Clinical Pharmacology Review

NDA	203-985
Submission Date:	02/29/2012
PDUFA Date:	8/29/1012
Brand Name:	Afinitor® /Afinitor® DISPERZ™
Generic Name:	Everolimus
Formulation:	Afinitor DISPERZ (everolimus tablets for oral suspension): 2, 3, and 5 mg
	Afinitor® tablets: 2.5, 5, 7.5 and 10 mg
Submission Type; Code:	Original NDA; 000
Dosing regimen:	Therapeutic Drug Monitoring (TDM): starting dose of 4.5 mg/m^2/day and titrated to C_{min} of 5 to 15 ng/mL
Indication:	Tuberous sclerosis complex (TSC) who have Subependymal Giant Cell Astrocytoma (SEGA)
Sponsor:	Novartis
OCP Reviewer:	Jian Wang, Ph.D.
OCP Team Leader:	Hong Zhao, Ph.D.
Pharmacometrics Reviewer	Jian Wang, Ph.D.
Pharmacometrics Team Leader:	Christine Garnett, Pharm.D.
	Nitin Mehrotra, Ph.D.(Acting)
OCP Division:	Division of Clinical Pharmacology 5
OND Division:	Division of Drug Oncology Products 2

A required inter-divisional level briefing was held on August 1, 2012. The attendees are: Atik NAM Rahman, Shiew-Mei Huang, Hong Zhao, Nitin Mehrotra, Jian Wang, Ruby Leung, Lily mulugetha, Rachelle Lubin, Xinning Yang, Lyle Canda, An-Chi Lu, Sarah Schrieber, Jinoo Lee, Jenemiah Mamper, Jingyu Yu, Liang Zhao, Hoi Kei Kon, Dongyang Liu, Malako Lasana, Dionna Green, Rosane Charlob Orbach, Suresh Dodapangni, Martha Donoghue, Mehul Mehta, John Lazor.

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1 EXECUTIVE SUMMARY

Everolimus is an inhibitor of the human kinase mammalian target of rapamycin (mTOR). Afinitor®
tablets (Everolimus) have been approved for oral use in the treatment of advanced renal cell
carcinoma (RCC), adults with progressive neuroendocrine tumors of pancreatic origin (PNET) and
adults with renal angiomyolipoma and tuberous sclerosis complex (TSC). Based on the results of a
phase 2 trial (C2485), Afinitor is indicated under an accelerated approval, for the treatment of
adults and children ≥ 3 years of age with subependymal giant cell astrocytoma (SEGA) associated with
TSC who require therapeutic intervention but are not candidates for curative surgical resection.

This NDA is for a new age-appropriate formulation of Afinitor dispersible tablets (Afinitor®
DISPERZ™) for the treatment of children and adults with SEGA and TSC who require therapeutic
intervention but are not likely to be curatively resected, which was one of the components outlined
in the Written Request (WR) issued for Afinitor. The applicant also requests for a pediatric
exclusivity determination.

Clinical evidence in this application supporting the efficacy and safety of everolimus consists of
data from two clinical trials, M2301 and C2485. Results of the primary analysis of Study M2301
demonstrate the benefit of everolimus as assessed by best overall SEGA response (34.6% on
everolimus vs. 0% on placebo, p<0.000, N=117). Furthermore, longer-term follow-up data from
Study C2485 (median follow-up of 34.2 months) demonstrate that the positive effect on tumor
burden is sustained. Everolimus has an acceptable safety profile that is well characterized and
consistent with previous experience in the TSC setting, with the exception of a potential risk for
secondary amenorrhea.

The results of the data analyses support the proposed dose of 4.5 mg/m^2 as the recommended
starting dose, followed by dose titration to target range of 5-15 ng/mL. Although the 5-mg
dispersible tablet when administered as suspension in water showed 20-36% lower C_{max} as
compared to the 5 x 1-mg market formulation (FM) tablets and to the 5-mg final market image
(FMI) tablet, it is not likely to affect the efficacy response of everolimus since dosing of everolimus
in patients with TSC who have SEGA will be based on therapeutic drug monitoring (TDM) with
dose titration to attain a C_{min} within the target range of 5 to 15 ng/mL.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the
information contained in NDA 203-985. This NDA is considered acceptable from a clinical
pharmacology perspective.

Phase IV Requirement or Commitment

None.

Labeling Recommendations

Please see Section 3 - Detailed Labeling Recommendations.

Required Inter-Divisional CP Briefing was held on August 1, 2012 with the following attendees:

Signatures:

Reviewer: Jian Wang, Ph.D.
Division of Clinical Pharmacology 5

Team Leader: Hong Zhao, Ph.D.
Division of Clinical Pharmacology 5

Acting Team Leader: Nitin Mehrotra,
Ph.D., Division of Pharmacometrics

Division Director: Atik Rahman, Ph.D.
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - V Jarral; MTL - S Demko; MO - M Donoghue
       DCP-   Reviewer - J Wang; PM TL - C Garnett; N Mehrotra; H Zhao
       5:      Acting TL & DDD - B Booth; DD - A Rahman

1.2   CLINICAL PHARMACOLOGY SUMMARY

Background: Everolimus is a derivative of rapamycin which acts as a signal transduction inhibitor. It targets mTOR (mammalian target of rapamycin), which regulates protein synthesis and cell growth, cell proliferation, angiogenesis and survival. Everolimus has been approved for oral use in the treatment of advanced renal cell carcinoma (RCC), adults with progressive neuroendocrine tumors of pancreatic origin (PNET) and adults with renal angiomyolipoma and tuberous sclerosis complex (TSC). Everolimus has also been approved as an immunosuppressant for transplantation under NDA 21-560 (allogeneic kidney transplant).

Clinical Pharmacology Studies: Clinical pharmacology data are from four studies, two clinical efficacy and safety studies in patients with TSC who have SEGA (M2301 and C2485) and two bioequivalent studies in healthy subjects with MF/FMI everolimus tablets and the dispersible tablet (X2105 and X2106). Of note, data from Study C2485 were previously reviewed by FDA and led to the accelerated approval of Afinitor for the treatment of patients with TSC who have SEGA.

Target Trough Levels: An exposure-response relationship for efficacy is evident based on data in the pivotal study M2301. An increased efficacy response with increased average C_{min} was observed and the effect reached plateau at $C_{min} \geq 5$ ng/ml. There was a significant portion (44%) of patients with their C_{min} below 5 ng/mL even though the target range was 5-15 ng/mL. Based on an indirect response model derived using the continuous data, the typical decrease in SEGA volumes for C_{min} of 3 ng/mL was 29.8% (95% CI: 22.5%-35.6%). Combined safety data from M2301 and C2485 indicate that there is no relationship between C_{min} and Grade 3+ infections or stomatitis, both of which are related to everolimus treatment, and the incidence is consistently low when C_{min} is up to 14.6 ng/mL. Under the submissions for PNET and RCC indications, there were no specific safety concerns when C_{min} was up to 135 ng/mL. Overall, the results of the data analyses support the proposed dose of 4.5 mg/m^2 as the recommended starting dose, followed by dose titration to target range of 5-15 ng/mL.

Bioequivalence Studies: Data from Study X2105 and Study X2106 indicate that $AUC_{0-\infty}$ of the 5-mg dispersible tablet when administered as suspension in water was equivalent to the 5 x 1-mg MF tablets and to the 5-mg FMI tablet. Although C_{max} of the 5-mg dispersible tablet was 64% of that of the 5 x 1-mg MF tablets and 80% of that of 5-mg FMI tablet, predicted C_{min} values at steady-state are similar after daily administration of all the three formulations. The lower C_{max} of the dispersible tablet when administered in suspension is not likely to affect the efficacy response of everolimus since its dosing in patients with TSC who have SEGA will be based on therapeutic drug monitoring (TDM) with dose titration to attain a C_{min} within the target range of 5 to 15 ng/mL.

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 NDA submission will be addressed below. Please see Clinical Pharmacology Review for NDA 22-334 by Dr. Julie Bullock in DARRTS (dated 03/09/2009) and by Drs. Nitin Mehrotra & Elimika Pfuma (dated 10/15/2010, 02/03/2012) 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 (E-R) relationship for efficacy. In pivotal trial M2301, everolimus was administered orally at a starting dose of $4.5 mg/m^2/day$, and subsequently titrated, subject to tolerability, to attain whole blood trough concentrations of 5-15 ng/mL. Average steady state C_{min} concentrations in the core treatment phase and % reduction in SEGA tumor volumes were the variables utilized in the analysis. Exposure data were divided into sextiles with 13 patients in each quantile. An increased response with increased average C_{min} was observed and the response reached plateau at $C_{min} \geq 5$ ng/ml (**Figure 1**). The second quantile had unusual highest response rate, which could not be logically explained in this model. The observed E-R relationship provides supportive evidence of effectiveness for everolimus in treatment of SEGA.
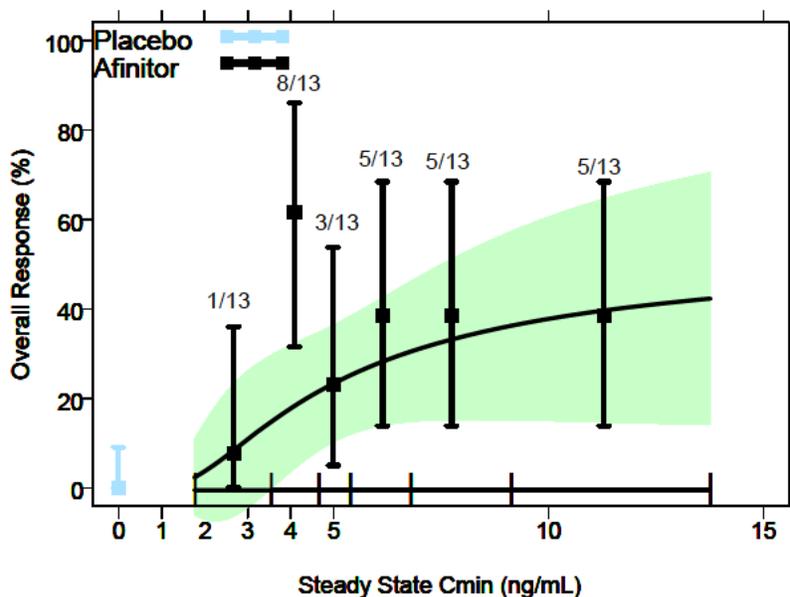
Figure 1: Exposure-response relationship of everolimus for percent reduction in SEGA tumor volume at 6 month. The numbers adjacent to each of the quantile represent the C_{min} range. The numbers represent number of patients with positive response/total number of patients in respective quantiles.

