
Clinical Pharmacology Review

NDA	22-334 (IND 66279)
Submission Date:	30th April 2010
Brand Name:	Afinitor®
Generic Name:	Everolimus (RAD001)
Formulation:	2.5, 5 and 10 mg tablets
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Sponsor:	Novartis
Submission Type; Code:	sNDA; 22334/71
Dosing regimen:	Therapeutic Drug Monitoring (TDM): [REDACTED] (b) (4)
Indication:	Orphan Indication: Subependymal giant cell astrocytoma associated with tuberous sclerosis

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1 EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology Divisions of Clinical Pharmacology 5 and Pharamcometrics have reviewed NDA 22-334 and find the application acceptable from a clinical pharmacology perspective provided that an agreement is reached regarding the concentration target for therapeutic drug monitoring (TDM) and dose-adjustments for specific populations.

1.2 CLINICAL PHARMACOLOGY SUMMARY

Everolimus (Afinitor[®]) is an inhibitor of the human kinase mammalian target of rapamycin (mTOR). Afinitor[®] is currently indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib at a fixed dose of 10 mg once daily.

In the current supplemental NDA submission, the sponsor seeks accelerated approval of Afinitor[®] for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS). Everolimus has orphan drug designation for this indication. TS is estimated to affect 25,000 to 40,000 people in the US and one to two million worldwide. SEGAs occur in 5–20% of patients with TS and primarily affect children and adolescents. There is no drug approved for this indication and the only treatment option for patients with SEGA is brain surgery.

The sponsor submitted data from a single non-randomized, open-label, single-center phase 2 trial in 28 patients to support this indication. The confirmatory phase 3 placebo-controlled trial is ongoing. In the phase 2 trial, SEGA patients were treated with 3 mg/m²/day everolimus titrated to a target trough concentration of 5–15 ng/ml.

Significant reduction in primary SEGA tumor volume from baseline was observed at month 6 (median reduction 0.8 cm³, p <0.001) with 79% of patients experiencing reductions ≥ 30%. Significant exposure-response relationship for reduction in SEGA tumor volume provides evidence of effectiveness in a single-arm trial. Stomatitis and infections were the most common adverse events observed and are consistent with the previously reported toxicity profile of everolimus.

The sponsor proposed individualized dosing with TDM (b) (4). TDM is proposed for this indication since most of the patients will be on concomitant enzyme-inducing antiepileptic drugs and everolimus is a substrate of CYP3A4. There was no clear rationale behind the selection of target trough concentration range of (b) (4) for the TDM. (b) (4)

The exposure-efficacy analysis supported the lower limit of the target range of 5 ng/ml. The upper limit of (b) (4) was not justified because there was no additional reduction in tumor volume with trough concentrations >3 ng/ml and >90% of the observed data were below 10 ng/ml in the core treatment phase. Thus, a target range of 5–10 ng/ml for TDM is recommended. Some of the patients exhibited tumor re-growth during the follow-up phase. Analysis relating

tumor re-growth with exposures does not indicate that lower exposures are responsible for this phenomenon.

A conclusive exposure-safety relationship for stomatitis, infections and upper respiratory infections could not be identified probably due to few patients (N=28) in the safety database. Most of the patients experienced Grade 1 or 2 adverse events.

In healthy volunteer studies, everolimus exposures were significantly increased when Afinitor was taken with moderate CYP3A4 or Pgp inhibitors (reviewed in the original NDA). The sponsor has proposed a 50% lower starting dose for patients taking moderate CYP3A4 or Pgp inhibitors. For patient with BSA <1.2 m², starting dose reduction is not possible due to the unavailability of lower dose strengths. Pharmacokinetic simulations support alternate-day dosing for these patients.

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2 QUESTION BASED REVIEW

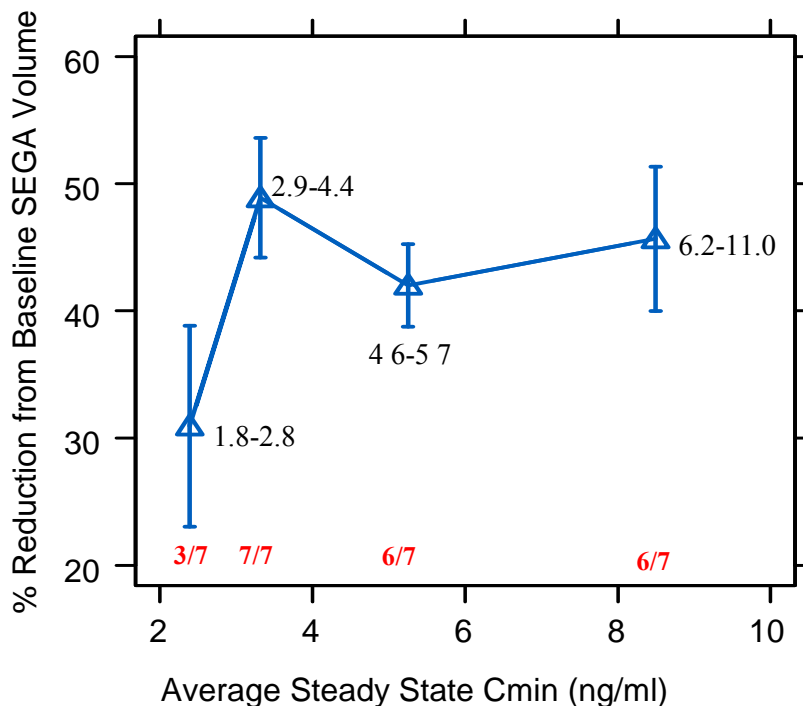
Afinitor® has been reviewed previously under NDA 22-334 for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib (submission 06/27/08). For brevity, only QBR questions regarding this current sNDA submission will be addressed below. Please see Clinical Pharmacology Review for NDA 22-334 by Dr. Julie Bullock in DAARTs dated 03/09/2009 for more details.

2.1 KEY REVIEW QUESTIONS

2.1.1 Is there evidence of exposure-response for efficacy?

Yes, there is evidence of an exposure-response relationship for efficacy. Average steady state C_{min} concentrations in the core treatment phase and % reduction in SEGA tumor volume were the variables utilized in the analysis. Exposure data were divided into quartiles with seven patients in each quartile. An increased response with increased average C_{min} was observed with no additional benefit at $C_{min} \geq 3$ ng/ml (**Figure 1**). CART (Classification and regression tree) analysis identified 2.8 ng/ml as the optimal C_{min} breakpoint that maximally distinguished the response. Considering $\geq 30\%$ reduction in SEGA tumor volume as response, 3/7 (42%) of patients were responders in the lowest quartile compared to 19/21 (90%) responders in the other three quartiles ($P < 0.05$ when response in the first quartile was compared to the other three quartiles). In the absence of a placebo arm in the current trial, the observed exposure-response relationship provides supportive evidence of effectiveness for everolimus in treatment of SEGA.

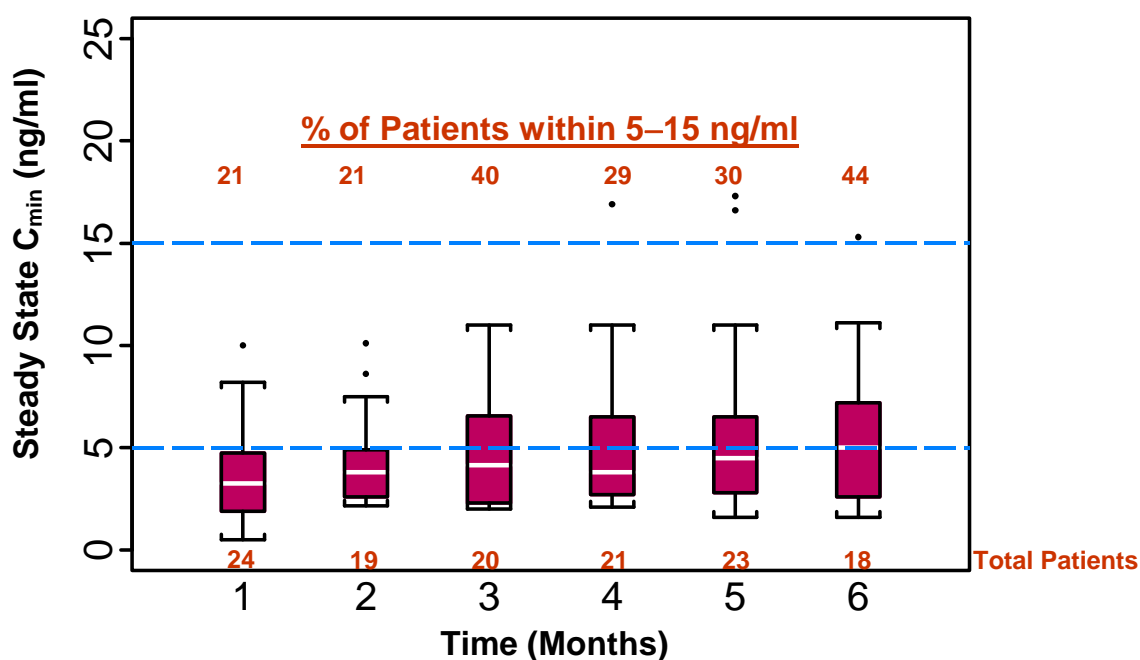
Figure 1: Exposure-response relationship of everolimus for percent reduction in SEGA tumor volume at 6 month. The numbers adjacent to each of the quartile represent the C_{min} range. Data are shown as Mean \pm SE. The numbers in red above the x-axis represents number of patients with $\geq 30\%$ response/total number of patients in respective quartiles.



2.1.2 Did TDM achieve target everolimus concentrations (5–15 ng/ml)?

No, less than half of the patients had steady state C_{min} within the concentration range of 5–15 ng/ml during the core treatment phase (6 months) in the phase 2 trial. **Figure 2** below shows the distribution of steady state C_{min} along with the % of patients within the 5–15 ng/ml range during core treatment phase. The observed data showed that only 21–44% of the patients were within the target range with most of the patients with steady state $C_{min} < 5$ ng/ml.

Figure 2: Box plot showing steady state C_{min} over time for the phase 2 trial. The blue dashed lines indicate the $(b) (4)$ target range (5–15 ng/ml). The numbers in red below the boxes represent the number of patients for which steady state C_{min} was available for respective months. The numbers in red above the dashed line represent the percentage of patients at each month within the target range.



2.1.3 Does exposure-response for efficacy support the $(b) (4)$ everolimus target?

The exposure-response relationship for efficacy supports the lower limit of everolimus target trough concentration of 5 ng/ml $(b) (4)$. The exposure-response relationship for % reduction in SEGA tumor volume shows that the mean % reduction in tumor volume is higher in patients with $C_{min} > 3$ ng/ml. Patients who had $C_{min} < 3$ ng/ml had approximately 30% mean reduction in tumor volume compared to 46% in patients who had average $C_{min} > 3$ ng/ml (**Figure 1**). Moreover, greater than 90% of patients were considered responders (defined as percent reduction $\geq 30\%$) at $C_{min} > 3$ or 5 ng/ml compared to 50% responders if $C_{min} < 3$ ng/ml (**Table 1**). A 90% response rate at $C_{min} > 3$ ng/ml is reassuring and supports the lower limit of 5 ng/ml.

Table 1. Responder Analysis by C_{min} Cutoff of 3 and 5 ng/ml

C_{min}, ng/ml (N)	Proportion of Patients with ≥ 30% Reduction in SEGA Tumor Volume
≥ 5 (N=12)	11 (92%)
≥ 3 (N=20)*	18 (90%)
< 3 (N=8) *	4 (50%)

* P <0.05 when comparing proportion of responders (≥ 30% tumor reduction) between these two groups

Although the data shows response at C_{min} >3 ng/ml, the lower limit of 5 ng/ml is appropriate because of the following two reasons:

1. Intra-individual variability in C_{min} is approximately 32% (range 9–83%). Therefore, some patients might fall below 3 ng/ml and loose response.
2. The exposure-response relationship is steep with an inflection point around 3 ng/ml (**Figure 1** and **Table 6**).

Thus, it is better to keep the lower limit of the target range in the flat region of the exposure-response curve to avoid a patients C_{min} falling below 3 ng/ml.

