of age, gender or other factors on clearance. As shown in Figure 3, the exposures (AUC_{ss}) to 75-mg/m^2 temsirolimus in pediatrics are similar for subjects of different sizes as measured by BSA. Therefore, the BSA-based dosing regimen is acceptable.

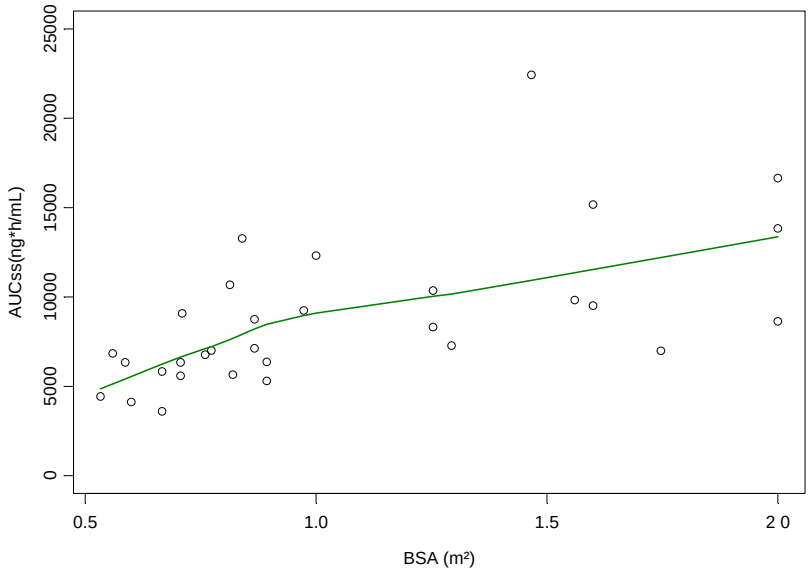
For sirolimus, however, there was no additional effect of WT on apparent clearance (CL/fm). The exposures (AUC_{ss}) to sirolimus in pediatric patients increase with increasing BSA (Figure 4).

Figure 3. Individual Temsirolimus AUC_{ss} *vs.* BSA in Pediatrics



Note: AUC_{ss} is calculated based on the post-hoc estimates of individual CL from population PK model (run171)

Figure 4. Individual Sirolimus AUC_{ss} *vs.* BSA in Pediatrics



Note: AUC_{ss} is calculated based on the post-hoc estimates of individual CL from population PK model (run525)

4.1.2 What is the difference in the exposure to temsirolimus and sirolimus between pediatric subjects with relapsed/refractory solid tumors at 75-mg/m^2 weekly dose and adult patients with RCC at 25-mg flat dose?

The observed exposures to temsirolimus and sirolimus are provided in Table 6 and Table 7, respectively, in patients with different ages. Table 6 shows that the mean exposure to temsirolimus in pediatrics receiving 75-mg/m^2 dose is approximately 6-fold higher than the mean exposure in adults at 25-mg flat dose. The increased pediatric exposure is due to administration of higher doses compared to adults, *i.e.*, 25-mg flat dose is approximately 14.4 mg/m^2 for 1.73 m^2. The between-subject variability in exposure (AUC and Cmax) to temsirolimus is higher in pediatrics compared to adults.

Table 7 shows that the exposure to sirolimus in pediatrics receiving 75-mg/m^2 dose is approximately 2-fold higher than that in adults at 25-mg dose. The between-subject variability in AUC for sirolimus in pediatrics is higher in pediatrics compared to adults. But the between-subject variability in Cmax for sirolimus in pediatrics is comparable to adults.

Table 6. PK Parameters of Temsirolimus 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	25[a]	8025±5993, 75%[c]	1327±669, 50%[d]
Adult	25-mg[b]	11	1349±232, 17%	443±109, 25%

[a] Excludes two patients with unexplained high concentrations (subject ID 204 and 231)
[b] 25-mg flat dose is 14.4 mg/m^2 for BSA of 1.73 m^2
[c] Geometric mean (cv%)of AUC: 6364 (68%)
[d] Geometric mean (cv%)of Cmax: 1107(72%)

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."

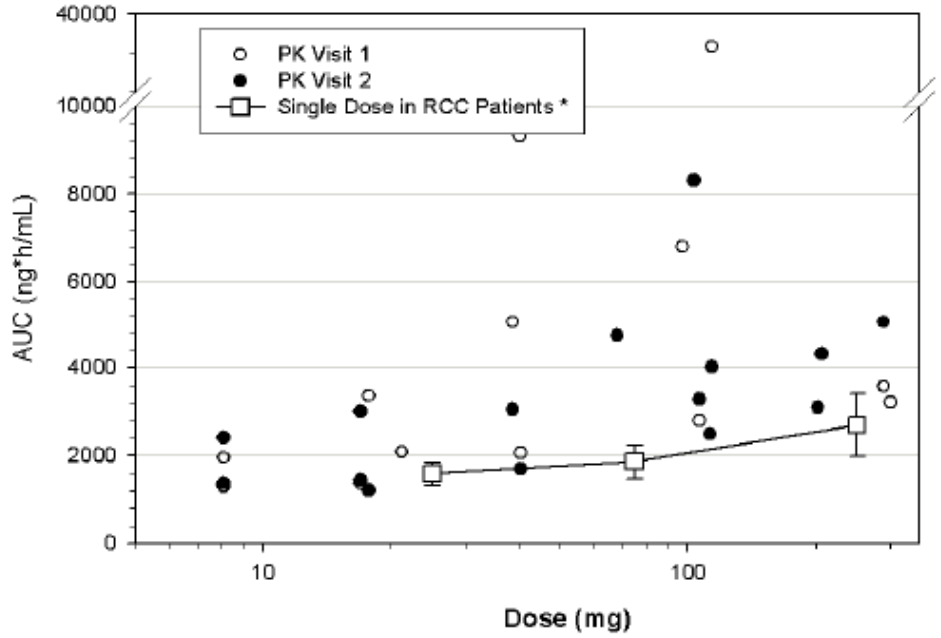
Table 8. Summary of Pharmacokinetic Parameters of Temsirolimus and Sirolimus in Healthy Subjects, and Adult and Pediatric Patients Following IV Treatment with Temsirolimus

