

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203985Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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## Clinical Pharmacology Review

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

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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, Jino 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<sup>®</sup> 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  $\geq 3$  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<sup>®</sup> DISPERZ<sup>™</sup>) 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  $4.5 \text{ mg/m}^2$  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  $C_{\text{max}}$  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  $C_{\text{min}}$  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:**

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

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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<sup>2</sup> 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.

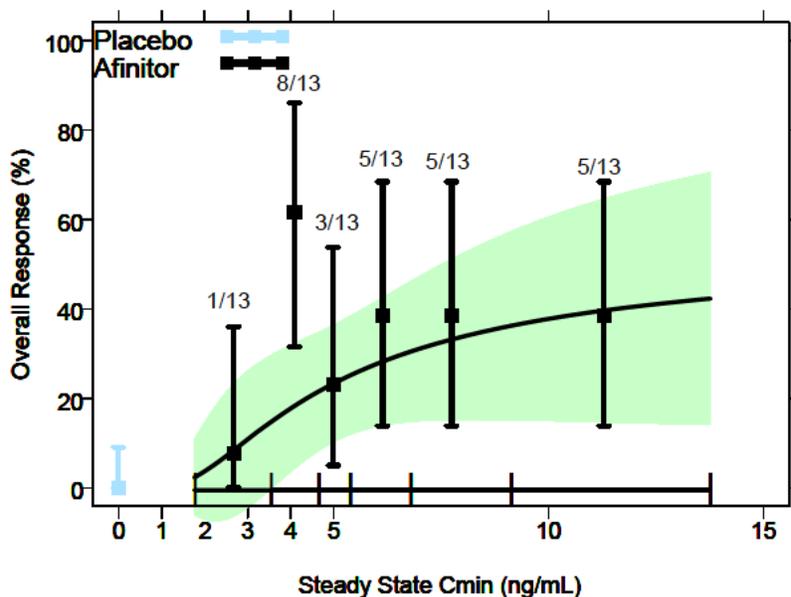
## 2 QUESTION BASED REVIEW

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 4.5mg/m<sup>2</sup>/day, and subsequently titrated, subject to tolerability, to attain whole blood trough concentrations of 5-15 ng/mL. Average steady state C<sub>min</sub> 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<sub>min</sub> was observed and the response reached plateau at C<sub>min</sub> ≥ 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.

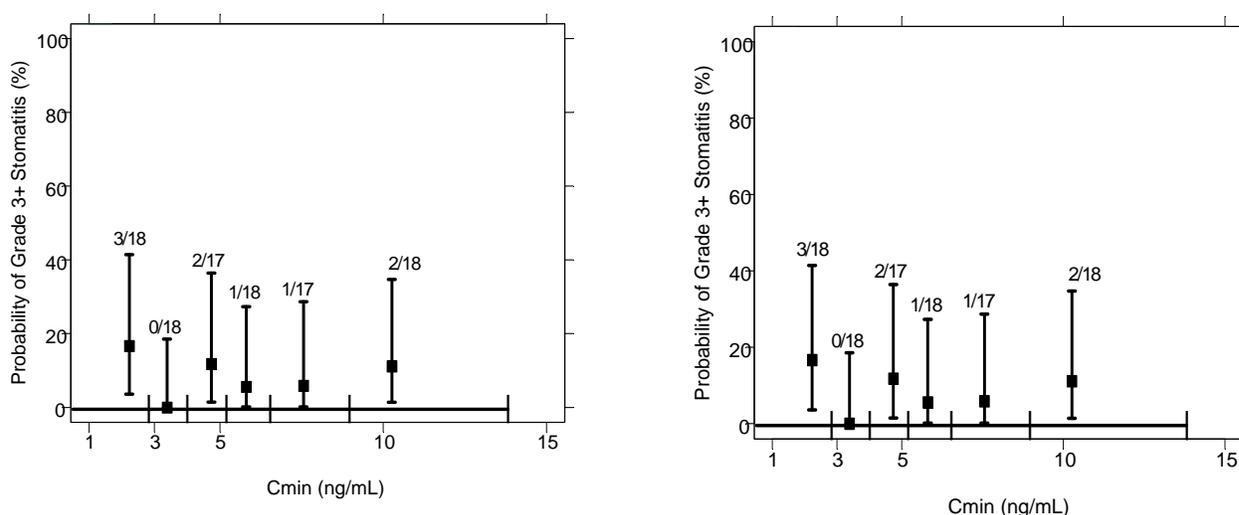


**Figure 1:** Exposure-response relationship of everolimus for percent reduction in SEGA tumor volume at 6 month. The numbers adjacent to each of the quantile represent the C<sub>min</sub> range. The numbers represent number of patients with positive response/total number of patients in respective quantiles.

### 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.

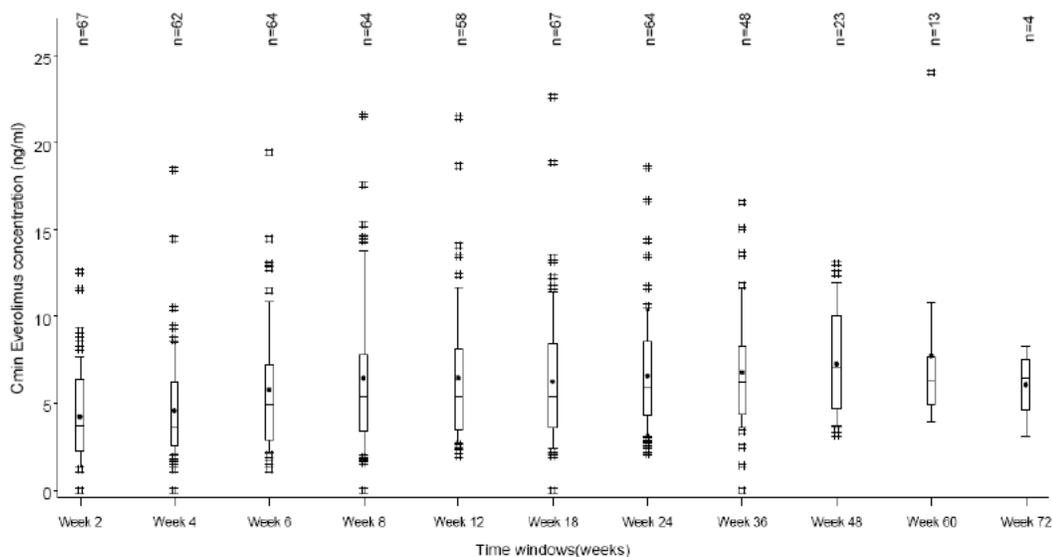
**Table 1: C<sub>min</sub>, Number of Patients on EIAED and Response Rate by Average C<sub>min</sub> Range**

Group	Median C <sub>min</sub> ,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<sup>2</sup> 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) ng/mL 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) ng/mL 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 given that there are limited dose strengths for both formulations.