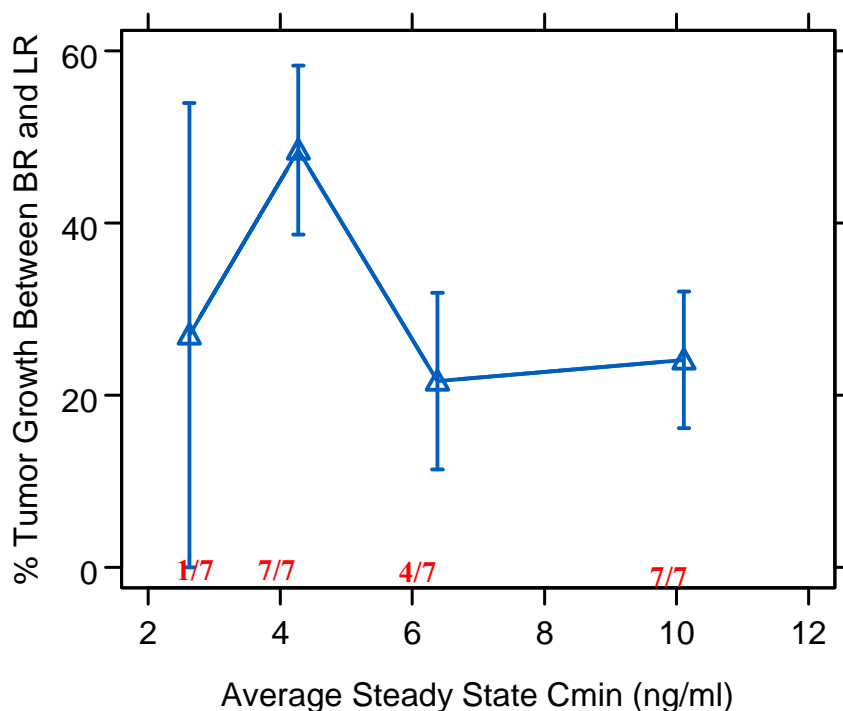
- (b) (4)
1. No additional reduction was observed in tumor volume at C_{min} ≥3 ng/ml.
 2. Only 12/125 of concentrations (< 10%) from 6 patients were above 10 ng/ml in the core treatment phase. (b) (4)

The recommended target range of 5–10 ng/ml is supported by the exposure-efficacy relationship and safety experience.

2.1.4 Is tumor re-growth after the core treatment phase associated with lower exposures?

The tumor re-growth in patients after the core treatment phase does not seem to be associated with lower exposures. Nineteen patients had measured last response (LR) that was worse than the best response (BR) during the treatment period. These patients were classified as patients with tumor re-growth which was defined as the % increase in SEGA tumor volume from BR. For the purpose of relating exposures with tumor re-growth, the steady state average C_{min} between BR and LR was used for the patients with tumor re-growth while the steady state C_{min} over the entire treatment period was utilized for patients with no tumor re-growth. Exposure data was then divided into quartiles with seven patients in each quartile and plotted against % increase in tumor volume from BR. There was no visible trend to indicate that tumor re-growth is associated with lower exposures (**Figure 3**). The analysis repeated with rate of tumor re-growth between BR and LR (defined as tumor re-growth divided by time between BR and LR in years) as the dependent variable resulted in the same outcome (**Table 7**).

Figure 3: Exposure-tumor re-growth relationship of everolimus. Data are shown as Mean \pm SE. The numbers in red above the x-axis represent number of patients with tumor re-growth/total number of patients in respective quartiles.



Patients with or without tumor re-growth were also examined at an individual level to investigate if tumor re-growth is associated with lower exposures. The data indicated that:

- 54% (7/13) patients with low average C_{min} (< 5 ng/ml) had tumor re-growth (representative plots from 4 patients, **Figure 14**).
- At the same time, the remaining 46 % (6/13) patients with average C_{min} < 5 ng/ml had sustained reduction in SEGA tumor volume without any tumor re-growth (representative plots from 4 patients, **Figure 13**).

In summary, there is lack of evidence to indicate that lower exposures might be responsible for tumor re-growth. There may be other pharmacodynamic reasons responsible for these findings.

The dose interruptions during the study were also considered as a potential reason for tumor re-growth. The patients who were considered to have no re-growth between the best response and the last response were compared to those that had some re-growth (3–189% re-growth). Considering the half-life of the drug is about 25–39 hours, a washout period of 7 days was used as a cutoff. In patients with no tumor re-growth, 2/9 (22%) had a dose interruption longer than 7 days (8 and 14 days) during the study. In patients with tumor re-growth, 14/19 (74%) patients had dose interruptions longer than 7 days (8–118 days) during the study, with 10/19 (53%) having dose interruptions longer than 7 days (8–18 days) during the period of re-growth. However, no relationship was observed between % dose interruption during the dosing period or dose interruption duration and % of tumor re-growth.

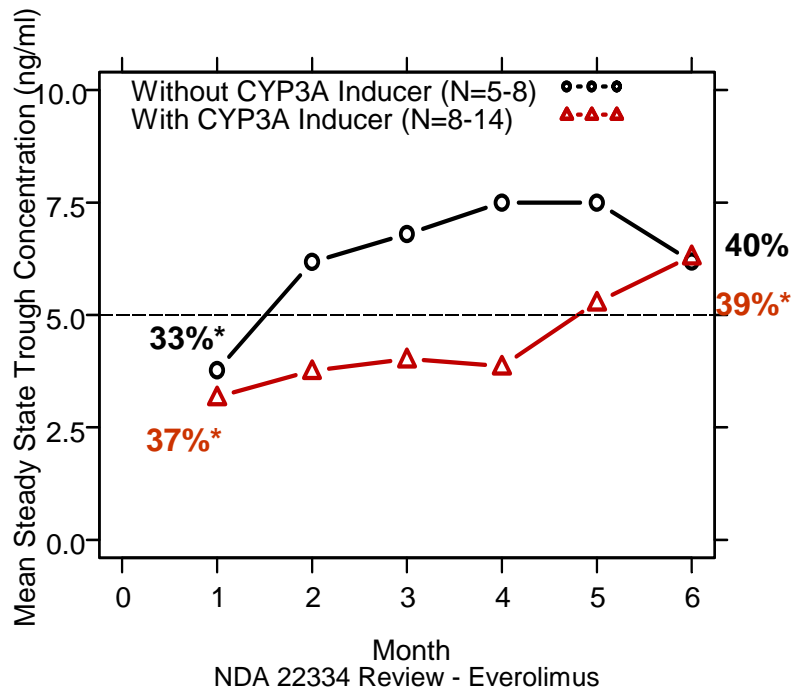
2.1.5 Is the starting dose and titration scheme appropriate for patients taking concomitant enzyme-inducing anti-epileptic drugs (EIAED)?

Patients on CYP3A4 inducers may need a higher starting dose and frequent titration scheme to reach the target of 5 ng/ml earlier. In the phase 2 trial, on an average, patients on CYP3A4 inducers did not reach the lower limit of the proposed target, 5 ng/ml, until the fifth month. **Figure 4** below shows the time course of C_{min} stratified by use of EIAED depicting that patients with concomitant EIAED reach target later.

The % reduction in SEGA tumor volume at 3 and 6 month was similar between the two groups indicating similar efficacy. This is also in accordance with the exposure-efficacy analysis that showed that the average % reduction in SEGA tumor volume remains constant at concentrations above 3 ng/ml. However, patients do not reach the lower limit of the proposed target, 5 ng/ml, until the fifth month which might warrant a need for higher dose/titration scheme in these patients. The sponsor does propose a higher starting dose if concomitant CYP3A4 inducers are used (see proposed label, section 3).

The titration scheme used in the trial is different from what is proposed in the label. The frequency of titration was not specified in the trial and doses were titrated approximately every month to achieve the target. In the label, the sponsor proposes every two week titration schedule to achieve the target. This frequent titration scheme will allow the patients to reach the 5 ng/ml target earlier. We also recommend doubling the dose in patients requiring strong CYP3A4 inducers since it is known from a dedicated drug-drug interaction study in healthy volunteers that exposures are decreased by ~ 65%. Moreover, in the trial, majority of patients on inducers had concentrations below 5 ng/ml at the first month so doubling the dose would still keep them in the target range. It should also be noted that the sponsor is evaluating a starting dose of 4.5 mg/m²/day (50% higher than the current proposed dose) in the Phase 3 trial.

Figure 4: Time course of steady state C_{min} over time for everolimus 3 mg/m²/day dosing regimen in the phase 2 trial. The black dashed line indicates the lower limit of the target, 5 ng/ml. Only mean concentrations are plotted for better visualization. Numbers against * indicate percent reduction in SEGA tumor volume at 3 and 6 months for the two groups.



2.2 GENERAL ATTRIBUTES

2.2.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

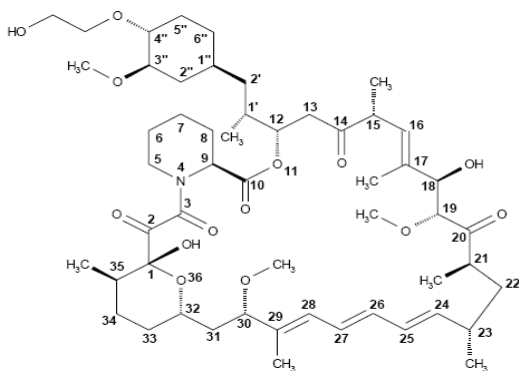
Everolimus is an mTOR inhibitor that was approved for advanced RCC after failure of treatment with sunitinib or sorafenib in 2009 under the trade name Afinitor® and for prophylaxis of organ rejection in kidney transplant in 2010 under the trade name Zortress®. Afinitor is approved at a fixed dose of 10 mg daily in RCC. Zortress is approved at a starting dose of 0.75 mg BID with titration to plasma trough concentrations of 3–8 ng/ml using therapeutic drug monitoring (TDM) in kidney transplant.

A written request (WR) dated 04/01/10 asked the sponsor to submit information from 2 studies for pediatric information: 1) a non-randomized, open-label phase 2 study of everolimus for the treatment of patients with SEGA associated with TSC, and 2) a randomized, double-blind, placebo-controlled phase 3 study of everolimus for the treatment of patients with SEGA associated with TSC. The current submission contains the phase 2 study report (study 1 in WR) which is an investigator initiated study (C2485) conducted at Cincinnati Children's Hospital (IND 70895). At a pre-sNDA meeting on 11/29/09, the FDA agreed to review the data from the single arm Phase 2 study for Subpart H approval as long as the sponsor would complete recruitment to their Phase 3 trial prior to the action date for the supplemental application. A short description of the phase 2 study (C2485) submitted for accelerated approval with key findings is summarized in 4.3. The current sNDA application is submitted under the Afinitor NDA 22334.

2.2.2 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

- Structural formula:



- Established name: Afinitor
- Molecular Weight: 958.2

- Molecular Formula: C₅₃H₈₃NO₁₄
- 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-(2hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-azatricyclo[30.3.1.0^{4,9}] - hexatriaconta16,24,26,28-tetraene-2,3,10,14,20-pentaone.
- Formulation: Afinitor is supplied as tablets for oral administration containing 2.5, 5 and 10 mg of everolimus together with butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone and lactose anhydrous as inactive ingredients.

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

The sponsor is seeking approval of Afinitor for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS). Tuberous sclerosis is an autosomal dominant condition involving the *TSC1* and/or *TSC2* genes and when either is deficient, mTORC1 is constitutively upregulated, leading to hamartoma formation throughout the body. Everolimus is an mTOR inhibitor, specifically targeting the mTOR-raptor signal transduction complex (mTORC1). The sponsor claims that restoration of the signaling balance through the administration of everolimus will show that further SEGA growth can be inhibited and that regression may also be achieved.

2.2.4 What are the proposed dosage and route of administration?

The sponsor proposes individualized dosing with a starting dose of (b) (4) administered orally with dose titration every 2 weeks until a steady state trough concentration of (b) (4) is achieved. Since the drug is formulated as 2.5, 5 and 10 mg tablets, the sponsor proposes a flat starting dose based on BSA cutoffs as mentioned in the table below:

BSA (m ²)	Starting Daily Dose (mg)
(b) (4)	2.5
1.3 – 2.1	5
≥ 2.2	7.5

Reviewer's Comments: The sponsor's proposed dosing regimen and titration scheme appears acceptable. The starting daily dose proposed by the sponsor is slightly different from the way it was studied in the trial. The starting doses in the C2485 study were 2.5 mg for patients with a BSA of 0.66 - 0.96 m², 5 mg for BSA of 0.97 - 2.16 m² and 7.5 mg for BSA of 1.97 - 2.60 m². One patient with a BSA of 0.58 m² had a starting dose of 2.5 mg QOD.