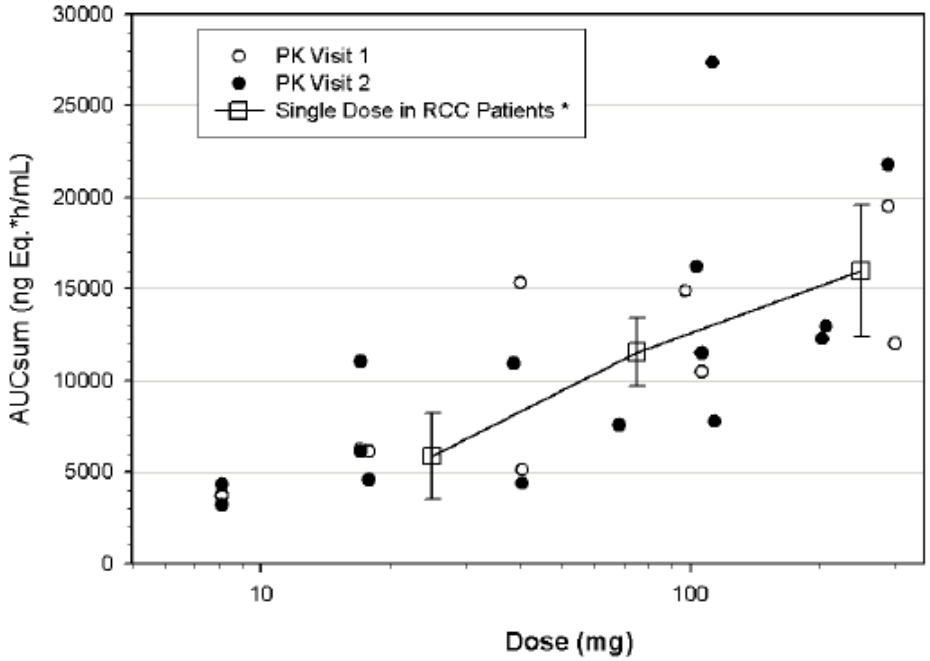
Pharmacokinetic Parameters	Healthy Adult Subjects Single-dose (N=51)	Adult Patients Single-dose (N=13)[a]	Adult Patients Multiple-dose (N=11)[b]	Pediatric Patients Multiple-dose (N=35)[c,d]
Dose	25 mg	25 mg	25 mg	75 mg/m^2
Temsirolimus				
C_{max} (ng/mL)	592.4 ± 101.9	585.4 ± 83.1	443.0 ± 109.2	6280 ± 21000
$t_{1/2}$ (h)	17.7 ± 4.5	17.3 ± 5.9	NC	30.65 ± 13.63
AUC[e] (ng·h/mL)	2276 ± 340	1627 ± 425	1349 ±231.8	13900 ± 24100
CL (L/h)[f]	11.4 ± 2.4	16.2 ± 3.5	19.0 ± 3.0	14.3 ± 14.0
Sirolimus				
C_{max} (ng/mL)	57.4 ± 14.3	55.4 ± 31.8	34.5 ± 19.3	163 ± 70.7
$t_{1/2}$ (h)	73.3 ± 23.2	54.6 ± 1.5	NC	43.86 ± 18.18
AUC (ng·h/mL) [e]	5479 ± 1799	4151 ± 1600	3793 ± 1466	8350 ± 4860
CL/f_m (L/h) [f]	4.9 ±1.2	6.9 ± 2.6	7.4 ±2.5	9.76 ± 3.40
Composite				
AUCsum (ng eq's·h/mL)	7755 ± 1874	5778 ±1722	5141 ± 1345	15464 ± 10488[g]

a: For C_{max} N=5; $t_{1/2}$ N=2
b: For temsirolimus C_{max} N=7; sirolimus C_{max} N=3
c: For temsirolimus $t_{1/2}$ N=26; AUC and CL/f_m N=31
d: For sirolimus $t_{1/2}$ N=32; AUC and CL N=34
e: AUC denotes AUC (evaluated from 0 to infinity) for single dose, and steady-state AUC for multiple dose
f: CL/f_m denotes quotient of clearance and unknown fraction of parent drug metabolized
g: For AUCsum, as reported from part 1 of study (N=3)
Abbreviation: NC = Not calculated; no subjects provided data
Source.= Adult Subjects and Patients from Temsirolimus RCC eCTD, module 2.7.2, Table 3.1-2. Pediatric Patients Multiple Dose from CSR-76631, Table 11-1 and 11-2.

Source: Sponsor's NDA 022088 S-014, Pediatric Supplement for Torisel – Response to FDA Request for Clinical Pharmacology Information (31 Jan 2012), Page 2

Figure 5. Individual AUC, and AUC_{sum} Versus Flat Dose in Pediatric Subjects (Study 3066K1-139-WW) and Adult Subjects With Renal Cell Carcinoma (Study 3066K1-200-US)





Source: Sponsor's NDA 022088 S-014, Pediatric Supplement for Torisel – Response to FDA Request for Clinical Pharmacology Information (31 Jan 2012), Page 3

Reviewer's Comments:

1. [redacted] (b) (4)

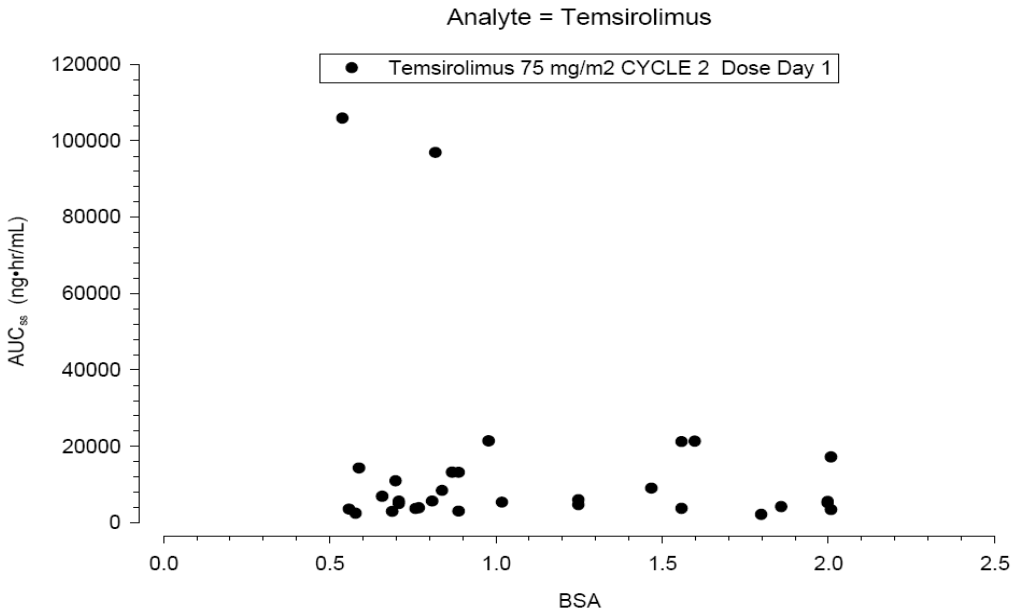
   *Figure 5 provided by sponsor suggests some pediatric subjects with approximately 25-mg flat dose had a comparable exposure as adults with 25-mg dose. There is no observed exposure data for pediatric population at 25-mg or any other flat dose. Based on the population PK model, the typical exposure of temsirolimus at 25-mg flat dose for a pediatric subject decreases by half from 4797 to 2464 ng*h/ml when the body weight increases from 10 to 50 kg. Therefore, it's not reasonable to consider the exposure in pediatric subjects with low BSA or body weight as representative in overall pediatric population at flat dose. Instead, the comparison of observed exposure of temsirolimus and sirolimus should be made in the context of the respective dosing scheme for adults (25-mg flat dose) and pediatric population (75 mg/m^2) as presented in section 1.1.2.*