2.1.2 Is there evidence of exposure-response for safety?

To assess the E-R relationship for safety, the patients for whom the trough concentrations were available from the two Trials C2485 and M2301 were combined and then divided into six quantiles and % subjects having adverse events (AEs) were plotted against each quantile. C_{min} here is the trough concentration at the time of assessment of the AEs. Selection of AEs to be assessed was based on the clinical relevance after discussion with the medical reviewer. Infections and stomatitis were two of the most common AEs observed.

There is no relationship between C_{min} and Grade 3+ infections or stomatitis (**Figure 2**). Further analyses indicated that there were no E-R relationships for all grades of these AEs in Trials C2485 and M2301.
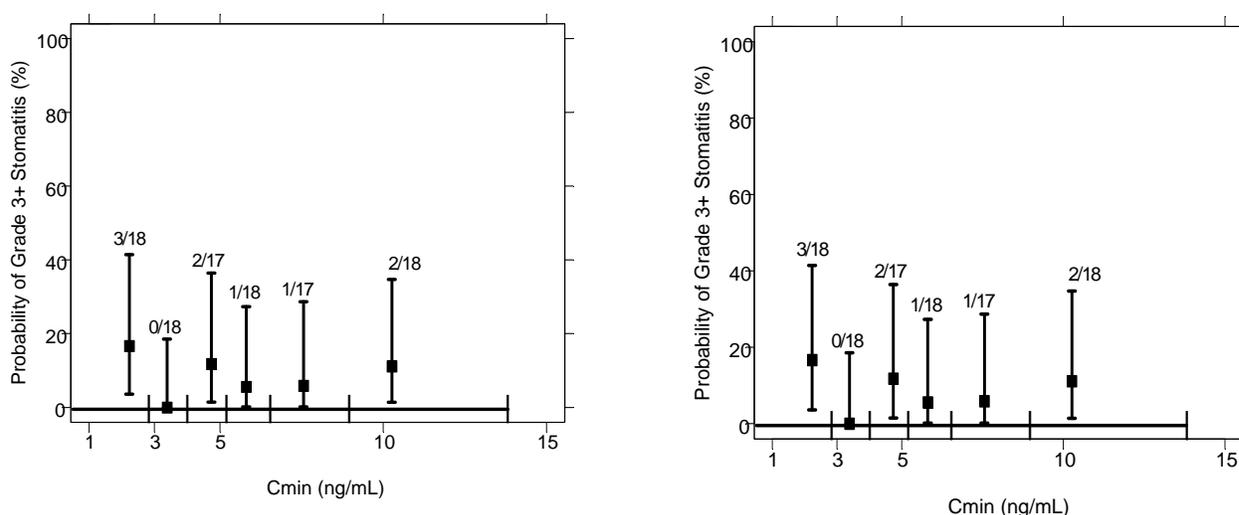
Figure 2: Percent adverse events in each quantile.

2.1.3 Did patients with TDM achieve target everolimus concentrations (5–15 ng/ml)?

No. In the phase 3 trial M2301, 44% of the patients had average C_{min} below the target concentration range of 5-15 ng/ml during the core treatment phase (6 months). **Table 1** below shows C_{min}, number of patients on Enzyme-Inducing Anti-Epileptic Drugs (EIAED) and response rate (RR) in each subgroup as divided by C_{min} range with cutoff value at 3, 5, 10, 15 ng/mL. No significant differences were found between each subgroup with regard to gender, or co-administration of EIAEDs. In the phase 2 trial M2485, less than half of the patients had overall C_{min} within the target concentration range of 5–15 ng/ml during the core treatment phase (6 months) (See Dr. Nitin Mehrotra's review, 10/15/2010). The observed data from the Phase 2 trial showed that only 21–44% of the patients had their steady state C_{min} within the target range with most of the patients having steady state $C_{min} < 5$ ng/mL.

Table 1: Cmin, Number of Patients on EIAED and Response Rate by Average Cmin Range

Group	Median Cmin,ng/mL (Range)	# Patients on EIAED	Female /Male	Response rate %
0-3	2.6 (1.8, 2.9)	3/11	4/7	9.1 (1/11)
3-5	4.5 (3.4, 4.9)	5/23	7/16	43.5 (10/23)
5-10	6.8 (5.8, 9.9)	7/35	14/21	37.1 (13/35)
10-15	12.2 (11.3,13.8)	0/9	4/5	33.3 (3/9)

Following an initial starting dose of 4.5 mg/m^2 daily and subsequent dose adjustment based on TDM, median everolimus trough concentrations were within the 3.7 to 7.1 ng/mL ranging from Week 2 to Week 48 (**Table 2,**, **Figure 3**).

Table 2: Everolimus Pre-dose Concentrations by Time Points in Study M2301

	Study Week								
	2	4	6	8	12	18	24	36	48
n	67	62	64	64	58	67	64	48	23
Mean (SD)	4.2 (2.7)	4.6 (3.2)	5.8 (3.7)	6.4 (4.4)	6.5 (4.0)	6.3 (4.0)	6.6 (3.4)	6.8 (3.4)	7.3 (3.1)
CV% mean	63.9	69.8	63.5	68.8	62.1	64.4	52.1	50.2	42.7
Geo-mean	4.0	4.0	4.8	5.4	5.5	5.5	5.8	6.2	6.7
CV% geo-mean	58.9	61.5	70.1	71.6	61.4	61.0	52.9	51.4	45.4
Median	3.7	3.7	4.9	5.4	5.4	5.4	6.0	6.2	7.1
Range	0.0-12.6	0.0-18.5	1.2-19.5	0.0-21.6	2.0-21.5	0.0-22.7	2.1-18.6	0.0-16.6	3.2-13.1
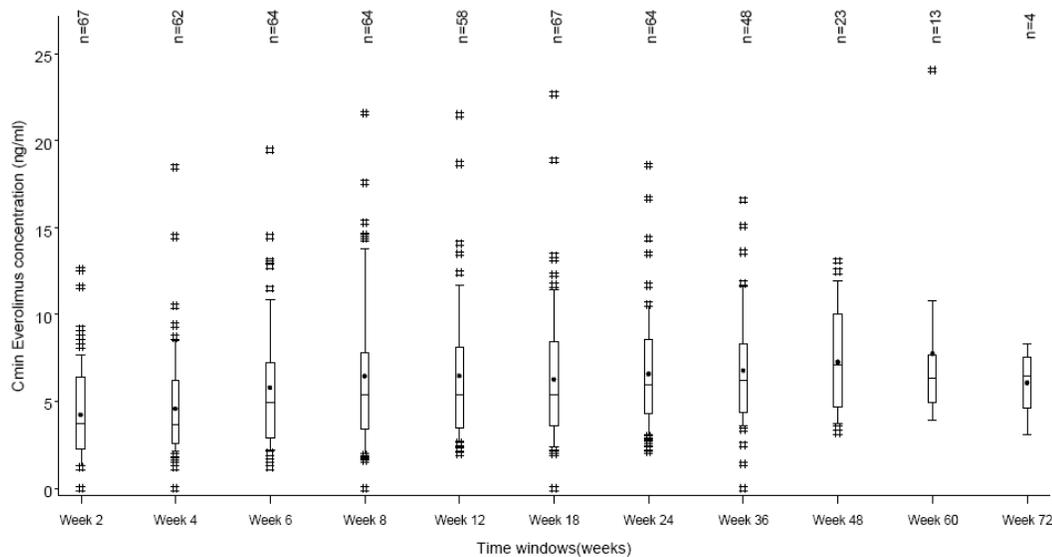
- # Indicates values that lie outside the P10 and P90
- Medians are displayed as a line, means are displayed as dots, boxes are drawn from P25 to P75 and whiskers extend from P10 to P90.

Figure 3: Box-plot of concentration-time profile for everolimus at pre-dose (trough) by time window.

2.1.4 Does exposure-response data support the 5–15 ng/ml everolimus target?

In the current submission, the applicant proposed ▊▊▊ (b) (4) as the target trough levels for TDM. The reviewer's recommendation of 5 ng/mL instead of the proposed ▊▊▊ (b) (4) as the lower limit is based on the following evidences:

1) An exposure-response (E-R) analysis using E_{max} logistic regression showed that SEGA tumor response reached a plateau when $C_{min} > 5$ ng/mL (**Figure 1**).
2) In Trial M2301, a large portion (44%) of patients was below 5 ng/mL even though the target range was set at 5-15 ng/mL. One would reasonably expect that more than 50% of patients would fall below ▊▊▊ (b) (4) if a lower limit of target were set to ▊▊▊ (b) (4).
3) The E-R relationship is steep with an inflection point around 3 ng/mL (Study C2485). Thus, it is better to keep the lower limit of the target range in the flat region of the E-R curve to avoid a patient's C_{min} falling below 3 ng/mL.
4) Based on indirect response model by the continuous data, a typical patient requires approximately 7.5 ng/mL to achieve a 50% tumor reduction; however, the typical decrease in SEGA volumes at C_{min} of 3 ng/mL was 29.8% (95% CI: 22.5%-35.6%) (see Appendix).
5) There is no safety concern at 5-15 ng/mL concentration range.

