CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203985
Priority or Standard	Priority
Submit Date(s)	February 29, 2012
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Division / Office	DOP2/OHOP
Reviewer Name(s)	Martha Donoghue, MD Suzanne Demko, PA (CDTL)
Review Completion Date	August 3, 2012
Established Name	everolimus
(Proposed) Trade Name	Afinitor Disperz
Therapeutic Class	m-TOR Inhibitor
Applicant	Novartis
Formulation(s)	2 mg, 3 mg, and 5 mg tablets for oral suspension
Dosing Regimen	Starting dose 4.5 mg/m^2/day with dose adjustments as needed to achieve and maintain everolimus trough concentrations between 5-15 ng/mL
Indication(s)	Subependymal Giant Cell Astrocytoma (SEGA) that requires therapeutic intervention

	but cannot be curatively resected
Intended Population(s)	Children and adults with SEGA associated with TSC

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

We recommend approval of new drug application (NDA) 203985 for the indication listed below:

Afinitor® and Afinitor Disperz® are indicated in pediatric and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.

This NDA also revises the product label to include the following results in patients with SEGA:

- updated results from Study CRAD001C4285 (Study C2485). Study C2485 is the single arm study (n = 28) that provided data supporting the October 29, 2010 accelerated (Subpart H) approval of Afinitor (everolimus) for the treatment of patients with SEGA associated with TSC who require therapeutic intervention but are not candidates for curative surgical resection (NDA 22,334, Supplement 006)

- results of the primary analysis of Study CRAD001M2301 (Study M2301), a randomized trial comparing the SEGA response rate in patients receiving everolimus to the SEGA response rate in patients receiving placebo (n = 117).

The data submitted to this NDA do not reflect patient follow-up of sufficient duration to fulfill the outstanding postmarketing requirements necessary to convert the status of this marketing authorization from accelerated approval to full approval.

This NDA also included outstanding analyses and data required to fulfill the terms of the Written Request issued by FDA on April 1, 2010 and a request for Pediatric Exclusivity Determination. Based on review of the data submitted, the review teams for this NDA concluded that the Applicant fulfilled the requirements of the Written Request. On July 10, 2012, the NDA review teams met with the FDA Pediatric Exclusivity Board and formally recommended that pediatric exclusivity be awarded to the Applicant. After reviewing the terms of the Pediatric Written Request and a summary of the contents of NDA 203985, the Pediatric Exclusivity Board concurred with this recommendation.

1.2 Risk Benefit Assessment

On October 29, 2010, FDA granted accelerated (Subpart H) approval to Afinitor supplemental New Drug Application (sNDA) 22,334, Supplement 006 for the treatment of patients with SEGA associated with TSC who require therapeutic intervention but are not candidates for curative surgical resection. Accelerated approval was based on safety and efficacy data from a prospective, single arm, single institution study (Study C2485).

This NDA included data to support the approval of a new dosage form of everolimus, Afinitor Disperz (everolimus tablets for oral suspension) for use in patients with SEGA. Development of an age-appropriate pediatric formulation is required to fulfill the terms of the pediatric Written Request for Afinitor issued by FDA on April 1, 2010. Afinitor Disperz (everolimus tablets for oral suspension) is available in 2 mg, 3 mg, and 5 mg strengths.

The clinical, clinical pharmacology, and chemistry and manufacturing review teams concluded that Afinitor Disperz is an age-appropriate formulation for pediatric patients. Previously approved Afinitor labeling included instructions for preparation of a suspension in 30 mL water using Afinitor Tablets for oral administration, which are available in 2.5 mg, 5 mg, 7.5 mg, and 10 mg unscored tablets. Afinitor Disperz offers several advantages to young pediatric patients who are unable to swallow Afinitor Tablets. First, Afinitor Disperz is available in smaller dosage increments compared to the Afinitor tablets, thus permitting administration of a lower dose (2 mg) and the capacity for 1 mg incremental dose adjustments. Additionally, the Applicant provided data demonstrating that preparation of a suspension with Afinitor Disperz requires less time (less than 3 minutes for Afinitor Disperz compared to approximately 6 minutes for Afinitor), less water (5 ml for Afinitor Disperz compared to 30 ml for Afinitor), and less manipulation compared to the previously-labeled procedures for preparation of a suspension with Afinitor Tablets.

This NDA also included the following data and analyses to fulfill the outstanding requirements of the Pediatric Written Request issued by FDA on April 1, 2010:

- Data from two pharmacology studies conducted in healthy adult subjects to establish bioequivalence between a single 5 mg tablet for oral suspension and five of the 1 mg market formulation (MF) tablets used in Study M2301 (Study X2105) and between the 5 mg tablet for oral suspension and the 5 mg “final market image” tablet (FMI) currently approved for commercial use and also used in study C2485 (X2106).
- Updated data and clinical study report from study C2485 (data cut-off December 30, 2010 compared to December 9, 2009 data cut-off used for the primary analysis).

- Data and clinical study report from the primary analysis of Study M2301, a randomized trial in 117 pediatric and adult patients with SEGA associated with TSC.

After reviewing the data from Study X2105 and X2106, the clinical pharmacology review team concluded that everolimus tablets for oral suspension were not bioequivalent to the MF or FMI formulations. Study X2105 and Study X2106 demonstrated that the formulations are comparable with respect to Area Under the Curve (AUC), but the C_{max} of the everolimus tablets for oral suspension was lower compared to the C_{max} of the MF and FMI tablets. However, the clinical pharmacology review teams predicted that the C_{min} of the everolimus tablets for oral suspension, MF tablets, and FMI tablets would be similar at steady data based on analysis of the data. Additionally, the clinical and clinical pharmacology review teams concluded that the lower C_{max} of the everolimus tablets for oral suspension was not likely to affect efficacy in patients with SEGA because dosing is based on therapeutic drug monitoring of everolimus serum trough levels. The FDA clinical and clinical pharmacology review teams ultimately decided that the bioavailability of everolimus tablets for oral suspension was sufficiently similar to the bioavailability of the formulations approved for commercial use (FMI) and the formulations used in prior clinical trials of everolimus (MF) in patients with SEGA to support approval of Afinitor Disperz (everolimus tablets for oral suspension).

Study C2485 provided the basis for the accelerated approval of everolimus for the treatment of patients with SEGA who require therapeutic intervention but are not candidates for curative surgical resection. Study C2485 was conducted in 28 patients with TSC who had at least one SEGA tumor with evidence of serial growth on MRI. In this study, patients received adult formulation everolimus tablets at a dose of 3 mg/m^2/day, with subsequent dose adjustments to achieve and maintain an everolimus trough level of 5-15 ng/mL. At the time of accelerated approval, the median duration of treatment was 24.4 months (range 4.7 months to 37.3 months). The primary endpoint of Study C2485 was the change from baseline in the volume of the primary SEGA tumor at 6 months, as determined by central radiology review. At 6 months, 9 of 28 patients (32%, 95% CI: 16% - 52%) had at least a 50% reduction in tumor volume of their largest SEGA tumor. The median duration of response for the 9 responding patients was 266 days (range: 97 to 946 days).

Overall, the updated safety and efficacy data from Study C2485 and primary analyses of Study M2301 submitted to this NDA are consistent with the results of the primary analysis of Study C2485 that provided the basis for the 2010 accelerated approval. Additionally, the new clinical data from these studies enable better characterization of the consistency of objective SEGA tumor

response, durability of this response, and adverse event profile of everolimus in children and adults with TSC who require treatment for SEGA.

FDA clinical reviewers of NDA 22334, Supplement 6 recommended the 2010 accelerated approval of everolimus for the treatment of SEGA, noting that the primary analysis of Study C2485 "demonstrated a favorable benefit:risk profile for everolimus treatment in patients with subependymal giant cell astrocytoma associated with tuberous sclerosis (TS)." FDA reviewers considered the results of Study C2485 to be "clinically significant, especially for SEGAs whose anatomic location predisposes them to have the propensity to cause obstruction of CSF circulation and/or pressure effects on the surrounding brain tissue." The updated data from Study C2485, which reflect an additional year of follow-up of the 25 patients who remained on everolimus at the time of the original analysis, provide additional evidence of the durability of response and tolerability of everolimus in this patient population. As of December 31, 2010, the median duration of treatment was 34.2 months (range 4.7 to 47.1 months), and the median duration of response for the 9 patients who exhibited an objective response was 360 days (range 97 to 1191 days). Seven of these nine patients had maintained a ≥ 50% reduction in SEGA volume at the time of the updated data cut-off.

Study M2301 provides additional evidence of a favorable benefit:risk profile for everolimus in the treatment of patients with SEGA that requires therapeutic intervention but cannot be curatively resected. Study M2301 was a randomized (2:1), double-blind, placebo-controlled trial of everolimus conducted in 117 pediatric and adult patients with SEGA and TSC. Eligible patients had at least one SEGA lesion ≥ 1 cm in longest diameter based on local MRI assessment and one or more of the following: serial radiological evidence of SEGA growth, a new SEGA lesion ≥ 1 cm in longest diameter, or new or worsening hydrocephalus. Patients randomized to the treatment arm received everolimus 1 mg MF tablets at a starting dose of 4.5 mg/m^2/day, with subsequent dose adjustments as needed to achieve and maintain everolimus trough concentrations of 5 to 15 ng/mL. Patients received everolimus or matched placebo until disease progression or unacceptable toxicity. MRI scans were obtained at baseline, 12, 24, and 48 weeks, and annually thereafter. The primary efficacy endpoint was SEGA response rate based on independent central radiology review. SEGA response was defined as a ≥ 50% reduction in the sum of the SEGA volume of target lesions relative to baseline, in the absence of unequivocal worsening of non-target SEGA lesions, a new SEGA lesion ≥ 1 cm, or new or worsening hydrocephalus. Analysis of SEGA response rate was limited to the blinded treatment period which ended 6 months after the last patient was randomized.

A total of 78 patients were randomized to everolimus and 39 patients were randomized to placebo. The median age of patients enrolled was 9.5 years (range 0.8 to 26 years).

The SEGA response rate was statistically significantly higher in everolimus-treated patients. There were 27 (35%) patients with SEGA responses in the everolimus arm and no SEGA responses in the placebo arm ($p<0.0001$; 95% CI: 24%, 46% for the everolimus arm and 0%, 9% for the placebo arm). At the time of the primary analysis, the median duration of response was 5.3 months (range 2.1 to 8.4 months). With a median follow-up of 8.4 months, SEGA progression was observed in 6 of 39 (15.4%) patients in the placebo arm; no patients in the everolimus arm exhibited SEGA progression.

At the proposed dose and schedule, the safety profile of everolimus in children and adult patients with SEGA enrolled in Study C2485 and Study M2301 was generally similar to that previously described in the approved label for Afinitor. The most common adverse event in both studies was stomatitis. In both studies, the rate of patient discontinuations was low and there were no patient deaths reported for either study.

In Study M2301, no adverse reactions resulted in discontinuation of everolimus during the double-blind treatment period. Dose interruptions or reductions due to adverse reactions occurred in 56% of everolimus-treated patients. The most common adverse reaction leading to dose adjustment was stomatitis. The most common adverse reactions reported for everolimus (incidence ≥ 20%) were: stomatitis (62%); pyrexia (23%); anxiety, aggression, or other behavioral disturbance (21%); and rash (21%). The most common Grade 3-4 adverse reactions (incidence ≥ 2%) were stomatitis (9%, all Grade 3), pyrexia (6%, all Grade 3), pneumonia (3%), gastroenteritis (4%), aggression (3%), agitation (3%), and amenorrhea (3%). The most common key laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia and elevated partial thromboplastin time. The most common Grade 3-4 laboratory abnormality (incidence ≥ 3%) was neutropenia (9%). Serious adverse events (SAEs) were reported for 19 (24%) of patients in the everolimus group and 5 (13%) patients in the placebo group during the double blind treatment period. Infections were the most common type of serious adverse event.

In summary, the data submitted to this NDA support the approval of Afinitor Disperz for the treatment of pediatric and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected. Additionally, the data and analyses submitted by the Applicant fulfill the terms of the Pediatric Written Request for Afinitor; therefore, Pediatric Exclusivity has been granted to the Applicant. Finally, the updated data from Study C2485 and

primary analysis of Study M2301 support a favorable benefit:risk assessment for the treatment of patients with SEGA that requires therapeutic intervention but cannot be curatively resected.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

The clinical team does not recommend additional postmarket requirements or commitments based upon review of this application. At the time of accelerated approval of Afinitor for the treatment of patients with SEGA associated with TSC, the following post market requirements were established under 21 CFR 314.510 to further verify and describe clinical benefit of everolimus in the treatment of patients with SEGA associated with TSC:

PMR 1700-1:

Submit the final report (at least 4 years of follow-up) and datasets from M2301, a randomized, double-blind, placebo-controlled, multi-center phase 3 trial evaluating treatment with everolimus versus placebo in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

The Applicant agreed to conduct this trial according to the following schedule:
Final Protocol Submission: January 2011
Trial Completion: September 2014
Final Report and Dataset Submission: March 2015.