2. *The AUC_{sum} (arithmetic summation of AUCs of temsirolimus and sirolimus) is not a validated total exposure metrics which can be related to the overall pharmacological effect, because temsirolimus and sirolimus may have very different pharmacological effect on the target.*

3. *As shown in* Figure 6*, there are two outliers (one 1 years old toddler and one 6 years old child) with unusually high exposures (AUC) of temsirolimus (>88,000 ng*hr/mL, which also contributed substantially to the between subject variability in the summary statistic in Table 8.* Figure 7 *suggests that the unusually high exposure is driven by two extreme peak concentrations of subject 204 and 231 around day 21, which are approximately 100-fold higher than others and maybe measurements errors. The PK parameters of temsirolimus after excluding these two subjects are provided in* Table 6.

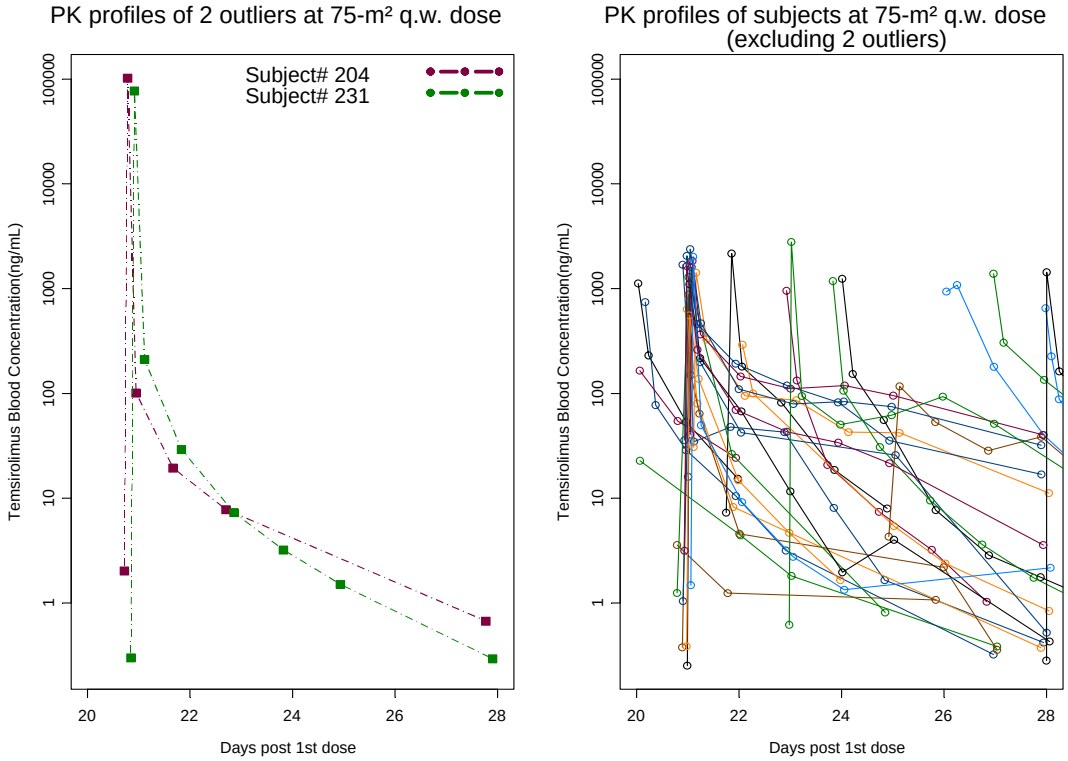
4. *Based on the prediction by the population PK models, the AUCss in a typical pediatric subject of 8 year old, white male, weight of 23.5 kg, and BSA of 0.89 m^2 for temsirolimus and sirolimus are 5474 ng*h/mL (CL=12.2 L/h, t1/2β = 32.6 h) and 6990 ng*h/mL (CL=9.5 L/h, t1/2β = 57.4 h), respectively. These predictions are comparable with the summary profiles by NCA in Table 6.*

Figure 6. Individual Temsirolimus AUCss in Whole Blood *vs.* BSA



Source: Sponsor's Clinical Study Report CSR-76631, Page 594

Figure 7. Individual PK profiles of Pediatric Patients with RCC at 75 mg/m^2 dose Temsirolimus



6.2 POPULATION PK ANALYSIS

6.2.1 Data

The population PK study included the data collected from part 1 and part 2 of the pediatric study. The overview of the data is given in Table 9.

Table 9. Number of Subjects and Pharmacokinetic Samples Included in the Population Pharmacokinetic Analysis

	Temsirolimus	Sirolimus
Subjects in PPK analysis	55	55
Post-dose PK samples available	485	485
Sample not reported	3	6
Outliers excluded from the analysis [b]	23	2
Post-dose samples <LLOQ [a]	60 (12.4%)	4 (0.8%)
Post-dose samples >=LLOQ included in the analysis	399	473

[a] LLOQ = lower limit of quantitation, 0.25 ng/mL. The percentage is calculated using the number of post-dose available samples as denominator.
[b] Outliers are listed in Attachment 1.2

Source: Sponsor's Population Pharmacokinetics Report of Temsirolimus RPT-10021

6.2.2 Method

In previous population PK study in CSR-70829, a mechanistic model that includes saturable specific tissue and blood cell binding was used to characterize temsirolimus PK in adults. However, due to poor fit of the pediatric PK data to this mechanistic model, a two-compartment model with IV infusion input and first-order elimination from the central compartment was chosen for temsirolimus as structure model for pediatric population.

A two-compartment model with first-order absorption (i.e., formation of sirolimus) and first-order elimination was used for sirolimus. For the sirolimus model, the temsirolimus dose was used to generate apparent population parameters. The exponential error model was used to describe the inter-subject variability in PK parameters. Proportional error model was used to describe the residual variability.