- *In the study patients with BSA 0.66 - 0.96 m² started at 2.5 mg and 5 patients with a BSA between 0.97 and 1.24 m² had a starting dose of 5 mg. The 5 patients with a BSA < 1.3 m² receiving 5 mg had the first trough concentration measured at steady state of 2.4, 2.7, 3.3, 4.8 and 10.4 ng/ml, respectively. The patients with trough concentrations of 2.4 and*

2.7 ng/ml were on CYP3A4 enzyme inducing antiepileptic drugs (EIAED). The concentrations in the 5 patients are either below or in the target range suggesting the 5 mg may be appropriate for these patients. The sponsor does not provide rationale for picking the starting dose of 2.5 mg for patients with a BSA of 0.97 to 1.2 m². However, this may be acceptable considering the sponsor is being more conservative and TDM will be used for the patients to achieve trough concentrations in the target range. (b) (4)

the drug will only be used in patients aged 3 years or older. Study C2485 did not include patients younger than 3 years old but the ongoing phase 3 study will study patients that are 1 year or older.

- The proposed starting dose of 5 mg for BSA of 1.3 – 2.1 m² appears acceptable since patients with BSA of 0.97 - 2.16 m² in the study received the starting dose of 5 mg. Only 1 patient in this study with a BSA of less than 2.2 m² (1.97 m²) received a starting dose of 7.5 mg and this patient achieved a trough concentration of 4.2 ng/ml while on an EIAED.
- All the other patients in the study with a BSA less than 2.1 received a starting dose of 2.5 or 5 mg, so starting dose of 7.5 mg appears acceptable for patients with BSA ≥ 2.2m².

In summary, the sponsor's proposed dosing regimen and titration scheme appears reasonable. We recommend doubling the starting dose in patients requiring concomitant use of strong CYP3A4 inducers (2.1.5).

2.3 GENERAL CLINICAL PHARMACOLOGY

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

One Phase 2 study (C2485) was submitted to support dosing or claims. C2485 is a prospective, non-randomized, open-label, investigator-initiated, single-center study designed to evaluate the safety and efficacy of everolimus in patients (N=28) with SEGA associated with TS. The median age (range) of patients in the study was 11 (3–34 years) with BSA ranging from 0.6 - 2.6 m². TDM was utilized in this study to achieve a target trough concentration of 5 - 15 ng/ml. The starting dose was 3 mg/m²/day titrated to achieve the target range (5 - 15 ng/ml).

Duration of treatment included a six-month core treatment phase after which patients were able to transition into a long-term extension. Treatment was to continue for as long as therapeutic benefit was evident without significant adverse effect or risk to the patient.

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

The primary efficacy endpoint was change in SEGA volume from baseline to 6 month as determined by independent central review. An additional measurement of SEGA volume was

also taken at 3 months from the initiation of the study. Volumetric assessment of the tumor was performed using Magnetic Resonance Imaging (MRI). Current approaches for classifying tumor response are typically based on anatomical measurements in either one- (Response Evaluation Criteria in Solid Tumors [RECIST]) or two-dimensions (World Health Organization [WHO]). There are no currently validated criteria for assessing SEGA hamartomas. Sponsor states that recent studies have demonstrated that volumetric measurement of target lesions using MRI allows for a more accurate assessment of lesion response to treatment and provides a better approximation of actual tumor volume than diameter-based measurements.

Secondary efficacy endpoints included: seizure frequency, as assessed by 24-hr video-EEG monitoring; Quality of Life (QoL) as assessed by a standardized Quality of Life in Children with Epilepsy (QOLCE) questionnaire; neuropsychometric functioning as assessed by a battery of age-appropriate tests; response of facial angiofibromas; magnetic resonance spectroscopy (MRS) to measure reduction in choline and myoinositol peaks.

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

Everolimus is the main circulating moiety and it has 6 main metabolites detected in human blood which are about 100 times less active than everolimus itself. PK samples in the current submission were analyzed only for the parent drug using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method. The method is similar to the method used for everolimus (Zortress) TDM in the renal transplant indication and is discussed in greater detail in 2.6.1.

2.3.4 Exposure-response

There was evidence of exposure-response relationship for efficacy. Exposure-response for safety could not be identified probably because of a small safety database of 28 patients. The most common adverse reactions observed were stomatitis and infections (mainly upper respiratory track infections (URI)) and were grade 1 or 2. There were 10 patients who experienced grade 3 adverse reactions and one patient experienced a grade 4 adverse reaction (convulsions).

2.3.4.1 Is there evidence of an exposure-response relationship for efficacy?

Please refer to 2.1.1 and 4.2.1 for details.

2.3.4.2 Is there an evidence of exposure-response for safety?

The data is limited to support exposure-safety relationship for stomatitis, infections or upper respiratory track infections:

- The safety dataset only comprised of 28 patients.

- Most the patients experienced these AEs, thus it is difficult to discern any relationship with exposures.
- The range of C_{min} may not be wide enough to explore exposure-safety relationship.

Since the safety database only had 28 patients in the safety database the average C_{min} exposures were divided by median to form low and high exposure group to see if there was a trend of increasing adverse events with higher exposures. In study C2485, 22/28 patients had stomatitis or URI and 25/28 experienced infections at least once during the treatment period. There seems to be some trend for stomatitis and infections, but the data is limited to establish any concrete relationship. It is also important to note that most of the adverse events were Grade 1 or 2 and dose interruptions rather than dose reduction appeared to be the favored method for managing AEs in this single-center study, with a median of 2 interruptions per patient (range: 0 to 15). Interruptions lasted for between 1 and 131 days. The toxicity profile of everolimus in SEGA was similar to what has been observed and reported in the approved label for Afinitor for the renal cell carcinoma indication.

Table 2. Exposure-safety relationships for most common adverse events.

Exposure Group	Mean C_{min} (Range) ng/ml	Adverse Event	Proportion of Patients with all grades AE's (%)	Proportion of patients with AEs \geq Grade 3
Low (Below median C_{min})	2.9 (1.8 - 4.4)	Stomatitis	10/14 (71)	1/14
High (Above median C_{min})	6.9 (4.6 - 11)		12/14 (86)	0/14
Low (Below median C_{min})	2.9 (1.8 - 4.4)	Infections and Infestations	11/14 (79)	2/14
High (Above median C_{min})	6.9 (4.6 - 11)		14/14 (100)	2/14
Low (Below median C_{min})	2.9 (1.8 - 4.4)	URI	11/14	0/14
High (Above median C_{min})	6.9 (4.6 - 11)		11/14	0/14

2.3.4.3 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?

There was no clear rationale for dosing regimen (b) (4) and target range (b) (4) selection. The maximum tolerated dose established in for pediatric patients with refractory or recurrent solid tumors was found to be 5 mg/m² (Fouladi, et al 2007). A dose titration is used in the SEGA population because a significant number of patients require concurrent enzyme inducing antiepileptic drugs (EIAEDs) and everolimus is a substrate of CYP3A4. The initial everolimus target concentration that the investigator assumed from biomarker data in RCC and rapamycin (sirolimus) data was 10 – 15 ng/ml (10 – 35 ng/ml in preliminary RCC PK/PD studies). This information was used for everolimus TDM without any clear justification. However despite dose adjustments some SEGA patients failed to achieve the target dose level although some experienced the radiologic response. This led to the revision of target rough concentrations of 5 – 15 ng/ml. The 3 mg/m²/day dosing regimen is lower when compared to a single 10 mg QD dose for a 70 kg patient. The starting dose may not be that critical in TDM as the patient trough levels will be titrated to a fixed target. However, the target range is not supported by the study C2485 and should be changed (b) (4) to 5 - 10 ng/ml to be consistent with the exposure-efficacy relationship and safety experience based on the observed data in the trial (See 2.1.2, 2.1.3 and 4.1.1.1 for details).

2.3.5 What are the pharmacokinetic characteristics of the drug and its major metabolites?

In adult patients with advanced solid tumors, peak everolimus concentrations are reached 1 to 2 hours after administration of oral doses ranging from 5 mg to 70 mg. Following single doses, C_{max} is dose-proportional between 5 mg and 10 mg. At doses of 20 mg and higher, the increase in C_{max} is less than dose-proportional, however AUC shows dose-proportionality over the 5 mg to 70 mg dose range. Steady state is achieved within two weeks following once daily dosing with a mean elimination half-life of 25 – 39 hours. In healthy subjects, high fat meals reduced systemic exposure of Afinitor 10 mg tablet with everolimus AUC reduced by 22% and the peak plasma concentration C_{max} reduced by 54%. Food, however, had no significant effect on the post absorption phase concentration-time profile. Following the administration of a 3 mg single dose of radio-labeled everolimus in patients who were receiving cyclosporine, 80% of the radioactivity was recovered from the feces, while 5% was excreted in the urine. The parent substance was not detected in urine or feces.

The sponsor states that C_{min} is proportional over the BSA-normalized dose range of 1.5 to 14.6 mg/m². A model-based method was used to analyze trough level data from Study C2485. The relationship between C_{min} and BSA-normalized dose was evaluated using a mixed model with logarithmized-C_{min} as the dependent variable, logarithmized dose

(mg/m²) as a fixed effect, and patient as a random effect. The model was of the form $\ln(C_{\min}) = \alpha + \beta \cdot \ln(\text{dose}) + \text{error}$. Coefficient β was estimated along with the 90% confidence interval (CI). Based on the sponsor's analysis the dose-proportionality coefficient β was 1.066 (90% CI 0.928 to 1.205) for all data, 1.16 (90% CI 0.838 to 1.481) with patients who had received CYP3A4 inducer/inhibitor co-medication excluded (69 samples), 1.055 (90% CI 0.893 to 1.216) for patients who had received CYP3A4 inducers (128 samples) and β was 0.726 (90% CI 0.487 to 0.965) for patients who had received CYP3A4 inhibitors (40 samples). The sponsor concluded that dose proportionality exists irrespective of the use of CYP3A4 inducers or inhibitors. The reviewer agrees with the sponsor's analysis and conclusion.

2.4 INTRINSIC FACTORS

2.4.1 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?

Dosage regimen adjustments were proposed for patients taking concomitant CYP3A4 inducers, CYP3A4 inhibitors or patients with moderate hepatic impairment.

2.4.1.1 Hepatic Impairment

A study was conducted under the transplant NDA in healthy patients and patients with moderate hepatic impairment. 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 21-560 (b) (4)). It was seen that average AUC was increased by 2-fold in patients with moderate hepatic impairment compared to patients with normal hepatic function. In RCC, it is recommended that the dose is decreased from 10 to 5 mg daily in patients with moderate hepatic impairment (Child Pugh class B) but everolimus was not studied in severe hepatic impairment.

The sponsor proposes (b) (4) in patients with moderate hepatic impairment (Child-Pugh class B). However, it may be acceptable to use the same starting dose in patients with moderate hepatic impairment and in those with normal hepatic function. The two fold higher exposures in moderate hepatic impaired patients with the same starting dose appear acceptable since we are aiming for a target (5 - 10 ng/ml). Moreover, based on the observed data, the average trough concentration for the first month was below 5 ng/ml (**Figure 2**) so 2-fold higher exposures may still fall within the target. More importantly, subsequent TDM can be utilized to individualize dosing. At that time, dose can be reduced by 50% to maintain 5-10 ng/ml target range.