PMR 1700-2:

Submit the long-term (at least 5 years) follow-up efficacy and safety data from C2485, a single-arm, single-institution, phase 2 trial evaluating treatment with everolimus in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

The Applicant agreed to conduct this trial according to the following schedule:
Final Protocol Submission: March 2011
Trial Completion: March 2014
Final Report and Dataset Submission: November 2014.

Additionally, under Section 505(o)(3), the Applicant is required to conduct the following postmarketing studies and clinical trials to assess the long-term effects of everolimus on the growth and development of pediatric patients:

PMR 1700-3:
To evaluate the potential for serious risk of adverse long-term effects of Afinitor® (everolimus) on growth for pediatric patients, submit long-term follow-up data on patients enrolled on M2301, a randomized, double-blind, placebo-controlled, multi-center phase 3 trial evaluating treatment with Afinitor® (everolimus) versus placebo in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

All patients must be evaluated for growth and development milestones annually while still treated in the extension phase of M2301 (minimum of 4 years after randomization of the last patient). Evaluations must include the following: growth as measured by weight, height (measured with a stadiometer), height standard deviation scores (SDS), height velocity, height velocity SDS, age at thelarche (females), age at adrenarche (males), age at menarche (females), and Tanner Stage progression. Results of each evaluation must be documented. Luteinizing and follicle stimulating hormones (LH, FSH), and testosterone levels in boys and LH, FSH and estradiol levels in girls must be measured in patients who have not developed secondary sexual characteristics by age 13 in girls and 14 in boys. Descriptive statistics (including mean and standard deviation values) of on-study data for growth velocity must be presented. Growth velocity during the trial should be compared with growth velocity at baseline (if pre-baseline data are available). Provide analyses of height and weight data that assess measures of central tendency and outlier analyses using height and weight z-scores.

The Applicant agreed to conduct this trial according to the following schedule:
Final Protocol Submission: January 2011
Trial Completion Date: September 2014
Final Report and Dataset Submission: March 2015.

PMR 1700-4:
To evaluate the potential for serious risk of adverse long-term effects of Afinitor® (everolimus) on growth for pediatric patients, submit long-term follow-up data on patients enrolled on C2485, a single-arm, single-institution, phase 2 trial evaluating treatment with Afinitor® (everolimus) in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

All patients must be evaluated for growth and development milestones annually while still treated in the extension phase of C2485 (at least 5 years). Evaluations must include the following: growth as measured by weight, height (measured with a stadiometer), height standard deviation scores (SDS), height velocity, height

velocity SDS, age at thelarche (females), age at adrenarche (males), age at menarche (females), and Tanner Stage progression. Luteinizing and follicle stimulating hormones (LH, FSH), and testosterone levels in boys and LH, FSH and estradiol levels in girls must be measured in patients who have not developed secondary sexual characteristics by age 13 in girls and 14 in boys. Descriptive statistics (including mean and standard deviation values) of on-study data for growth velocity must be presented. Growth velocity during the trial should be compared with growth velocity at baseline (if pre-baseline data are available). Provide analyses of height and weight data that assess measures of central tendency and outlier analyses using height and weight z-scores.

The Applicant agreed to conduct this trial according to the following schedule:
Final Protocol Submission: March 2011
Trial Completion Date: March 2014
Final Report and Dataset Submission: November 2014.

2 Introduction and Regulatory Background

Tuberous sclerosis Complex (TSC) is an autosomal dominant condition caused by inherited or sporadic mutations of the TSC1 or TSC2 genes. Patients with TSC typically develop hamartomatous tumors in multiple organ systems, including the central nervous system, lung, kidney, and skin. TSC affects approximately 1 in 6,000 to 10,000 live births, 25,000 to 40,000 people in the United States, and 1 to 2 million people worldwide[1,2,3].

The pathophysiology of TSC remains incompletely understood. However, it is known that the characteristic features of TSC arise due to aberrant activation of cellular pathways normally regulated by hamartin and tuberin. Hamartin and tuberin, encoded by the TSC1 and TSC2 genes, respectively, form a tumor suppressor complex within the cell that acts via several intermediate cellular signaling pathways. By promoting the conversion of Rheb (Ras homologue enriched in brain) from its active GTP-bound state into an inactive GDP-bound state, the hamartin-tuberin complex inhibits activity of the mammalian target of Rapamycin (mTOR) pathway. mTOR is a major effector of cell growth. The signs and symptoms of TSC arise from constitutive activation of the mTOR pathway resulting from upregulation of RHEB due to dysfunctional activity of the hamartin/tuberin complex [3, 4].

Although the genetic mutations resulting in TSC manifestations can be identified by laboratory tests, the diagnosis of TSC is based on clinical criteria established at the 1998 Tuberous Sclerosis Complex Consensus Conference[5]. At this conference, the revised diagnostic criteria for TSC were subdivided into “major” and “minor” features:

The following criteria are considered “major features” of TSC:
- Facial angiofibromas or forehead plaques
- Three or more hypomelanotic macules
- Nontraumatic ungula or periungual fibromas
- Shagreen patch (connective tissue nevus)
- Multiple retinal nodular hamartomas
- Cortical tuber
- Subependymal nodules
- Subependymal giant cell astrocytoma (SEGA)
- Cardiac rhabdomyoma
- Lymphangioleiomyomatosis (also known as lymphangiomyomatosis)
- Renal angiomyolipoma.

The following criteria are considered “minor features” of TSC:
- Multiple randomly-distributed pits in dental enamel
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter radial migration lines
- Gingival fibromas
- Non-renal hamartomas
- Retinal achromic patch
- “Confetti” skin lesions (multiple 1 to 2 mm hypomelanotic macules)
- Multiple renal cysts.

The definitive diagnosis of TSC requires the presence of two major features. The only exception to this rule is in some women who have angiomyolipomas of the kidney associated with pulmonary lymphangiomyomatosis but no other TSC-related features and are not considered to have TSC. Children with one major plus one minor feature are classified as having probable TSC, while those with one major feature only, or two or more minor features but no major features are classified as possible TSC[3, 5, 6, 7].

SEGAs, classified as WHO Grade I tumors by histology, are generally characterized as discrete, slow growing tumors with low proliferative potential[8]. Diagnosis of SEGA is based on clinical and radiological findings. SEGA are typically slow-growing tumors that usually become symptomatic after causing obstructive hydrocephalus; this natural history has led to recommendations for periodic radiological evaluation of patients with SEGA[9,10,11,12].

Surgery is potentially curative. However, due to the location of SEGA tumors, surgery is not always possible. SEGAs are usually resected if they exhibit progressive growth, cause hydrocephalus or cause other symptoms. Although

there currently are no definitive guidelines regarding the optimal timing for surgical intervention for SEGA, experts generally recommend intervention when SEGA progression is documented by serial scans[13].

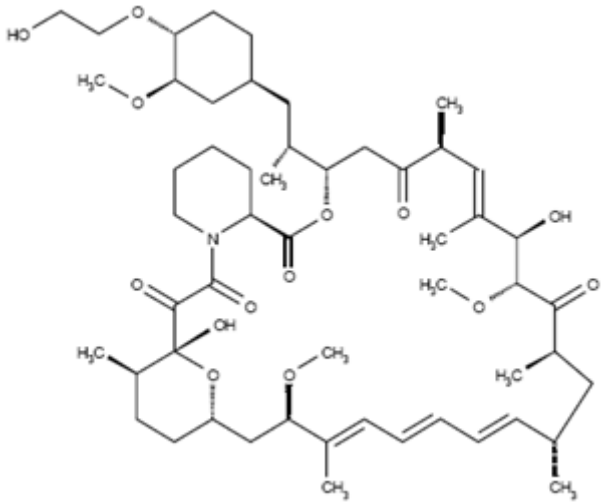
Although surgical resection has historically been the primary mode of treatment for SEGA, not all SEGA are amenable to curative resection. SEGA can also recur after surgical resection. Additionally, patients with SEGA may have multiple SEGA lesions, making surgery challenging. Finally, surgery for SEGA can result in significant morbidities, such as memory impairment, hemiparesis, infection and the requirement for ventriculoperitoneal shunts[14].

2.1 Product Information

Afinitor Disperz (everolimus tablets for oral suspension) is an inhibitor of mTOR, an antineoplastic agent. The chemical name of everolimus is (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone.

The molecular formula is $C_{53}H_{83}NO_{14}$ and the molecular weight is 958.2. The structural formula is shown in Figure 1:

Figure 1: Structural formula of everolimus



Afinitor Tablets are supplied for oral administration and contain 2.5 mg, 5 mg, 7.5 mg, or 10 mg of everolimus. Afinitor Tablets also contain butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, and anhydrous lactose as inactive ingredients.

Afinitor Disperz (everolimus tablets for oral suspension) is supplied for oral administration and contains 2 mg, 3 mg, or 5 mg of everolimus. Afinitor Disperz also contain butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, mannitol, microcrystalline cellulose, and colloidal silicon dioxide as inactive ingredients

2.2 Tables of Currently Available Treatments for Proposed Indications

FDA granted accelerated approval to Afinitor (everolimus) for the treatment of patients with SEGA associated with TSC who require therapeutic intervention but are not candidates for curative surgical resection. Afinitor (everolimus) is the sole FDA-approved treatment for SEGA associated with TSC (Table 1).

Table 1: Approved therapy for SEGA associated with TSC

Drug	Class	Date of Accelerated Approval	Specific Indication	Basis for Approval
Everolimus	mTOR inhibitor	10/29/2010	Patients with SEGA associated with TSC who require therapeutic intervention but are not candidates for curative surgical resection	At 6 months, ≥ 50% reduction in tumor volume of the largest SEGA lesion in 9 of 28 patients (32%; 95% CI: 16% to 52%) enrolled in a single prospective open label trial. Duration of response ranged from 97 to 946 days (median: 266 days). Enrolled patients were 3 years of age and older.

2.3 Availability of Proposed Active Ingredient in the United States

Afinitor (everolimus) tablets for oral administration are currently marketed and available in United States in 2.5 mg, 5 mg, 7.5 mg, and 10 mg unscored tablets (NDA 22334). Afinitor is currently approved for treatment of patients with the following conditions:

- Progressive neuroendocrine tumors of pancreatic origin (PNET) that are unresectable, locally advanced or metastatic.
- SEGA associated with TS who require therapeutic intervention but are not candidates for curative surgical resection. This was an accelerated approval.
- Advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

- Advanced hormone receptor-positive breast cancer in postmenopausal women, after failure of treatment with letrozole or anastrozole, in combination with exemestane.

Everolimus is also marketed in 0.25 mg, 0.5 mg, and 0.75 mg tablets under the trade name ZORTRESS (NDA 021560) for prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant. This indication was approved on 4/20/10 in conjunction with a Risk Evaluation and Mitigation Strategy (REMS). The REMS includes a communication plan to inform healthcare providers about the risks of wound-healing complications, hyperlipidemia, proteinuria, graft thrombosis, as well as nephrotoxicity when ZORTRESS is co-administered with standard doses of cyclosporine. FDA has also approved a medication guide to inform patients of these risks.

2.4 Important Safety Issues With Consideration to Related Drugs

Section 5 of the Afinitor label contains the following warnings and precautions for healthcare providers to consider when prescribing Afinitor:

- Non--infectious pneumonitis: monitor for clinical symptoms or radiological changes and manage by dose reduction or discontinuation, along with potential treatment with corticosteroids
- Increased risk of infections: monitor for signs and symptoms of infection and treat promptly
- Oral ulceration, including mouth ulcers, stomatitis, and oral mucositis
- Renal failure
- Laboratory test alterations including elevations of serum creatinine, blood glucose and lipids and decreases in hemoglobin, neutrophil count, and platelet count
- Avoidance of live vaccines and close contact with recipients of live vaccines
- Potential fetal harm when used during pregnancy.

Other safety issues identified with the other approved mTOR inhibitors include

- Hypersensitivity reactions, angioedema, interstitial lung disease, excess fluid accumulation, impaired or delayed wound healing, increased risk of calcineurin inhibitor-induced HUS/TTP/TMA and potential for increased risk for development of infection and the development of lymphoma with Rapamune (sirolimus)[15].

- Hypersensitivity and infusion reactions, interstitial lung disease, bowel perforation, abnormal wound healing with Torisel (temsirolimus). Additionally, temsirolimus is contraindicated in patients with bilirubin levels over 1.5 times the upper limit of normal; dose reduction is advised when temsirolimus is administered to patients with mild hepatic impairment[16].

Additional safety issues identified with rapamycin-related drugs include anemia, apthous stomatitis, lymphopenia, immunosuppression and risk of infection, hyperlipidemia, hyperglycemia, and renal dysfunction.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2 summarizes the pertinent regulatory activities related to submission of this NDA. The Applicant has pursued development of everolimus for multiple clinical indications since 1996. The Applicant initiated clinical development for the first of multiple oncologic indications in 2002. FDA approved everolimus under the trade name Afinitor (NDA 22334) on March 30, 2009 for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. On May 5, 2011, FDA approved Afinitor for the treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease. On July 20, 2012, the FDA approved Afinitor for the treatment of postmenopausal women with advanced hormone receptor-positive HER2-negative breast cancer in combination with exemestane after failure or treatment with letrozole or anastrozole.