A forward stepwise regression (model building) followed by a backward stepwise regression (model reduction) was performed based on the likelihood ratio test (LRT). The covariate selection process was also aided by use of diagnostic plots. Log-transformed concentrations were used in the population PK analysis to stabilize the model.

6.2.3 Results

The summary for the final population PK model for temsirolimus and sirolimus in pediatric population is presented in Table 10 and Table 11.

Table 10. Summary of temsirolimus Population PK Parameters in the Final Model from Study 3066K1-139-US (run171)

Parameters		Estimate (RSE%) [a]
CL (L/hr)	θ1	20.3 (22)
WT on CL [b]	θ6	0.413 (43.8)
Dose on CL [b]	θ9	0.505 (27.3)
V1 (L)	θ2	44.1 (18.1)
V2 (L)	θ3	232 (12.4)
Dose on V2 [c]	θ25	0.483 (18.9)
Q (L/hr)	θ4	22.5 (23.7)
WT on Q [d]	θ30	0.953 (19.7)
BSV of CL (CV%)	η1	57.0 (32.6)
BSV of V1 (CV%)	η2	109.5 (28.1)
BSV of V2 (CV%)	η3	52.4 (43.3)
BSV of Q (CV%)	η4	32.2 (128.8)
Correlation between CL and V1		0.339
Correlation between V1 and V2		0.881
Proportional residual error (CV%)	θ5	64.5 (5.4)

Source: Attachment 16 and Appendix 2

[a] Parameter estimates are presented as mean (RSE% = [SE ÷ mean]*100%).

[b] $CL\ (L/hr) = 20.3*(WT/70)^{0.413} * (Dose/75)^{0.505}$

[c] $V2\ (L) = 232*(Dose/75)^{0.483}$

[d] $Q\ (L/hr) = 22.5*(WT/70)^{0.953}$

Sources: Sponsor's Population Pharmacokinetics Report of Temsirolimus RPT-10021, Page 36

Table 11. Summary of Sirolimus Population PK Parameters in the Final Model from Study 3066K1-139-US (run525)

Parameters		Estimate (RSE%) [a]
CL/F (L/hr)	θ1	9.76 (7)
Dose on CL/F [b]	θ7	0.187 (29.4)
V2/F (L)	θ2	703 (7.9)
WT on V2/F [c]	θ10	0.477 (11.7)
Q/F (L/hr)	θ3	1.13 (32.8)
V3/F (L)	θ4	74.8 (25.4)
Ka (hr^{-1})	θ5	1.60 (23.8)
BSV of V2/F (CV%)	η1	39.0 (24.9)
BSV of CL/F (CV%)	η2	39.4 (27.4)
BSV of Q/F (CV%)	η3	0.0 (fixed)
BSV of V3/F (CV%)	η4	59.6 (65.6)
BSV of Ka/F (CV%)	η5	71.1 (20.4)
BOV of Ka/F (CV%)	η6, η7	same as above
BOV of V2/F (CV%)	η8, η9	8.1 (192.1)
BOV of CL/F (CV%)	η10, η11	7.7 (82.1)
Correlation between CL/F and V2/F		0.958
Proportional residual error (CV%)	θ6	24.6 (2.1)

Source: Appendix 6

[a] Parameter estimates are presented as mean (RSE% = [SE ÷ mean]*100%).

[b] $CL/F\ (L/hr) = 9.76 * (Dose/75)^{0.187}$

[c] $V2/F\ (L) = 703 * (WT/70)^{0.477}$

Source: Sponsor's Population Pharmacokinetics Report of Temsirolimus RPT-10021, Page 41

Figure 8. Temsirolimus Goodness of Fit Diagnostic Plots of PK Data from Study 3066K1-139-US in the Final PK Model (run171)

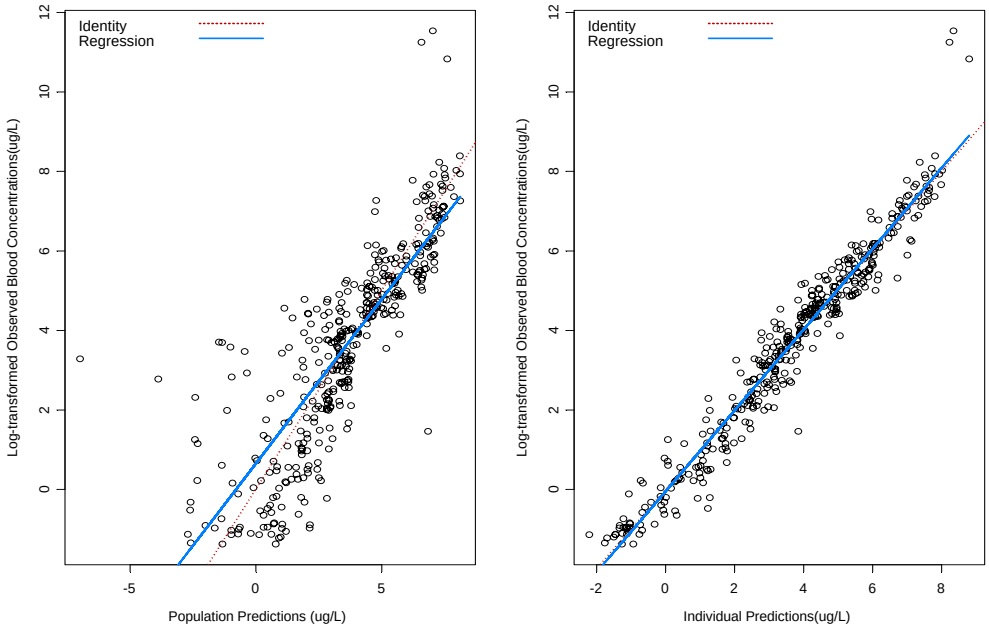
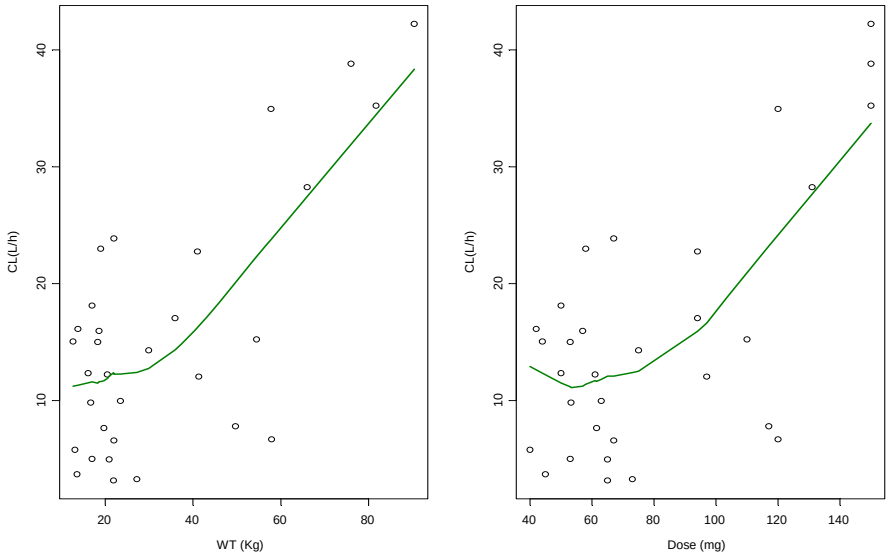