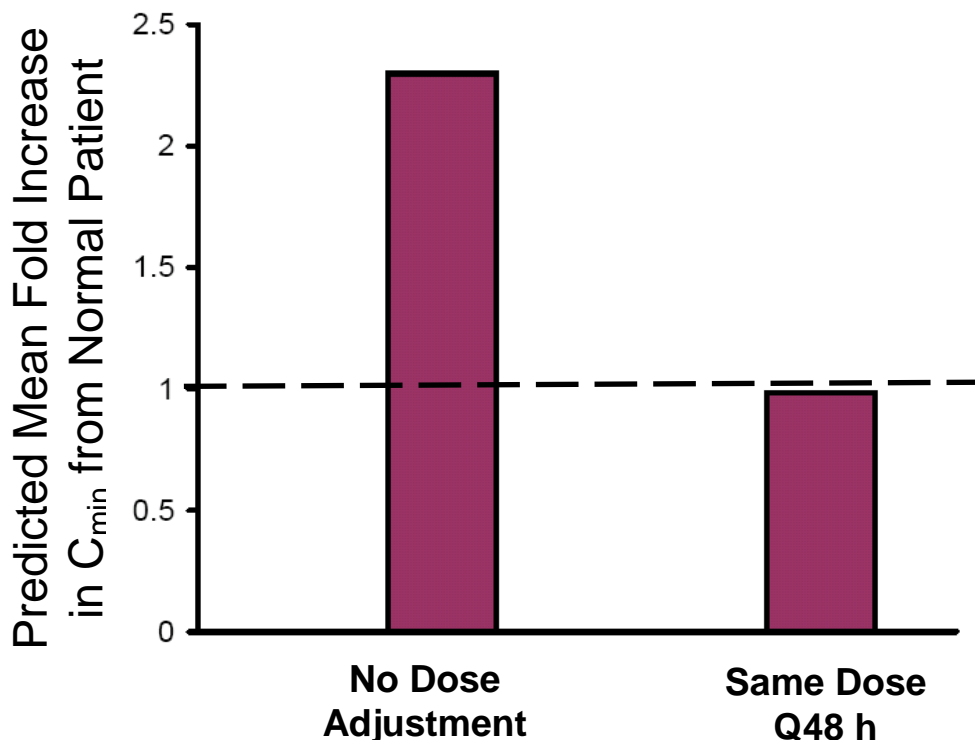
However, during subsequent TDM, if dose reduction is required in patients taking 2.5 mg daily dose, a lower strength tablet is not available.

Simulations were conducted using sponsor's population PK model to explore alternate day (Q48 h) dosing regimen. Steady state C_{min} for a typical adult patient was simulated with a 5 mg daily dose. The choice of dose for simulation is not important here. The 5 mg daily dose was chosen as it approximates to a 3 mg/m²/day dose for an adult with BSA of 1.8 m². The focus here was to calculate the relative fold increase in hepatic impaired patient compared to a typical adult patient for proposing dose adjustments in SEGA patients. Simulation was also conducted for the same patient for the two other scenarios:

- Hepatic impairment (clearance decreased by half) and no dose adjustment.
- Hepatic impairment (clearance decreased by half) and same dose every 48 h. The idea is to explore this alternate day dosing regimen if it matches C_{min} of the typical adult patient.

Figure 5 shows the mean fold increase in moderate hepatic impaired patient relative to normal patient for the above two scenarios. It can be seen that giving same dose Q48 h in a moderately hepatic impaired patient will produce similar C_{min} to a typical adult patient. Thus, we recommend that if trough levels assessed at week 2 are higher than the target, then alternate day dosing with 2.5 mg should be considered.

Figure 5: Predicted mean fold increase in C_{min} of a moderate hepatic impaired patient relative to normal patient for two scenarios: No dose adjustment and same starting dose every 48h. Dashed line represents similar exposures to typical normal adult patient.



2.5 EXTRINSIC FACTORS

2.5.1 Drug-drug interactions

The steady-state C_{max} and AUC estimates of everolimus were significantly increased by co-administration of single dose cyclosporine (CYP3A4/P-gp inhibitor). Multiple-dose ketoconazole (strong CYP3A4 inhibitor) administration to healthy volunteers significantly increased single dose estimates of everolimus C_{max} , AUC, and half-life. The current Afinitor label recommends that strong inhibitors of CYP3A4 or PgP not be co-administered with everolimus while 2.5 mg everolimus dose should be administered to patients taking moderate CYP3A4 or PgP inhibitors with an option to increase it to 5 mg based on patient tolerance.

According to the current approved Afinitor label, in healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP3A4, decreased everolimus AUC and C_{max} by 64% and 58% respectively, compared to everolimus treatment alone. Thus, strong CYP3A4 inducers should be avoided, but if needed an increase in the dose of Afinitor may be considered.

2.5.1.1 What are the dose modifications proposed in subjects on concomitant CYP3A4 inducers?

The sponsor proposes to avoid the use of concomitant strong CYP3A4 inducers. If patients require co-administration of a strong CYP3A4 inducer (EIAEDs), increasing the dose may be considered to achieve (b) (4). We recommend doubling the dose in patients requiring concomitant use of strong CYP3A4 inducers (2.1.5).

2.5.1.2 What are the dose modifications proposed in subjects on concomitant CYP3A4 inhibitors?

The sponsor proposes that strong CYP3A4 or PgP inhibitors be avoided, but if a moderate CYP3A4 or PgP inhibitors are required, caution should be used and the dose reduced by 50% to maintain trough concentrations of (b) (4). The dose adjustment for a reduction of the dose in patients that start on a dose of 2.5 mg daily is addressed below considering a lower strength tablet is not available.

Simulations were conducted to investigate two possible scenarios here:

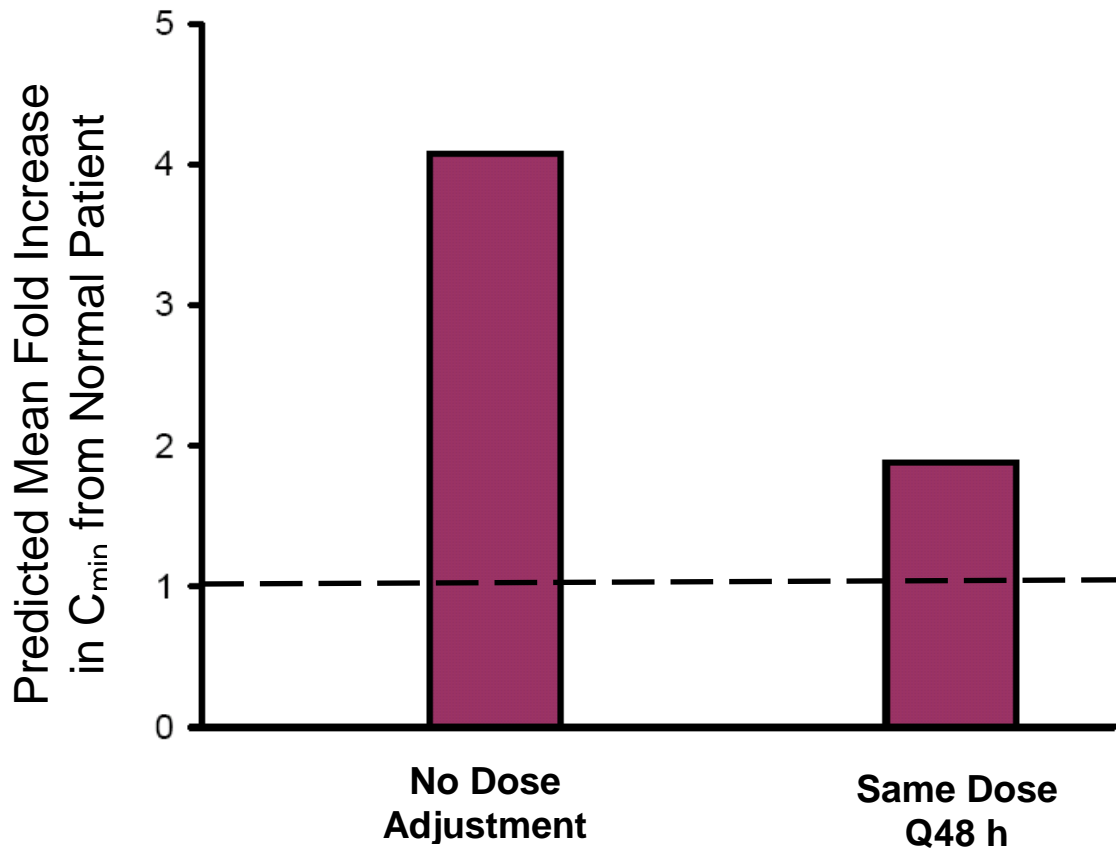
- ❖ Patients starting on 2.5 mg and on moderate CYP3A4 or PgP inhibitors
As described above, steady state C_{min} for a typical adult patient was simulated with a 5 mg daily dose (~ dose $3\text{mg}/\text{m}^2/\text{day}$ for adult with BSA of 1.8m^2). The focus here was to calculate the relative fold increase in patients on moderate CYP3A4 or PgP inhibitors compared to typical adult patient for proposing dose adjustments in SEGA patients. Simulation was also conducted for the same patient for the two sub-scenarios:

- Concomitant administration of moderate CYP3A4 inhibitors (clearance decreased by ~ 4 fold) and no dose adjustment.
- Concomitant administration of moderate CYP3A4 inhibitors (clearance decreased by ~ 4 fold) and same dose every 48 h.

Figure 6 shows the mean predicted fold increase in patient taking moderate CYP3A4 inhibitor relative to normal patient for the above two sub-scenarios: No dose adjustment and same dose every 48 h. It can be seen from

Figure 6 that even though giving same dose every other day to these patients will not compensate for 4-fold higher exposures, it will reduce the exposures by two-fold. Thus we recommend that if use of moderate CYP3A4 inhibitors cannot be avoided, alternate day dosing with 2.5 mg can be used with caution. Subsequent dosing should be individualized based on TDM.

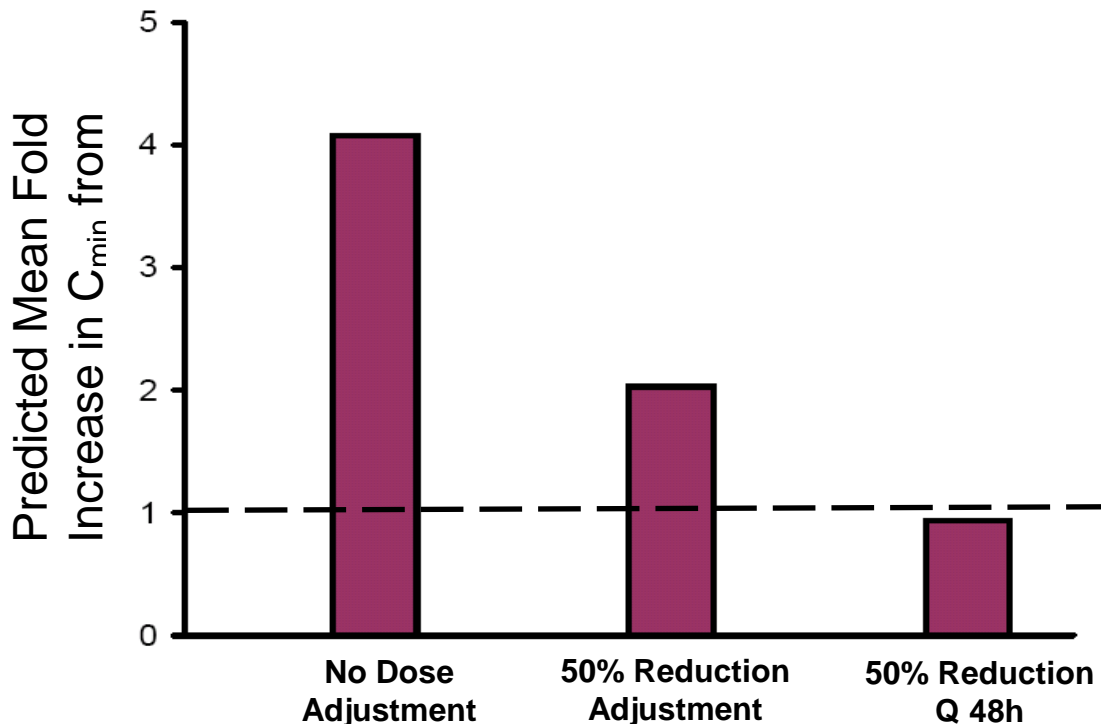
Figure 6: Predicted mean fold increase in C_{min} of a patient on 2.5 mg starting dose taking moderate CYP3A4 inhibitors relative to normal patient for two scenarios: No dose adjustment and same starting dose every 48 h. Dashed line represents similar exposures to typical normal adult patient.