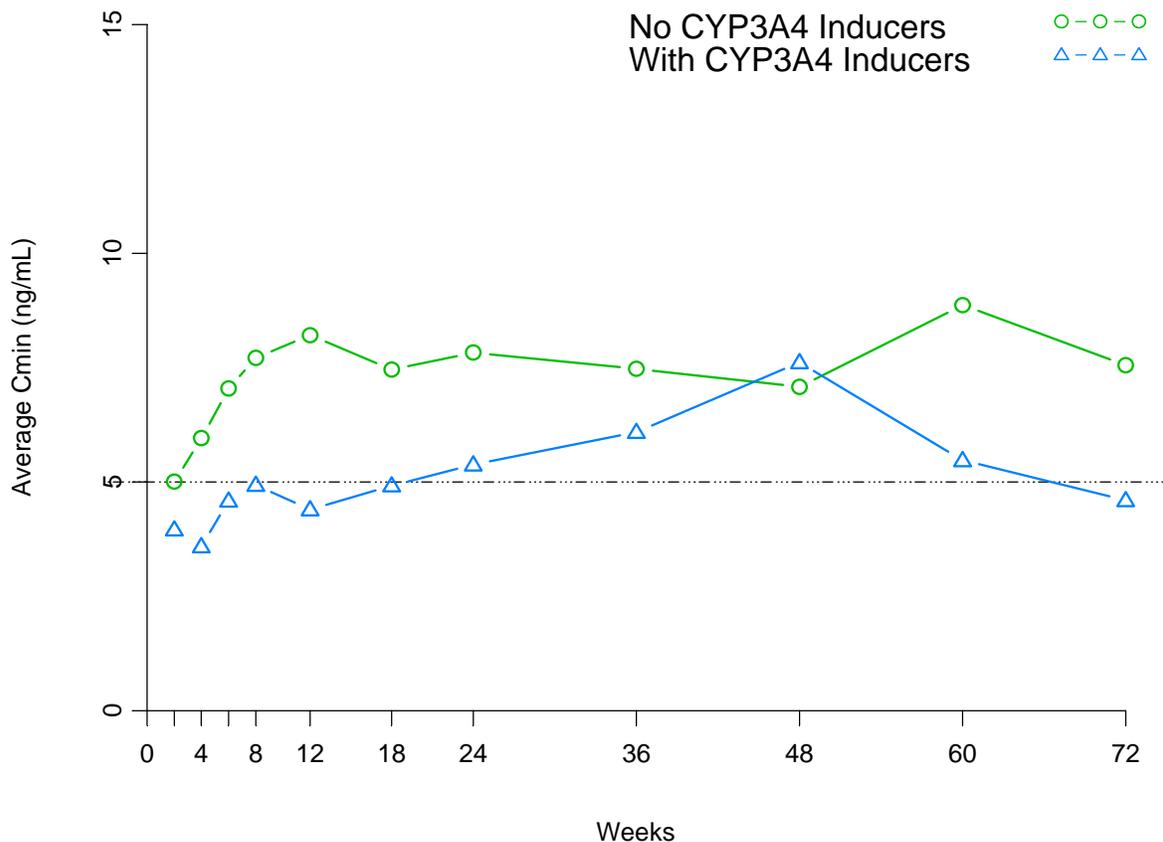
Overall, the recommended target  $C_{\min}$  range of 5–15 ng/mL is supported by the E-R relationship for efficacy and safety experience.

### **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<sup>2</sup>/day, patients on CYP3A4 inducers did not reach the lower limit of the proposed target, 5 ng/mL, until the 24<sup>th</sup> 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<sup>2</sup>/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<sup>2</sup>/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<sup>2</sup>/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<sup>2</sup>/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.

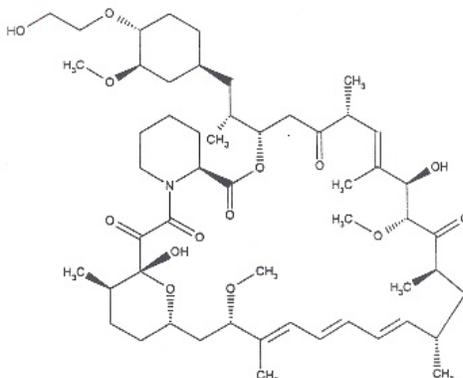
- The 4.5-mg/m<sup>2</sup>/day starting dose is acceptable as data from a Phase 1 pediatric oncology study concluded that the maximum tolerated dose (MTD) in children is 5 mg/m<sup>2</sup>/day (Fouladi et al 2007).
- The geometric mean C<sub>min</sub> (range) values normalized to mg/m<sup>2</sup> dose 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/m<sup>2</sup> should deliver C<sub>min</sub> 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<sub>min</sub> value is close to the recommended target C<sub>min</sub> 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<sub>53</sub>H<sub>83</sub>NO<sub>14</sub>
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-dioxo-4-azatricyclo[30.3.1.0<sup>4,9</sup>]-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?

The applicant proposed the following dose recommendation:

(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.

(b)

**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 <sup>2</sup> /day, and subsequently titrated, subject to tolerability, to attain whole blood trough concentrations of 5-15 ng/mL.	C <sub>min</sub> 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 <sup>2</sup> /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.	C <sub>min</sub> 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**

	<b>C2485</b>	<b>M2301</b>
Trial	Phase II	Phase III
N	28	117
Age	≥3 yrs	Any age
Formulation	2.5, 5-mg MF tablet 5-mg FMI tablet	1-mg MF tablet
Primary endpoint	reduction in SEGA tumor volume	SEGA response rate
Initial dose	3 mg/m <sup>2</sup> /day	4.5 mg/m <sup>2</sup> /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<sup>2</sup> to 14.4 mg/m<sup>2</sup>. 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<sup>2</sup>) 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  $\beta$  was estimated along with the 90% confidence interval (CI). Based on the sponsor's analysis the dose-proportionality coefficient  $\beta$  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<sup>2</sup> to 14.4 mg/m<sup>2</sup>.”*

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?

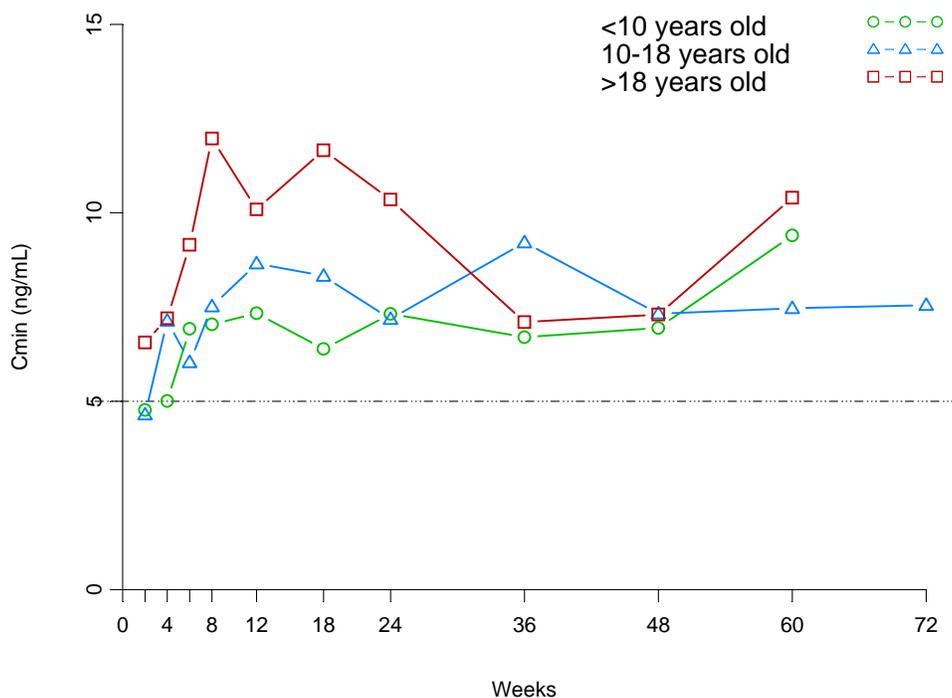
Population PK analyses indicate that body surface area (BSA) and presence of CYP3A inducers are significant covariates for everolimus clearance. Age, body mass index (BMI), baseline sum of target SEGA volumes, and sex have no statistically significant effects on clearance after incorporation of BSA and 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  $C_{min}$  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)
$C_{min}$	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<sup>2</sup>/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)
$AUC_{0-\infty}$ (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