Figure 9. Temsirolimus Total CL vs WT and Dose
(Population PK study (run171))



* CL is the post-hoc estimates of individual CL from population PK model(run171)

Figure 10. Sirolimus Goodness of Fit Diagnostic Plots of PK Data from Study 3066K1-139-US in the Final PK Model (run525)

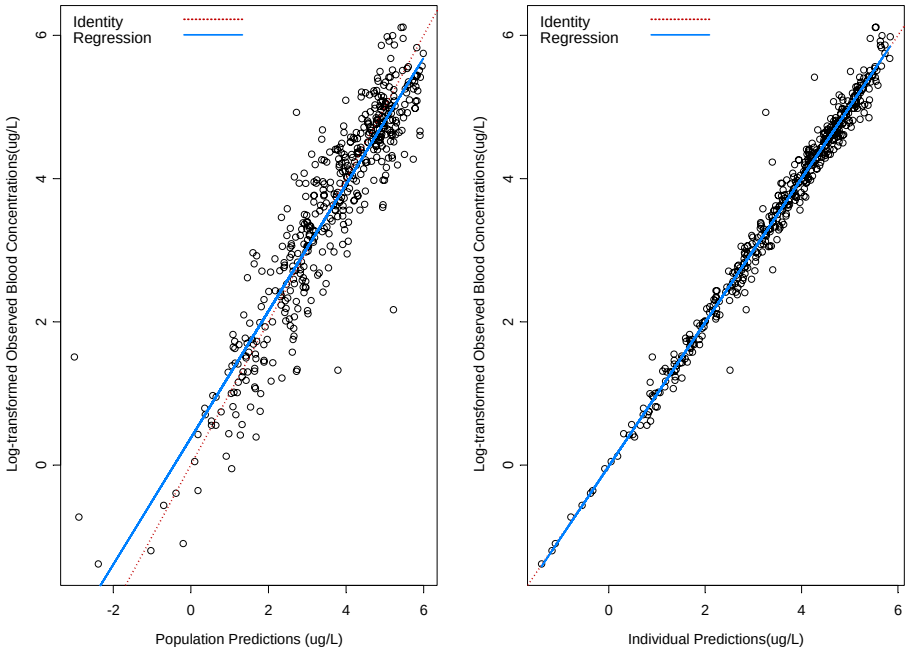
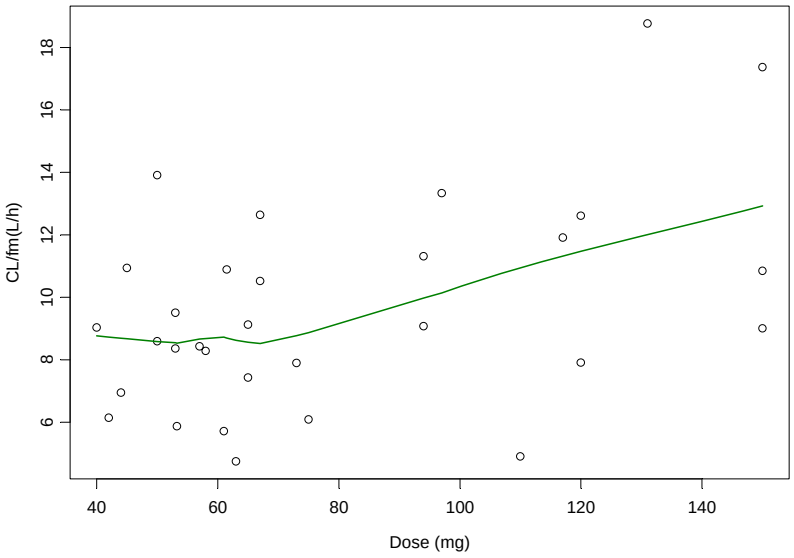
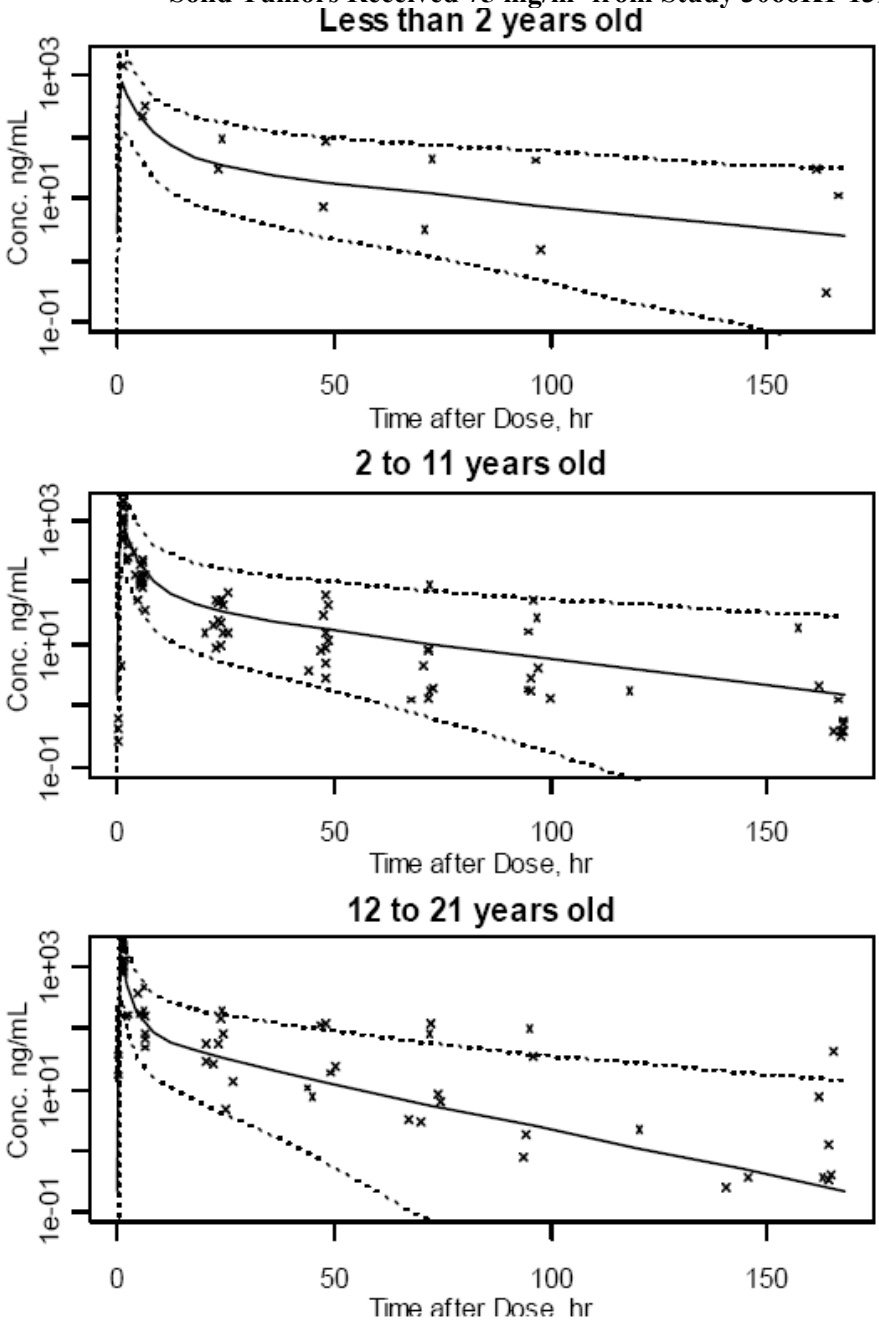