The clinical development program for treatment of diseases associated with Tuberous Sclerosis Complex (TSC) began with the filing of investigator-sponsored IND 70,895 for the study of everolimus in patients with angiomyolipomata associated with TSC in 2004. An investigator-sponsored study of everolimus in patients with SEGA associated with TS (Study C2485) was submitted to FDA under IND 70,895 in August 2006, and the first patient was enrolled in January 2007.

At an End of Phase 2 (EOP2) meeting with FDA (under the Applicant's commercial IND 66, 279) on October 2, 2007, the Applicant proposed to conduct two registrational randomized phase III studies in patients with TSC, M2301 (for SEGA) and M2302 [for renal angiomyolipoma or sporadic lymphangioleiomyomatosis (LAM)]. After receiving FDA feedback at this meeting, the Applicant revised both protocols and submitted them for Special Protocol Assessment (SPA). However, although the Applicant chose to conduct Study M2301 and M2302, the Applicant subsequently withdrew the request for SPA for both studies.

While these studies were being conducted, an analysis showing favorable results from the single arm investigator-sponsored study conducted in TSC patients with SEGA (Study C2485) prompted the Applicant to reassess the initial plans for registration in patients with TSC who have SEGA. After discussion with FDA, Novartis submitted an sNDA based on data from Study C2485, which resulted in the October 29, 2010 accelerated approval of everolimus (Afinitor) for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) who require therapeutic intervention but are not candidates for curative surgical resection (sNDA 22334, Supplement 6). Accelerated approval was based on SEGA response rate observed in patients enrolled in Study C2485. The approval letter included two clinical postmarketing requirements (PMRs) to verify the clinical benefit of everolimus in patients with SEGA associated with TSC and two additional PMRs to assess the effects of long-term use of everolimus on the growth and development of pediatric patients.

On April 1, 2010, prior to submission of the sNDA (Supplement 6) by Novartis that resulted in the accelerated approval of Afinitor for the treatment of patients with SEGA, FDA issued a Written Request (WR) for the study of everolimus in pediatric patients with TSC and SEGA. In order to fulfill the terms of the WR, the Applicant is required to submit updated study results from Study C2485, in addition to results of randomized Study M2301. Additionally, the Applicant agreed to develop an age-appropriate formulation of everolimus for pediatric patients with SEGA.

On April 26, 2012, FDA granted accelerated approval for the treatment of renal angiomyolipomas in adult patients with TSC based upon evidence of durable reduction in tumor size. The Applicant is required to complete the ongoing trial CRAD001M2302 entitled “A Randomized, Double-Blind, Placebo-Controlled Study of RAD001 in the Treatment of Angiomyolipoma in Patients with Tuberous Sclerosis Complex (TSC) or Sporadic Lymphangioleiomyomatosis (LAM)” to further verify and describe the clinical outcomes of the duration of objective responses, incidence of nephrectomy and renal embolization four years after randomization of the last patient in the study.

Everolimus is also marketed under the trade name Zortress (NDA 021560). FDA approved Zortress (everolimus) on April 20, 2010 (NDA 021560) for the prophylaxis of organ rejection in adult patients at low to moderate immunologic risk receiving a kidney transplant.

Table 2: Key regulatory activities prior to submission of NDA 203985

Date	Nature of Regulatory Activity
	Prior Approvals of Non-TSC Related Indications
3/30/2009	*NDA approval* of Afinitor (NDA 22334) for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.
4/20/2010	*NDA approval* of Zortress (NDA 21560) for the prophylaxis of organ rejection in adult patients at low to moderate immunologic risk receiving a kidney transplant.
5/5/2011	*sNDA approval* of Afinitor (NDA 22334) for the treatment of patients with progressive neuroendocrine tumors of pancreatic origin (PNET) with unresectable, locally advanced, or metastatic disease
	Clinical Development for TSC-Related Indications
10/2/2007	EOP2 meeting to discuss Phase III Study M2302 (for renal angiomyolipoma or sporadic lymphangioleiomyomatosis) and Study M2301 (SEGA). • Novartis provided a rationale for use of volumetric assessment of tumor response as an endpoint for SEGA, and stated that annual incidence of hydrocephalus and SEGA-related surgery are not feasible as study endpoints because there are no reliable historical estimates of these outcomes in patients with SEGA.
4/7/2008	Study M2301 protocol submitted for SPA evaluation.
11/13/2008	Novartis withdrew SPA request for Study M2301.
3/12/2009	Protocol for Study M2301 submitted to FDA.
8/25/2009	Applicant submitted Amendment 1 to Study M2301 to FDA.
9/29/2009	pre-sNDA meeting: FDA agreed to review data from investigator-sponsored single-arm study C2485 for a SEGA indication.
12/9/2009	Cutoff date for data analysis in study C2485 (date of 12-month assessment of last patient enrolled).
4/1/2010	WR for study of everolimus in patients with SEGA and TSC. • WR specified submission of data from studies C2485 (at least 28 patients, including a minimum of 22 patients less than 18 years of age), and M2301 (at least 99 patients, including a minimum of 74 patients less than 18 years of age), and development of an age-appropriate formulation.
4/16/2010	Applicant submitted response to FDA accepting the terms of the WR Applicant submitted Amendment 2 to Study M2301 to FDA
10/29/2010	Accelerated approval of NDA 22334, Supplement 6 (SE1-006) for Afinitor in the treatment of patients with SEGA who require therapeutic intervention but are not candidates for curative surgical resection based on study C2485.

Date	Nature of Regulatory Activity
1/27/2011	Applicant submitted Amendment 3 to Study M2301 to FDA.
3/9/2011	Applicant submitted Amendment 4 to Study M2301 to FDA.
9/27/2011	Pre-sNDA meeting to discuss filing strategy and content and format of planned NDA for treatment of SEGA, (b) (4) • FDA recommended that the (b) (4) • FDA stated that conversion to full approval for the SEGA indication would not be considered in the absence of long-term safety and efficacy data described in the PMRs issued at the time of the accelerated approval for SEGA. "The complete long term follow up data required as part of the PMRs issued at the time of accelerated approval must be submitted prior to any consideration of changes to labeling or conversion to full approval." • Novartis agreed to submit data from M2301 and C2485, data from bioequivalence studies (X2105 and X2106), and CMC information to support a "pediatric-appropriate" dispersible formulation in and NDA to satisfy the requirements outlined in the Written Request. • FDA stated that separate labeling for the new dispersible formulation would be acceptable, and that the final determination regarding whether the terms of the WR were satisfied is made by the Pediatric Exclusivity Board. • FDA stated that filing of these submissions and any changes to labeling would be review issues.
4/26/2012	Accelerated approval of sNDA 22-334 Supplement 17 for the treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC) not requiring immediate surgery. Labeling revision approved to include new renal angiomyolipoma indication and rewording of indication statement: *adults and children ≥ 3 years of age* with SEGA associated with TSC who require therapeutic intervention but are not candidates for curative surgical resection based on study C2485.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This NDA submission was of adequate quality to permit review of the application.

3.2 Compliance with Good Clinical Practices

Study C2485 and Study M2301 contained statements indicating that they were conducted in accordance with the declaration of Helsinki.

For Study M2301, an independent data monitoring committee (IDMC) conducted safety analyses every 6 months to review the safety of everolimus. IDMC analyses were conducted independently from the trial team, who remained blinded during the study. The IDMC did not perform statistical testing or efficacy analyses. The IDMC met three times during the course of the study; each time the IDMC concluded that the trial should continue without modification. The original protocol and all amendments were reviewed and approved by the local IRB.

A DSMB monitored the conduct of study C2485. The original protocol and all amendments were reviewed and approved by the local IRB. During review of efficacy Supplement 6, FDA's Division of Scientific Investigation (DSI) inspected the single study site of C2485. Although this inspection revealed some regulatory violations, these violations were relatively few, minor in nature, and not considered to materially impact the integrity of data (see Dr. Amir Shahlaee's review of sNDA 22334 SE1-006, dated October 26, 2010, for additional details regarding this inspection and the data integrity of study C2485).

A review of Study M2301 conducted by Novartis revealed a low rate of major protocol deviations (0.9%) that have the potential to impact analysis of the primary endpoint. One major protocol deviation occurred in a patient randomized to placebo (patient 0600/00018). This patient received a medication pack that differed from that assigned by the interactive web response system (IWRS) for 25 days. After unblinding, it was determined that this medication pack contained placebo, which was originally assigned by IWRS. However, this patient was excluded from the per-protocol analysis set.

Minor protocol deviations occurred in the majority of patients in both treatment arms during the double blind treatment period (79.5% and 61.5% of everolimus and placebo patients, respectively). However, these deviations consisted primarily of PK sampling outside of the approved protocol time-window (38.5% versus 20.5% for the everolimus and placebo group, respectively), and co-administration of CYP3A4 or PgP inhibitors/inducers (33.3% versus 28.2% for the everolimus and placebo group, respectively; these protocol deviations were considered to be minor issues by the Applicant.

Clinical comment: Section 6.7.3 of the Study M2301 protocol indicated that drugs or substances known to be inhibitors, inducers or substrates of CYP3A4 or P-glycoprotein other than enzyme-inducing antiepileptic drugs were not allowed

on study or should be avoided, unless use of the drug was "necessary" or "essential" and "no substitute is available." Because this is a clinical judgment call, it is not surprising that subjects frequently remained on such drugs. Additionally, drug levels were adjusted based on therapeutic drug monitoring, so everolimus dose would be adjusted in these patients if drug interactions resulted in everolimus levels outside of the targeted therapeutic window. The Office of Clinical Pharmacology concluded that the protocol deviations relating to PK sampling did not materially impact the conduct and results of this study.

3.3 Financial Disclosures

No clinical investigators involved in Study C2485 or Study M2301 were full or part-time employees of Novartis. All investigators participating in Study C2485 and Study M2301 provided financial disclosure information. In the original NDA submission, Novartis provided a Form 3454 for Study RAD001C2485 (Study C2485) and Study CRAD001M2301. This form certified that Novartis did not enter any financial arrangement with the listed investigators participating in either study whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Novartis also certified that each listed investigator did not disclose a proprietary interest in the investigational product (everolimus) or a significant equity holding in Novartis as defined in 21 CFR 54.2(b). Additionally, Novartis certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

The list of investigators without a disclosable financial arrangement or interest included every investigator involved in either study, with one exception. Novartis submitted Form 3455 and attached documentation describing a disclosable financial interest for Dr. (b) (6) who was (b) (6) (b) (6). Dr. (b) (6) included documentation of the following financial relationships with Novartis:

1. Dr. (b) (6) was the principal investigator or sub-investigator for (b) (6) investigator-initiated and industry-sponsored studies involving everolimus funded by Novartis.
2. Dr. (b) (6) stated that there is a consulting agreement between Novartis and (b) (6) for his services involving everolimus clinical development, FDA approval, and subsequent marketing activities (in excess of $25,000).
3. Dr. (b) (6) has received honorarium associated with speaking engagements.

In the forms provided, Novartis indicated that they did not enter into any financial arrangement with Dr. (b) (6) whereby the value of the compensation to the clinical

investigator for conducting the study could be influenced by the outcome of the study. Novartis also indicated that Dr. (b) (6) did not have any significant equity interest [as defined in 21 CFR 54.2(b)] in Novartis, and did not have a proprietary interest in everolimus.

Reviewer comment: Additionally, the risk of bias is mitigated because the radiographic determination of the primary endpoint, SEGA response, was made by an independent blinded central review panel.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see the Office of New Drug Quality Assessment reviews by Dr. Sue-Ching Lin and Dr. Kareen Riviere for comprehensive information regarding the chemistry, manufacturing and controls (CMC) and biopharmaceutical issues addressed during review of this NDA.

The CMC reviewer concluded that this NDA was approvable, pending an acceptable overall recommendation from the Office of Compliance for the inspections of the manufacturing and testing facilities for the drug substance and drug product. However, the CMC review team identified a deficiency in the stability data provided in this application. On July 13, 2012 the Applicant submitted an amendment informing FDA that the container closure system proposed for the marketed product (i.e., the commercial blister package) was different than the container closure system used in the registration stability studies. Based on the provided stability data, ONDQA recommended granting an 18-month expiration dating period for the drug product when stored at the proposed controlled room temperature and protected from light and moisture. As described in Dr. Lin's review, the Applicant agreed to the following postmarketing commitment (PMC):

> *Novartis will conduct pre-validation as well as validation activities for the blistering process for the container closure system that will be used for the US market. The USP <671> Water Vapor Transmission Rate test (WVTR) will be performed with blister cards derived from Pre-Validation trials. The most stringent requirement, Class A <0.5 mg/day, will need to be met before proceeding with validation and launch activities. To bridge the registration stability and the launch batches Novartis will ensure that the WVTR result is comparable to that measured for the registration stability batches. Because water uptake is the most critical*

attribute as relates to stability of the Afinitor Tablets for Oral Suspension an acceptable WVTR result in combination with successful pre-validation and validation on the packaging process will provide assurance that the registration stability data is bridged to the intended commercial product. Novartis will provide the comparable USP<671> WVTR data before the end of November. Novartis also commits to submitting the 3 months accelerated stability data on the first 3 commercial batches before the end of May 2013.