The reviewer agrees with the proposed 15 ng/ml as the upper limit of everolimus target trough concentration based on the following evidences:
1) There is no E-R relationship for safety by the combined data from the trials C2485 and M2301.
2) Previous selection of ▊▊▊ (b) (4) is because of lacking the safety data in the ▊▊▊ (b) (4) range (See Dr. Mehrotra's review). The current analysis has a total of 10 of 78 patients with their C_{min}

in the range of 10-15 ng/mL. Incidence of SAEs in this group is consistently as low as those patients with $C_{min} < 10$ ng/mL.

3) In the submissions for PNET and RCC indications, there were no safety concerns when C_{min} was up to 135 ng/mL (Refer to Drs. Earp and Mehrotra's review).

4) Selection of 15 ng/mL rather than ▒▒▒▒ (b) (4) provides more space to adjust the doses give that there are limited dose strengths for both formulations.

Overall, the recommended target C_{min} range of 5–15 ng/mL is supported by the E-R relationship for efficacy and safety experience.

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

The reviewer's analysis indicated that patients on CYP3A4 inducers may need a higher starting dose and frequent titration scheme to reach the target of 5 ng/mL earlier.

– In M2301 trial with a starting dose of 4.5 mg/m^2/day, patients on CYP3A4 inducers did not reach the lower limit of the proposed target, 5 ng/mL, until the 24th week (the sixth month). In addition, their C_{min} were slightly dropped below 5 ng/mL in Weeks 18 and 72. In contrast, patients who did not receive CYP3A4 inducers did reach the lower limit of target range at the second week and continually maintained within the target range of 5-15 ng/mL. **Figure 4** shows the time course of C_{min} stratified by the use of CYP3A4 inducers (EIAED) and CYP3A4 inhibitors depicting those patients with concomitant EIAED reaching target later. The response rate is not significantly different between the two groups (**Figure 8**).

– In the phase 2 trial C2485 with a starting dose of 3 mg/ m^2/day, patients on CYP3A4 inducers did not reach the lower limit of the proposed target, 5 ng/mL, until the fifth month. The frequency of titration was not specified in the trial and doses were titrated approximately every month to achieve the target, which is different from what is proposed in the product label.

In summary, as in the clinical trial patients did not reach the lower limit of the proposed target, 5 ng/mL until the second month, this warrants a need for higher dose/titration scheme in these patients. In addition, it is known from a dedicated drug-drug interaction study in healthy volunteers that co-administration of rifampin, a strong CYP3A4 inducer, decreased everolimus exposure by ~ 65%. These data support the recommendation of doubling the starting dose in patients requiring strong CYP3A4 inducers (see proposed labeling, Section 3). The proposed every two week titration schedule to achieve the target appears reasonable since the frequent titration scheme will allow the patients to reach the 5 ng/mL target earlier.
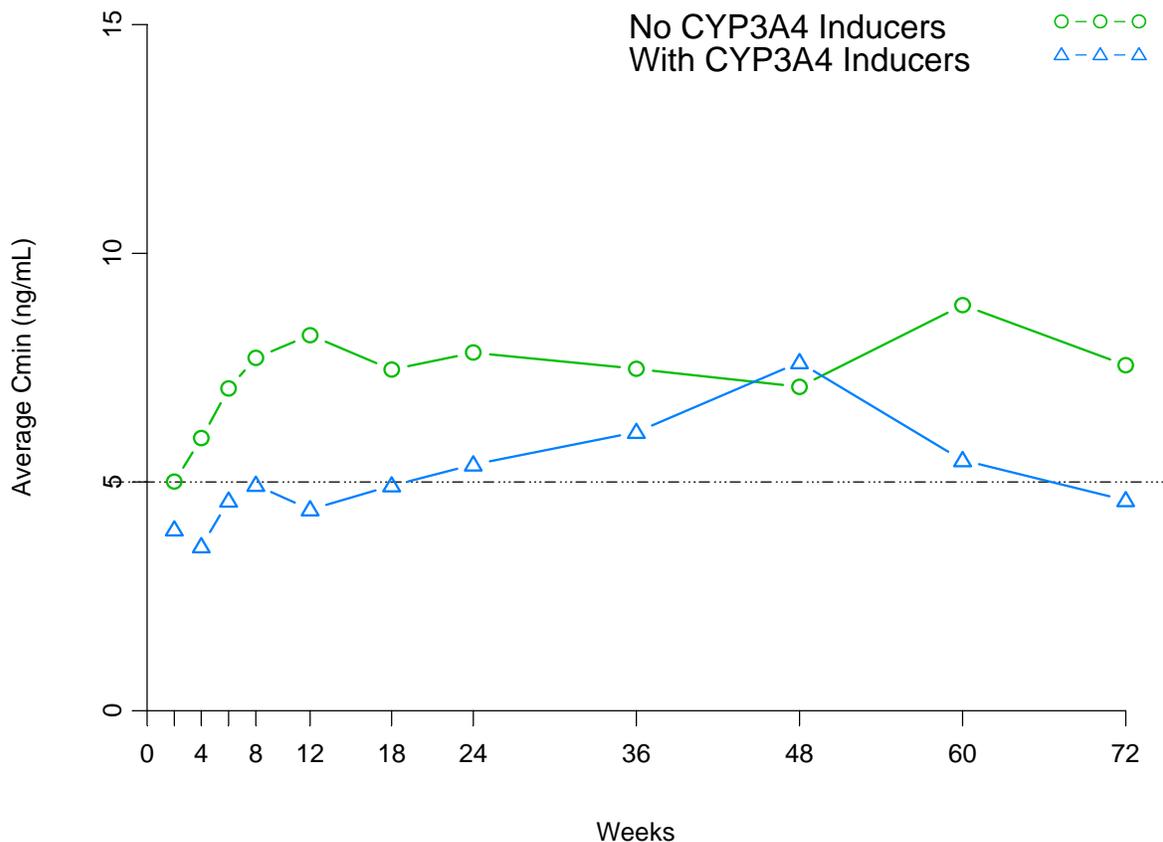
Figure 4: Time course of steady state C_{min} over time for everolimus 4.5 mg/m^2/day dosing regimen in the phase 3 trial. The black dashed line indicates the lower limit of the target, 5 ng/mL. Only mean concentrations are plotted for better visualization.

Note:
 – PK samples collected in the absence of co-medication with any CYP3A4/PgP inducer or inhibitor: N= 45, n=35, 34, 36, 37, 34, 36, 39, 28, 14, 9, 2 for corresponding timepoints
 – PK samples collected with co-administration of a CYP3A4/PgP inducer and without co-administration of any CYP3A4/PgP inhibitor N= 39, n=34, 31, 28, 27, 23, 31, 26, 21, 10, 4, 2 for corresponding timepoints

2.1.6   Is the starting dose and titration scheme appropriate for patients not taking concomitant enzyme-inducing anti-epileptic drugs (EIAED)?

Yes. The dose of 4.5 mg/m^2/day is recommended as starting dose based on the following data observed in Study M2301:

 – The higher starting dose proposed for the trial was enable patients to reach the target trough concentration as early as the second week (**Figure 4**). In the phase 2 trial C2485 with a starting dose of 3 mg/m^2/day, on an average, patients on CYP3A4 inducers did not reach the

lower limit of the proposed target, 5 ng/mL, until the second month.

– The 4.5-mg/m²/day starting dose is acceptable as data from a Phase 1 pediatric oncology study concluded that the maximum tolerated dose (MTD) in children is 5 mg/m²/day (Fouladi et al 2007).

– The geometric mean C_{min} (range) values normalized to mg/m² dose were 1.0, 1.3, 2.1 ng/mL for patients not taking CYP3A4/PgP inducer with ages < 10 yr, 10-18 yr, and > 18 yr, respectively. Thus, a starting dose of 4.5 mg/m² should deliver C_{min} values of 4.4 ng/mL, 5.7 ng/mL, and 9.6 ng/mL in patients within the respective age groups. The lowest C_{min} value is close to the recommended target C_{min} lower range.

2.2 GENERAL ATTRIBUTES

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

Physico-chemical properties
1. Structural formula:
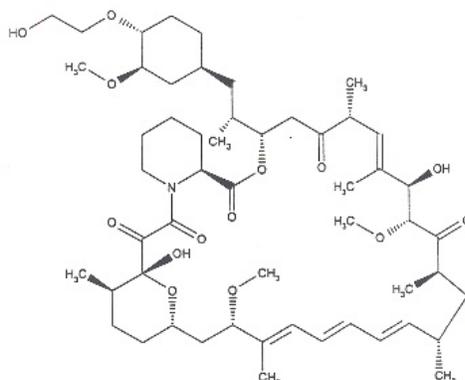
2. Established name: everolimus
3. Molecular Weight: 958.25 g/mol
4. Molecular Formula: $C_{53}H_{83}NO_{14}$
5. Chemical Name: (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R),-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.0⁴ᐟ⁹]-hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone

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

Everolimus is a signal transduction inhibitor targeting mammalian target of rapamycin (mTOR), an enzyme that regulates cell growth, proliferation, angiogenesis and survival. The indication is for the treatment of patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) and require therapeutic intervention but are not likely to be cured by surgery.

2.2.3 What are the proposed dosage and route of administration?

(b) (4)

(b) (4)

The labeling will recommend as follows:

(b) (4)

Administer AFINITOR Tablets or AFINITOR DISPERZ orally once daily at the same time every day. Administer either consistently with food or consistently without food (See Section 3 for details).

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?

Clinical pharmacology data from four studies are included in the current submission; two studies conducted in patients with TSC who have SEGA (M2301 and C2485) and another two studies conducted in healthy subjects to evaluate the bioequivalence (BE) between the MF/FMI everolimus tablets and the dispersible tablet (X2105 and X2106). **Table 3** provides an overview of these clinical studies. Of note, data from Study C2485 were previously submitted to FDA and have led to the accelerated approval of Afinitor for the treatment of patients with TSC who have SEGA. **Table 4** summarizes the major difference between trial M2301 and trial C2485.