- ❖ Patients starting on 5 mg and on moderate CYP3A4 or PgP inhibitors:
The sponsor recommends a 50% reduction in dose in a patient with a starting dose of 5 mg and on CYP3A4 inhibitors. Again, steady state C_{min} for a typical adult patient was simulated with a 5 mg daily dose (\sim dose $3\text{mg}/\text{m}^2/\text{day}$ for adult with BSA of 1.8m^2). Simulation was also conducted for the same patient for the three sub-scenarios:
 - Concomitant administration of moderate CYP3A4 inhibitors (clearance decreased by \sim 4 fold) and no dose adjustment
 - Concomitant administration of moderate CYP3A4 inhibitors (clearance decreased by \sim 4 fold) and 50% reduction in dose.
 - Concomitant administration of moderate CYP3A4 inhibitors (clearance decreased by \sim 4 fold) and 50% reduction in dose given every 48 h.

Figure 7 shows the mean predicted fold increase in a patient taking moderate CYP3A4 inhibitor relative to a patient for the above three sub-scenarios. It can be seen from Figure 7 that reducing the dose by 50% will still result in 2-fold higher C_{min} in these patients. However, 50% reduction in dose along with every 48 h administration will result in similar C_{min} . We recommend that it is reasonable to start with 50% dose reduction for these patients since two-fold higher exposures is acceptable considering that we are aiming for a target (5 - 10 ng/ml). Subsequently TDM can be utilized to maintain target trough of 5 - 10 ng/ml. During subsequent TDM, the option of alternate day dosing could be considered to achieve the target of 5-10 ng/ml.

Figure 7: Predicted mean fold increase in C_{min} of a patient on 5 mg starting dose taking moderate CYP3A4 inhibitors relative to normal patient for three scenarios: No dose adjustment, 50% dose reduction and 50% dose reduction every 48 h. Dashed line represents similar exposures to typical normal adult patient.



2.6 ANALYTICAL SECTION

2.6.1 What bioanalytical methods are used to assess concentrations?

The bioanalytical method that was used as of January 2009 in study C2485 is the same one used for Zortress TDM in kidney transplant and will be available to health care providers for TDM in this indication until a commercially available assay is approved. The concentrations of calibrators and controls changed in 2009 in the lots supplied by the manufacturer. The method details are contained below.

Table 3. Details of the Bioanalytical Method

Matrix	Human whole blood with K ₃ EDTA anticoagulant
Sample Volume Required	125 µL
Storage Conditions	Lyophilized: Stable for 36 months at 5°C Reconstituted: Stable for one week at 5°C Stable for 30 days at -20°C
Concentration Range	0.39 - 88.8 ng/mL (Feb 2007 to Dec 2008) 1.20 - 44.9 ng/mL (Jan 2009 to Dec 2009)
HPLC Procedure	Reversed-phase liquid
Detection	Triple quadrupole mass spectrometry
Regression Type	Quadratic regression
Calibration Weighting	1/x ²
Inter-batch mean accuracy ranges	Standards: 95.8 – 105% Quality Controls: 96.3 -101%
Inter-batch mean precision ranges	Standards: ≤ 12.6% Quality Controls: ≤ 6.22%
Bench top stability	24.1 hours
Freeze thaw stability	2 cycles
Reinjection reproducibility	48.2 hours
Dilutions	5x and 10x
QC	<p>Sample batch acceptance from 21 Feb 2007 to 02 Jun 2009:</p> <ul style="list-style-type: none"> • Bias within the range of ±20% for at least 2/3 of the individual values. • At least two thirds of the QC samples at all levels must deviate ≤20% from their respective nominal value. • At least 50% of the QC samples at each level must deviate ≤20% from their respective nominal value. <p>If QC acceptance criteria are not met, all data from the run are rejected.</p> <p>Sample batch acceptance from 02 Jun 2009 to Dec 11 2009:</p>

	<ul style="list-style-type: none">• Bias within the range of $\pm 15\%$ for at least 2/3 of the individual values.• At least two thirds of the QC samples at all levels must deviate $\leq 15\%$ from their respective nominal value.• At least 50% of the QC samples at each level must deviate $\leq 15\%$ from their respective nominal value. <p>If QC acceptance criteria are not met, all data from the run are rejected.</p>
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3 DETAILED LABELING RECOMMENDATIONS

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)

4 APPENDIX

4.1 SPONSOR'S ANALYSIS

4.1.1 Exposure-Response Analysis

Sponsor conducted exploratory exposure-response analysis for efficacy (tumor change from baseline) and safety endpoints (infections and stomatitis).

4.1.1.1 Efficacy

Higher C_{\min} values appeared to be associated with a larger reduction in SEGA volume (**Figure 8**). The relationship is less evident for patients with baseline SEGA volumes $< 1 \text{ cm}^3$.

Primary SEGA volume at Month 6

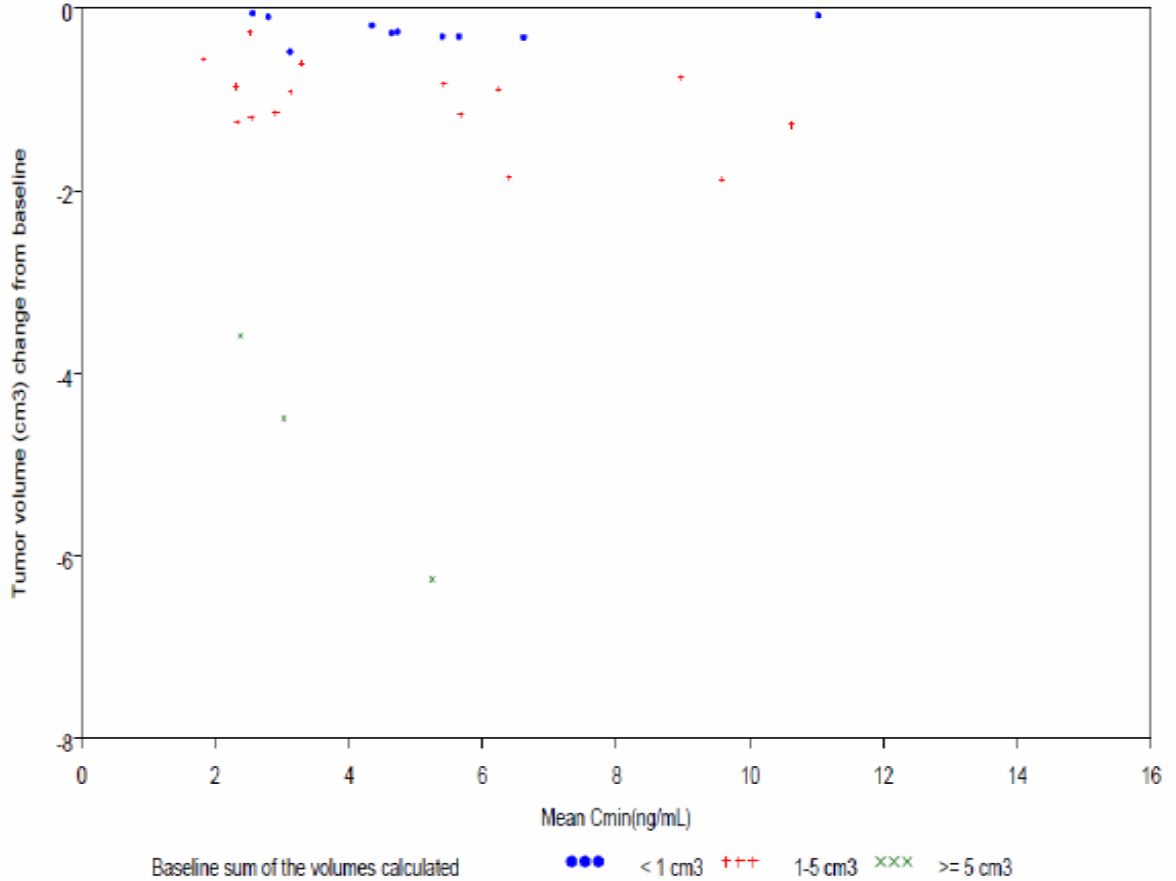
The relationship between SEGA volume and C_{\min} values was investigated using a linear model. Baseline tumor volume was included as a covariate and was found to be significant indicating that reduction in SEGA volume was positively correlated with baseline tumor size. There was also a significant interaction between baseline tumor size and volume reduction suggesting that the exposure-response relationship is different for differing baseline volumes.

The exposure-response relationship was then investigated in three subgroups defined by baseline SEGA volume: $> 5 \text{ cm}^3$, $1\text{-}5 \text{ cm}^3$, and $< 1 \text{ cm}^3$. The relationship between reduction in SEGA volume and C_{\min} was more evident for patients with baseline SEGA volumes of between 1 and 5 cm^3 and $> 5 \text{ cm}^3$. These analyses were considered to be exploratory and no multiplicity adjustment was performed.

Primary SEGA volume data using all time points in the study

Similar results were obtained when investigating the exposure-response relationship using repeated measurements for patients, that is, their SEGA volume change at each MRI assessment and the average C_{\min} between the time of that tumor assessment and the previous one. The relationship between reduction in SEGA volume and C_{\min} was more evident for patients with baseline SEGA volume of between 1 and 5 cm^3 ($p=0.0551$). Relationships were not statistically significant for patients with baseline SEGA volumes $< 1 \text{ cm}^3$ or $> 5 \text{ cm}^3$. These analyses were again considered to be exploratory and no multiplicity adjustment was performed.

Figure 8: Relationship between reduction in SEGA volume and C_{min} - PK Sample Set 3 - Safety Population. C_{min} at Month 6 = average of all C_{min} readings during the initial 6 months



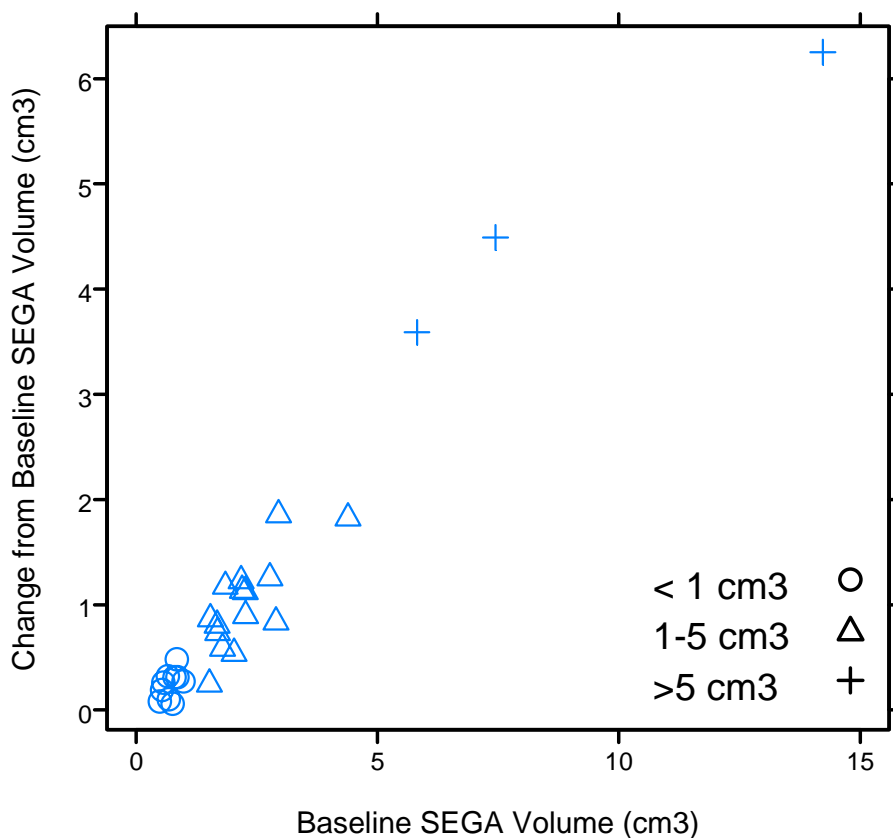
Reviewer's Comments:

The exploratory analysis conducted by the sponsor seems reasonable. There are a few specific comments about the analysis:

- *There were only 28 patients in the study with only 3 patients in the $> 5\text{cm}^3$ baseline SEGA tumor volume subgroup. Therefore it is not feasible to perform exposure-response analysis for different subgroups (based on baseline tumor size). Moreover, the cutoffs for these subgroups (< 1 , $1-5$ and $\geq 5\text{cm}^3$) based on baseline tumor sizes are arbitrary. Therefore, assuming that the shape of exposure-response curve will not be different among the three baseline tumor size subgroups, reviewer performed exposure-response analysis using data from all 28 patients. The absolute change in SEGA tumor volume was positively correlated to baseline tumor size (**Figure 9**). Therefore, % change from baseline SEGA tumor volume as apposed to absolute change from baseline was used as the response variable which corrects for different baseline tumor volume among patients.*

- Reviewer performed additional exposure-response analysis based on responder status (considering $\geq 30\%$ or 50% reduction in SEGA tumor volume as definition of responder).
- Sponsor did not address the reasons behind tumor growth in some patients after the core-treatment phase. Reviewer's analysis focused on whether lower exposures may be associated with tumor growth. See 4.2.1 for more details.
- PK sample set 2 was utilized for all the analysis since PK sample set 3 included samples that were not confirmed to be at steady state.