The CMC review team recommended that the expiration dating period be extended to 24 months upon fulfillment of the PMC.

Additionally, the ONDQA review team determined that the Applicant's proposed dissolution method was not discriminating, and therefore not acceptable. The ONDQA Biopharmaceutics Team requested that the Applicant use phosphate pH 4.5 as the dissolution medium because it is biorelevant and discriminating. Additionally the ONDQA Biopharmaceutics Team asked the Applicant to provide complete dissolution profile data using phosphate buffer pH 4.5 for the clinical batches of the proposed product. During a teleconference held on July 25, 2012, the Applicant acknowledged the Agency's recommendations and agreed to conduct additional studies to develop a discriminating dissolution method. The Applicant agreed to a postmarketing commitment to submit a dissolution method development report on or before February 29, 2013 and a Prior Approval Supplement (including the revised dissolution method and information to support the dissolution acceptance criterion) on or before August 29, 2013. FDA agreed to review the dissolution development report and provide feedback to the Applicant within 30 days of its submission.

Novartis originally proposed the generic name (b) (4) for Afinitor Disperz. The ONDQA review team concluded that this was not an acceptable name; the Applicant and ONDQA subsequently agreed to use the generic name "everolimus tablets for oral suspension" for Afinitor Disperz.

The Applicant requested a biowaver for the 2 mg and 3 mg strengths of Afinitor Disperz. ONDQA determined that the Applicant provided sufficient data to meet the requirements of CFR 320.22(d)(2); therefore a biowaiver was granted for the 2 mg and 3 mg strengths.

Reviewer note: At this time of this review, the facility inspection reports and conclusions based on these inspections have not been finalized; it is not yet known whether problems have been identified during inspection of the drug manufacturing facility that would impact the approvability of the application.

4.2 Clinical Microbiology

There were no significant clinical microbiology issues identified with this supplemental application. The microbiology review completed on March 22, 2012 recommended approval of this application.

4.3 Preclinical Pharmacology/Toxicology

There were no significant preclinical pharmacology/toxicology issues identified with this application.

4.4 Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) reviewer, Jian Wang, PhD, conducted an extensive review of the pharmacokinetic data, including analysis of biocomparability between the Afinitor DISPERZ tablets and the market formulation tablets, the relationship between everolimus trough levels and toxicity, as well as the relationship between everolimus trough levels and SEGA response. Please refer to Dr. Wang's review for details regarding the OCP evaluation of this application. The OCP review team concluded that at everolimus target trough levels between 5-15 ng/ml, there was not a consistent exposure-response relationship between everolimus trough levels and toxicity or efficacy in patients with SEGA.

The Applicant originally proposed a target everolimus trough levels between (b) (4) (b) (4). Although SEGA responses were observed in patients with average steady state C_{mins} of less than 5 ng/mL, the clinical and clinical pharmacology review teams proposed that the target trough concentration range be 5 – 15 ng/mL. Please see Section 7.2.2 of this review and the OCP review of this application for details regarding the rationale for the 5-15 ng/mL target trough concentration range.

There is currently not an approved test kit for measuring everolimus trough levels in patients with SEGA (unlike Zortress, for which there is an approved test kit to monitor everolimus levels in the adult transplant population). Because dosage of everolimus in SEGA is based on therapeutic drug monitoring, the clinical review team consulted with the Center for Devices and Radiological Health (CDRH) to obtain advice regarding whether the current recommendation for use of a "validated test" for measuring everolimus trough levels was sufficient. CDRH concluded that it was not necessary to require the Applicant to develop a commercially available test kit for measuring everolimus trough levels in patients with SEGA because of the relatively wide therapeutic range, the relative tolerability of everolimus in the SEGA population at the proposed dose and schedule, and lack of a strong relationship between everolimus trough levels and toxicity.

4.4.1 Mechanism of Action

Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation with mTOR complex 1 (mTORC1) and thus inhibition of mTOR kinase activity. Everolimus reduces the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP1), downstream effectors of mTOR, involved in protein synthesis. S6K1 is a substrate of mTORC1 and phosphorylates the activation domain 1 of the estrogen receptor which results in ligand-independent activation of the receptor. In addition, everolimus inhibits the expression of hypoxia-inducible factor (e.g., HIF-1) and reduces the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in *in vitro* and/or *in vivo* studies.

Two regulators of mTORC1 signaling are the oncogene suppressors tuberin-sclerosis complexes 1 and 2 (*TSC1*, *TSC2*). Loss or inactivation of either *TSC1* or *TSC2* leads to activation of downstream signaling. In TSC, inactivating mutations in either the *TSC1* or the *TSC2* gene lead to hamartoma formation throughout the body.

4.4.2 Pharmacodynamics

In patients with SEGA, higher everolimus trough concentrations appeared to be associated with larger reductions in SEGA volume. However, because responses were observed at trough concentrations as low as 5 ng/mL, it is unclear whether additional dose increases within the 5 -15 ng/mL range are necessary or beneficial.

Current Afinitor labeling contains information regarding a randomized, placebo-controlled, crossover study in which 59 healthy subjects received a single oral dose of Afinitor (20 mg and 50 mg) and placebo. In this study, there was no indication of a QT/QTc prolonging effect of Afinitor after administration of single doses up to 50 mg.

4.4.3 Pharmacokinetics

Current Afinitor labeling includes the following summaries of PK studies that the Applicant had previously submitted to NDA 22334.

- In patients with advanced solid tumors, steady-state concentrations of everolimus were achieved within 2 weeks following once-daily dosing.

- In healthy subjects, high fat meals reduced systemic exposure to Afinitor 10 mg tablets (as measured by AUC) by 22% and the peak blood concentration C_{max} by 54%. Light fat meals reduced AUC by 32% and C_{max} by 42%. However, food had no apparent effect on the post absorption phase concentration-time profile.

- The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given AFINITOR 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

- Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100-times less activity than everolimus itself. *In vitro*, everolimus competitively inhibited the metabolism of CYP3A4 and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan.

- No specific excretion studies have been undertaken in cancer patients. Following the administration of a 3 mg single dose of radiolabeled everolimus in patients who were receiving cyclosporine, 80% of the radioactivity was recovered from the feces, while 5% was excreted in the urine. The parent substance was not detected in urine or feces. The mean elimination half-life of everolimus is approximately 30 hours.

- The safety, tolerability and pharmacokinetics of Afinitor were evaluated in a single oral dose study of everolimus in subjects with impaired hepatic function relative to subjects with normal hepatic function. Compared to normal subjects (N=13), there was a 1.8-fold, 3.2-fold, and 3.6-fold increase in exposure (i.e. AUC) for subjects with mild (Child-Pugh class A, N=6), moderate (Child-Pugh class B, N=9), and severe (Child-Pugh class C, N=6) hepatic impairment, respectively. In another study, the average AUC of everolimus in eight subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in eight subjects with normal hepatic function.

- In a population pharmacokinetic evaluation in cancer patients, no relationship was apparent between oral clearance and patient age or gender. In patients with SEGA, the geometric mean C_{min} values normalized to mg/m^2 dose in patients aged < 10 years and 10 to 18 years were lower by 54% and 40%, respectively, than those observed in adults (> 18 years of age), suggesting that everolimus clearance normalized to body surface area was higher in pediatric patients as compared to adults.

This application contained new data and analyses of two randomized open label crossover bioequivalency studies in healthy adult subjects comparing the bioavailability of Afinitor Disperz to the adult formulation everolimus tablets (Study 1X2105 and Study 1X2106). In patients with SEGA and TSC, everolimus C_{min} was approximately dose-proportional within the dose range from 1.35 mg/m^2 to 14.4 mg/m^2. In healthy adult subjects, the $AUC_{0-\infty}$ of Afinitor Disperz (everolimus tablets for oral suspension) was equivalent to the $AUC_{0-\infty}$ of Afinitor (everolimus) Tablets. The predicted trough concentrations at steady-state were similar after daily administration. However, the C_{max} of the suspension formulation was 20-36% lower than that of Afinitor Tablets

Reviewer note: the clinical and clinical pharmacology review teams concluded that the lower C_{max} of the dispersible tablet was not likely to affect the efficacy in patients with SEGA because dosing is based on therapeutic drug monitoring. The FDA clinical and clinical pharmacology review teams ultimately decided that the bioavailability of everolimus tablets for oral suspension was sufficiently similar to the bioavailability of the formulations approved for commercial use (FMI) and the formulations used in prior clinical trials of everolimus (MF) in patients with SEGA to support the approval of Afinitor Disperz (everolimus tablets for oral suspension).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3 lists the clinical trials that provided support for this application.

Table 3: Clinical trials providing support for NDA 203985

Study Number	Population	Design
M2301	Patients of any age with worsening SEGA and TSC (N = 117)	Randomized (2:1) multicenter double-blind placebo-controlled study. 1º endpoint: SEGA response rate
C2485	Patients ≥ 3 years of age with worsening SEGA and TSC. (N = 28)	Single arm, single center investigator-sponsored study. 1º endpoint: change from baseline of primary SEGA lesion
1X2105	Healthy adult subjects (N=54)	Randomized, open label crossover bioequivalency study (one 5mg tab for oral suspension vs. five 1 mg tablets for oral use)
1X2106	Healthy adult subjects (N=54)	Randomized, open label crossover bioequivalency study (one 5mg tab for oral suspension vs. one 5 mg tablets for oral use)

5.2 Review Strategy

The clinical review of safety and efficacy of Afinitor in the treatment of pediatric and adult patients with SEGA focused on review of the data from the primary analysis of Study M2301, in addition to updated data from Study C2485. FDA clinical review included exploratory analyses of raw data contained in the electronic submission in addition to review of the case report forms and clinical study reports contained in the NDA. The key review materials and activities are outlined below:

- Comprehensive review of the data, case report forms, and clinical study reports for Study M2301 and Study C2485 contained in the February 29, 2012 NDA submission.
- Review of the Applicant's subsequent electronic submissions in response to FDA information inquiries.
- The major efficacy and safety analyses contained in proposed labeling and clinical study reports were reproduced or audited using the raw datasets and SAS or JMP programming.
- The data and study reports contained in the 120-day safety update submitted by the Applicant on May 4, 2012 were reviewed, analyzed, and incorporated into the safety review. This safety update included approximately 4.5 months of additional safety data from study M2301 that were not included in the original NDA submission on February 29, 2012.
- Additionally, safety data included in the integrated summary of safety were examined to look for additional safety signals relevant to the SEGA population that were not evident from analyses of data from studies M2301 and C2485.
- Review of relevant published literature.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study CRAD001M2301 (Study M2301)

Study CRAD001M2301 (hereafter referred to as "Study M2301"), entitled "A randomized double-blind placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with Tuberous Sclerosis Complex (TSC)" is an industry-sponsored trial that was conducted in 24 sites in 10 countries. The 305 study report contains data from the first patient visit on August 10, 2009 until the date of primary data cut-off, March 2, 2011. This study remains ongoing.

Table 4 shows the dates that the initial protocol and each amendment were submitted to the FDA. Sections 5.3.1.1 through Sections 5.3.1.9 summarize the final design of Study M2301, with details regarding important protocol amendments described subsequently.

Table 4: Dates of submission of protocol and protocol amendments for Study M2301

Protocol or Amendment	Submission Date
Original Protocol	3/12/2009
Amendment 1	8/25/2009
Amendment 2	4/16/2010

Protocol or Amendment	Submission Date
Amendment 3	1/27/2011
Amendment 4	3/9/2011

5.3.1.1 Study Design

Study M2301 is a double-blind, randomized, parallel group, placebo-controlled multicenter trial comparing a once daily oral dose of everolimus compared to matching placebo in patients with TSC who have SEGA that investigators deemed to be worsening (see eligibility criteria described in Section 5.3.1.3 of this review for details regarding factors used to made a determination of SEGA worsening).

Patients who met the eligibility criteria were randomized in a 2:1 ratio to receive everolimus or matching placebo. Randomization was stratified by presence or absence of use of enzyme-inducing anti-epileptic drugs at randomization.

Figure 2, copied from the Applicant's NDA submission, summarizes the conduct of Study M2301. The trial had two distinct treatment phases: a core phase, and an open-label extension phase. Prior to the core treatment phase there was a pre-treatment phase, which consisted of a 28-day screening period pre-randomization during which an MRI of the brain and CT/MRI of the kidney were performed to evaluate SEGA lesions and verify patient eligibility.

The core phase started at the time of randomization of the first patient and continued until the last randomized patient was treated with everolimus or placebo for 6 months. The core treatment phase included a double blind treatment period and an open label period. The open label period applied to patients randomized to placebo who opted to commence everolimus therapy after experiencing SEGA progression while receiving placebo (determined by central review or "unequivocal progression" according to investigator assessment) during the blinded treatment phase.