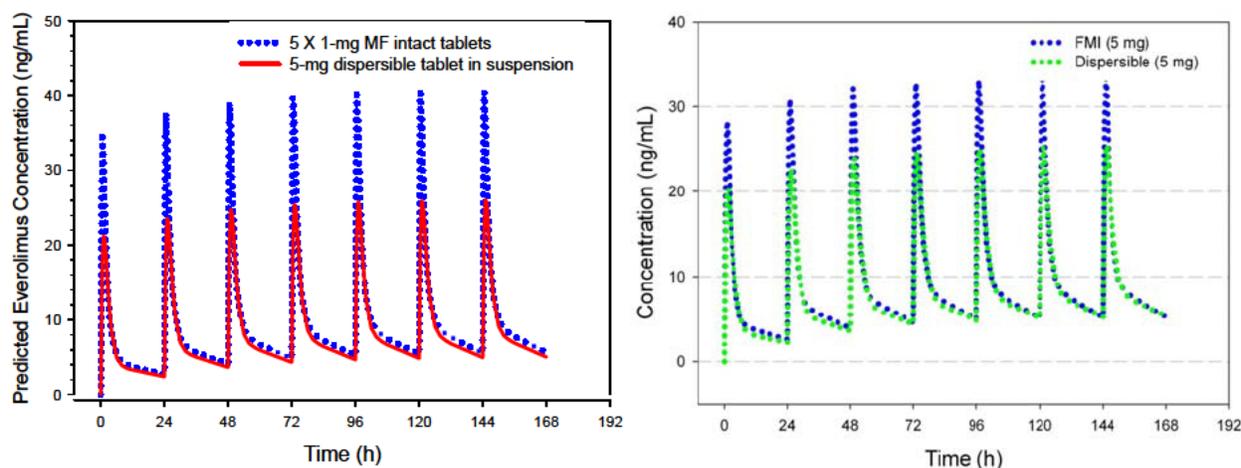
**X2106:** For the primary PK parameter  $AUC_{0-\infty}$ , the 90% confidence intervals of the ratio of geometric means for the comparison between 5-mg FMI intact tablet and 5-mg dispersible tablet suspended in water were within the BE boundaries of 0.8 and 1.25. However,  $C_{max}$  of the 5-mg dispersible 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 <sub>0-inf</sub> (ng.h/mL)	A	53	255	0.91 (0.862, 0.955)
	B	52	231	
C <sub>max</sub> (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<sub>min</sub>) 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<sub>0-inf</sub> 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<sub>max</sub> 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<sub>min</sub> 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<sub>min</sub> 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.

### **2 DOSAGE AND ADMINISTRATION**

(b) (4)

(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<sup>2</sup>, 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  $\geq 3$  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  $\geq 18$  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<sup>2</sup> to 14.4 mg/m<sup>2</sup>.

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<sup>2</sup> 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

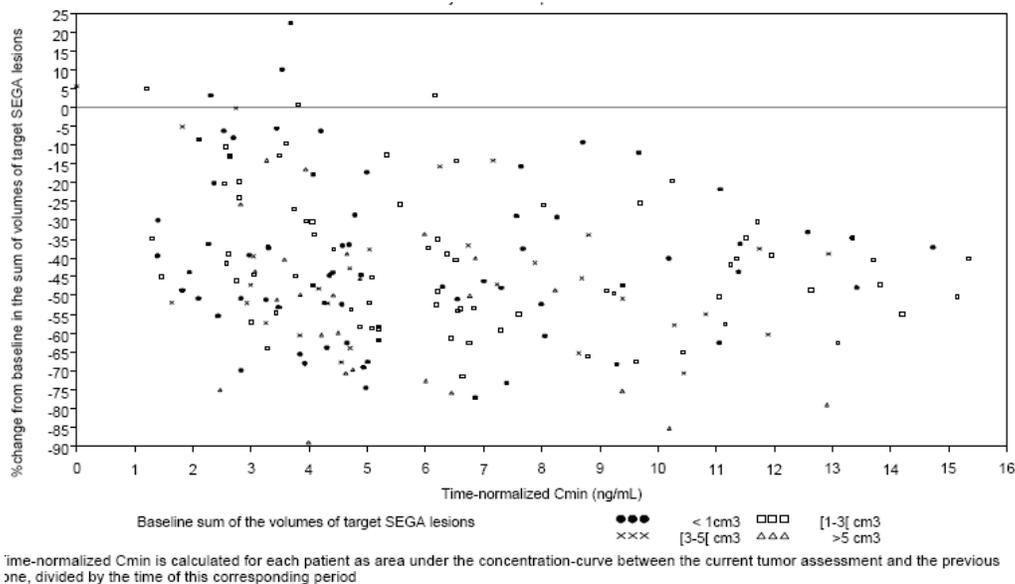
### 4.1 SPONSOR'S ANALYSIS

#### 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 C<sub>min</sub> (or C<sub>2h</sub>) and frequency of clinically notable adverse events, suggesting that higher everolimus exposure within the C<sub>min</sub> (up to 14.6 ng/mL) or C<sub>2h</sub> (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)

*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 of (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<sup>2</sup>), 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 C<sub>min</sub> for each individual for each day.

The typical maximum effect of the drug (I<sub>max</sub>) 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 C<sub>min</sub>=6.41 ng/mL (SE=1.01 ng/mL; 95% CI: 4.43-8.39 ng/mL, ). The typical decrease in SEGA volumes for C<sub>min</sub> = 3 ng/mL was 29.8% (95% CI: 22.5% to 35.6%). No covariates were identified that would predict IC<sub>50</sub>.

*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 C<sub>min</sub> and frequency of clinically notable adverse events. The sponsor states that higher everolimus exposure within the C<sub>min</sub> (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<sub>min</sub> Subgroups**

Grouping	Time-normalized C <sub>min</sub> * (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 C<sub>min</sub> 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 C<sub>min</sub> 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 C<sub>min</sub> 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  $C_{\min}$  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  $C_{\min}$  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  $C_{\min}$  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	<a href="\\Cdsub1\evsprod\NDA203985\0000\m5\datasets\rad001m2301poppk\analysis">\\Cdsub1\evsprod\NDA203985\0000\m5\datasets\rad001m2301poppk\analysis</a>
M2301	apknorm.xpt apkpd.xpt apkint.xpt actsass.xpt aaev.xpt	<a href="\\Cdsub1\evsprod\NDA203985\0000\m5\datasets\rad001m2301\analysis">\\Cdsub1\evsprod\NDA203985\0000\m5\datasets\rad001m2301\analysis</a>

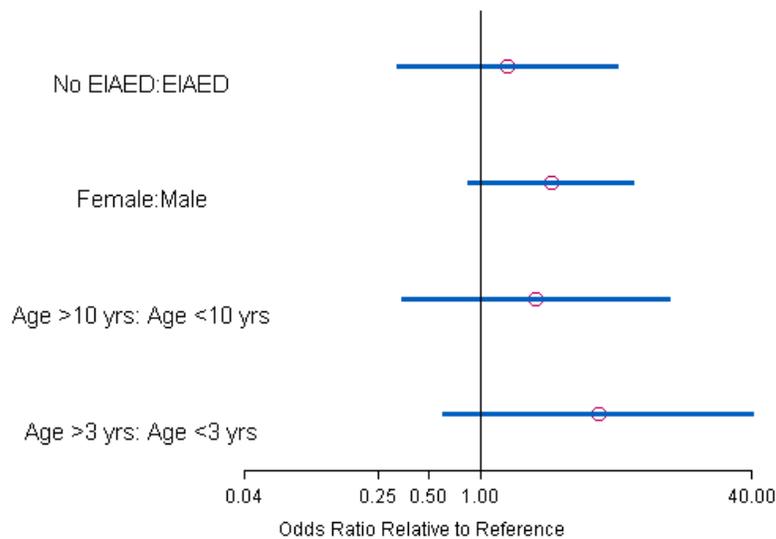
#### 4.2.1.4 Software

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**).