Table 3: Overview of Studies with a Clinical Pharmacology Data in the Current "TSC with SEGA" Submission

Study	Description	Clinical pharmacology data
M2301	A randomized, double-blind, placebo-controlled phase III study of everolimus to evaluate the safety and efficacy of everolimus in patients with TSC who have SEGA, irrespective of age. Everolimus was administered orally at a starting dose of 4.5mg/m^2/day, and subsequently titrated, subject to tolerability, to attain whole blood trough concentrations of 5-15 ng/mL.	Cmin and exposure-response relationships in patients with TSC who have SEGA
C2485	A prospective, non-randomized, open-label, investigator-initiated, phase-II study designed to evaluate the safety and efficacy of everolimus therapy in patients ≥3 years with TSC who have SEGA. Everolimus was administered orally at a starting dose of 3.0 mg/m^2/day (once-daily or on an alternate day regimen) and subsequently titrated, subject to tolerability, to attain whole blood trough concentrations of 5-15 ng/mL.	Cmin and exposure-response relationships in patients with TSC who have SEGA
X2105	A single-center, open-label, randomized, two-way cross-over study with 2 treatment periods and 2 treatment sequences conducted in 54 healthy subjects (male and female), aged 18 to 55 years. The subjects were randomly assigned to one of the 2 treatment sequences to receive the following treatments in two study periods: 1 × 5-mg dispersible tablet and the 5 × 1-mg MF tablets. Treatment periods were separated by a washout interval of 8 days. The study drug was administered to subjects under fasting conditions.	To determine the bioequivalence between the dispersible tablet and the 1-mg MF tablet.
X2106	A single-center, open-label, randomized, two-way cross-over study with 2 treatment periods and 2 treatment sequences conducted in 54 healthy subjects (male and female), aged 18 to 55 years. The subjects were randomly assigned to one of the 2 treatment sequences to receive the following treatments in two study periods: 1 × 5-mg dispersible tablet and the 1 × 5-mg FMI tablets. Treatment periods were separated by a washout interval of 8 days. The study drug was administered to subjects under fasting conditions.	To determine the bioequivalence between the dispersible tablet and the 5-mg FMI tablet.

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

Table 4: Comparison of Trials C2485 and M2301

	C2485	M2301
Trial	Phase II	Phase III
N	28	117
Age	>=3 yrs	Any age
Formulation	2.5, 5-mg MF tablet	1-mg MF tablet
	5-mg FMI tablet	
Primary endpoint	reduction in SEGA tumor volume	SEGA response rate
Initial dose	3 mg/m^2/day	4.5 mg/m^2/day
TDM Cmin range	5-15 ng/mL	5-15 ng/mL

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 of this study was the SEGA response rate, defined as the proportion of patients with a best overall SEGA response of 'SEGA response' which was confirmed with a second scan performed approximately 12 weeks later (and no sooner than 8 weeks later), was defined as follows:
• A reduction in SEGA volume of ≥ 50% relative to baseline, where SEGA volume was the sum of the volumes of all target SEGA lesions identified at baseline
• No unequivocal worsening of non-target SEGA lesions, no new SEGA lesions (≥ 1 cm in longest diameter), and no new or worsening hydrocephalus

There were three key secondary efficacy endpoints in this study:
• The absolute change in frequency of total seizure events per 24 hours from baseline to Week 24
• Time to SEGA progression
• Skin lesion response rate

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 six 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 for the renal transplant indication and is discussed in greater detail in review by Dr. Bullock.

2.3.4   Exposure-response

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

Please refer to 2.1.1 and 4.2.1 for details.

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

Please refer to 2.1.2 and 4.2.2 for details.

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?

Please refer to 2.1.3, 2.1.4 and 4.2 for details.

2.3.5   Pharmacokinetic characteristics of the drug and its major metabolites

The applicant states that C_{min} is proportional over the dose range of 1.35 mg/m^2 to 14.4 mg/m^2. A model-based method was used to analyze trough level data from Study M2301. 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/m^2) as a fixed effect, and patient as a random effect. The model was of the form $\ln(C_{min}) = \alpha + \beta*\ln(dose) + error$. Coefficient β was estimated along with the 90% confidence interval (CI). Based on the sponsor's analysis the dose-proportionality coefficient β was 1.107 (90% CI 1.03 to 1.19). The reviewer agrees with the applicant's analysis and conclusion.

The following is added in the labeling Section 12.3:

"*Dose Proportionality in Patients with SEGA and TSC: In patients with SEGA and TSC, everolimus C_{min} was approximately dose-proportional within the dose range from 1.35 mg/m^2 to 14.4 mg/m^2.*"

The following is adapted from the currently FDA-approved Afinitor labeling and previous NDA 22334 review:

(b) (4)

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?

Population PK analyses indicate that body surface area (BSA) and presence of CYP3A inducers are significant covariates for everolimus clearance. Age, body mass index (BMI), baseline sum of target SEGA volumes, and sex have no statistically significant effects on clearance after incorporation of BSA and presence of CYP3A inducers in the final model.

At the absence of CYP3A4/PgP inhibitors or inducers, the geometric mean C_{min} values normalized to mg/m^2 dose in patients aged < 10 years and 10 to 18 years were significantly lower by 54% and 40%, respectively, than those observed in adults (> 18 years of age), suggesting that everolimus clearance normalized to body surface area was higher in pediatric patients as compared to adults (**Table 5**).

Table 5: Geometric Mean Cmin Divided by Age Groups at the Absence of CYP3A4/PgP Inhibitors or Inducers

PK Parameter	Group	Age (Years)	N	Geometric mean (ng/mL per mg/m^2)	Ratio of geometric means (90% CI)
Cmin	A	> 18	46	2.13	
	B	10-18	92	1.27	B:A: 0.60 [0.38,0.92]
	C	<10	194	0.97	C:A: 0.46 [0.31,0.68]

The effect of age on everolimus exposure was analyzed in patients who was not on any CYP3A4 inducers or inhibitors. For patients with < 10 years of age and patients with 10-18 years of age, the average C_{min} at Week 2 is 4.8 ng/mL (n=22) and 4.6 ng/mL (n=8), respectively (**Figure 5**). The C_{min} is continuously maintained above 5 ng/mL in the following weeks. These results indicate that dose adjustment may not be necessary with regard to age.
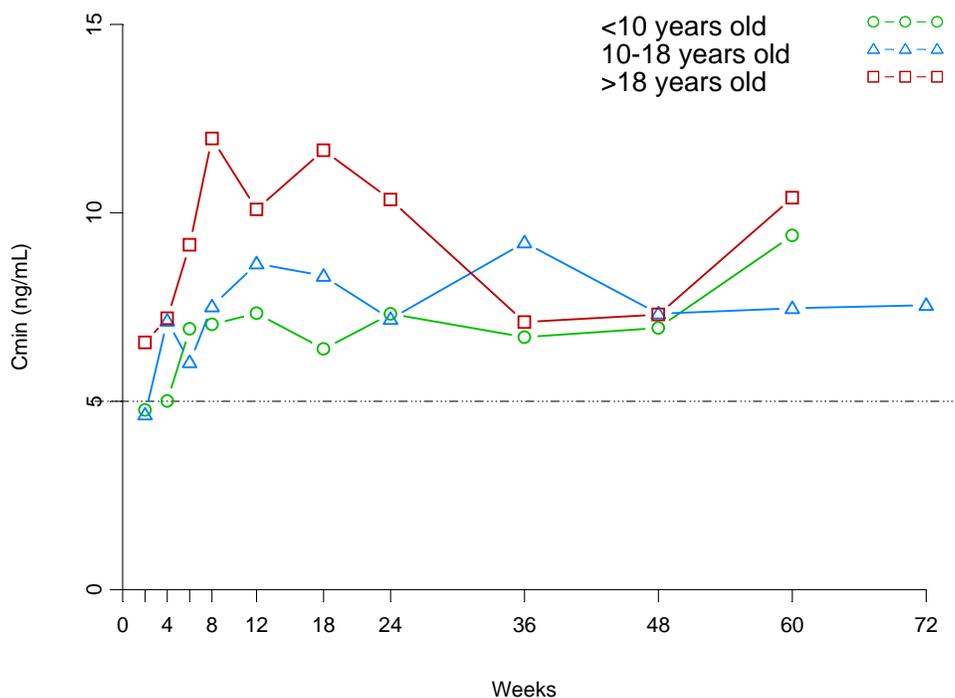
Figure 5: Time course of steady state C_{min} over time for everolimus 4.5 mg/m^2/day dosing regimen in patients who were not taking CYP3A4 inducers or inhibitors. The black dashed line indicates the lower limit of the target, 5 ng/mL. Only mean concentrations are plotted for better visualization.

Reviewer's comment: This analysis indicated that everolimus exposure is varied by different age groups, supporting the use of TDM to achieve best efficacy.

2.4.2   **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.**

The dose adjustments for patients taking concomitant CYP3A4 inducers or CYP3A4 inhibitors were approved by FDA previously and there are no changes in the current submission.

As for hepatic impairment, previous approved labeling recommends the following:

(b) (4)

At the review of the current NDA submission, the medical reviewer recommends reducing the starting dose of AFINITOR DISPERZ or AFINITOR by approximately 50% (instead of avoid use) in patients with SEGA who have severe hepatic impairment (Child-Pugh class C). Subsequent dosing should be based on therapeutic drug monitoring. This recommendation is more consistent with the dose adjustment in the RCC or PNET indication. The reviewer agrees with the above recommendation, taking into consideration of the safety profile discussed above and the wide target range of trough concentration for TDM.

2.5   GENERAL BIOPHARMACEUTICS

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

Everolimus is a low permeability drug based on the *in vitro* permeability study using Caco-2 cell monolayers. The reported everolimus solubility is < 0.01% (0.1 mg/mL) in water, 0.1 N HCl, and citrate buffer (pH 2.0 - 10.0).