The primary analysis for the core phase was performed using all data up to the data cut-off date (March 2, 2011), which was defined as 6 months after the last patient was randomized. This application contains data from the core phase of the trial. On May 4, 2012, the Applicant submitted a safety update that included additional safety data through July 18, 2011.

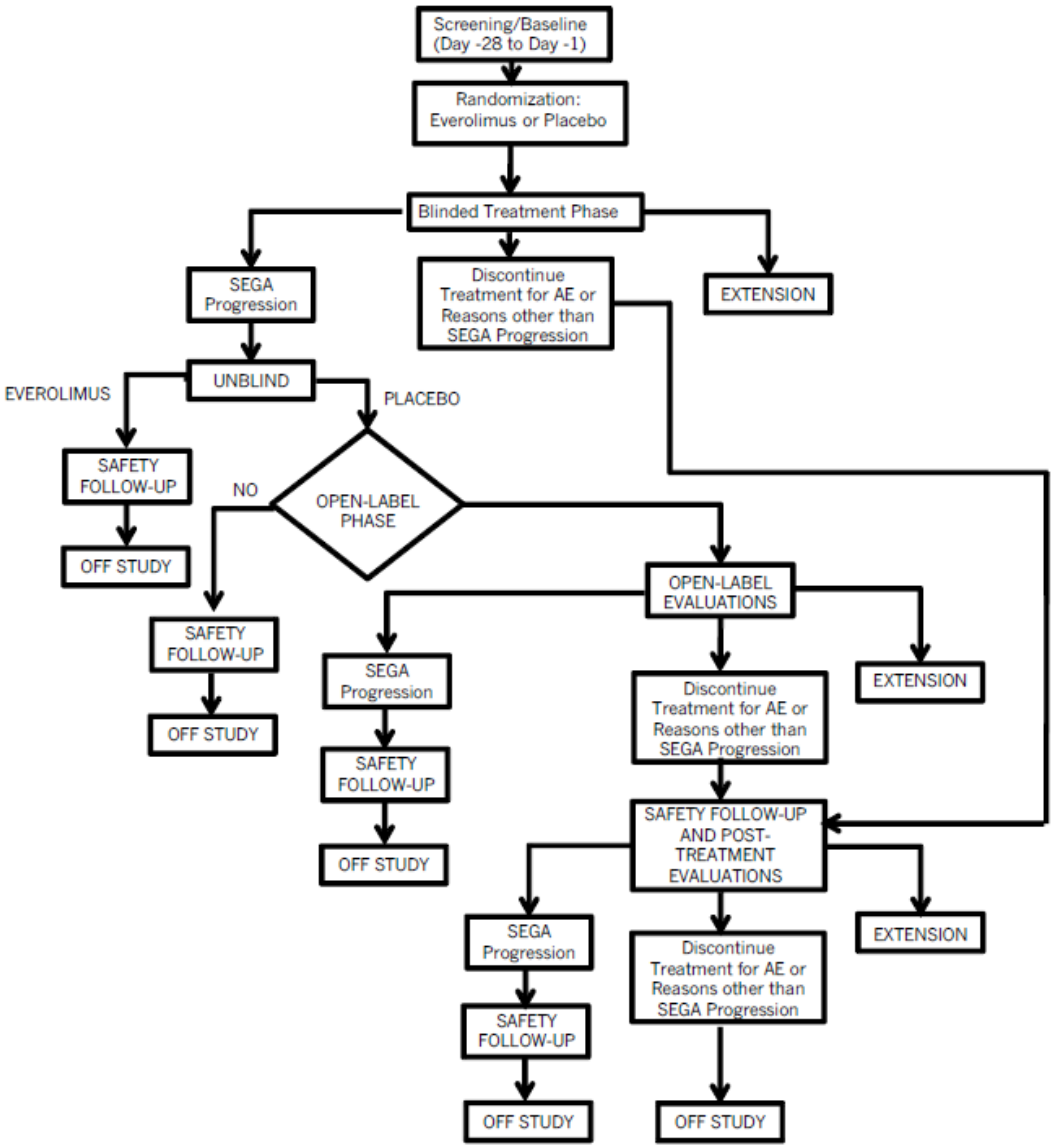
The M2301 protocol included a plan for commencement of an extension phase if the primary analysis of data derived from the core treatment (double blind) phase demonstrated superiority of everolimus over placebo in achievement of a SEGA response (≥50% reduction in the sums of the volumes of SEGA target lesions).

In the extension phase, all patients randomized to either treatment arm who remained on study therapy could be treated with open label everolimus until disease progression, unacceptable toxicity, withdrawal of consent, or end of the extension phase, whichever comes first. The extension phase is planned to continue until 4 years after the last patient was randomized.

Reviewer comment: the use of placebo as the control arm in Study M2301 appears reasonable and ethically appropriate for the following reasons.

- *The study protocol excluded enrollment of patients that required immediate surgical intervention.*
- *Surgery was not considered an appropriate control arm in this population due to the potential for surgical morbidity.*
- *There was no active pharmacologic comparator that had been shown to benefit to patients with TSC at the time this study was initiated (the first patient visit for Study M2301 occurred on August 10, 2009, and everolimus was granted accelerated approval for the treatment of SEGA on October 29, 2010).*
- *Because Study C2485 was a small single arm trial, the incorporation of a placebo control arm into this study enabled the first comparative analyses of safety and efficacy data of everolimus compared to the natural history of the disease in patients with SEGA associated with TSC.*
- *SEGA are slow-growing tumors, and Study M2301 permitted patients to crossover at the first radiologic sign of progression.*

Figure 2: Schematic of conduct of Study M2301 (copied from Applicant's NDA submission)



Safety Follow-Up: Collection of AEs and SAEs that occur within 28 days of treatment discontinuation. SAEs suspected to be related to study drug were collected for an additional 8 weeks (56 days).

Post-Treatment Evaluations: MRI of the brain (and MRI/CT of the kidneys, if applicable) annually

Open-Label Evaluations: MRI of the brain (and MRI/CT of the kidneys, if applicable) was to be done 12, 24, and 48 weeks after the start of open-label everolimus and annually thereafter. Safety and efficacy assessments were to be carried out as in the blinded treatment phase (with the exception of biomarker assessments, which were not performed in the open-label phase).

The trial was supported by an Interactive Web Response System (IWRS) for randomization and trial medication management, a central laboratory for analysis of blood samples, an independent central radiology review for blinded

assessment of the primary efficacy endpoint, and an Independent Data Monitoring Committee (IDMC) for ongoing assessment of safety.

5.3.1.2 Study Objectives

The primary objective of Study M2301 was to compare the SEGA response rate in the everolimus arm to the response rate in the placebo arm in patients with TSC-associated with SEGA.

Secondary objectives included comparison of the following parameters in the two treatment arms:

- Change from baseline in frequency of epileptiform events
- Time to SEGA progression (TTSP)
- Skin lesion response rate
- Change from baseline in plasma angiogenic molecules (e.g. vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF), placental growth factor (PLGF), soluble VEGF receptor-1, and soluble VEGF receptor-2)
- Renal function assessed using calculated creatinine clearance
- Safety profile.

Additional secondary objectives included the characterization of pharmacokinetics (PK) of everolimus in patients with SEGA and evaluation of the time to SEGA response, duration of SEGA response, and the duration of skin lesion response in patients receiving everolimus.

There were multiple exploratory objectives, including assessment of changes in the following parameters compared to baseline: anti-convulsant therapy, severity of seizures, and neuropsychological assessments and cognitive function. Additionally, correlation between SEGA tumor volume and longest diameter, occurrence of SEGA-related surgery and time to SEGA-related surgery, correlation between mutation analysis of TSC1 and TSC2 genes with SEGA response and progression, and the relationship between everolimus concentration and safety/efficacy endpoints were also assessed.

5.3.1.3 Eligibility Criteria

The target population consisted of patients of any age with a definitive diagnosis of TSC who required intervention for worsening SEGA tumors, as evidenced by evidenced by at least one of the following conditions prior to randomization:

- Serial SEGA growth
- Presence of a new SEGA lesion
- New or worsening hydrocephalus.

Inclusion Criteria (copied from the protocol with some modifications for brevity)

- Children or adults of any age
- Clinically definitive diagnosis of TSC according to modified Gomez Criteria
- At least one SEGA lesion of ≥ 1 cm in its longest diameter using MRI
- A recent (within 28 days of randomization) MRI of the brain which showed one of the following changes between an earlier (pre-baseline) MRI:
  - Serial growth, as defined by a ≥ 25% increase in SEGA volume
  - Presence of a new SEGA lesion ≥ 1 cm in its longest diameter
  - New or worsening hydrocephalus
- If of childbearing potential, a negative pregnancy test
- For sexually active, pre-menopausal women, willingness to use adequate contraceptive measures while on study and for up to 8 weeks after ending treatment
- Provision of informed consent

Exclusion Criteria (copied from the protocol with some modifications for brevity)

- Patients for whom SEGA related surgery is likely to be required, in the opinion of the investigator
- History of myocardial infarction, angina, or stroke-related to atherosclerosis
- Known impaired lung function
- Evidence of end-organ dysfunction as evidenced by one or more of the following
  - Transaminase levels > 2.5 times the upper limit of normal (ULN)
  - Serum bilirubin > 1.5 times the ULN
  - Hemoglobin < 9 g/dL
  - Platelet count < 80,000/mm^3
  - Absolute neutrophil count < 1,000/mm^3
  - Serum creatinine > 1.5 X ULN
- Pregnancy or lactation
- Infection at the time of randomization or known human immunodeficiency virus seropositivity
- Prior history of organ transplantation
- Surgery involving entry into a body cavity or requiring sutures within 2 months prior to randomization
- Prior therapy with mTOR inhibitors such as sirolimus, temsirolimus or everolimus
- Bleeding diathesis or requirement for oral anti-Vitamin K medication except for low-dose warfarin
- Malignancy in the past few years, other than squamous or basal cell skin cancer
- Inability to undergo MRI assessment

- Any severe or uncontrolled medical conditions which would cause unacceptable safety risks or compromise ability to comply with the study protocol, such as:
  - Uncontrolled hyperlipidemia or diabetes mellitus
  - Impairment of gastrointestinal function that may significantly alter absorption of study drug
  - Skin, mucosa, ocular, or gastrointestinal disorders of ≥ Grade 1 severity

5.3.1.4 Treatment Plan

In study M2301, the investigational drug used was everolimus 1.0 mg immediate-release tablets. Patients randomized to the control arm received a matching placebo tablet. Both everolimus and placebo were provided by Novartis Drug Supply Management and dispensed by study center personnel on an outpatient basis. Patients were provided with a 5-week supply of study drug on Treatment Day 1, Week 4, and Week 8 for self-administration at home. At later visits, study drug was supplied on an as-needed basis. On days when PK-sampling was required, everolimus or placebo was administered by the investigator at the study site after the PK sample was obtained.

Patients received a starting dose of 4.5 mg/m^2 of everolimus or matching placebo, rounded to the nearest milligram, orally with a glass of water once daily at the same time each day in the morning after a light breakfast, starting on Day 1. Patients unable to swallow tablets were instructed to suspend the tablets by stirring them gently in approximately 30 ml water just prior to administration. Patients ingesting the suspension were also instructed to rinse the glass with 30mL of water and ingest the resulting mixture.

Dosing was titrated to achieve everolimus trough levels between 5-15 ng/mL. Trough levels of everolimus or matching placebo were collected by the local laboratory 2 weeks after initiation of therapy, at each clinic visit, and 1-2 weeks after starting an increased dose at a new level, any decrease in an enzyme-inducing drug, or any increase in an enzyme-inhibiting agent. A central laboratory measured trough levels from samples sent by the local laboratories and uploaded the trough level information for each patient directly into IWRS. Based on the everolimus PK information (or a randomized schema for patients receiving placebo), IWRS instructed investigators to either maintain, reduce, or increase dosing to achieve everolimus target trough levels between 5– 15 ng/mL.

The protocol also included provisions for study drug interruption and dose modification for toxicities. If necessary, doses were increased by approximately 33% increments, and doses were decreased by 25 – 50% increments. If treatment was interrupted due to toxicity, study drug was resumed only if the

toxicity resolved or improved to Grade 1 severity within 6 weeks. Study drug was then resumed at the initial dose or a lower dose level depending on the toxicity type and grade. Study therapy was discontinued if toxicities did not resolve or improve to Grade 1 levels within 6 weeks. Additionally, study therapy was discontinued in patients requiring more than two dose reductions due to an adverse event.

Table 5 and Table 6, copied from the protocol submitted to this NDA, outline the everolimus dose modification guidelines for non-hematologic toxicities, respectively.