Figure 11. Sirolimus Total CL vs. Dose



* CL is the post-hoc estimates of individual CL from population PK model(run525)

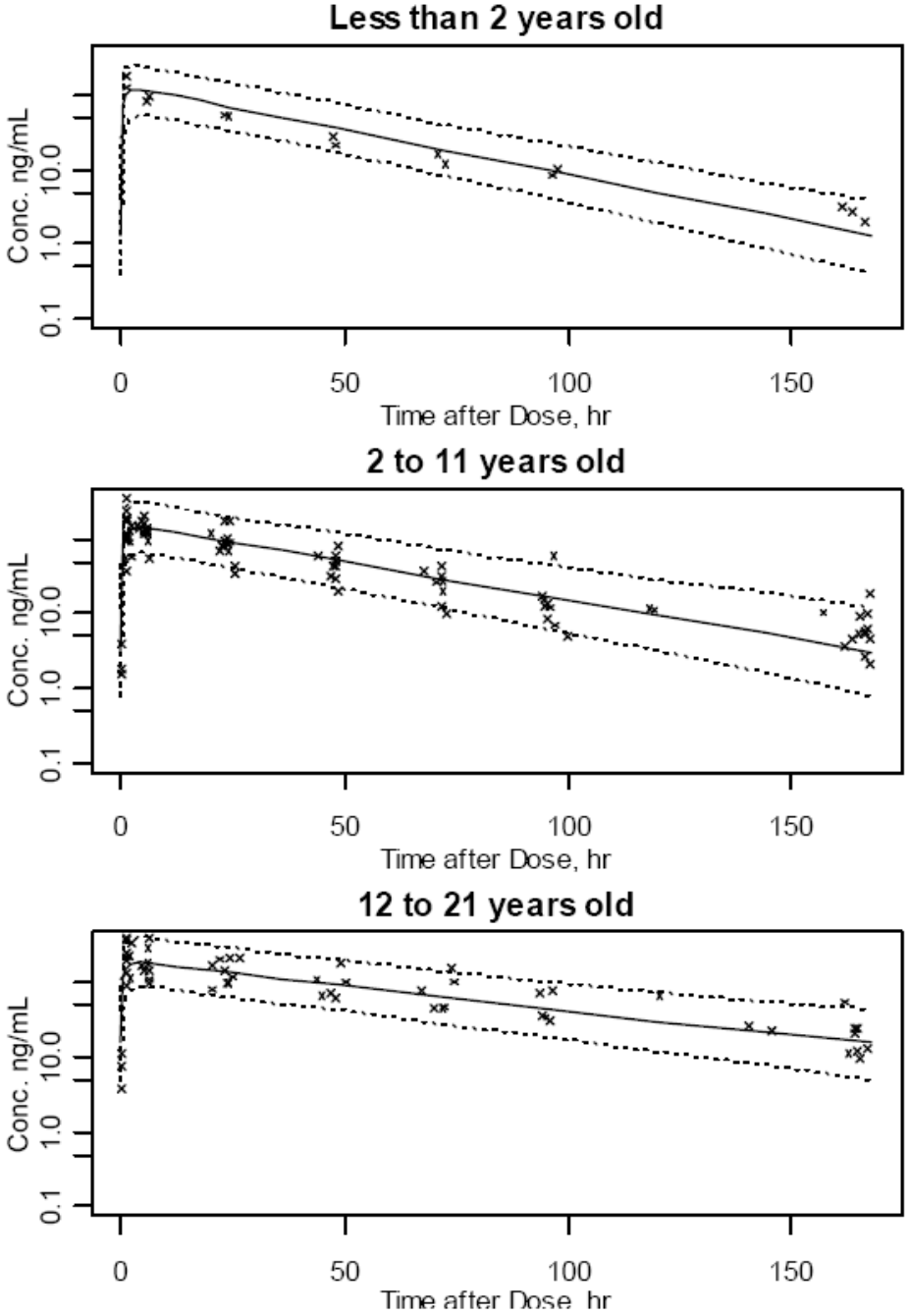
Figure 12. Visual Predictive Check: Semi-log Plots of Model-Predicted and Observed Whole Blood Concentrations of Temsirolimus at Steady-State in Pediatric Subjects with Relapsed/Refractory Solid Tumors Received 75 mg/m^2 from Study 3066K1-139-US



*The solid line is the model-predicted median and the two dashed lines are the model-predicted 95% confidence interval. The x markers are the observed whole blood concentrations.