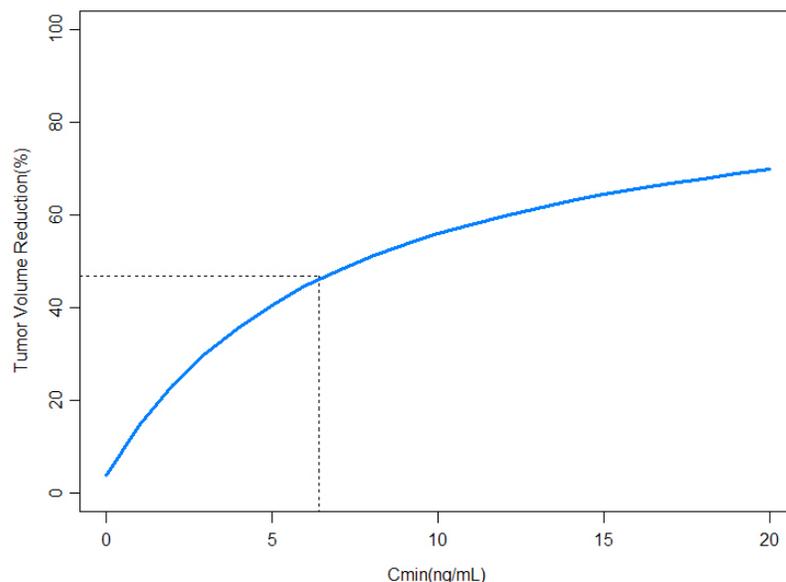


**Figure 8: Estimated Odds Ratios of the Full Logistic Regression Model of SEGA Response. The horizontal error bars depict the estimated 95% confidence intervals.**

##### *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.**

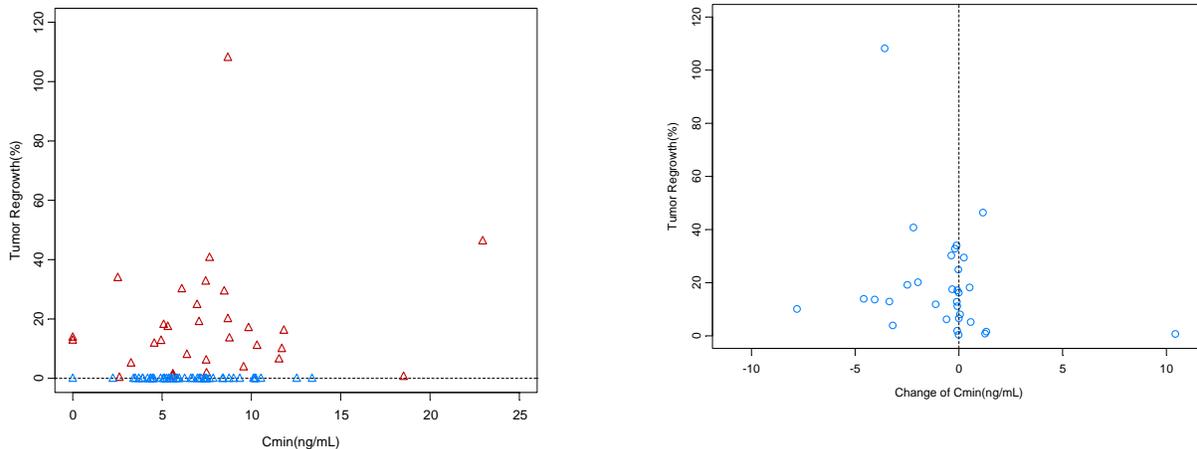
### *SEGA Tumor Rebound*

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 effectiveness 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.



**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	<a href="\\Cdsub1\evsprod\NDA203985\0000\m5\datasets\rad001m2301\analysis">\\Cdsub1\evsprod\NDA203985\0000\m5\datasets\rad001m2301\analysis</a>
C2485	apkpd.xpt aaev.xpt	<a href="\\Cdsub1\evsprod\NDA022334\0064\m5\datasets\rad001c2485\analysis">\\Cdsub1\evsprod\NDA022334\0064\m5\datasets\rad001c2485\analysis</a>

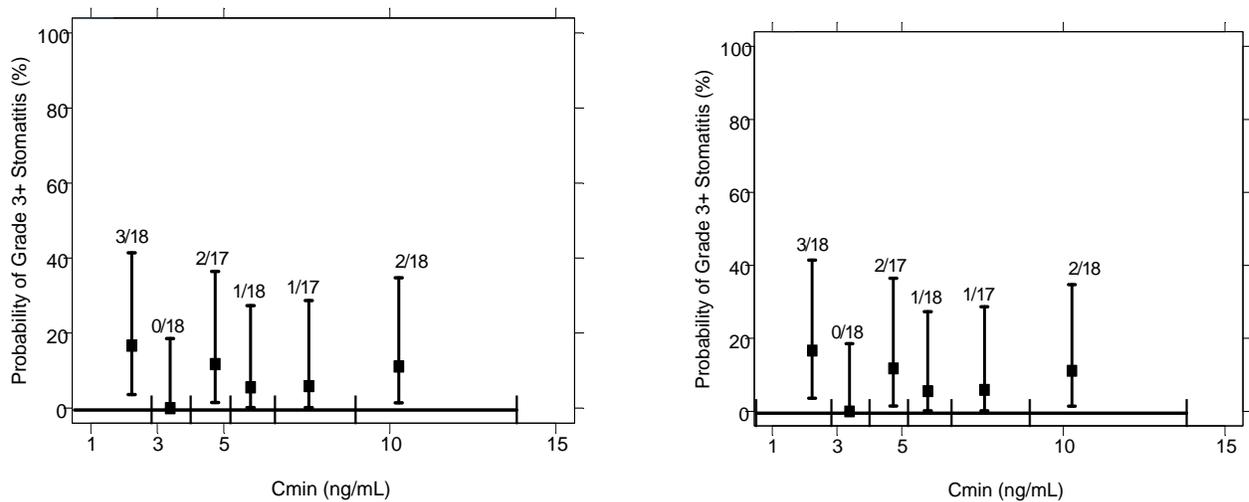
#### 4.2.2.4 Software

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. C<sub>min</sub> 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 C<sub>min</sub> 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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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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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

**BIOPHARMACEUTICS REVIEW**  
**Office of New Drug Quality Assessment**

<b>Application No.:</b>	NDA 203-985	<b>Reviewer:</b> Kareen Riviere, Ph.D.	
<b>Submission Dates:</b>	February 29, 2012; April 12, 2012; April 16, 2012; July 19, 2012		
<b>Division:</b>	Oncology Products 2	<b>Team Leader:</b> Angelica Dorantes, Ph.D.	
<b>Applicant:</b>	Novartis Pharmaceuticals	<b>Secondary Signature:</b> Sandra Suarez-Sharp, Ph.D.	
<b>Trade Name:</b>	Afinitor® DISPERZ™	<b>Date Assigned:</b>	March 8, 2012
<b>Generic Name:</b>	Everolimus tablets for oral suspension	<b>Date of Review:</b>	August 3, 2012
<b>Indication:</b>	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	<b>Type of Submission:</b> Original 505(b)(1) New Drug Application	
<b>Formulation/strengths:</b>	IR Tablets for oral suspension/ 2mg, 3mg, and 5mg		
<b>Route of Administration:</b>	Oral		

**SUBMISSION:**

This is a 505(b)(1) New Drug Application for immediate release dispersible tablets containing 2 mg, 3 mg, and 5 mg of everolimus. The proposed 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.

This submission includes a drug product development section, a dissolution development report with a proposed dissolution specification and acceptance criterion and comparative dissolution data supporting the BA/BE waiver request for the 2 mg and 3 mg strengths.

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criterion, as well as the acceptability of the BA/BE waiver request for the 2 mg and 3 mg strengths based on dissolution profile comparisons.