Table 5: Everolimus dose modification guidelines for non-hematologic toxicities (copied from Applicant's submission)

Toxicity	Actions
Pneumonitis	See Table 6-3
Hyperlipidemia and/or hypertriglyceridemia	Any grade: Treat according to best clinical practice. No specific dose reductions are needed.
Hyperglycemia	Any grade: Treat according to best clinical practice. No specific dose reductions are needed.
Stomatitis	Grade 2: Interrupt study drug until resolution to ≤ grade 1. Restart at the same dose. Grade 3: Interrupt study drug until recovery to grade ≤1. Reintroduce study drug at the next lower dose level**. Discontinue study drug if stomatitis doesn't recover to ≤grade 1 within 4 weeks. Grade 4: Discontinue study drug.
Other Toxicities	Grade 2 and 3 Interrupt administration until resolution to ≤ grade 1. Restart at the same dose. Grade 4 Hold study drug until recovery to ≤ grade 1. Reintroduce study drug at the lower dose level**, if available.
Toxicity requiring interruption for >6 weeks	Permanently discontinue treatment.
No specific dose adjustments are recommended for Grade 1 toxicity. However, physicians should always manage patients according to their medical judgment based on the particular clinical circumstances. ** To determine the next lowest dose level, please refer to Table 6-4. Due to rounding, the next lowest dose level may not result in an actual dose reduction (e.g. previous dose calculation was 4.4 mg resulting in a dose of 4 mg/d and the dose at the next lowest level results in a dose calculation of 3.6, still resulting in a 4 mg/d dose). In such cases, the patient's dose should be lowered by 1 mg.	

Table 6: Everolimus dose modification guidelines for hematologic toxicities (copied from Applicant's submission)

Toxicity	Actions
Thrombocytopenia Platelet count	≥ 75000/mm^3: No change 50000/ mm3 to 75000/ mm^3 Hold study drug until recovery to ≥ 75000/mm^3 Reintroduce study drug at the same dose level < 50000/ mm^3 Hold study drug until recovery to ≥ 75000/mm^3 Reintroduce everolimus at the next lower dose level**, if available.
Absolute Neutrophil Count (ANC)	≥ 1000/ mm^3: No change 500/ mm^3 to 1000/ mm^3 Hold study drug until recovery to ≥ 1000/mm^3 Reintroduce study drug at the same dose level < 500/ mm^3 Hold until recovery to ≥ 1000/ mm^3. Reintroduce study drug at the next lowest dose level**, if available.
Febrile neutropenia	Hold further dosing until ANC ≥ 1250/mm^3 and no fever. Then resume dosing at the next lower dose level** if available.
Toxicity requiring interruption for > 6 weeks	Discontinue study treatment.
Physicians should always manage patients according to their medical judgment based on the particular clinical circumstances.	

Table 7, copied from the protocol submitted to this NDA, outlines the guidelines for management of non-infectious pneumonitis that were used in Study M2301.

Table 7: Guidelines for management of non-infectious pneumonitis in Study M2301 (copied from Applicant's submission)

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Study Treatment Dose Adjustment
Grade 1	CT scans with lung windows. Repeat CT scan at least every 12 weeks until return to within normal limits.	No specific therapy is required.	Administer 100% of study treatment dose.
Grade 2	CT scan with lung windows. Consider pulmonary function testing including spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat CT scan at least every 12 weeks until return to within normal limits. Consider bronchoscopy with biopsy and /or BAL	Symptomatic only. Consider corticosteroids if symptoms are troublesome.	Reduce study treatment dose by 1 dose level** (see Table 6-4) until recovery to ≤ Grade 1. Study treatment may also be interrupted if symptoms are troublesome. Patients will discontinue study treatment if they fail to recover to ≤ Grade 1 within 3 weeks.
Grade 3	CT scan with lung windows and pulmonary function testing including spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every 8 weeks until return to within normal limits. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to ≤ Grade 1. May restart study treatment within 3 weeks at a reduced dose (by one level**) if evidence of clinical benefit.
Grade 4	CT scan with lung windows and required pulmonary function testing including spirometry, DL_{CO}, and room air O_2 saturation at rest. Repeat at least every 8 weeks until return to within normal limits. Bronchoscopy with biopsy and/or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.
**To determine the next lowest dose level, please refer to Table 6-4. Due to rounding, the next lowest dose level may not result in an actual dose reduction (e.g. previous dose calculation was 4.4 mg resulting in a dose of 4 mg/d and the dose at the next lowest level results in a dose calculation of 3.6, still resulting in a 4 mg/d dose). In such cases, the patient's dose should be lowered by 1 mg.			

5.3.1.5 Concomitant Therapies

The Study M2301 protocol contained the following guidelines regarding the use of concomitant medications.

- Investigational or commercial antiproliferative agents other than everolimus were prohibited.

- Investigators were instructed to avoid co-administration of consumption of the following drugs or foods known to affect activity of cytochrome P450 or P-glycoprotein (PgP):
  - Moderate or strong inhibitors of cytochrome P450 3A4 (CYP3A4)
  - Inhibitors of PgP
  - Strong inducers of CYP3A4 other than anti-epileptics
  - Seville orange, star fruit, grapefruit and other juices known to affect CYP 450 and PgP activity
- Investigators were instructed to avoid administration of live vaccines during study therapy.

5.3.1.6 Protocol-Specified Discontinuation Criteria

The Study M2301 protocol indicated that patients could discontinue study treatment for any of the following reasons: adverse event (s), abnormal laboratory value (s), abnormal test procedure result (s), SEGA progression, protocol deviation, withdrawal of consent, lost to follow up, administrative problems, death, commencement of new therapy for SEGA, completion of treatment during the extension phase, and if the primary analysis of the core phase data indicated that the extension phase should not open. Irrespective of the reason for study therapy discontinuation, patients were required to have an additional evaluation 28 days after the last dose of study treatment. The protocol also indicated that patients could withdraw from the study at any time.

5.3.1.7 Schedule of Assessments for Study M2301

The schedule of assessments for the blinded and open label periods of the core treatment phase of Study M2301 are outlined in Table 8 and Table 9, respectively (copied from the Applicant's NDA submission).

Table 8: Schedule of assessments for blinded treatment period of core phase of Study M2301 (copied from Applicant's submission)

Assessment	Screening /Baseline	Treatment Day 1	2 wks	4 wks	6 wks	8 wks	12 wks	18 wks	24 wks	Every 12 wks thereafter	Every 24 wks thereafter	End of treatment	Follow-Up	Study Completion
Time point (days)	-14 to -1	0	14	28	42	56	84	126	168					Last
Visit no.	1	2	3	4	5	6	7	8	9			777 or 779		780
Written Informed Consent (S)	X													
Inclusion/Exclusion Criteria (D)	X													
IWRS Registration [a] (S)	X													
Demography (D)	X													
Medical History/Current Medical Conditions (D)	X													
Hepatitis screen and HIV history (D)	X													
Serum pregnancy test[b] (D)	X													
IWRS Randomization[c] (S)	X													
Vital signs (D)	X	X		X		X	X	X	X	X		X		

Schedule of assessments for blinded treatment period of core phase of Study M2301 (continued, copied from Applicant's submission)

Assessment	Screening /Baseline	Treatment Day 1	2 wks	4 wks	6 wks	8 wks	12 wks	18 wks	24 wks	Every 12 wks thereafter	Every 24 wks thereafter	End of treatment	Follow-Up	Study Completion
Time point (days)	-14 to -1	0	14	28	42	56	84	126	168					Last
Visit no.	1	2	3	4	5	6	7	8	9			777 or 779		780
Body Surface Area Calculation (D)		X		X		X	X	X	X	X				
Physical exam (including Neurological Exam)[d] (S)	X	X		X		X	X	X	X	X		X		
Performance status (WHO or Lansky)[e] (D)	X	X		X		X	X	X	X	X		X		
ECG[f] (D)	X											X		
Hematology[g] (D)	X		X	X	X	X	X	X	X	X		X		
Coagulation Studies (PTT/INR) (D)	X						X		X	X				
Serum Chemistry[h] (D)	X		X	X	X	X	X	X	X	X		X		
Serum Lipid Profile[i] (D)	X						X		X	X				
Urinalysis[j] (D)	X			X		X	X	X	X	X		X		
Prior/Current concomitant medications[k] (D)	Daily													
Adverse events[l] (D)	Daily													

Schedule of assessments for blinded treatment period of core phase of Study M2301 (continued, copied from Applicant's submission)

Assessment	Screening /Baseline	Treatment Day 1	2 wks	4 wks	6 wks	8 wks	12 wks	18 wks	24 wks	Every 12 wks thereafter	Every 24 wks thereafter	End of treatment	Follow-Up	Study Completion
Time point (days)	-14 to -1	0	14	28	42	56	84	126	168					Last
Visit no.	1	2	3	4	5	6	7	8	9			777 or 779		780
MRI of the Brain[m] (D)	X						X		X		X**	X		
MRI of the Kidney[n] (D)	X						X		X		X**	X		
Neuropsychological Assessments[o] (D)	X								X		X	X		
24 hour video EEG[p] (D)	X								X					
Seizure Severity Questionnaire[q](D)	X								X					
RAD001/placebo dosing (D)	Daily													
Biomarkers blood sampling[r] (D)	X				X			X		X	X*		X	
TSC1 and *TSC2* genetic analysis (D)	X													
PK blood sampling[s] (D)			X		X	X	X	X	X	X	X		X	
Pulmonary function tests[t] (D)	X	X	X		X	X	X	X	X	X	X		X	
Chest CT[u] (D)	Only to be done if clinically indicated													
Digital Photographs of Skin lesions[v] (D)	X	X						X		X	X		X	

Schedule of assessments for blinded treatment period of core phase of Study M2301 (continued, copied from Applicant's submission)

Assessment	Screening /Baseline	Treatment Day 1	2 wks	4 wks	6 wks	8 wks	12 wks	18 wks	24 wks	Every 12 wks thereafter	Every 24 wks thereafter	End of treatment	Follow-Up	Study Completion
Time point (days)	-14 to -1	0	14	28	42	56	84	126	168					Last
Visit no.	1	2	3	4	5	6	7	8	9			777 or 779		780
Physician's Global Assessment of Skin Lesions (D)								X		X	X		X	

* Biomarker samples will only be collected through week 48. An additional biomarker sample will be collected at the End of Treatment visit.

**MRI of Kidneys and Brain (if necessary) will be completed for all patients at baseline, 12, 24 and 48 weeks after the start of treatment and annually thereafter.

All visits must be completed within ± 7 days of scheduled visit, with the exception of the baseline visit which must be conducted no more than 14 days after the screening visit. All tests and procedures (i.e., MRIs, hematology labs, biochemistry labs) that occur within the 7 days before or after the scheduled visit will not constitute a protocol deviation.

a Patients should be registered through IWRS after informed consent is signed.

b Pregnancy test only to be performed in females of childbearing potential at local lab. Pregnancy test may be repeated during the study at the discretion of the investigator, if required.

c Patients should be randomized through IWRS, after all eligibility criteria have been confirmed, and no more than 7 days before Treatment Day 1.

d Significant findings from Physical Examination will be noted in the Relevant Medical history pages or Adverse Events pages.

e Performance status should be assessed using the WHO Performance Status for patients aged 13 years or older, and the Lansky Play Performance Status for patients aged from 0 to 12 years inclusive (at randomization). Patients assessed by Lansky Play Performance Status at screening should continue to be assessed with this tool throughout the trial, even after they have reached the age of 13 years (note that the tool has been designed for children up to the age of 18).

f ECG may be repeated at the investigator's discretion if there are signs or symptoms of cardiotoxicity. Significant findings will be noted in the Relevant Medical history pages or Adverse Events pages.

g Hematology must include: hemoglobin, hematocrit, platelets, red blood cell count (RBC) total white blood cell count (WBC) absolute & differential including neutrophils, lymphocytes, monocytes, eosinophils and basophils. Absolute Neutrophil Count will be calculated by the laboratory. PTT (INR) evaluation will be included at screening.