Sources: Sponsor's Population Pharmacokinetics Report of Temsirolimus RPT-10021, Page 124

Figure 13. Visual Predictive Check: Semi-log Plots of Model-Predicted and Observed Whole Blood Concentrations of Sirolimus at Steady-State in Pediatric Subjects with Relapsed/Refractory Solid Tumors Received 75 mg/m^2 from Study 3066K1-139-US



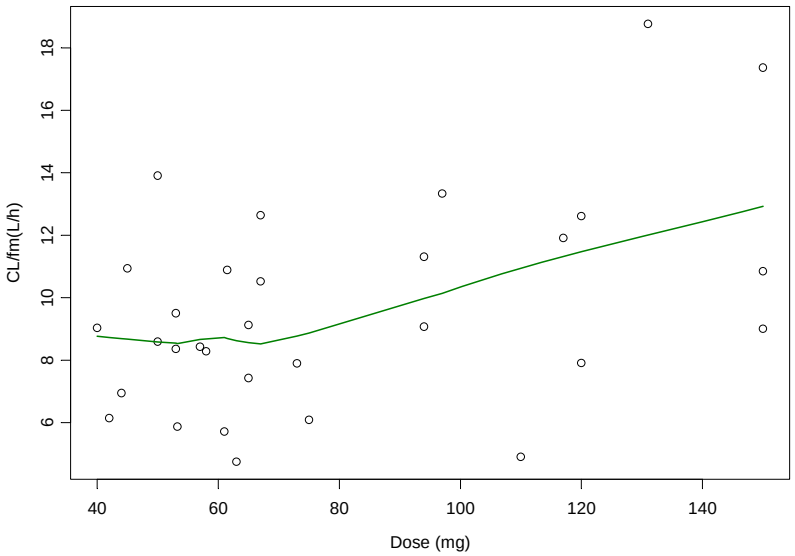
*The solid line is the model-predicted mean and the two dashed lines are the model-predicted 95% confidence interval. The x markers are the observed whole blood concentrations.

Sources: Sponsor's Population Pharmacokinetics Report of Temsirolimus RPT-10021, Page 173

Reviewer's Comment:
Population PK analysis indicated that the total clearance of temsirolimus and sirolimus increases with increasing dose, which is possibly due to the saturation of specific binding in the blood (Figure 9 and Figure 11). The clearance of temsirolimus also increases with body weight. But body weight has no additional effect on clearance of sirolimus after accounting for body weight in the model.

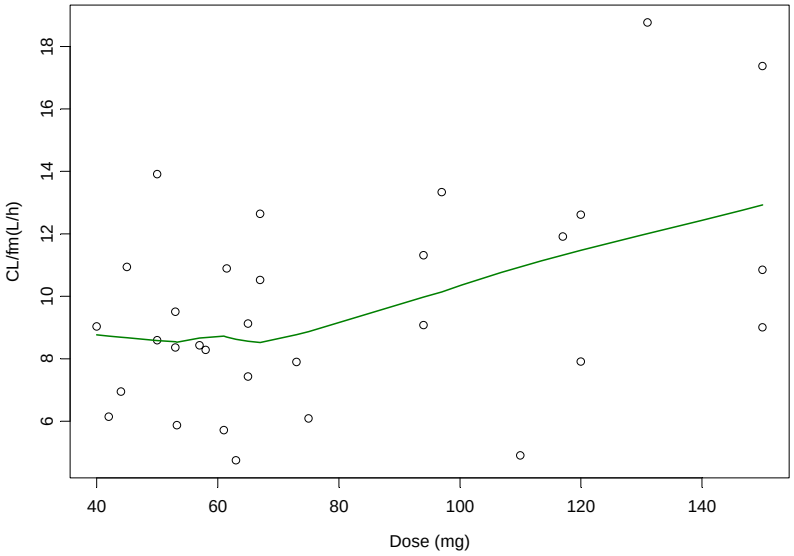
The diagnostic analyses suggest that the final population PK models are able to reasonably characterize temsirolimus and sirolimus PK profile (Figure 8 and Figure 10). The visual predictive check (VPC) suggests that the final population PK model provides acceptable predictive performance of the PK profiles of temsirolimus and sirolimus for all age groups in pediatric patients (Figure 12 and Figure 13). Therefore, the final population PK models of temsirolimus and sirolimus are acceptable.

Figure 11. Sirolimus Total CL vs. Dose



* CL is the post-hoc estimates of individual CL from population PK model(run525)

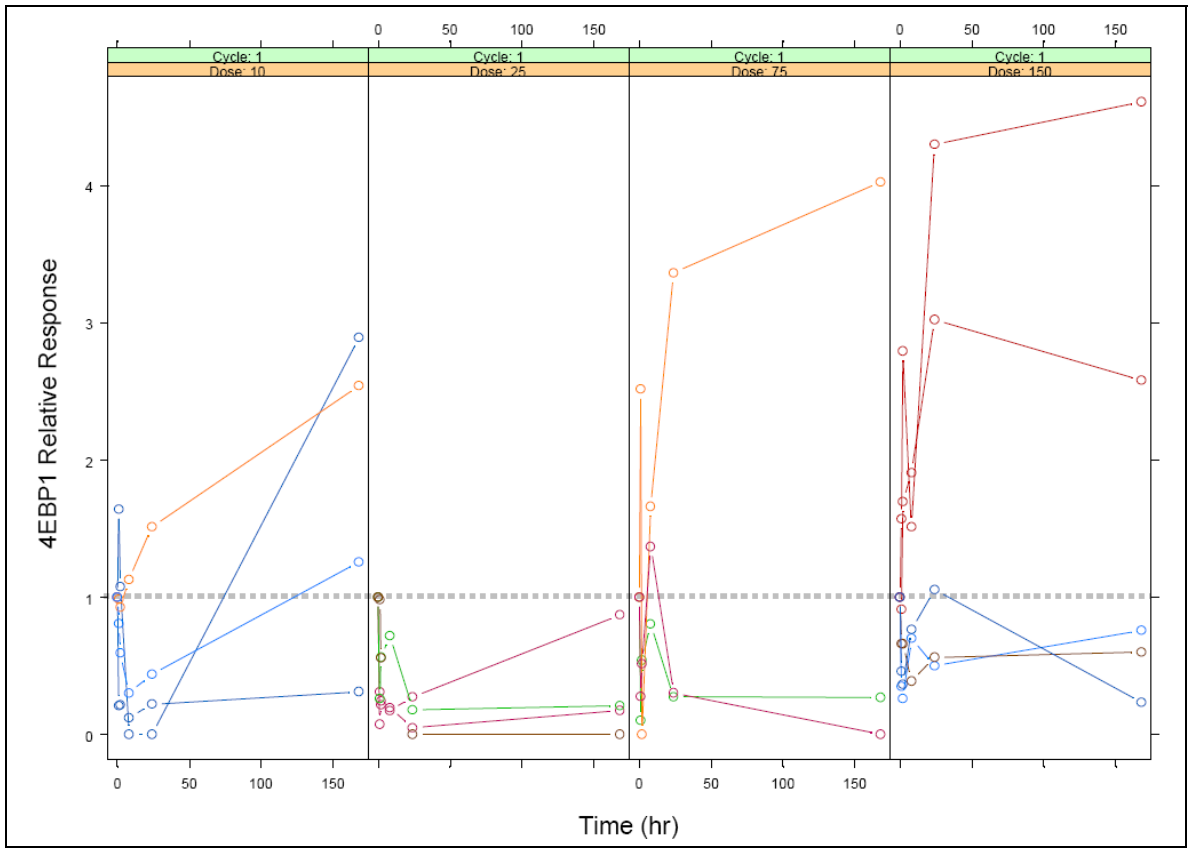
Figure 12
Figure 11. Sirolimus Total CL vs. Dose



* CL is the post-hoc estimates of individual CL from population PK model(run525)

Figure 12 Preliminary data analysis indicated that PD measurements by western blot assays were highly variable among the 3 biomarkers examined in part 1 of the study (See example in Figure 14). Given the high variability in the data and limited number of observations available (2-5 subjects for each dose group), no dose/exposure-response analysis was performed.