**A. Dissolution Method and Acceptance Criterion**

(b) (4)



(b) (4)

(b) (4)

**Kareen Riviere, Ph.D.**  
Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

**Sandra Suarez-Sharp, Ph.D.**  
Senior Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

cc: Dr. Angelica Dorantes, Dr. Richard Lostritto

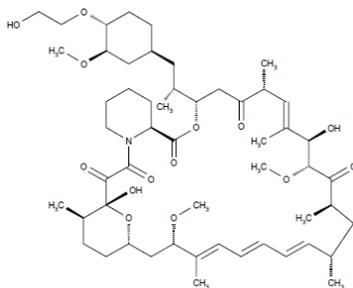
## ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

### 1. Background

Novartis is seeking approval for a pediatric-appropriate formulation of everolimus 2 mg, 3 mg, and 5 mg tablets. The Applicant has an approved IR tablet formulation (NDA 22334, 29-Oct-2010) on the market for the same proposed indication.

#### Drug Substance

Everolimus is a macrocyclic lactone with potent anti-proliferative and immunosuppressant properties which is derived by chemical modification from the natural product rapamycin. The structure of everolimus is shown in Figure 1.



**Figure 1.** Structure of everolimus

The solubility profile of everolimus is shown in Table 1. The drug substance is practically insoluble in water but is soluble in organic solvents. Additionally, it is unstable at temperatures above room temperature and is sensitive to light.

**Table 1.** Solubility Profile of Everolimus at 25±0.5°C

Solvent		Solubility % m/V [g/100 ml solution]
Methanol		>10 %
Ethanol		>10 %
Ethanol	95 %	>10 %
Isopropyl alcohol		>10 %
Ethanol 94 % / water	7 : 9	1.0 %
Acetone		>10 %
n-Octanol		10.1 %
Propylene glycol		>10 %
Hydrochloric acid	0.1 N	< 0.01 %
Buffer citrate (Titrisol™ MERCK)	pH 2.0	< 0.01 %
Buffer citrate (Titrisol™ MERCK)	pH 4.0	< 0.01 %
Buffer citrate (Titrisol™ MERCK)	pH 6.0	< 0.01 %
Buffer citrate (Titrisol™ MERCK)	pH 8.0	< 0.01 %
Buffer citrate (Titrisol™ MERCK)	pH 10.0	< 0.01 %
Acetonitrile		>10 %
Buffer pH 6.0 / sodium dodecylsulfate	0.4 %	0.6 %
Sodium dodecylsulfate	0.1 %	0.07 %
Sodium dodecylsulfate	0.2 %	0.3 %
Sodium dodecylsulfate	0.4 %	0.6 %
Water		< 0.01 %
Sodium chloride 0.9 % in water		< 0.01 %
Isopropyl acetate		>10 %
Ethyl acetate		>10 %
Ethyl acetate / n-heptane	4 : 6.5	2.3 %
Isopropyl acetate / heptane fractions	1 : 1	>10 %
n-Heptane		0.05 %
Acetonitrile / water 53 :47 (w/w)		>10 %
Isopropyl acetate / heptane fractions / water 785 :71 :15 (w/w) water saturated		>10 %

In the Applicant's April 16, 2012 submission they provided additional solubility data shown in Table 2.

**Table 2. Additional Solubility Data for Everolimus Drug Substance**

Solvent	Solubility after 48h by stirring at room temperature and HPLC [µg/ml]
Water	19
Phosphate buffer pH 4.5	14
Phosphate buffer pH 6.8	13

**Reviewer's Assessment:**

*The solubility of the drug substance is low in all the aqueous buffers tested.* (b) (4)

(b) (4)

**Drug Product**

RAD001 tablets are immediate release dosage forms for dispersion prior to oral administration. The manufacture of RAD001 2 mg, 3 mg and 5 mg tablets is (b) (4)

The composition of RAD001 tablets is shown in Table 3.

**Table 3. Composition of RAD001 2 mg, 3 mg and 5 mg Tablets**

Ingredient	Amount per 2mg tablet [mg]	Amount per 3mg tablet [mg]	Amount per 5mg tablet [mg]	Function	Reference to standards
(b) (4)	2.00	3.00	5.00	Active ingredient	Novartis monograph
(b) (4) Butylated hydroxytoluene/				(b) (4)	Ph. Eur., NF, JPE
Lactose monohydrate/ (b) (4)					Ph. Eur., NF, JP
Hypromellose (b) (4) (b) (4)					Ph. Eur., USP, JP
Mannitol (b) (4)					Ph. Eur., USP, JP
Cellulose microcrystalline/ (b) (4)					Ph. Eur., NF, JP
Croscopovidone					Ph. Eur., NF, JPE
Magnesium stearate					Ph. Eur., NF, JP
(b) (4) s/ Colloidal silicon dioxide/ (b) (4)					Ph. Eur., NF, JP
(b) (4) (b) (4)					Ph. Eur., USP
					Ph. Eur., NF
					Ph. Eur., NF
Tablet	250.00	375.00	625.00		

(b) (4)

**Reviewer's Assessment:**

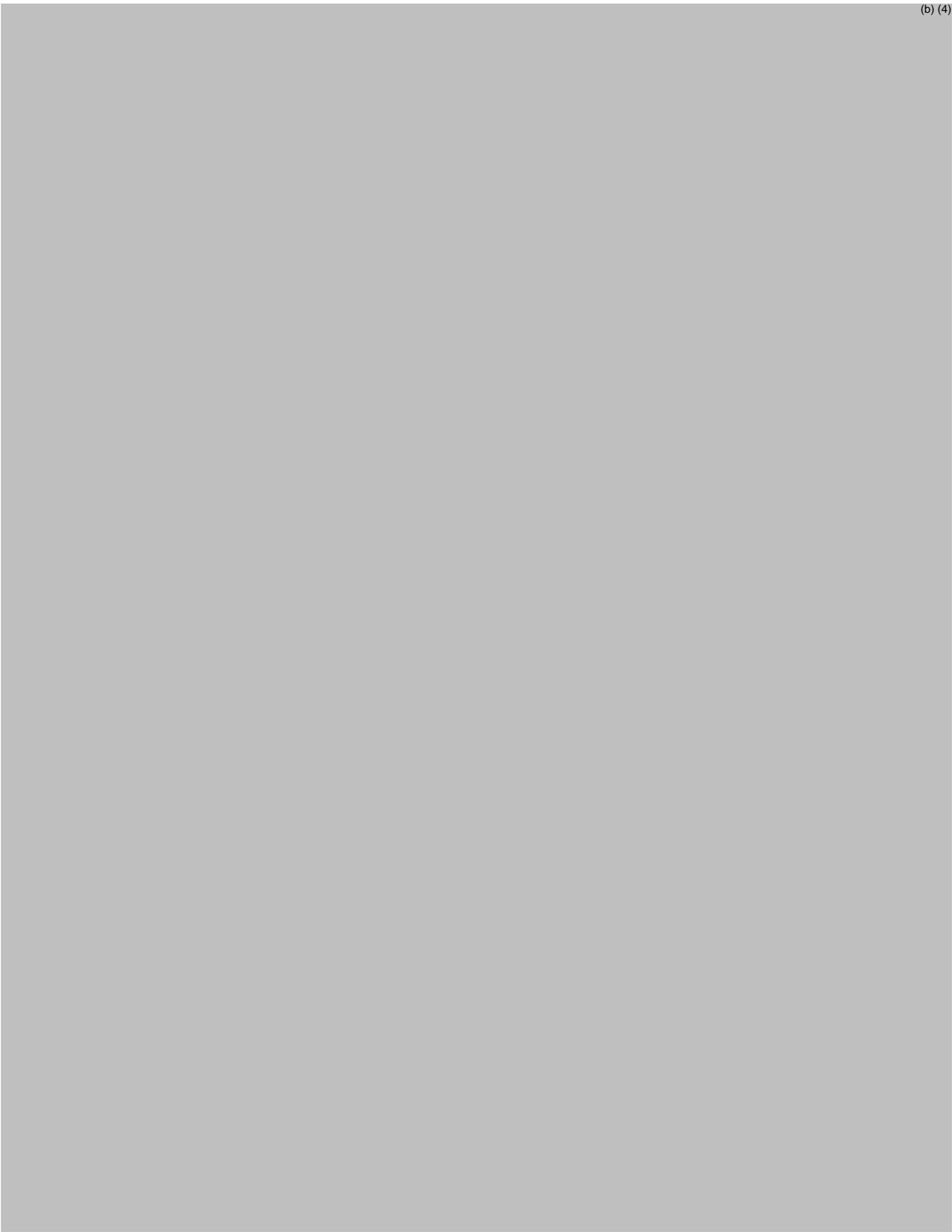
*The three proposed strengths are (b) (4) in active and inactive ingredients.*