2.5.2   Is the dispersible tablet bioequivalent to the MF/FMI tablet?

Everolimus formulations used in the studies included in the current submission are listed in **Table 6**. The final market image (FMI) tablet is the approved market formulation, and the market formulation (MF) tablet is the formulation used generally in clinical studies. The review by Dr. Bullock states that previous study C2119 has demonstrated the bioequivalence (BE) between the FMI and MF formulations. In addition to the regular FMI/MF tablets, the proposed age-appropriate dispersible tablets were used in the BE Studies X2105 and X2106.

The current market product for the SEGA indication is the everolimus FMI tablet with strengths of 2.5-mg and 5-mg. To satisfy the agreement for an age-appropriate formulation in the Pediatric Investigational Plan and the Written Request, the applicant developed the 2-mg, 3-mg, and 5-mg dispersible tablets for the TSC with SEGA indication. The 2-mg, 3-mg and 5-mg dispersible tablets are proportional in composition.

Note: In previous BE Study C2121: the bioavailability of 5 x 1-mg FM tablets administered as a suspension in water relative to that of 5 x 1-mg tablets administered as intact tablets was 88% (90% CI = 0.8 to 0.96). C_{max} of the suspension was 72% (90% CI = 0.63 to 0.82) that of the intact tablets.

Table 6: Everolimus Formulations Used in Studies Included in the Current Dossier for the SEGA Submission

	C2485	M2301	X2105	X2106
1-mg MF tablet		X	X	
2.5-mg MF tablet	X			
5-mg MF tablet	X			
5-mg FMI tablet	X			X
2-mg dispersible tablet				
3-mg dispersible tablet				
5-mg dispersible tablet			X	X

Study X2105 was conducted to assess the BE between the 1-mg MF tablet used in the Phase 3 SEGA study M2301 and the 5-mg dispersible tablet intended for marketing. Study X2106 was conducted to assess the BE between the 5-mg MF tablet used in Phase 2 SEGA study C2485 and the 5-mg dispersible tablet intended for marketing.

X2105: For the primary PK parameter $AUC_{0-\infty}$, the 90% confidence intervals of the ratio of geometric means for the comparison between 5 x 1-mg MF intact tablets and 1 x 5-mg dispersible tablet suspended in water were within the BE boundaries of 0.8 and 1.25. However, C_{max} of the 1 x 5-mg dispersible tablet suspended in water was only 64% that of the 5 x 1-mg MF intact tablets (**Table 7**).

Table 7: Results of Study X2105

PK parameters	Treatment	N	Geometric mean	Ratio of geometric means (B:A) (90% CI)
AUC_{0-inf} (ng.h/mL)	A	51	255	0.86 (0.802, 0.926)
	B	51	220	
C_{max} (ng/mL)	A	51	39.8	0.64 (0.599, 0.679)
	B	51	25.4	

A = 5 x 1-mg intact tablets, B = 1 x 5-mg dispersible tablet suspended in water

X2106: For the primary PK parameter $AUC_{0-\infty}$, the 90% confidence intervals of the ratio of geometric means for the comparison between 5-mg FMI intact tablet and 5-mg dispersible tablet suspended in water were within the BE boundaries of 0.8 and 1.25. However, C_{max} of the 5-mg dispersible tablet suspended in water was only 80% that of the 5-mg FMI intact tablets (**Table 8**).

Table 8: Results of Study X2106

PK parameters	Treatment	N	Geometric mean	Ratio of geometric means (B:A) (90% CI)
AUC_{0-inf} (ng.h/mL)	A	53	255	0.91 (0.862, 0.955)
	B	52	231	
C_{max} (ng/mL)	A	53	32.0	0.80 (0.754, 0.859)
	B	53	25.8	

A = 1 x 5-mg intact tablet, B = 1 x 5-mg dispersible tablet suspended in water

Simulation: Predicted pre-dose trough (C_{min}) concentrations are similar after daily administration of 5 x 1-mg intact tablets, 5-mg intact tablet, and 5-mg dispersible tablet (**Figure 6**).
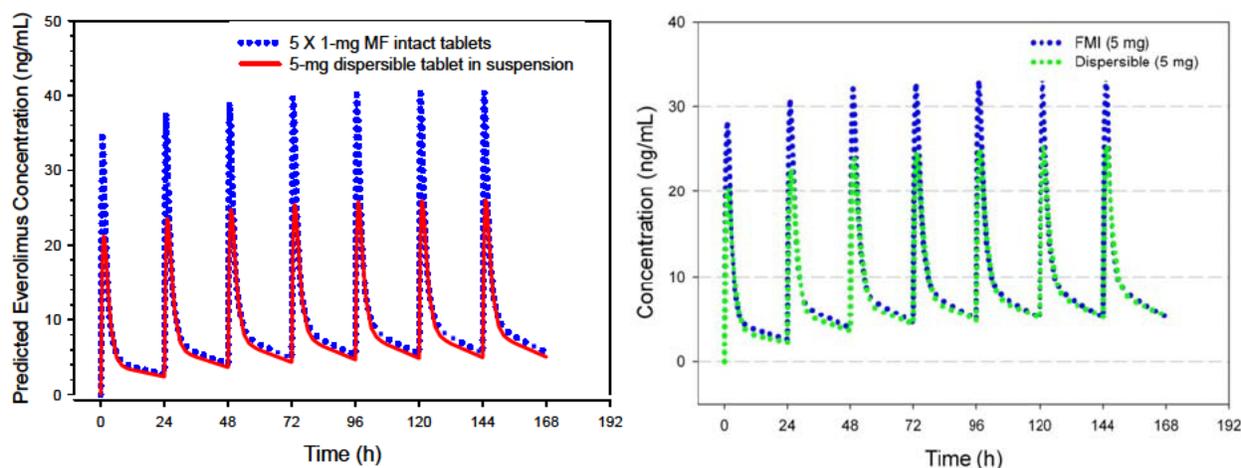
Figure 6: Predicted steady-state everolimus concentration-time profiles of daily administration of 5 x 1-mg intact tablets, 5-mg intact tablet, and 5-mg dispersible tablet

In summary:

- AUC_{0-inf} of 5-mg dispersible tablet when administered as suspension in water was equivalent to 5 x 1-mg intact tablets and to 5-mg intact tablet.

- C_{max} of 5-mg dispersible tablet in suspension was 64% and 80% of 5 x 1-mg intact tablets and 5-mg intact tablet, respectively.

- Predicted C_{min} values at steady-state are similar after daily administration of 5-mg dispersible tablets in suspension, 5 x 1-mg intact tablets, and 5-mg intact tablet.

- Dosing of everolimus in patients with SEGA will be based on therapeutic drug monitoring with dose titration to maintain C_{min} within target range to ensure equivalent therapeutic

effect.

2.5.3   Is the lowest tablet strength of 2 mg is appropriate for the SEGA indication?

The lowest tablet strength of 2 mg is appropriate for the SEGA indication based on the following reasons:
- For the 78 patients on the everolimus arm in Study M2301, the median duration of exposure up to the 02-Mar-2011 data cut-off was 41.9 weeks (range: 24.0 to 78.9). Only four patients (5.1%) have been administered a 1-mg/day dose for a median of 41 days (range: 22 to 198).
- Data in Study M2301 indicated that a 2 mg dose delivered median pre-dose concentration of 3.5 ng/mL with range of 2.0 - 9.9 ng/mL in patients.

3   DETAILED LABELING RECOMMENDATIONS

3.1 SPONSOR'S PROPOSAL

The sponsor proposed the following labeling changes (submission date: 02/29/2012). For brevity, only relevant sections are included.