Schedule of assessments for blinded treatment period of core phase of Study M2301 (continued, copied from Applicant's submission)

h Serum Chemistry must include: total LDH, fasting glucose, sodium, magnesium, phosphate, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, uric acid, calcium.

i Serum Lipid profile must include: total cholesterol, triglycerides, LDL, and HDL. Assessment should be repeated every 12 weeks.

j Standard urinalysis dipstick assessment must include: pH, protein, glucose, blood, ketones, and leukocytes.

k Medications taken within the 30 days prior to starting treatment and up to 30 days after last dose should be documented on the appropriate CRF.

lAEs should be recorded on the AE CRF from the time of starting study treatment and up to 28 days after last dose (until the follow-up visit). All SAEs occurring within 28 days of study treatment discontinuation (until the follow-up visit), regardless of causality, should be captured on AE CRF. SAEs with suspected causality to study drug should be captured for an additional 8 weeks (56 days) after follow-up visit (for a total of 12 weeks (84 days) after treatment discontinuation).

m MRI of the brain should be performed at screening/baseline, at 12, 24 and 48 weeks after start of study treatment, and annually thereafter, unless observation of SEGA response warrants a confirmation no sooner than 4 weeks after observation. MRI is not required at 18 weeks.

n MRI of the kidneys should be performed at screening/baseline for all patients. For all patients with at least one angiomyolipoma with longest diameter ≥ 1.0 cm at screening , MRI of the kidneys should be repeated at 12, 24 and 48 weeks after start of study treatment, and annually thereafter, unless observation of response warrants a confirmation no sooner than 4 weeks after observation. MRI of the kidneys is not required at 18 weeks.

o One of the following assessments must be conducted: Wechsler Pre-School and Primary Scale of Intelligence, Wechsler Abbreviated Scale of Intelligence or the Vineland Adaptive Behavior Scale. The test that is administered will depend on the patient's age at randomization, the patient's cognitive/behavioral status, and whether the assessment is available in the patient's native language. In addition, neuropsychological Assessments, that are routinely performed on these patients according to standard clinical practice, are encouraged. These assessments are recommended to be performed at baseline, 24 weeks and every 24 weeks thereafter. However, neuropsychological assessments may be administered more or less frequently, based on the investigator's and/or psychologist's discretion.

p 24 hour video EEG to be conducted at screening/baseline and week 24, and sent for an independent central review (screening/baseline EEG should only be performed once it has been confirmed that the patient is eligible to be randomized).

q Seizure Severity Questionnaire to be filled out for patients being treated with antiepileptics at baseline, whenever available in the patient's native language.

r A biomarker sample will be collected at screening/baseline, and at 4 weeks, 12 weeks, 24 weeks, 36 weeks, 48 weeks and at end of treatment. No additional biomarker samples will be collected.

s Blood samples for trough RAD001 levels will be collected from all patients pre-dose at every visit starting at week 2 (Visit 3) and until discontinuation of study drug. In addition, a blood sample for Cmax will be collected 2.0 hours (± 30 mins) after dosing at week 2 (Visit 3) and 2 weeks after any dose adjustment.

t Pulmonary Function tests will be assessed for all patients in the clinic at each visit and will include spirometry (FEV1), DLco and room air O2 saturation at rest and will be performed and interpreted using the ATS/ERS guidelines (Brusasco et al, 2005). *Patients unable to perform a pulmonary function test (e.g. younger children, patients with developmental delay) will have a baseline chest CT scan performed. In the event that they develop signs and or symptoms suggestive of non-infectious pneumonitis, follow-up chest CT scans should be performed as clinically indicated.

u Chest CT should be performed as clinically indicated.

v For patients with skin lesions at screening/baseline: Skin lesions will be photographed together with a calliper or a ruler, using a digital camera. Skin lesion photographs will be taken at baseline, 12 and 24 weeks after start of study treatment, and every 12 weeks thereafter.

Table 9: Schedule of assessments for open label period of core treatment phase and extension phase of Study M2301 (copied from Applicant's submission)

NOTE: To be followed for patients who are initiating RAD001 for the first time:

Assessment	Baseline	Treatment Day 1	2 weeks	4 weeks	6 weeks	8 weeks	12 weeks	18 weeks	24 weeks	Every 12 weeks thereafter	Every 24 weeks thereafter	End of treatment	Follow-Up	Study Completion
Time point (days)	-28 to -1	0	14	28	42	56	84	126	168					Last
Visit no.	101	102	103	104	105	106	107	108	109			778 or 779		780
Vital signs (D)	X	X		X		X	X	X	X	X		X		
Body Surface Area Calculation (D)		X		X		X	X	X	X	X				
Physical exam (including Neurological Exam)[a] (S)	X	X		X		X	X	X	X	X		X		
Performance status (WHO or Lansky)[b] (D)	X	X		X		X	X	X	X	X		X		
ECG[c] (D)	X											X		
Hematology[d] (D)	X		X	X	X	X	X	X	X	X		X		
Coagulation Studies (PTT/INR) (D)	X						X		X	X				
Serum Chemistry[e] (D)	X		X	X	X	X	X	X	X	X		X		
Serum Lipid Profile[f] (D)	X						X		X	X				
Urinalysis[g] (D)	X			X		X	X	X	X	X		X		

Schedule of assessments for open label period of core treatment phase and extension phase of Study M2301
(continued, copied from Applicant's submission)

Assessment	Baseline	Treatment Day 1	2 weeks	4 weeks	6 weeks	8 weeks	12 weeks	18 weeks	24 weeks	Every 12 weeks thereafter	Every 24 weeks thereafter	End of treatment	Follow-Up	Study Completion
Time point (days)	-28 to -1	0	14	28	42	56	84	126	168					Last
Visit no.	101	102	103	104	105	106	107	108	109			778 or 779		780
Prior/Current concomitant medications[h] (D)	Daily													
Adverse events[i] (D)	Daily													
MRI of the Brain[j] (D)	X						X		X		X*	X		
MRI of the Kidney[k] (D)	X						X		X		X*	X		
Neuropsychological Assessments[l] (D)	X								X		X	X		
24 hour video EEG[m] (D)	X								X					
Seizure Severity Questionnaire[n] (D)	X								X					
RAD001 dosing (D)	Daily													
PK blood sampling[o] (D)			X	X	X	X	X	X	X	X		X		
Pulmonary function tests[p] (D)	X	X	X	X	X	X	X	X	X	X		X		
Chest CT[q] (D)	Only to be done if clinically indicated													
Digital Photographs of Skin lesions[r] (D)	X	X					X		X	X		X		
Physician's Global Assessment of Skin Lesions (D)							X		X	X		X		

*The most recent MRIs of the brain and kidney (if followed) from the core phase of the study will be used as the baseline (if completed within 28 days of initiating RAD001) Additional MRIs of the brain will be conducted at 12, 24 and 48 weeks after start of open-label RAD001, and annually thereafter. MRI of the kidneys would only be conducted if the patient had angiomyolipoma with longest diameter ≥ 1.0 cm at screening during the blinded phase.

Schedule of assessments for open label period of core treatment phase and extension phase of Study M2301
(continued, copied from Applicant's submission)

All visits must be completed within ± 7 days of scheduled visit, with the exception of the baseline visit which must be conducted no more than 28 days after the blinded End of Treatment Visit. All tests and procedures (i.e., MRIs, hematology labs, biochemistry labs) that occur within the 7 days before or after the scheduled visit will not constitute a protocol deviation.

[a] Significant changes from last Physical Examination conducted in the blinded phase will be noted in the Adverse Events pages.

[b] Performance status should be assessed using the WHO Performance Status for patients aged 13 years or older, and the Lansky Play Performance Status for patients aged from 0 to 12 years inclusive (at randomization). Patients assessed by Lansky Play Performance Status at baseline should continue to be assessed with this tool throughout the trial, even after they have reached the age of 13 years (note that the tool has been designed for children up to the age of 18).

[c] ECG may be repeated at the investigator's discretion if there are signs or symptoms of cardiotoxicity. Significant findings will be noted in the Relevant Medical history pages or Adverse Events pages.

[d] Hematology must include: hemoglobin, hematocrit, platelets, red blood cell count (RBC) total white blood cell count (WBC) absolute & differential including neutrophils, lymphocytes, monocytes, eosinophils and basophils. Absolute Neutrophil Count will be calculated by the laboratory. PTT (INR) evaluation will be included at baseline.

[e] Serum Chemistry must include: total LDH, fasting glucose, sodium, magnesium, phosphate, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, uric acid, calcium.

[f] Serum Lipid profile must include: total cholesterol, triglycerides, LDL, and HDL. Assessment should be repeated every 12 weeks.

[g] Standard urinalysis dipstick assessment must include: pH, protein, glucose, blood, ketones, and leukocytes.

h Medications taken within the 30 days prior to starting treatment and up to 30 days after last dose should be documented on the appropriate CRF.

[i] AEs will continue to be recorded on the AE CRF up to 28 days after last dose (until the follow-up visit). All SAEs occurring within 28 days of study treatment discontinuation (until the follow-up visit), regardless of causality, should be captured on AE CRF. SAEs with suspected causality to study drug should be captured for an additional 8 weeks (56 days) after follow-up visit (for a total of 12 weeks (84 days) after treatment discontinuation).

[j] MRI of the brain should be performed at 12, 24 and 48 weeks after start of study treatment, and annually thereafter, unless observation of SEGA response warrants a confirmation no sooner than 4 weeks after observation. MRI is not required at 18 weeks.

[k] For all patients with at least one angiomyolipoma with longest diameter ≥ 1.0 cm at screening of the blinded phase, MRI of the kidneys should be repeated at 12, 24 and 48 weeks after start of study treatment, and annually thereafter, unless observation of response warrants a confirmation no sooner than 4 weeks after observation. MRI of the kidneys is not required at 18 weeks.

[l] One of the following assessments must be conducted: Wechsler Pre-School and Primary Scale of Intelligence, Wechsler Abbreviated Scale of Intelligence or the Vineland Adaptive Behavior Scale. The test that is administered will depend on the patient's age at randomization, the patient's cognitive/behavioral status, and whether the assessment is available in the patient's native language. In addition, neuropsychological Assessments, that are routinely performed on these patients according to standard clinical practice, are encouraged. These assessments are recommended to be performed at baseline, 24 weeks and every 24 weeks thereafter. However, neuropsychological assessments may be administered more or less frequently, based on the investigator's and/or psychologist's discretion.

Schedule of assessments for open label period of core treatment phase and extension phase of Study M2301
(continued, copied from Applicant's
submission)

[m] 24 hour video EEG to be conducted at baseline (if more than 28 days has passed since the patient's previous video EEG) and week 24, and sent for an independent central review.

[n] Seizure Severity Questionnaire to be filled out for patients being treated with antiepileptics at baseline, whenever available in the patient's native language.

[o] Blood samples for trough RAD001 levels will be collected from all patients pre-dose at every visit starting at week 2 (Visit 103) and until discontinuation of study drug. In addition, a blood sample for C_{max} will be collected 2.0 hours (± 30 mins) after dosing at week 2 (Visit 103) and 2 weeks after any dose adjustment.

[p] Pulmonary Function tests will be assessed for all patients in the clinic at each visit and will include spirometry (FEV_1), DL_{co} and room air O_2 saturation at rest and will be performed and interpreted using the ATS/ERS guidelines (Brusasco et al, 2005). *Patients unable to perform a pulmonary function test (e.g. younger children, patients with developmental delay) will have a baseline chest CT scan performed. In the event that they develop signs and or symptoms suggestive of non-infectious pneumonitis, follow-up chest CT scans should be performed as clinically indicated.

[q] Chest CT should be performed as clinically indicated.

[r] For patients with skin lesions at baseline: Skin lesions will be photographed together with a calliper or a ruler, using a digital camera. Skin lesion photographs will be taken at baseline, 12 and 24 weeks after start of study treatment, and every 12 weeks thereafter.

5.3.1.8 Statistical Design of Study M2301

Please see the FDA statistical review by Dr. Weishi Yuan, for additional details regarding the statistical design and analysis of Study M2301. The data cut-off for the primary analysis of Study M2301 was 6 months after the last patient was randomized. All data up to the data cut-off date were included in the final analysis, but the statistical analyses focused on data from the double-blind phase of the trial; data collected during the open label phase were reported in separate analyses. The full analysis set (FAS), consisting of all randomized patients, was the primary population used in the efficacy assessments. The safety set consisted of all patients who received at least one dose of study drug during the double-blind period. The per-protocol set (PPS) consisted of all patients from the FAS without major protocol deviations who received blinded study drug for at least 50% of the days in the first 12 weeks of therapy.

All 117 patients in the full analysis set were included in the safety set. Four patients were excluded from the PPS (3 in the everolimus arm and 1 in the placebo arm). The Independent Review Committee did not confirm the presence of a target SEGA lesion for two patients in the everolimus arm: Patient 0500_00006 and Patient 0600_00007; an additional patient was excluded from the PPS due to insufficient treatment exposure. One patient in the placebo arm was excluded form the PPS because they received a different medication pack (also placebo) from the one assigned by IWRS for a period of 25 days.

Primary Efficacy Endpoint

The primary efficacy endpoint of Study M2301 was the SEGA response rate, defined as the proportion of patients with a SEGA response by independent central radiological (IRC). In order to qualify as a SEGA response, the IRC had to concur that the following two conditions were met, based on review of two scans, performed approximately 8-12 weeks apart:

- A reduction in sum of the volumes of all target SEGA lesions of ≥ 50% relative to baseline.
- Absence of unequivocal worsening of non-target SEGA lesions, new SEGA lesions (≥ 1 cm in longest diameter) or worsening hydrocephalus (defined by IRC assessment of changes in ventricular configuration, periventricular edema, and cerebrospinal fluid flow dynamics).

Target lesions, which were required to have at least one dimension measuring 1 cm or longer, were identified and recorded at baseline. SEGA volume measurements were obtained through brain MRIs performed during screening, and 12, 24, and 48 weeks after starting study therapy. Thereafter, MRIs were

performed annually. MRIs were obtained locally and then sent for independent central radiology review within 2 days of the scan for estimation of volume at each time point.

Comparison of SEGA response rates in the everolimus and placebo arms was performed using a Cochran-Mantel-Haenszel (CMH) test with a one-sided alpha of 2.5%. The test was stratified by presence or absence of use of EIAEDs.