(b) (4)

(b) (4)

(b) (4)





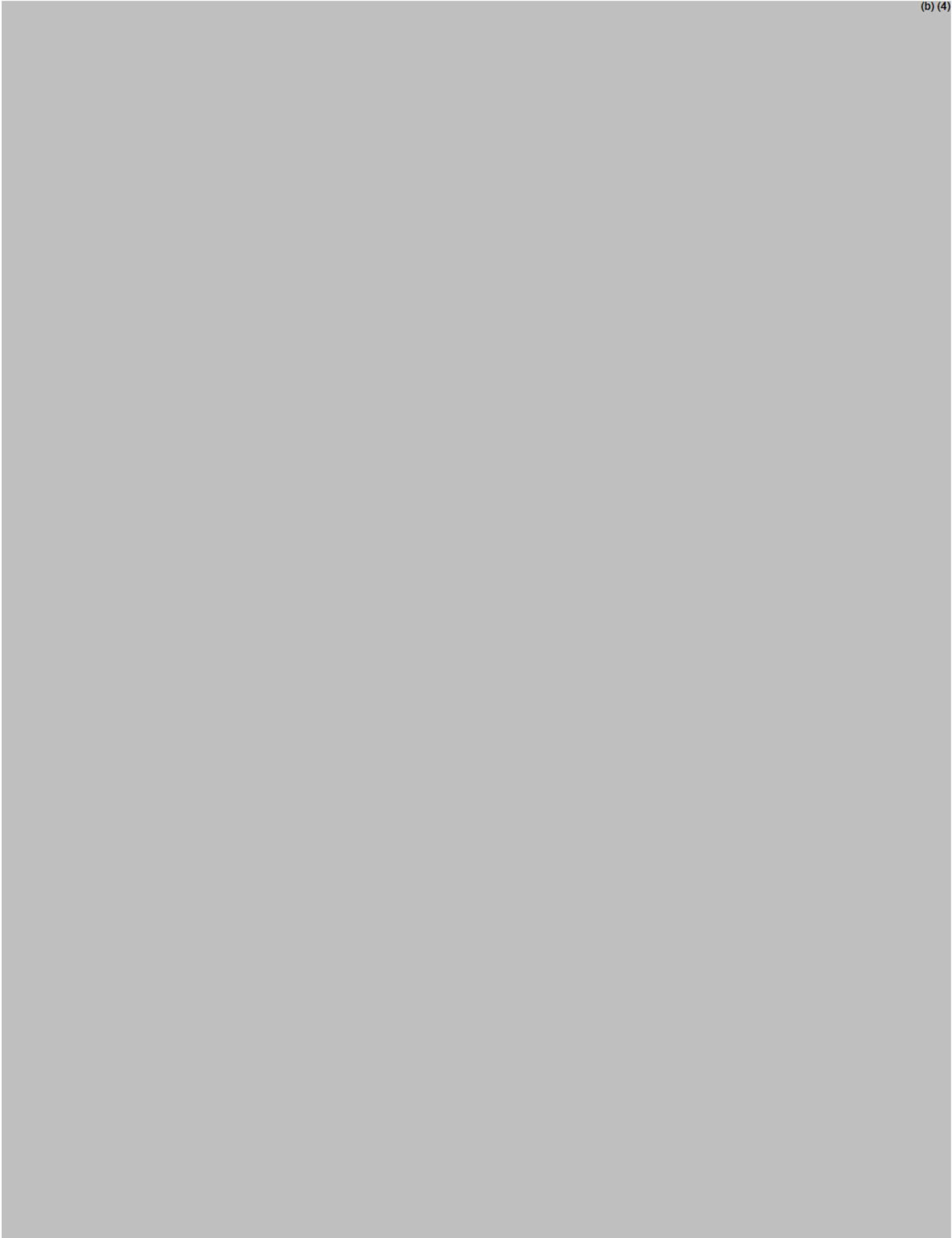


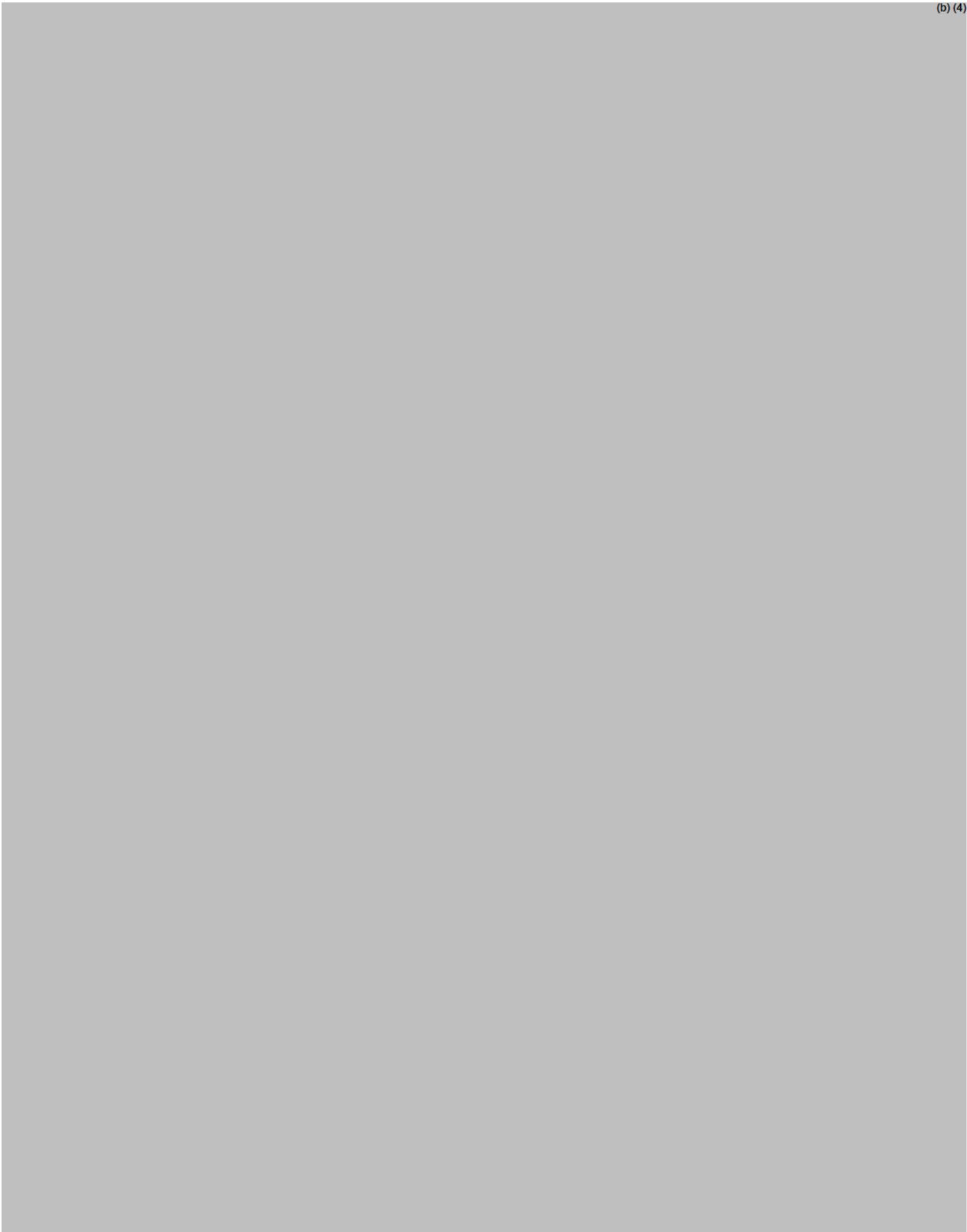
[Redacted] (b) (4)