(b) (4)
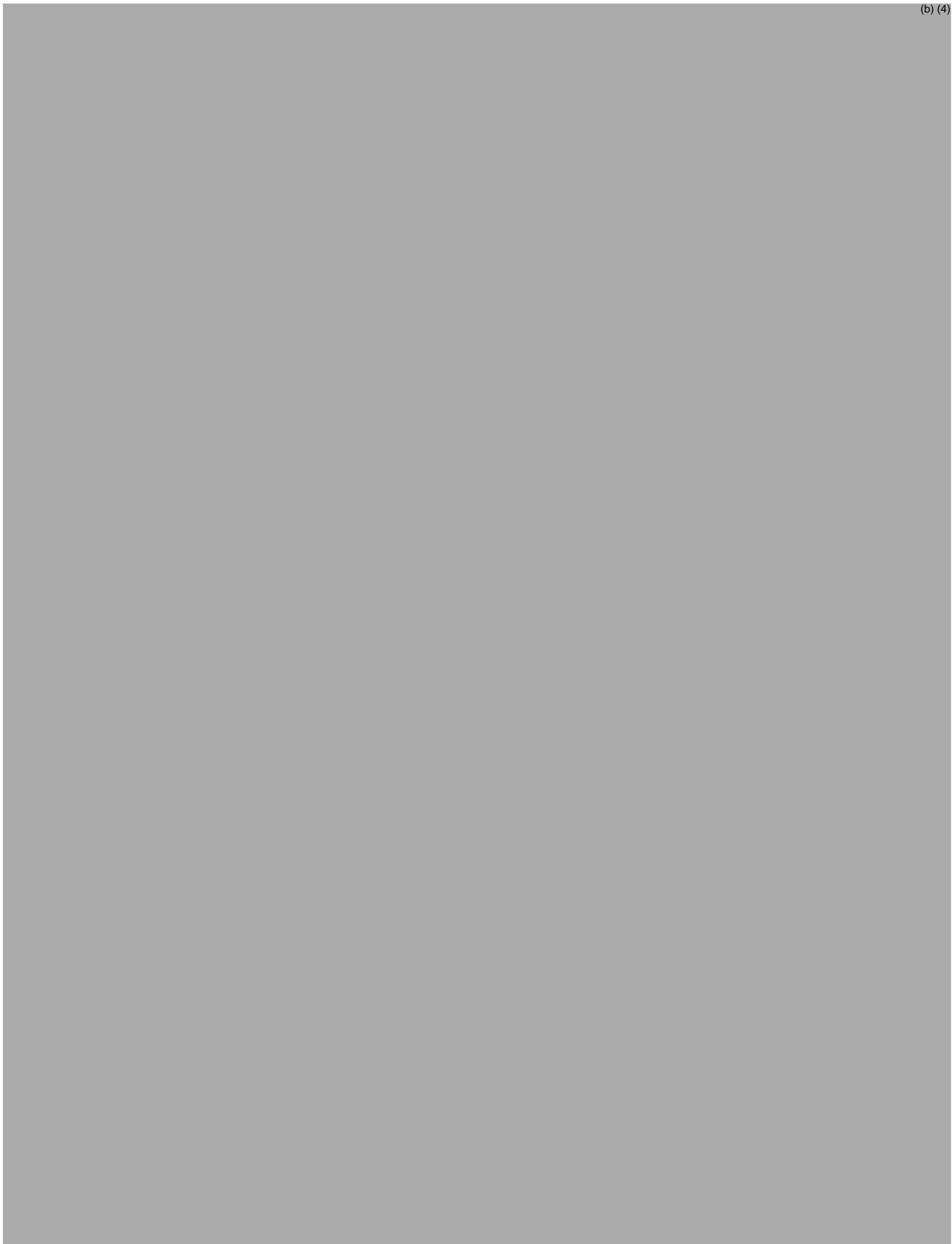
3.2 AGENCY RECOMMENDATION

FDA recommends the following labeling changes. For brevity, only sections that are relevant to clinical pharmacology are included.

2 DOSAGE AND ADMINISTRATION

AFINITOR is available in two formulations: tablets (AFINITOR Tablets) and tablets for oral suspension (AFINITOR DISPERZ). AFINITOR DISPERZ is recommended only for the treatment of patients with SEGA and TSC in conjunction with therapeutic drug monitoring [see Clinical Pharmacology (12.3)].

2.3 Recommended Dose in Subependymal Giant Cell Astrocytoma with TSC

The recommended starting dose is 4.5 mg/m^2, once daily. Round dose to the nearest strength of either AFINITOR Tablets or AFINITOR DISPERZ.

Use therapeutic drug monitoring to guide subsequent dosing [see Dosage and Administration (2.4)]. Adjust dose at two week intervals, as needed to achieve and maintain trough concentrations of 5 to 15 ng/mL [see Dosage and Administration (2.3, 2.4, 2.5)].

Continue treatment until disease progression or unacceptable toxicity occurs. The optimal duration of therapy is unknown.

2.4 Therapeutic Drug Monitoring in Subependymal Giant Cell Astrocytoma with TSC

Monitor everolimus whole blood trough levels routinely in all patients. When possible, use the same assay and laboratory for therapeutic drug monitoring throughout treatment.

Assess trough concentrations approximately two weeks after initiation of treatment, a change in dose, a change in co-administration of CYP3A4 and/or PgP inducers or inhibitors, a change in hepatic function, or a change in formulation between AFINITOR Tablets and AFINITOR DISPERZ. Once a stable dose is determined, monitor monthly for 6 months and then every 3 months for the duration of AFINITOR treatment.

Titrate the dose to attain trough concentrations of 5 to 15 ng/mL.

- For trough concentrations less than 5 ng/mL, increase the daily dose by 2.5 mg (in patients taking AFINITOR Tablets) or 2 mg (in patients taking AFINITOR DISPERZ).
- For trough concentrations greater than 15 ng/mL, reduce the daily dose by 2.5 mg (in patients taking AFINITOR Tablets) or 2 mg (in patients taking AFINITOR DISPERZ).
- If dose reduction is required for patients receiving the lowest available strength, administer every other day.

2.5 Dose Modifications in Subependymal Giant Cell Astrocytoma with TSC

Hepatic Impairment
- Reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50% in patients with SEGA who have severe hepatic impairment (Child-Pugh class C). Adjustment to the starting dose for patients with SEGA who have mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment may not be needed. Subsequent dosing should be based on therapeutic drug monitoring.
- Assess everolimus trough concentrations approximately two weeks after commencing treatment, a change in dose, or any change in hepatic function [see Dosage and Administration (2.3, 2.4)].

CYP3A4 and/or P-glycoprotein (PgP) Inhibitors
Avoid the use of concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) in patients receiving AFINITOR Tablets or AFINITOR DISPERZ [see Warnings and Precautions (5.7) and Drug Interactions (7.1)].

For patients who require treatment with moderate CYP3A4 and/or PgP inhibitors (e.g., amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem):
Reduce the AFINITOR Tablets or AFINITOR DISPERZ dose by approximately 50%. Administer every other day if dose reduction is required for patients receiving the lowest available strength.
- Assess everolimus trough concentrations approximately two weeks after dose reduction [see Dosage and Administration (2.3, 2.4)].
- Resume the dose that was used prior to initiating the CYP3A4 and/or PgP inhibitor 2-3 days after discontinuation of a moderate inhibitor. Assess the everolimus trough concentration approximately two weeks later [see Dosage and Administration (2.3, 2.4)].

Do not ingest foods or nutritional supplements (e.g., grapefruit, grapefruit juice) that are known to inhibit cytochrome P450 or PgP activity.

Strong CYP3A4 Inducers
Avoid the use of concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) if alternative therapy is available [see Warnings and Precautions (5.7) and Drug Interactions (7.2)]. For patients who require treatment with a strong CYP3A4 inducer:
- Double the dose of AFINITOR Tablets or AFINITOR DISPERZ.
- Assess the everolimus trough concentration two weeks after doubling the dose and adjust the dose if necessary to maintain a trough concentration of 5 to 15 ng/mL [see Dosage and Administration (2.3, 2.4)].
- Return the AFINITOR Tablets or AFINITOR DISPERZ dose to that used prior to initiating the strong CYP3A4 inducer if the strong inducer is discontinued, and assess the everolimus trough concentrations approximately two weeks later [see Dosage and Administration (2.3, 2.4)].

Do not ingest foods or nutritional supplements (e.g., St. John's Wort (Hypericum perforatum)) that are known to induce cytochrome P450 activity.

5.8 Hepatic Impairment

For patients with SEGA and mild or moderate hepatic impairment, adjust the dose of AFINITOR or AFINITOR DISPERZ based on therapeutic drug monitoring. For patients with SEGA and severe hepatic impairment, reduce the starting dose of AFINITOR or AFINITOR DISPERZ by approximately 50% and adjust subsequent doses based on therapeutic drug monitoring [see Dosage and Administration (2.4, 2.5)].

8.4 PEDIATRIC USE

Pediatric use of AFINITOR and AFINITOR DISPERZ is recommended for patients 1 year of age and older with TSC for the treatment of SEGA that requires therapeutic intervention but cannot be curatively resected. The safety and effectiveness of AFINITOR and AFINITOR DISPERZ have not been established in pediatric patients with renal angiomyolipoma with TSC in the absence of SEGA.

The effectiveness of AFINITOR in pediatric patients with SEGA was established in two clinical trials based on demonstration of durable objective response, as evidenced by reduction in SEGA tumor volume *[see Clinical Studies (14.5)]*. Improvement in disease-related symptoms and overall survival in pediatric patients with SEGA has not been demonstrated. The long term effects of AFINITOR on growth and pubertal development are unknown.

Study 1 was a randomized, double blind, multicenter trial comparing AFINITOR (n=78) to placebo (n=39) in pediatric and adult patients. The median age was 9.5 years (range 0.8 to 26 years). At the time of randomization, a total of 20 patients were < 3 years of age, 54 patients were 3 to < 12 years of age, 27 patients were 12 to < 18 years of age, and 16 patients were > 18 year of age. The overall nature, type, and frequency of adverse reactions across the age groups evaluated were similar, with the exception of a higher per patient incidence of infectious serious adverse events in patients < 3 years of age. A total of 6 of 13 (46%) patients < 3 years of age had at least one infectious serious adverse event due to infection, compared to 2 of 7 (29%) patients treated with placebo. No patient in any age group discontinued AFINITOR due to infection *[see Adverse Reactions (6.5)]*. Subgroup analyses showed reduction in SEGA volume with AFINITOR treatment in all pediatric age subgroups.

Study 2 was an open label, single arm, single-center trial of AFINITOR (N=28) in patients aged ≥ 3 years; median age was 11 years (range 3 to 34 years). A total of 16 patients were 3 to < 12 years, 6 patients were 12 to < 18 years, and 6 patients were ≥ 18 years. The frequency of adverse reactions across the age-groups was generally similar *[see Adverse Reactions (6.5)]*. Subgroup analyses showed reduction in SEGA volume with AFINITOR treatment in all pediatric age subgroups.

Everolimus clearance normalized to body surface area was higher in pediatric patients than in adults with SEGA *[see Clinical Pharmacology (12.3)]*.The recommended starting dose and subsequent requirement for therapeutic drug monitoring to achieve and maintain trough concentrations of 5 to 15 ng/mL are the same for adult and pediatric patients with SEGA *[see Dosage and Administration (2.3, 2.4)]*.

8.7 Hepatic Impairment

For patients with SEGA who have severe hepatic impairment (Child-Pugh class C), reduce the starting dose of AFINITOR or AFINITOR DISPERZ by approximately 50%. For patients with SEGA who have mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, adjustment to the starting dose may not be needed. Subsequent dosing should be based on therapeutic drug monitoring [see Dosage and Administration (2.4, 2.5)].

12.2 Pharmacodynamics

Exposure Response Relationships

In patients with SEGA, higher everolimus trough concentrations appear to be associated with larger reductions in SEGA volume. However, as responses have been observed at trough concentrations as low as 5 ng/mL, once acceptable efficacy has been achieved, additional dose increase may not be necessary.

12.3 Pharmacokinetics

Absorption

Dose Proportionality in Patients with SEGA and TSC: In patients with SEGA and TSC, everolimus C_{min} was approximately dose-proportional within the dose range from 1.35 mg/m^2 to 14.4 mg/m^2.