Figure 14. PD time-course change in Whole Blood Following Temsirolimus IV after 1st weekly dose



Sources: Sponsor's Clinical Study Report CSR-76631

7 REVIEWER'S ANALYSIS

7.1.1 Data Sets

Data sets used are summarized in Table 12.

Table 12. Analysis Data Sets

Study Number	Name	Link to EDR
RPT-10021	NONMEM input data sets	\\cdsesub1\EVSPROD\NDA022088\\0086\m5 \datasets\10021\analysis\datasets\nm.xpt

7.1.2 Software

Plotting was performed in S-Plus Version 2.6. NONMEM 7.2 with gfortran compiler (Icon, Ellicott City, MD) was used to reproduce the sponsor's population PK models for temsirolimus and sirolimus.

7.1.3 Models

Details about the models were provided in Table 10 and Table 11.

7.1.4 Results

The clearance of temsirolimus is dependent on WT and dose. Age is also highly correlated to WT, BSA and dose in this pediatrics study. The variability of exposures to temsirolimus in pediatrics is very high (Table 13). Therefore, the exposure to temsirolimus in different age groups can not be well characterized. The rationale of excluding outliers and corresponding results by reviewer were discussed at section 3.1. The exposures to sirolimus appear to increase with age (Table 14). The variability in each age group is comparable with adults.

Table 13. PK Parameters of Temsirolimus in Pediatric Patients with Relapsed/Refractory Solid Tumors including outliers

Age (y)	n	Mean AUC(ng*h/mL),CV% Geometric Mean, CV%	Mean Cmax (ng/mL), CV% Geometric Mean, CV%
0-2	2	60100, 108% 38797, 142%	39160, 136% 10450, 282%
3-6	11	13650, 203% 6297, 101%	10226, 298% 1229, 170%
7-18	14	9506, 75% 7560, 74%	1518, 43% 1384, 46%
0-18	27	14942, 171% 7812, 98%	7854, 302% 1531, 136%

[a] *25-mg is 14.4 mg/m^2 for BSA of 1.73 m^2*

Table 14. PK Parameters of Sirolimus in Pediatric Patients with Relapsed/Refractory Solid Tumors including outliers

Age (y)	n	Mean AUC(ng*h/mL),CV% Geometric Mean, CV%	Mean Cmax (ng/mL), CV% Geometric Mean, CV%
0-2	2	3925, 7% 3921, 7%	152, 23% 150, 23%
3-6	11	6757, 46% 6284, 38%	167, 46% 153, 42%
7-18	17	9046, 65% 7932, 49%	161, 48% 147, 43%

[a.] *25-mg is 14.4 mg/m^2 for BSA of 1.73 m^2*

8 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
run171.ctl	Final model temsirolimus	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Torisel_NDA_022088_JYU \PPK_Analyses \Modeling\Reviewer
run525.ctl	Final model sirolimus	Same as above
diag171.ssc	Code for basic GOF Plot	Same as above
diag525.ssc	Code for basic GOF Plot	Same as above

9 NDA FILING AND REVIEW FORM

General Information About the Submission

NDA Number	22088	**Brand Name**	Torisel®
DCP Division (I, II, III, IV, V)	V	**Generic Name**	Temsirolimus injection
Medical Division	Oncology	**Drug Class**	Inhibitor of mTOR
OCP Reviewer	Jeanne Fourie Zirkelbach, PhD	**Indication(s)**	Advanced renal cell carcinoma
OCP Team Leader	Qi Liu, PhD	**Dosage Form**	TORISEL injection, 25 mg/mL supplied with DILUENT for TORISEL
Date of Submission	12/2/2011	**Dosing Regimen**	25 mg infused over a 30-60 minute period once per week.
Due Date of OCP Review		**Route of Administration**	Intravenous infusion over 30-60 minutes
Standard PDUFA Due Date	//2012	**Sponsor**	Wyeth

Clinical Pharmacology Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				

Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**	**1**	Whole blood temsirolimus and sirolimus concentrations. Method validation not included but reference to applicant's internal protocol's is made. An IR clarified that the method validations were submitted as part of the original NDA submission (000).
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**x**	**2**	**2**	3066K1-139-US –- Single dose and multiple dose whole blood PK of temsirolimus and sirolimus– Part 1 dose escalation portion of trial.
multiple dose:	**x**	**2**	**2**	3066K1-139-US – Multiple dose whole blood PK of temsirolimus and sirolimus with once-weekly IV treatment. Part 2 at 75 mg/m2 dose IV.
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
geriatrics:				
renal impairment:				
hepatic impairment:				
pediatrics:	**x**	**1**	**1**	3066K1-139-US – Dose escalation (Part 1) and efficacy (Part2) of temsirolimus in children with relapsed/refractory neuroblastoma, high-grade gliomas and rhabdomyosarcoma.
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**x**	**1**	**1**	Report 10021 – Integrated PopPK analysis of temsirolimus in pediatric subjects with relapsed/refractory solid tumors.
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				

solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
QTC studies:				
In-Vitro Release BE				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Biliary Elimination				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable?	**X**	
Comments sent to firm?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	**J Fourie Zirkelbach, Ph.D.**	
Secondary reviewer Signature and Date	**Q Liu, Ph.D.**	

CC: HFD-150 (CSO – **Y Adkins;** MTL– **E Maher;** MO –**P Kluetz**)

HFD-860 (Reviewer – J Fourie Zirkelbach; TL – Q Liu; DDD - B Booth; DD - A Rahman)

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

/s/

JEANNE FOURIE ZIRKELBACH
05/07/2012

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05/07/2012

CHRISTINE E GARNETT
05/08/2012

QI LIU
05/08/2012