***Reviewer's Assessment:***

[Redacted] (b) (4)

[Redacted] (b) (4)







**Reviewer's Assessment of the Dissolution Method:**

*The Applicant tested whether the proposed dissolution method can detect changes in three critical manufacturing variables: compression force, particle size distribution, and solid dispersion concentration (which affects particle size distribution). The data in Figures 12-16 show that the proposed method cannot discriminate changes in these variables.*

*The Applicant did not test the discriminating ability of phosphate buffer pH4.5. From the data in Figure 2 above, phosphate buffer pH4.5 appears to be discriminating and biorelevant since non-BE batches fail f2 testing*

*whereas BE batches pass f2 testing. 900 mL of pH.4.5 provides 2.5 times what is required in order to form a saturated solution. This is just short of the 3x recommendation by the dissolution guidance. Perhaps if the dissolution volume were 1000 mL, sink conditions can be fulfilled. Therefore, pH4.5 phosphate buffer should be used as the dissolution medium.*

*The following Biopharmaceutics comment was conveyed to the Applicant in an IR letter dated June 20, 2012.*

**FDA Comment 1**

Your proposed dissolution method is not discriminating and therefore not acceptable. We recommend that you use phosphate buffer pH 4.5 as your dissolution medium because it is biorelevant and discriminating (Figure 2-13 in 3.2.P.2 demonstrates that non-BE batches fail f2 testing in phosphate buffer pH 4.5. Figure 2-16 in 3.2.P.2 demonstrates that BE batches pass f2 testing in pH 4.5).

**Applicant's Response**

Novartis recognizes the Agency's concern with the proposed dissolution method. The current dissolution method using the pH 4.5 buffer has been used to establish comparative dissolution profiles of a clinical batch used in the bioequivalence studies X2105 and X2106. In order to qualify the method for routine Quality Control testing a full method development and validation program is required that complies with late phase requirements. To date, the pH 4.5 buffer method has only been used during development to evaluate a small number of batches therefore the data pool is very limited. Additional batches will need to be analyzed in order to verify the robustness of the method and to evaluate its suitability for routine quality control testing. Additional data are also needed for specification setting.

Novartis believes that the proposed method using water and 0.4% SDS is suitable for its intended use and is the best method to ensure consistent lot to lot quality at this time. Novartis would like to discuss options for further dissolution method development with the Agency and the potential for a post approval commitment to provide an updated method and specification.

*In a teleconference held with the Applicant on July 25, 2012, the Agency stated that the dissolution method would be accepted on an interim basis provided that the Applicant agrees to update the dissolution method as a post-marketing commitment. Refer to the PMR/PMC document in the Appendix for more details on the data/information the Applicant agreed to provide to the Agency after the action date.*

**3. Acceptance Criterion**

The proposed dissolution acceptance criterion is shown below.

Proposed Dissolution Acceptance Criterion

<b>Acceptance criterion</b>
Q = (b) (4) t 15 minutes

*The following Biopharmaceutics comment was conveyed to the Applicant in an IR letter dated March 19, 2012.*

**FDA Comment 2**

Provide the complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for the proposed product.

**Applicant's Response**

As requested the complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches is provided. The specification sampling time point was selected

**Reviewer's Assessment:**

*The Applicant provided 12 month stability data for three batches of each strength using the proposed dissolution method. All batches pass the proposed acceptance criterion. However, since the Team recommends that the dissolution method be modified, it follows that the dissolution acceptance criterion should also be modified to suit the revised method. The following Biopharmaceutics comment was conveyed to the Applicant in an IR letter dated June 20, 2012.*

**FDA Comment 2**

Provide complete dissolution profile data (raw data and mean values) using phosphate buffer pH 4.5 for the clinical batches of the proposed product.

**Applicant's Response**

Please note that there was only one batch (X121EG) of Tablets for Oral Suspension used in the two clinical studies X2105 and X2106 (bioequivalence studies). As requested, the dissolution profile including raw data as well as mean values and standard deviations of this batch are provided using the phosphate buffer pH 4.5.

Dissolution Rate in Phosphate Buffer pH 4.5, 900 ml				
RAD001 (% release) Batch X121EG				
Tablet	10 min	15 min	20 min	30 min (b) (4)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Average	68.02	75.50	79.95	84.60
RSD (%)	1.88	2.24	1.60	0.96

*In a teleconference held with the Applicant on July 25, 2012 the Agency stated that the dissolution acceptance criterion would be accepted on an interim basis provided that the Applicant agrees to update the dissolution acceptance criterion as a post-marketing commitment. Refer to the PMR/PMC document in the Appendix for more details on the data/information the Applicant agreed to provide to the Agency after the action date.*

**4. Biowaiver Request for the 2mg and 3 mg Strengths**

The Applicant is seeking a waiver for in-vivo bioavailability studies for the proposed 2 mg and 3 mg strengths of the proposed product in accordance with 21 CFR 320.22(d)(2).

The Applicant compared the dissolution profiles of the 2 mg and 3 mg strengths to the 5mg strength in three media (water + 0.4% SDS, phosphate buffer pH 4.5, and phosphate buffer pH 6.8) using the paddle method (refer to Figures 17 and 18). Since RAD001 is not stable enough in acidic media up to pH 3 during the analysis of the samples, the Applicant did not conduct comparative dissolution studies at pH 1. Instead the Applicant used water + 0.4% SDS as the third dissolution medium.



In water + 0.4% SDS, all three dosage strengths released more than (b) (4) drug in 15 minutes. Thus, the f2 value cannot be calculated. The Applicant calculated an f2 value of 65 when comparing the dissolution profiles of 2 mg and 5 mg strengths in pH 4.5 buffer, and an f2 value of 72 when comparing the dissolution profiles of 3 mg and 5 mg strengths in pH 4.5 buffer. Additionally, the Applicant calculated f2 value of 58 when comparing the dissolution profiles of 2 mg and 5 mg strengths in pH 6.8 buffer, and an f2 value of 57 when comparing the dissolution profiles of 3 mg and 5 mg strengths in pH 6.8 buffer.

**Reviewer’s Assessment:**

***The Applicant requested a biowaiver for the 2 mg and 3 mg strengths. According to the CFR 320.22(d)(2) requirements and the BA/BE Guidance, a biowaiver may be granted for the lower strength products as long as all of the following conditions are met:***

- ***The lower strengths and highest strength product have the same dosage form;***
- ***There is BA data for the highest strength;***
- ***The lower strength products are proportionally similar in active and inactive ingredients to the highest strength product; and***
- ***The lower strengths and highest strength product have similar dissolution profiles in three media (pH 1.2, 4.5, and 6.8).***

***The lower strengths are in the same dosage form as the 5mg strength. The 2 mg and 3 mg strengths are proportionally similar in active and inactive ingredients (refer to Table 1). There is BA/BE data for the 5mg strength (refer to Tables 4 and 5). Additionally, the lower strengths and highest strength product have f2 similar dissolution profiles in water + 0.4% SDS, pH 4.5 buffer, and pH 6.8 buffer (refer to Reviewer’s Tables 1-3) . It is acceptable to substitute water + 0.4% SDS for pH 1.2 buffer since the drug substance is not soluble in acidic media up to pH 3.***

**Reviewer’s Table 1. f2 Similarity Factor in Water + 0.4% SDS**

Strength Comparison	Applicant’s f2 value	Reviewer’s f2 Value
2 mg vs. 5mg	-	-
3 mg vs. 5mg	-	-