Relative bioavailability of AFINITOR DISPERZ (everolimus tablets for oral suspension): The $AUC_{0-\infty}$ of AFINITOR DISPERZ was equivalent to that of AFINITOR Tablets; the C_{max} of this formulation was 20-36% lower than that of AFINITOR Tablets. The predicted trough concentrations at steady-state were similar after daily administration.

Effects of Age and Gender

In patients with SEGA, the geometric mean C_{min} values normalized to mg/m^2 dose in patients aged < 10 years and 10 to 18 years were lower by 54% and 40%, respectively, than those observed in adults (> 18 years of age), suggesting that everolimus clearance normalized to body surface area was higher in pediatric patients as compared to adults.

4 APPENDICES

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

The relationship between everolimus exposure and absolute change from baseline in sum of volumes of target SEGA lesions was investigated by a linear mixed model including the sum of volumes at baseline, the log-transformed time-normalized C_{min} between the previous and the current brain CT/MRI assessment as fixed effect and patient as random effect. Results of linear mixed model analysis of the SEGA volume-C_{min} relationship indicate that the relationship between percent change from baseline in SEGA lesion volume and C_{min} was statistically significant with a 12.98% (95% CI= -18.16%, -7.46%) tumor size reduction for a 2-fold C_{min} increase.
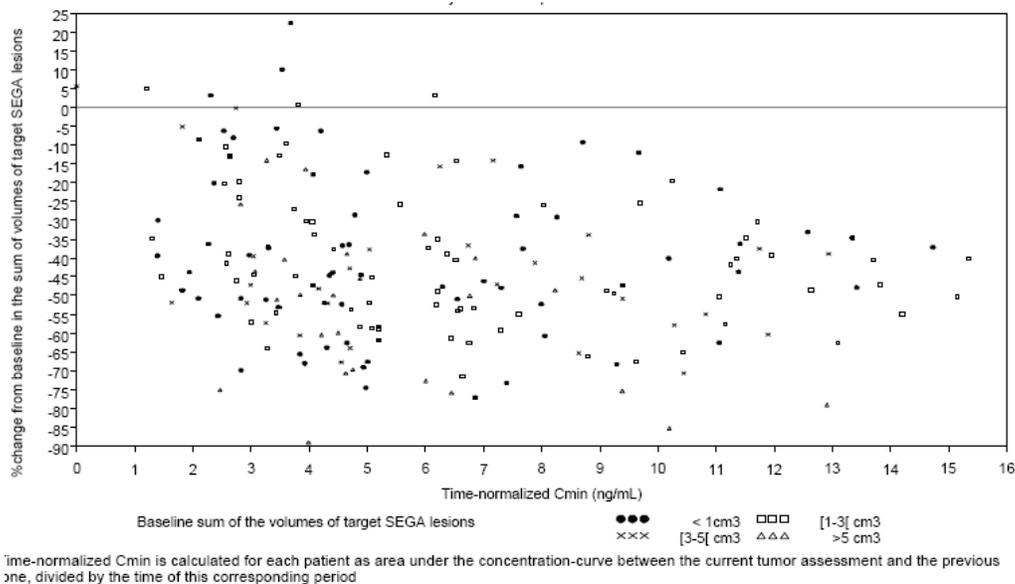
Figure 7: Relationship between percent change from baseline in SEGA volume and C_{min}

There was no apparent relationship between time normalized Cmin (or C2h) and frequency of clinically notable adverse events, suggesting that higher everolimus exposure within the Cmin (up to 14.6 ng/mL) or C2h (up to 63.4 ng/mL) ranges observed in this study was not indicative of a higher risk of adverse events.

Based on this analysis, the sponsor proposed labeling states that   (b) (4)

                                                                                                        (b) (4)

Reviewer's comment:

The exposure-response relationship appears nonlinear based on FDA's logistic regression analysis and indirect response model. The reviewer proposed to remove this labeling statement and keep the original labeling statement with a change (b) (4) *to 5 ng/mL for the lower limit of the target range. See labeling section for details.*

Indirect response model

In another analysis, target SEGA volumes were modeled by an indirect response model based on actual daily dosing history, including dose changes and interruptions. The analysis included 78 patients randomized to the everolimus arm for the double-blind treatment phase of Study M2301. Both treatment arms (placebo and everolimus) were used for the analysis, as well as baseline and pre-baseline values of sum of target SEGA volumes. The time-varying covariates included age (years), body weight (kg), body surface area (m^2), an indicator for CYP3A or PgP inducers, and an indicator for CYP3A or PgP inhibitors. Covariates incorporated with values at baseline include sex, race, prior anti-SEGA surgery, and sum of target SEGA volumes.

NONMEM with METHOD=1 INTERACTION was used for modeling. A zero dose was imputed on the days of dose interruptions in order to have NONMEM compute the Cmin for each individual for each day.

The typical maximum effect of the drug (Imax) was estimated as 93.5% (SE=5.15%). A typical decrease in SEGA volumes of 50% of 93.5% (half the maximal effect), or 47%, is estimated at pharmacodynamic steady state based on daily Cmin=6.41 ng/mL(SE=1.01 ng/mL; 95% CI: 4.43-8.39 ng/mL,). The typical decrease in SEGA volumes for Cmin = 3 ng/mL was 29.8% (95% CI: 22.5% to 35.6%). No covariates were identified that would predict IC_{50}.

Reviewer's comment:

The reviewer re-analyzed the data and further simulated the data based on the final model. The value of the model to guide clinical practice is limited since no covariates are found to affect response.

4.1.1.2 Safety
There was no apparent relationship between time-normalized Cmin and frequency of clinically notable adverse events. The sponsor states that higher everolimus exposure within the Cmin (up to 14.6 ng/mL) or ranges observed in study M2301 was not indicative of a higher risk of adverse events.

Table 9: Clinically Notable Adverse Events in Patients by Time-normalized C_{min} Subgroups

Grouping	Time-normalized C_{min} * (ng/mL) subgroups		
	< 5 ng/mL N = 34 (%)	5-10 ng/mL N = 35 (%)	> 10 ng/mL N = 9 (%)
Cytopenia	3 (8.8)	7 (20.0)	2 (22.2)
Hemorrhages	2 (5.9)	3 (8.6)	2 (22.2)
Hypersensitivity reactions (anaphylactic reaction)	1 (2.9)	1 (2.9)	0 (0.0)
Infections and infestations	27 (79.4)	23 (65.7)	6 (66.7)
Non infectious pneumonitis	0 (0.0)	1 (2.9)	0 (0.0)
Rash and similar events	9 (26.5)	3 (8.6)	1 (11.1)
Renal events	0 (0.0)	0 (0.0)	1 (11.1)
Stomatitis/oral mucositis/ulcers	20 (58.8)	21 (60.0)	5 (55.6)
Amenorrhoea	1 (2.9)	0 (0.0)	2 (22.2)

Reviewer's comment: the highest Cmin in this analysis is 14.6 ng/mL and there is only one observation between 14-15 ng/mL. The reviewer is concerned about the insufficient data in this higher Cmin range. However, the safety data from RCC and PNET submission are compelling evidence to support a target range up to 15 ng/mL.

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:

- Characterize the exposure-response relationship for efficacy and safety to evaluate the proposed 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.

- Simulate SEGA response based on the final model using Cmin within the proposed target concentration range.

- Assess variability by evaluating the effects of covariates, including the baseline sum of target SEGA volumes.

4.2.1.2 Methods

Logistic regression

A multivariate logistic regression based on log-linear model was conducted to identify the covariates that predict response. The following covariates were included in the analysis: body weight, age, sex, baseline tumor volumes. Several models including linear, log-linear and E_{max} models were tested. Logistic regression using the E_{max} model appeared to describe the data better as compared to linear or log-linear logistic regression models. Average steady state Cmin was utilized as the exposure variable to conduct the primary exposure-response analysis.

Indirect response model

The NONMEM objective function values and diagnostic plots were used to assess goodness of fit and suggest covariates to add to the model (**Error! Reference source not found.**). Covariates were also examined graphically for their decrease of variability by plotting individual estimates versus the covariates age, BSA, BMI, baseline SEGA volume, sex, and concomitant medications.

Simulation of the percentage decrease of sum of target SEGA volumes over 48 weeks was performed for values of steady-state Cmin in the range of 3-15 ng/mL (**Figure 9**).

Tumor Rebound

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. Tumor re-growth during any of the two consecutive assessments were also explored for its potential relationship to Cmin decrease during the time period.

Steady state C_{min} between BR and LR was calculated for the patient in which tumor grew back. Tumor growth was quantified as % increase in tumor from BR.

4.2.1.3 Datasets

Study Number	Name	Link to EDR
M2301	pkpd.xpt	\\Cdsesub1\evsprod\NDA203985\0000\m5\datasets\rad001 m2301poppk\analysis
M2301	apknorm.xpt apkpd.xpt apkint.xpt actsass.xpt aaev.xpt	\\Cdsesub1\evsprod\NDA203985\0000\m5\datasets\rad 001m2301\analysis

4.2.1.4 Software

NONMEM 7.1, SAS 9.2 and S-PLUS 7.0 were used for analyses.