Figure 9: Relationship between baseline SEGA tumor volume and change from baseline at the end of six months



4.1.1.2 Safety

Subgroup analysis of AEs by everolimus trough concentration was not indicative of an increased risk with higher C_{\min} . With data from only 2 patients in the highest trough concentration range, this column is not considered to be informative.

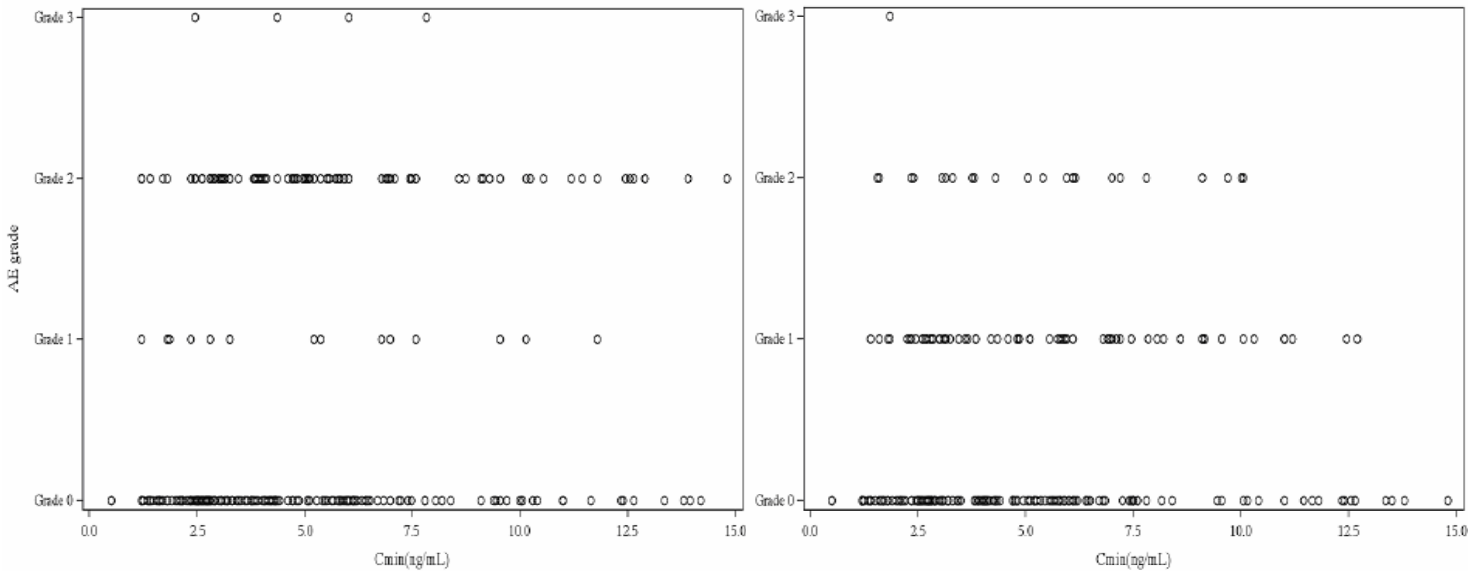
Table 4. Adverse events by everolimus trough concentration and preferred Term: PK Sample Set 3 - Safety Population

MedDRA preferred term	Everolimus					
	$C_{min} < 5$ ng/mL N=13 n (%)		$C_{min} 5-10$ ng/mL N=13 n (%)		$C_{min} > 10$ ng/mL N=2 n (%)	
Any AE	13	(100.0)	13	(100.0)	2	(100.0)
Upper respiratory tract infection	10	(76.9)	10	(76.9)	2	(100.0)
Stomatitis	9	(69.2)	11	(84.6)	2	(100.0)
Sinusitis	5	(38.5)	5	(38.5)	1	(50.0)
Convulsion	4	(30.8)	3	(23.1)	0	
Dermatitis acneiform	4	(30.8)	3	(23.1)	0	
Otitis media	4	(30.8)	6	(46.2)	0	
Personality change	4	(30.8)	1	(7.7)	0	
Pyrexia	4	(30.8)	6	(46.2)	0	
Body tinea	3	(23.1)	1	(7.7)	1	(50.0)
Cough	3	(23.1)	2	(15.4)	0	
Diarrhoea	3	(23.1)	2	(15.4)	2	(100.0)
Vomiting	3	(23.1)	2	(15.4)	1	(50.0)
Cellulitis	2	(15.4)	4	(30.8)	0	
Headache	1	(7.7)	4	(30.8)	0	
Rash	1	(7.7)	4	(30.8)	0	
Gastroenteritis	1	(7.7)	3	(23.1)	0	
Gastric infection	0		3	(23.1)	0	

Source: [Post-text Table 14.2-4.6.2.3](#)

No relationship was evident between the grading (severity) of infections and stomatitis, the two most frequently reported AEs, and C_{min} (**Figure 10**).

Figure 10: Exposure-response relationship between AEs and C_{min} - PK Sample Set 3 - Safety Population



Reviewer's Comments:

- *PK sample set 2 was utilized for the entire reviewer's analysis since PK sample set 3 included samples that were not confirmed to be at steady state.*
- *The cutoff of 0-5, 5-10 and >10 may not be appropriate especially when only two patients fall into the > 10 ng/ml group. Since the safety dataset comprised of only 28 patients, the reviewer used median exposure as the cutoff to form low and high exposure group and then conducted exposure-safety analysis for most common AEs.*
- *Individual patients who either discontinued due to adverse event or had SAEs were examined separately for exposure levels.*

4.2 REVIEWER'S ANALYSIS

4.2.1 Exposure-Response Analysis for Efficacy

4.2.1.1 Objectives

The primary objectives for these analyses were to:

- Explore exposure-response relationship for efficacy as a supportive evidence of effectiveness.
- Investigate the ability of therapeutic drug monitoring to achieve target everolimus trough concentrations in Study C2485.
- Explore the exposure-response relationship for efficacy to evaluate the (b) (4) everolimus target trough concentration range of 5 to 15 ng/ml.
- Explore if tumor re-growth in some patients after the core treatment phase was due to low exposures.

4.2.1.2 Methods

Sponsor provided 3 types of trough concentrations as part of the PK dataset. The PK sample analyses were done using 3 PK sets; first with samples at steady state and within 22 to 26 hours post dose (N=33 from 18 patients), the second included the samples in set 1 and some at steady state but in an unknown time after post dose (N=217 from 28 patients) and the third set included samples that were not confirmed as steady state concentrations (N=223 from 28 patients). PK sample set 2 was used for further analysis since PK sample set 1 comprised of very few samples.

Average C_{\min} over a period of 6 months was utilized as the exposure variable to conduct the primary exposure-response analysis. Five patients did not meet the eligibility criteria for inclusion in the trial. The primary exposure-response analysis was repeated excluding these five patients to assess the impact on exposure-response. Percent reduction in SEGA tumor volume from baseline as apposed to absolute change from baseline was used as the response variable to account for differences in baseline tumor volume.

Several sensitivity analyses were also conducted to ascertain the validity of exposure-response relationship:

- Scenario 1: % reduction in SEGA tumor volume at six months vs Month 6 steady state C_{min} (N=18 patients)
- Scenario 2: % reduction in SEGA tumor volume at 6 months and the average C_{min} between the time of 6 month tumor assessment and the previous MRI (N=27 patients).
- Scenario 3: % reduction in SEGA tumor volume at 3 and 6 month MRI assessment and the corresponding average C_{min} at 3 and 6 month (N=38 data points from 23 patients). Each data point was treated as different patient.

The best response (BR) and last response (LR) was considered to define patients with tumor re-growth. If LR was lower than BR, the patient was classified as having tumor growth. If last response was the best response, then the patient was assumed to have sustained reduction in tumor over the entire period. Steady state C_{min} between BR and LR was calculated for the patient in which tumor grew back while average steady state C_{min} over the entire treatment cycle was calculated for patients in which there was no growth of tumor. Tumor growth was quantified as % increase in tumor from BR and was calculated as:

$$\% \text{ Tumor Growth between BR and LR} = \left(\frac{BR - LR}{BR} \right) \times 100$$

Exposure-tumor growth relationship was graphically visualized for any trends. The same analysis was conducted using rate of tumor growth instead of % tumor growth. Rate of tumor growth was calculated by dividing % tumor growth by time between BR and LR in years. For patients in whom there was no tumor growth both % tumor growth and rate of tumor growth were zero since LR was the BR in these patients.

4.2.1.3 Datasets

Study Number	Name	Link to EDR
C2485	avis.xpt	\\cdsesub1\evsprod\NDA022334\0064\m5\datasets\rad001c2485\analysis
	apkpd.xpt	
	apkresp.xpt	

4.2.1.4 Software

SAS 9.2 and S-PLUS 7.0 were used for analyses.

4.2.1.5 Model

CART analysis was performed to identify an optimal C_{min} breakpoint which maximally distinguished the response (> 30% reduction in SEGA tumor volume). Fischer exact test was performed to distinguish proportion of responders by different C_{min} cutoff points.

4.2.1.6 Results

In the absence of placebo arm in the C2485 trial, exposure-efficacy analysis provides supportive evidence of effectiveness. It can be seen from **Figure 1** and **Figure 11** that there is increase in response with increasing trough concentrations with no additional benefit at $C_{\min} > 3$ ng/ml.

Figure 11: Average steady state C_{\min} over six month vs % reduction in SEGA tumor volume relationship for 28 patients. The two vertical bars represent the 3 and 5 ng/ml cutoff. The plot is stratified by baseline tumor size with legend depicting the three categories of baseline tumor size. Each symbol represents individual patient.

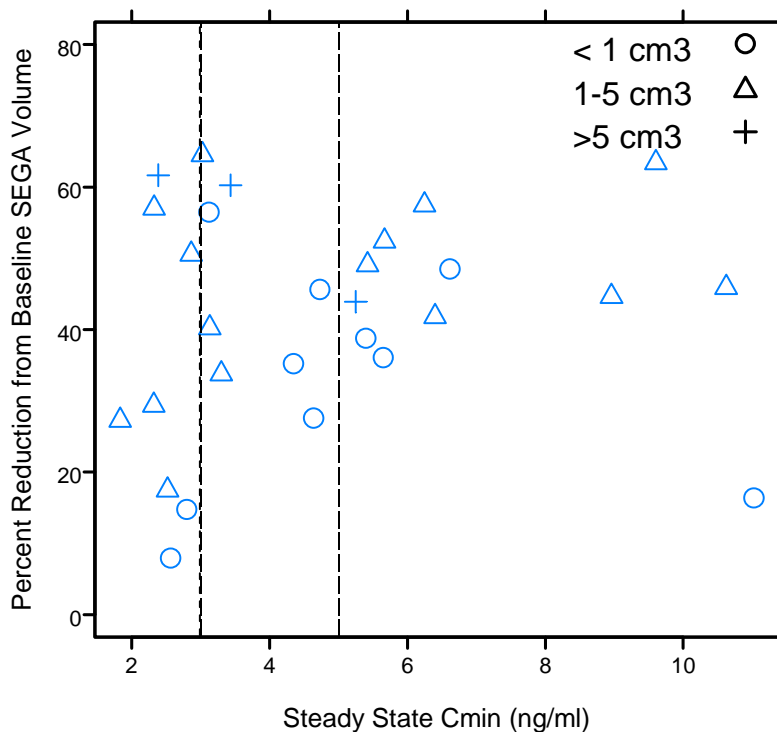


Table 6 below shows the results of the sensitivity analysis described above that was conducted to confirm exposure-efficacy relationship. The analysis shows that higher average response was observed if $C_{\min} > 3$ ng/ml with no additional benefit of increasing C_{\min} thus supporting the 5 ng/ml lower limit of the target range. The responder analysis by C_{\min} cutoff was also performed with $\geq 50\%$ as the definition of responder (**Table 5**). IN this case, there was no relationship seen when the data was stratified by C_{\min} cutoffs of 3 and 5 ng/ml. This may be due to few patients ($N=9/28$, 32%) who had more than 50% reduction in tumor volume.