**Reviewer’s Table 2. f2 Similarity Factor in pH 4.5**

Strength Comparison	Applicant’s f2 value	Reviewer’s f2 Value
2 mg vs. 5mg	65	67
3 mg vs. 5mg	72	72

**Reviewer’s Table 3. f2 Similarity Factor in pH 6.8**

Strength Comparison	Applicant’s f2 value	Reviewer’s f2 Value
2 mg vs. 5mg	58	58
3 mg vs. 5mg	57	58

***The Applicant has provided sufficient data to meet the requirements of CFR 320.22(d)(2). Therefore, a biowaiver is granted for the 2 mg and 3 mg strengths.***

**APPENDIX**

**PMR/PMC Development Template**

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

---

NDA/BLA #	NDA 203985	
Product Name:	Afinitor Disperz® Tablet for Oral Suspension	
PMR/PMC Description:	Dissolution Method Development Report and Prior Approval Supplement (including the revised dissolution method and information to support the dissolution acceptance criterion)	
PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>N/A</u>
	Study/Trial Completion:	<u>N/A</u>
	Final Report Submission:	<u>02/29/2013</u>
	Other: Prior Approval Supplement Submission:	<u>08/29/2013</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Applicant will conduct additional studies to develop a discriminating dissolution method. In an email to Ms. Jewell Martin (ONDQA Product Quality Regulatory Project Manager) dated July 25, 2012, the Applicant agreed to submit a dissolution development report to the Agency by 02/29/2013. (b) (4)

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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KAREEN RIVIERE  
08/03/2012

SANDRA SUAREZ  
08/03/2012

**CLINICAL PHARMACOLOGY  
FILING FORM/CHECKLIST FOR NDA # 203-985**

**Office of Clinical Pharmacology**

**New Drug Application Filing and Review Form**

***General Information About the Submission***

	Information		Information
<b>NDA/BLA Number</b>	203-985	<b>Brand Name</b>	Afinitor DISPERZ
<b>OCP Division (I, II, III, IV, V)</b>	V	<b>Generic Name</b>	Everolimus
<b>Medical Division</b>	Oncology	<b>Drug Class</b>	mTOR inhibitor
<b>OCP Reviewer</b>	Jian Wang, Ph.D.	<b>Indication(s)</b>	Tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA)
<b>OCP Team Leader</b>	Hong Zhao, Ph.D.	<b>Dosage Form</b>	2-mg, 3-mg, and 5-mg dispersible tablets
<b>Pharmacometrics Reviewer</b>	Jian Wang, Ph.D.	<b>Dosing Regimen</b>	4.5 mg/m <sup>2</sup> /day
<b>Pharmacometrics Team Leader</b>	Christine Garnett, Pharm.D.		
<b>Pharmacogenomics Reviewer</b>			
<b>Pharmacometrics Team Leader</b>			
<b>Date of Submission</b>	02/29/2012	<b>Route of Administration</b>	Oral
<b>Estimated Due Date of OCP Review</b>		<b>Sponsor</b>	Novartis
<b>Medical Division Due Date</b>	06/29/2012	<b>Priority Classification</b>	Priority
<b>PDUFA Due Date</b>	8/27/2012		

***Clin. Pharm. and Biopharm. Information***

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
<b>Mass balance:</b>				
<b>Isozyme characterization:</b>				
<b>Blood/plasma ratio:</b>				
<b>Plasma protein binding:</b>				
<b>Pharmacokinetics -</b>				
<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:	X	2		C2485, M2301
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

<b>Drug-drug interaction studies -</b>				
	In-vivo effects on primary drug:			
	In-vivo effects of primary drug:			
	In-vitro:			
<b>Subpopulation studies -</b>				
	ethnicity:			
	gender:			
	pediatrics:			
	geriatrics:			
	renal impairment:			
	hepatic impairment:			
<b>PD -</b>	QT Study:			
	Phase 2:	X	1	C2485
	Phase 3:	X	1	M2301
<b>PK/PD -</b>				
	Phase 1 and/or 2, proof of concept:	X	1	C2485
	Phase 3 clinical trial:	X	1	M2301
<b>Population Analyses -</b>				
	Data rich:			
	Data sparse:	X		M2301 (Cmin, C2h)
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
	solution as reference:			
	alternate formulation as reference:			
<b>Bioequivalence studies -</b>				
	traditional design; single / multi dose:	X	2	X2105, X2106
	replicate design; single / multi dose:			
<b>Food-drug interaction studies</b>				
		X		
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
	<b>Pediatric development plan</b>	X	2	M2301, C2485
	<b>Literature References</b>	X		
<b>Total Number of Studies</b>			4	M2301, C2485, X2105, X2106

On **initial** review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			X2105, X2106
2	Has the applicant provided metabolism and drug-drug interaction information?				
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?				
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?				
5	Has a rationale for dose selection been submitted?	X			

6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?				
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	X			The sponsor requested pediatric exclusivity determination
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X			M2301, C2485, X2105, X2106
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant. **N/A**

Jian Wang, Ph.D.	04/02/2012
<b>Clinical Pharmacology Reviewer</b>	<b>Date</b>
Hong Zhao, Ph.D.	04/02/2012
<b>Clinical Pharmacology Team Leader</b>	<b>Date</b>

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/s/  
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JIAN WANG  
04/05/2012

HONG ZHAO  
04/05/2012  
I concur.

**BIOPHARMACEUTICS FILING REVIEW**  
**Office of New Drug Quality Assessment**

<b>Application No.:</b>	NDA 203-985	<b>Reviewer:</b> Kareen Riviere, Ph.D.	
<b>Submission Date:</b>	February 29, 2012		
<b>Division:</b>	Oncology Products 2	<b>Acting Biopharmaceutics Supervisory Lead:</b> Angelica Dorantes, Ph.D.	
<b>Sponsor:</b>	Novartis Pharmaceuticals	<b>Secondary Signature:</b> Sandra Suarez-Sharp, Ph.D.	
<b>Trade Name:</b>	Afinitor® DISPERZ™	<b>Date Assigned:</b>	March 8, 2012
<b>Generic Name:</b>	Everolimus	<b>Date of Review:</b>	March 16, 2012
<b>Indication:</b>	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	<b>Type of Submission:</b> Original New Drug Application	
<b>Formulation/strengths:</b>	Dispersible tablets/2mg, 3mg and 5mg		
<b>Route of Administration:</b>	Oral		

**SUBMISSION:**

This is a 505(b)(1) New Drug Application for immediate release dispersible tablets containing 2 mg, 3 mg, and 5 mg of everolimus. The proposed 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. The Applicant has an Afinitor® (everolimus) IR tablet formulation (NDA 22-334; approved October 29, 2010) on the market for the same proposed indication.

**BIOPHARMACEUTIC INFORMATION:**

This submission includes a drug product development section, a dissolution development report with a proposed dissolution specification and acceptance criterion, BA/BE data comparing the 5 mg strength to the approved IR 1 mg and 5 mg tablets, and comparative dissolution data supporting the BA/BE waiver request for the 2 mg and 3 mg strengths.

The proposed dissolution method:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
(b) (4)				

The proposed acceptance criteria:

<b>Acceptance criterion</b>
Q = (b) (4) t 15 minutes

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criterion, as well as the acceptability of the BA/BE waiver request for the 2

mg and 3 mg strengths based on dissolution profile comparisons.

To aid in the review of the Applicant's submission, the following will be conveyed/requested:



**RECOMMENDATION:**

The ONDQA/Biopharmaceutics team has reviewed NDA 203-985 for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission. The above comments will be conveyed to the sponsor in an Information Request letter.

**Kareen Riviere, Ph.D.**

Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

**Sandra Suarez-Sharp, Ph.D.**

Senior Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

cc: Angelica Dorantes, Ph.D.

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/s/  
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KAREEN RIVIERE  
03/16/2012

SANDRA SUAREZ  
03/16/2012