4.2.1.5   Results

SEGA Response rate
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** that there is increase in response with increasing trough concentrations with no additional benefit at $C_{min} > 3$ ng/ml. Multivariate analyses showed that females or older patients have a trend of higher response than males or younger patients (**Figure 8**).
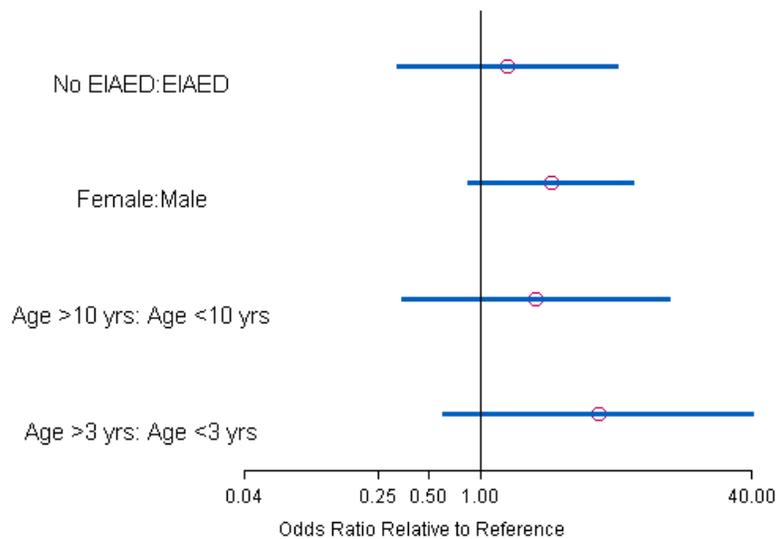
Figure 8: Estimated Odds Ratios of the Full Logistic Regression Model of SEGA Response. The horizontal error bars depict the estimated 95% confidence intervals.

SEGA Volume
There were 76 everolimus and 39 placebo patients contributing a total of 510 sums of target SEGA volumes to the analysis. An indirect response PK-PD model was developed to describe the exposure-efficacy relationship of everolimus in patients with TSC who have SEGA.

The estimated typical IC_{50} (6.41 ng/mL) and related 95% confidence interval (4.43-8.39 ng/mL) provides supportive evidence for the selection of the target concentration range 5-15 ng/mL(**Figure 9**).
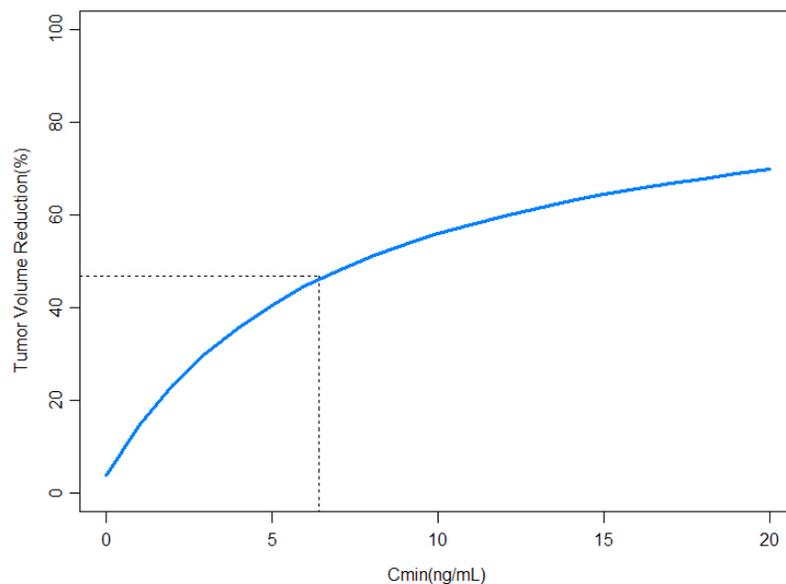
Figure 9: Simulation of typical sum of target SEGA volumes versus steady-state Cmin at Week 24 of post-treatment.

SEGA Tumor Rebound

The tumor re-growth in patients after the core treatment phase does not seem to be associated with lower exposures.

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. Drug exposure is indicated as predicted Cmin at the time of LR. Changes of Cmin between the time of LR and BR were calculated.

The data from both scenarios indicated that there is no clear relationship between Cmin and tumor rebound (**Figure 10**, left). A total of 31 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 or rebound which was defined as the % increase in SEGA tumor volume from BR. Among them, 68% of the patients (N=21 out of 31) had a decrease of Cmin from BR to LR. (**Figure 10**, right). There are 2 patients with no change of Cmin and 8 patients had an increase of Cmin. This observation provides supportive evidence for the effectivenees of everolimus in SEGA tumor reduction.

Although analyses showed that more than two third of the patient who suffered tumor rebound had decreased everolimus exposure during that time period, there is insufficient evidence to indicate that lower exposures might be responsible for tumor re-growth.

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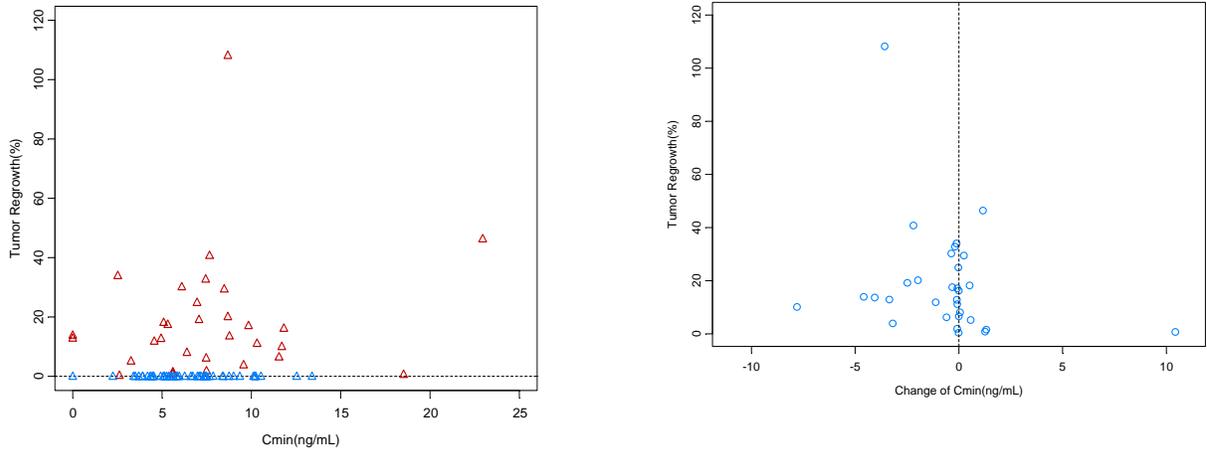
Figure 10: Exposure and tumor rebound relationship for everolimus. Left: Tumor rebound vs. everolimus exposure. LR was lower than BR (red) or the last response was the best response (blue). Right: Tumor rebound vs. change of Cmin from BR to LR.

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 proposed 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
M2301	apkpd.xpt aaev.xpt	\\Cdsesub1\evsprod\NDA203985\0000\m5\datasets\rad001m2301\analysis
C2485	apkpd.xpt aaev.xpt	\\cdsesub1\evsprod\NDA022334\0064\m5\datasets\rad001c2485\analysis

4.2.2.4 Software

S-PLUS 7.0 were used for analyses.

4.2.2.5 Results

To assess the exposure-safety relationship, the patients for whom the trough concentrations were available from the two Trials C2485 and M2301 were combined and then divided into 6 quantiles and % subjects having adverse events were plotted against each quantile. Cmin is the trough concentration at the time of assessment of the adverse events. Adverse events to be assessed were selected based on the clinical relevance and after discussion with the medical reviewer. Infections and stomatitis were two of the most common adverse events observed.

There is no relationship between Cmin and Grade 3+ infections or stomatitis (**Figure 11**). Further, there were no exposure response relationships for all grades of these adverse events in Trials C2485 and M2301.
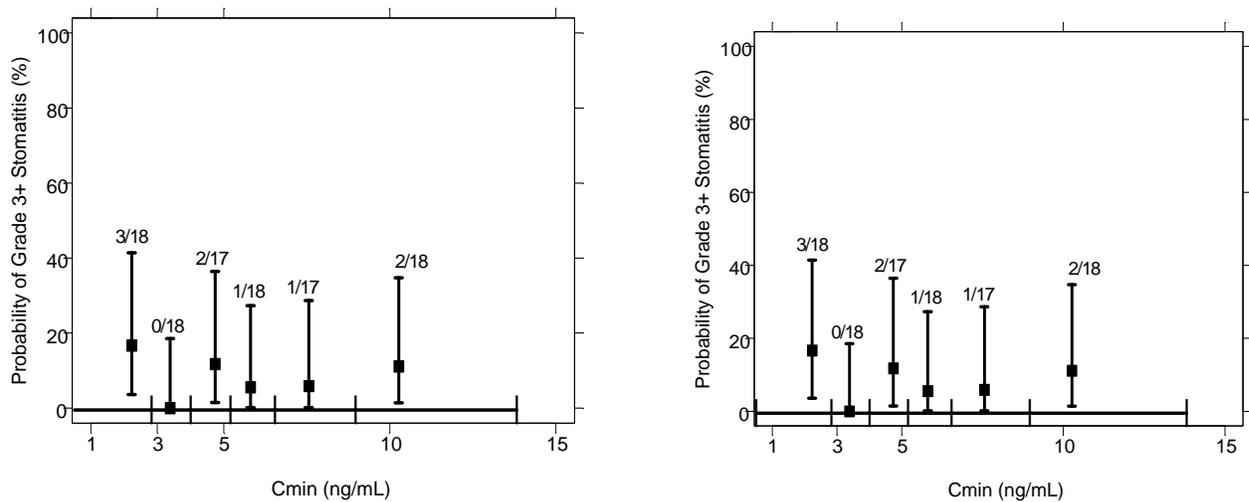
Figure 11: Exposure-safety relationships for most common adverse events.

In summary:
Data from Study M2301 suggest that higher everolimus Cmin was associated with a larger reduction from baseline in SEGA volume.

Within the everolimus Cmin exposure observed in the patients with SEGA in Studies C2485 and M2301, there were no apparent relationships between time-averaged Cmin and clinically notable adverse events, suggesting that higher Cmin was not associated with a higher safety risk within the everolimus ranges observed in the two studies.

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/s/

JIAN WANG
08/03/2012

NITIN MEHROTRA
08/03/2012
Christine Garnett was the pharmacometrics secondary reviewer for this application

HONG ZHAO
08/03/2012
I concur.

NAM ATIQUR RAHMAN
08/07/2012