Table 5. Responder ($\geq 30\%$ and 50% reduction in tumor volume) analysis by C_{\min} cutoff of 3 and 5 ng/ml.

C_{\min} , ng/ml (N)	Proportion of Patients with $\geq 30\%$ Reduction in SEGA Tumor Volume	Proportion of Patients with $\geq 50\%$ Reduction in SEGA Tumor Volume
≥ 5 (N=12)	11 (92%)	3 (25%)
≥ 3 (N=20)	18 (90%)	6 (33%)
< 3 (N=8)	4 (50%)	3 (38%)

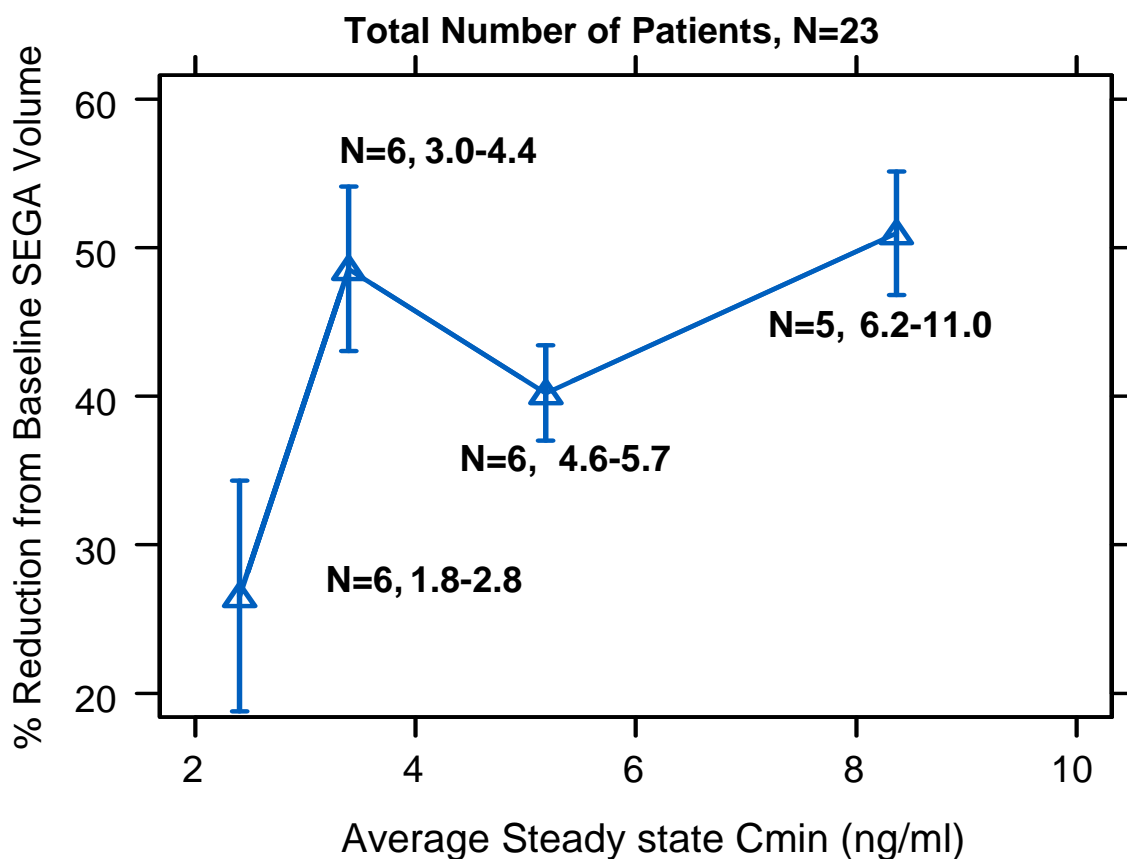
Table 6. Exposure-Efficacy analysis for various scenarios. The rows highlighted in grey represent the lowest quartile in each of the respective scenarios.

Primary Exposure-Response analysis with average six month C_{\min} vs Response		
Group (N)	Mean Concentration (Range) ng/ml	Median % Reduction in SEGA Tumor Volume
Quartile 1 (N=7)	2.4 (1.8-2.8)	28
Quartile 2 (N=7)	3.3 (2.9-4.4)	51
Quartile 3 (N=7)	5.3 (4.6-5.7)	44
Quartile 4 (N=7)	8.5 (6.3-11.0)	46
Scenario 1		
Quartile 1 (N=5)	2.2 (1.6-2.6)	30
Quartile 2 (N=4)	4 (3.6-4.5)	49
Quartile 3 (N=5)	6.1 (5.4-7.2)	46
Quartile 4 (N=4)	11.2 (8.2-15.3)	44
Scenario 2		
Quartile 1 (N=7)	2.7 (2.4-3)	30
Quartile 2 (N=6)	3.9 (3.1-4.6)	38
Quartile 3 (N=7)	5.9 (5.1-6.3)	46
Quartile 4 (N=7)	10.8 (6.5-16.6)	45
Scenario 3*		
Quartile 1 (N=9)	2.1 (1.6-2.3)	21
Quartile 2 (N=10)	3.3 (2.5-4.4)	42
Quartile 3 (N=10)	5.6 (4.5-7.1)	45
Quartile 4 (N=9)	10.1 (7.2-15.3)	45

* N=38 since this is combined analysis of Month 3 and 6 exposure-efficacy data. 18 subjects contributed to Month 6 while 20 subjects contributed towards Month 3 data.

The exposure-response analysis conducted after deleting 5 subjects with eligibility issues confirmed that average response was higher at average trough concentrations > 3 ng/ml (**Figure 12**).

Figure 12: Exposure-response relationship of everolimus for percent reduction in SEGA tumor volume at 6 month after deleting 5 patients with eligibility issues. The numbers adjacent to each of the quartile represent the number of patients and the C_{min} range. Data are shown as Mean \pm SE.



Nineteen patients were considered to have tumor re-growth based on the criteria described in the Methods section (4.2.1.2). There were some challenges in classifying patients with tumor growth. Since, there is lack of knowledge about the variability of tumor measurements, it was not clear for some patients with small tumors, if the measurement included noise or actual change in SEGA tumor volume. However, the analysis should not be affected as % reduction in SEGA tumor volume was taken for the patients with tumor growth instead of classifying patients categorically with growth/no growth. When individual patients were examined, there was no evidence that lower exposures may be associated with tumor re-growth. **Figure 13** shows patients with low C_{min} (patients in the first quartile from **Figure 3**) which showed no evidence of tumor growth. On the other hand, **Figure 14** depicts patients in first and second quartile with

low C_{min} but had tumor re-growth. Thus, there is something beyond exposures which might be resulting in tumor growth in some patients at low exposures when some patients at low exposures showed no evidence of tumor re-growth.

Figure 13: Representative plots of four patients from the first quartile of Figure 3 with low exposures but no tumor growth. Red line plot shows the SEGA tumor volume (Right y-axis) for the treatment period while black line plot represents the steady state C_{min} over time (Left y-axis).

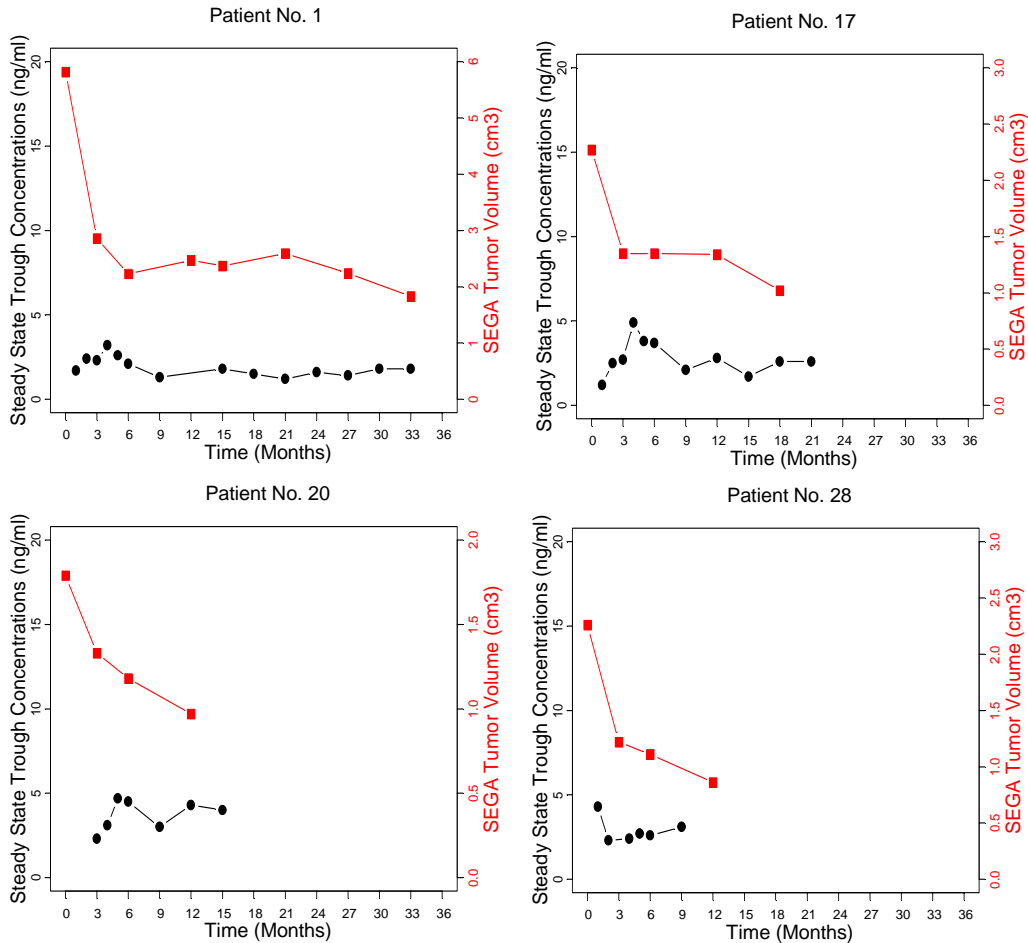
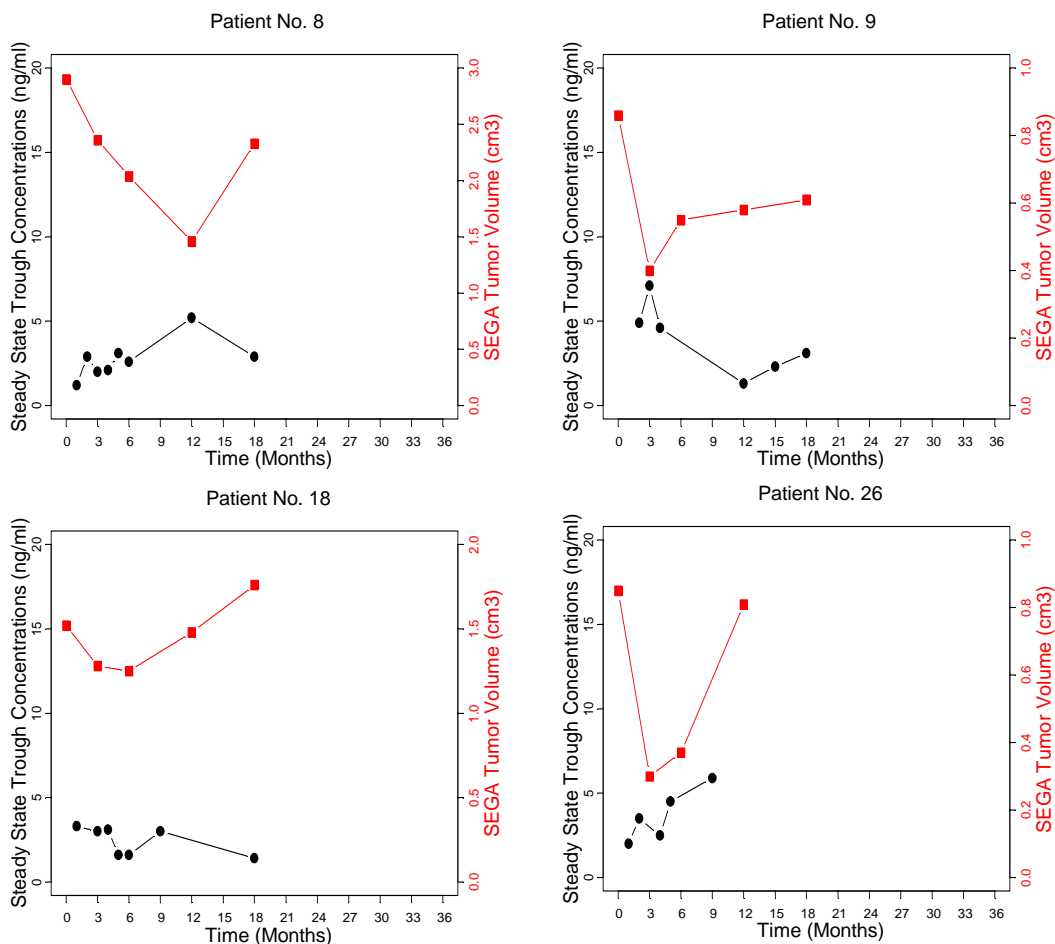


Figure 14: Representative plots of four patients from the first and second quartile of Figure 3 with low exposures having tumor growth. Red line plot shows the SEGA tumor volume (Right y-axis) for the treatment period while black line plot represents the steady state C_{min} over time (Left y-axis).



Time was then included in the analysis by calculating the annual rate of tumor re-growth instead of % of tumor re-growth between BR and LR for patients who had tumor growth. The rationale for this analysis is that two patients with similar % tumor growth but different time interval between BR and LR cannot be treated the same. No trend was observed with C_{min} and % tumor growth or rate of tumor growth suggesting that tumor growth cannot be solely attributed to lower exposures (Table 7).

Table 7. Exposure-response relationship of everolimus for percent increase in SEGA tumor volume /year. Data are shown as Mean ± SE.

Group (N)	Mean Concentration (Range) ng/ml	% Tumor growth from BR (Mean ± SE)	% Tumor growth from BR per year (Mean ± SE)
Quartile 1 (N=7)	2.6 (1.9-3.5)	27 ± 27	30 ± 30
Quartile 2 (N=7)	4.3 (3.8-5.3)	49 ± 9.8	64 ± 18.5
Quartile 3 (N=7)	6.3 (5.3-7.5)	22 ± 10.3	31 ± 17.5
Quartile 4 (N=7)	10.1 (8.2-10.9)	24 ± 7.9	38 ± 20.8

4.2.2 Exposure-Response Analysis for Safety

4.2.2.1 Objectives

The objective of this analysis was to explore the exposure-response for safety to evaluate the ^{(b) (4)} target trough concentration range of 5-15 ng/ml.

4.2.2.2 Methods

Stomatitis and infections were the most common adverse events observed in the analysis. Since we had only 28 patients in the safety database the average C_{min} exposures were divided by median to form low and high exposure group to see if there was a trend of increasing adverse events with higher exposures. Upper respiratory track infections (URI) which were common type of infections were also explored. The toxicity profile of everolimus in SEGA was similar to what has been observed and stated in the approved label for Afinitor for the renal cell carcinoma indication.

Since the safety dataset was small, patient who discontinued due to adverse events or had serious adverse events were also examined.

4.2.2.3 Datasets

Study Number	Name	Link to EDR
C2485	apkpd.xpt	\\cdsesub1\evsprod\NDA022334\0064\m5\datasets\rad001c2485\analysis
	aaev.xpt	

4.2.2.4 Software

SAS 9.2 and S-PLUS 7.0 were used for analyses.

4.2.2.5 Model

There was no modeling performed because safety data for only 28 patients was available.

Summary statistics of proportion of patients having AEs by C_{min} categories will be presented.

4.2.2.6 Results

The data is limited to support exposure-safety relationship for the most common adverse events:

- The safety dataset only comprised of 28 patients.
- Most the patients experienced these AEs, thus it is difficult to discern any relationship with exposures.
- The range of C_{min} may no be wide enough to explore exposure-safety relationship.

In study C2485, 22/28 patients had stomatitis or URI and 25/28 experienced infections at least once during the treatment period. There seems to be some trend for stomatitis and infections, but the data is limited to establish any concrete relationship (**Table 8**). It is also important to note that most of the adverse events were Grade 1 or 2 and were manageable by dose interruption/reductions. Infact, there was one Grade 3 stomatitis in the low exposure group while none of patients had grade 3 event in the high exposure group. There was no relationship of exposures and grade 3 AEs either as shown in sponsor's analysis.

Table 8. Exposure-safety relationships for most common adverse events.

Exposure Group	Mean C_{min} (Range) ng/ml	Adverse Event	Proportion of Patients with all grade AE's (%)	Proportion of patients with AEs \geq Grade 3
Low (Below median C_{min})	2.9 (1.8-4.4)	Stomatitis	10/14 (71)	1/14
High (Above median C_{min})	6.9 (4.6-11)		12/14 (86)	0/14
Low (Below median C_{min})	2.9 (1.8-4.4)	Infections and Infestations	11/14 (79)	2/14
High (Above median C_{min})	6.9 (4.6-11)		14/14 (100)	2/14
Low (Below median C_{min})	2.9 (1.8-4.4)	URI	11/14	0/14
High (Above median C_{min})	6.9 (4.6-11)		11/14	0/14

Patient 14 had multiple episodes of Grade 3 adverse reactions starting at Day 43, 47, 215, 271, 363, 471 of the treatment period but was part of the low exposure group with an average C_{min} of

4.4 ng/ml. There was no data on exposure available for this patient after 9 months (~270 days). Also, individually looking at patients who had serious adverse events or who discontinued due to adverse events also did not provide any additional information from an exposure-safety perspective. Patient No 15 had grade 4 convulsions but the adverse event was not attributed to everolimus.

4.3 INDIVIDUAL STUDY REPORT

TITLE OF STUDY: A non-randomized, open-label phase 2 study of everolimus for the treatment of patients with SEGA associated with tuberous sclerosis complex (TSC)

INVESTIGATOR / STUDY CENTER: Professor David Franz, MD / Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA.

STUDY PERIOD: 07-Jan-2007 to 09-Dec-2009

CLINICAL PHASE: 2

Primary Endpoint: Change from baseline in volume of primary SEGA lesion at 6 months.

Secondary Endpoints:

- Seizure frequency, as assessed by 24-hr video-EEG monitoring
- Quality of life (QoL) as assessed by a standardized QOLCE questionnaire
- Neuropsychometric functioning, as assessed by age-appropriate tests
- Rate, type, severity and causal relationship of adverse events to treatment

Statistical Methods: The primary analysis was performed using a non-parametric one-sided Wilcoxon signed rank test.

STUDY DESIGN:

This was a prospective, non-randomized, open-label, investigator-initiated, single-center study to evaluate the safety and efficacy of everolimus in 28 patients that are ≥ 3 years old with SEGA associated with TS. Patients received everolimus tablets at an initial starting dose of approximately 3 mg/m²/day (2.5, 5 or 7.5 mg) with titration to trough concentrations of 5 - 15 ng/ml, subject to tolerability. Study drug was self-administered orally (or administered by a caregiver) at the same time each day. The trial had a six-month core treatment phase after which patients were able to transition into a long-term extension. Treatment continues for as long as therapeutic benefit is evident without significant adverse effect or risk to the patient. During the core 6-month treatment phase, patients were instructed to visit the clinic at monthly intervals for a physical examination and blood collection for routine laboratory tests, urinalysis and evaluation of everolimus trough concentrations.

Patients unable to tolerate doses associated with the target 5 - 15 ng/ml trough concentration had their doses withheld or reduced by 25%. If trough concentrations of 5 - 15 ng/ml were not attained with the 3 mg/m²/day dose, the everolimus dose was escalated by 25% subject to tolerability.

Formulation: 2.5 and 5 mg tablets

ANALYSIS:

Pharmacokinetic Analysis: The investigator attempted to analyze PK samples for trough levels in all patients. The PK sample analyses were done using 3 PK sets; first with samples at steady state and within 22 to 26 hours post dose, the second included the samples in set 1 and some at steady state but in an unknown time after post dose and the third set included samples that were not confirmed as steady state concentrations.

Everolimus Assay: Everolimus concentrations in whole blood were determined by a liquid chromatography-mass spectroscopy (LC-MS) method following liquid extraction. The method used had a lower limit of quantitation (LLOQ) of 0.39 ng/ml for samples analyzed up to Dec-2008 and of 1.20 ng/ml from Jan-2009; this change resulted from the receipt of new quality control (QC) materials. The method used from Jan 2009 is similar to the one used in therapeutic drug monitoring for renal transplant (Zortress).

RESULTS: Twenty-eight evaluable patients were analyzed.

Pharmacokinetic Results: The table below summarizes the trough concentrations observed in all patients, in patients not on CYP3A4 inducers or inhibitors and in patients on a CYP3A4 inducer.

C _{min}	Everolimus whole blood trough concentrations (ng/mL)					
	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
All samples						
n	24	20	21	22	24	19
Mean (SD)	3.44 (2.14)	4.14 (2.32)	4.75 (2.86)	5.06 (3.72)	5.65 (4.15)	5.56 (3.57)
CV%, mean	62.3	56.1	60.1	73.4	73.5	64.1
Geometric mean	2.75	3.54	4.04	4.17	4.65	4.65
CV%, geometric mean	86.9	67.5	62.5	66.5	66.7	67.4
Median	3.3	3.7	3.9	3.5	4.3	4.5
Range						(b) (4)
Absence of CYP3A4 inducer or inhibitor						
n	7	6	5	8	7	7
Mean (SD)	3.77 (3.17)	5.25 (3.58)	6.80 (3.53)	7.50 (5.03)	7.50 (5.31)	6.19 (3.03)
CV%, mean	84.0	68.3	51.9	67.0	70.8	49.0
Geometric mean	2.67	3.81	6.06	6.12	5.66	5.40
CV%, geometric mean	127.1	137.9	59.0	78.2	96.0	68.7
Median	3.2	4.9	5.1	6.1	6.8	5.6
Range						(b) (4)
Presence of CYP3A4 inducer in previous 7 days						
n	15	14	15	13	16	11
Mean (SD)	3.08 (1.64)	3.66 (1.46)	4.21 (2.45)	3.58 (1.76)	4.90 (3.58)	5.33 (4.08)
CV%, mean	53.4	39.8	58.1	49.3	72.2	76.7
Geometric mean	2.59	3.43	3.63	3.25	4.25	4.32
CV%, geometric mean	76.2	38.0	59.6	46.3	55.4	71.7
Median	2.8	3.6	3.2	2.9	3.8	3.6
Range						(b) (4)

Based on data obtained at the 90-day analysis, no change in everolimus concentrations by time point was observed for the Safety Population; therefore, no changes were made to Table 11-19.

CV Coefficient of variation; SD Standard deviation

Source: C2485 90-day Update – Post-text Table 14.2-4.1.3 and C2485 90-day Update – Post-text Listing 14.2-4.1

EFFICACY RESULTS:

The sponsor reported as per independent central review:

- Reduction in primary SEGA volume from baseline to Month 6 (median 0.80 cm³, p<0.001)
 - 21 patients (75 %) experiencing reductions of ≥ 30%
 - 9 patients (32.1%) experiencing reductions of ≥ 50%.

- Tumor shrinkage during the initial 3 months of therapy from baseline
 - 17 patients (65.4%) with reductions of ≥ 30%
 - 10 patients (38.5%) with reductions of ≥ 50%.

SAFETY RESULTS: Stomatitis, upper respiratory tract infection, sinusitis, otitis media and pyrexia were the most common adverse events (AEs) reported in association with everolimus therapy, with a frequency ≥ 30% of patients. The majority of adverse events were grade 1 or grade 2. The grade 3 AEs were 2 cases of convulsions and single cases of stomatitis, sinusitis, vomiting, dizziness, decreased WBC, pneumonia, aspiration, viral bronchitis, cyclic neutropenia, sleep apnea syndrome, tooth infection, elevated AST and low ANC. A single grade 4 convulsion was also reported.

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/s/

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10/15/2010

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