Key Secondary Endpoints

The following three key secondary endpoints were analyzed for Study M2301:

- The absolute change in frequency of total seizures per 24 hours from baseline to Week 24
- Time to SEGA progression
- Skin lesion response rate.

These endpoints were tested after analysis of the primary endpoint using a pre-defined fixed-sequence testing procedure to control for multiplicity. A hierarchical testing sequence was included in the protocol; after testing of the primary endpoint of SEGA response rate, the first secondary endpoint tested was the change in total seizure frequency from baseline to Week 24, followed by time to SEGA progression and skin lesion response rate.

Change in Seizure Frequency

The absolute change from baseline to Week 24 in the number of seizures per 24 hour period, documented by 24-hour video EEG, was compared between the everolimus and placebo arms using the rank analysis of covariance (ANCOVA) method, with baseline seizure frequency as a covariate. The analysis was stratified by the use of EIAEDS, and the test was performed using a 2.5% significance level.

Time to SEGA Progression

Time to SEGA progression was defined as the time from the date of randomization to the date of the first documented SEGA progression as per Independent Central Review. SEGA progression was diagnosed if imaging documented one or more of the following conditions:

- ≥ 25% increase from nadir in SEGA volume, to a value greater than baseline SEGA volume
- Unequivocal worsening of non-target SEGA lesions
- Appearance of a new SEGA lesion ≥ 1 cm in longest diameter
- New or worsening hydrocephalus.

Time to SEGA progression was censored if SEGA progression was not observed before the cut-off date for the final analysis, the date a new therapy for treatment

of SEGA was initiated, or death, whichever occurred first. The censoring date was the date of the most recent MRI assessment before the first occurrence of any of these events. Time to SEGA progression was compared between the everolimus and placebo arms using a one-sided log-rank test stratified by use of EIAEDs at the 2.5% level.

Skin Lesion Response Rate
Digital photographs were used to document skin lesion response. Skin lesion response rate was defined as the proportion of patients with at least one skin lesion at baseline who exhibited a response (complete clinical response or partial response) using the Physician's Global Assessment of Clinical Condition (PGA). This assessment was designed to evaluate change in skin lesions as a whole. Responses were confirmed by at least two assessments performed at least 4 weeks apart. A complete clinical response required clinically absent skin disease. A partial response, corresponding to a PGA Grade of 3 ("moderate improvement"), 2 ("marked improvement") or 1 ("almost clear"), required overall improvement in skin lesions by at least 50% compared to baseline. Comparison of skin lesion response rates in the everolimus and placebo arms was performed using a CMH test with a one-sided alpha of 2.5%.

Additional Secondary Endpoints
The following additional secondary endpoints were evaluated in Study M2301:

- duration of SEGA response: time from first documented SEGA response until the first documented SEGA progression
- Time to SEGA response: time from randomization until the date of the first documented SEGA response
- Time to SEGA worsening: time from date of randomization to the date of first documented SEGA worsening
- Duration of skin lesion response: time from first skin lesion response until the date of the first skin lesion progression.
- Frequency of interictal epileptiform discharge (IED): absolute change from baseline to Week 24 in the number of IED events per 15 minutes in sleep and awake mode for each treatment group.

Exploratory Efficacy Endpoints
The following exploratory efficacy endpoints were also examined: correlation between volume and longest diameter of target SEGA lesions; changes in subependymal nodule (SEN) and tuber target lesions; angiomyolipoma response rate; change in left and right kidney volumes in patients with angiomyolipoma at baseline; change in neuropsychological assessments (WPPSI, WASI or VABS); and global change in the score of seizure severity (via the SSQ instrument). The protocol included a plan for comparison of the need for SEGA-related surgery in the everolimus and placebo groups; however, no patients required surgery, so this comparison was not performed.

5.3.1.9 Protocol Amendments for Study M2301

Four protocol amendments were issued for Study M2301. The important aspects of these amendments are summarized below:

Amendment 1 (0 patients, dated August 11, 2009)

- Added a requirement for the diagnosis of SEGA progression that target lesion volume had to increase to above the baseline value.
- Removed prior brain surgery from the exclusion criteria.
- Permitted renal disease to be assessed by CT or MRI.
- Permitted scans for confirmation of SEGA response to be performed up to 12 weeks after the initial SEGA response, instead of four weeks after the response.
- The requirement for assessment of pulmonary function testing (PFT) at every visit was removed. Instead, PFTs could be performed when clinically indicated.
- The screening period was increased from 14 to 21 days.

Amendment 2 (42 patients, dated April 2, 2010)

- Based on results from Study C2485, the target everolimus trough concentration range was changed from (b) (4) to 5-15 ng/mL.
- Guidance was provided regarding screening for hepatitis infections and exclusion of patients with active hepatitis.
- Evaluation of endocrine parameters and tanner staging was added to screen for low, age-adjusted testosterone levels and luteneizing hormone concentrations > 15 IU/L reported in the transplant setting. The amendment specified that endocrine testing should be performed every 12 weeks for girls and boys that did not exhibit secondary sexual characteristics by age 13 and 14, respectively.

Amendment 3 (117 patients, dated January 11, 2011)

- Frequency of assessments of growth and development parameters was changed to comply with the FDA postmarketing requirement issued with the 2010 accelerated approval for the SEGA indication.
- Additional guidelines for interruption of everolimus for patients with Hepatitis B reactivation and Hepatitis C flare were added.

Amendment 4 (117 patients, dated February 23, 2011)

- Addition of requirement for endocrine testing [FSH, LH, and estradiol (for females)] at baseline or the next scheduled visit, if not already performed.
- Frequency of endocrine sampling outlined as annually until the patient's 10th birthday, and every 12 weeks thereafter.

5.3.2 Study CRAD001C2485 (Study C2485)

For detailed information regarding the design of Study CRAD001C2485 (hereafter referred to as Study C2485), please see Dr. Amir Shahlaee's clinical review of sNDA 22334, Supplement 6 dated October 26, 2010. Study C2485 was an open-label, single-arm single-center, investigator-sponsored trial evaluating the safety and efficacy of everolimus in patients greater than or equal to 3 years of age with SEGA associated with TSC. Serial radiological evidence of SEGA growth was required for entry. In this study, change in SEGA volume was assessed by independent central radiology review at the end of the core 6-month treatment phase. In total, 28 patients received treatment with everolimus, and four patients had surgical resection of their SEGA lesions with subsequent re-growth prior to receiving everolimus treatment. After the core treatment phase, patients could continue to receive everolimus treatment by enrolling into an extension treatment phase where SEGA volume was assessed every 6 months. At 6 months, 9 of 28 patients (32%, 95% CI: 16% to 52%) had a ≥50% reduction in the tumor volume of their largest SEGA lesion. The duration of response for these 9 patients ranged from 97 to 946 days, with a median of 266 days. Seven patients had an ongoing volumetric reduction at the December 9, 2009 data cut-off date. The median duration of treatment was 24.4 months (range 4.7 to 37.3 months). This NDA included additional safety and efficacy data reflecting an additional year of follow up; the cut-off date for the updated analysis is December 31. 2010.

6 Review of Efficacy

Efficacy Summary

Study M2301 was a randomized (2:1), double-blind, placebo-controlled trial of everolimus conducted in 117 pediatric and adult patients with SEGA and TSC. Eligible patients had at least one SEGA lesion ≥ 1 cm in longest diameter based on local MRI assessment and one or more of the following: serial radiological evidence of SEGA growth, a new SEGA lesion ≥ 1 cm in longest diameter, or new or worsening hydrocephalus. Patients randomized to the treatment arm received everolimus 1 mg MF tablets at a starting dose of 4.5 mg/m^2/day, with subsequent dose adjustments as needed to achieve and maintain everolimus trough concentrations of 5 to 15 ng/mL. Patients received everolimus or matched placebo until disease progression or unacceptable toxicity. MRI scans were obtained at baseline, 12, 24, and 48 weeks, and annually thereafter. The primary efficacy endpoint was SEGA response rate based on independent central radiology review. SEGA response was defined as a ≥ 50% reduction in the sum of the SEGA volume of target lesions relative to baseline, in the absence of unequivocal worsening of non-target SEGA lesions, a new SEGA lesion ≥ 1 cm, or new or worsening hydrocephalus. Analysis of SEGA response rate was

limited to the blinded treatment period which ended 6 months after the last patient was randomized.

A total of 78 patients were randomized to everolimus and 39 patients were randomized to placebo. The median age of patients enrolled was 9.5 years (range 0.8 to 26 years). The SEGA response rate was statistically significantly higher in everolimus-treated patients. There were 27 (35%) patients with SEGA responses in the everolimus arm and no SEGA responses in the placebo arm ($p<0.0001$; 95% CI: 24%, 46% for the everolimus arm and 0%, 9% for the placebo arm). At the time of the primary analysis, the median duration of response was 5.3 months (range 2.1 to 8.4 months). With a median follow-up of 8.4 months, SEGA progression was observed in 6 of 39 (15.4%) patients in the placebo arm; no patients in the everolimus arm exhibited SEGA progression.

The updated data from Study C2485, reflecting an additional year of follow-up after the December 9, 2009 data cut-off used for the primary analysis, provides evidence of durability of objective tumor responses in patients with SEGA. At 6 months, 9 out of 28 patients (32%, 95% CI: 16% to 52%) had a ≥ 50% reduction in the tumor volume of their largest SEGA lesion. As of December 30, 2010, the median duration of treatment of patients enrolled in Study C2485 was 34.2 months (range 4.7-47.1 months). As of December 30, 2010, the median duration of response for the 9 patients who exhibited a SEGA response at 6 months was 360 days (range 97 to 1191 days); seven of these 9 patients had an ongoing volumetric reduction of ≥ 50% at the time of data-cut-off. No patient receiving everolimus has developed new a new SEGA lesion.

6.1 Indication

In this NDA, the sponsor proposed a slight rewording of the indication that was granted with the 2010 accelerated approval of Afinitor Tablets. FDA granted accelerated approval to Afinitor for the following indication on October 29, 2010:

> *Afinitor is indicated for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) who require therapeutic intervention but are not candidates for curative surgical resection.*
>
> *The effectiveness of AFINITOR is based on an analysis of change in SEGA volume. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated.*

This indication was revised on April 26, 2012:

> *Afinitor is indicated for the treatment of adults and children, ≥ 3 years of age with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection.*
>
> *The effectiveness of AFINITOR is based on an analysis of change in SEGA volume. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated.*

With this NDA, the sponsor proposed the following revisions to the approved indication:

6.1.1 Methods

This NDA included data supporting the primary efficacy analysis of Study M2301, in addition to updated efficacy data from Study C2485. Sections 6.1.2 through 6.1.7 of this review focus on the results of the primary analysis of Study M2301. The data from the primary analysis of Study C2485, previously submitted to NDA 22334 Supplement 6, provided the basis for the 2010 accelerated approval of Afinitor for the treatment of patients with SEGA associated with TSC who require therapeutic intervention but are not candidates for curative surgical resection. For a detailed discussion of the results of the primary analysis of Study C2485, see the FDA clinical review of NDA 22334 (supplement 6) dated October 26, 2010 by Dr. Amir Shahlaee. A review of the updated disposition of subjects enrolled in Study C2485 is provided in Section 6.1.3 (Subject Disposition) and a discussion of updated efficacy data from Study C2485 is provided in Section 6.1.9 (Discussion of Persistence of Efficacy and/or Tolerance Effects) of this review.

6.1.2 Demographics

Table 10 provides a summary of the demographic characteristics of patients enrolled in Study M2301

Table 10: Demographic characteristics of patients enrolled in Study M2301

Demographic Characteristic	Everolimus N = 78	Placebo N=39
Age (years)		
Mean (std dev)	10.1 (5.9)	10.3 (7.3)
Median (range)	9.5 (1.0-23.9)	7.1 (0.8-26.6)
Age group (years) n (%)		
< 3	13 (16.7)	7 (17.9)
3 to < 12	38 (48.7)	16 (41.0)
12 to < 18	17 (21.8)	10 (25.6)
≥ 18 years	10 (12.8)	6 (15.4)
Gender n (%)		
Male	49 (62.8)	18 (46.2)
Female	29 (37.2)	21 (53.8)
Race n (%)		
Caucasian	73 (93.6)	36 (92.3)
Black or African American	3 (3.8)	1 (2.6)
Pacific Islander or Native Hawaiian	1 (1.3)	0
Asian		
American Indian or Alaska Native	0	0
Other	1 (1.3)	2 (5.1)
Ethnicity n (%)		
Not Hispanic/Latino	76 (97.4)	35 (89.7)
Hispanic/Latino	2 (2.6)	4 (10.3)
Weight (kg)		
Mean (std dev)	38.7 (22.8)	39.5 (24.5)
Median (range)	31.4 (9.0 – 107.8)	27.1 (7.9 – 94.0)
BSA (m^2)		
Mean (std dev)	1.2 (0.5)	1.2 (0.5)
Median (range)	1.1 (0.4 – 2.2)	1.0 (0.4 – 2.1)

The treatment arms were well balanced with respect to all key demographic characteristics except gender; there was a higher percentage of male patients randomized to the everolimus arm (63%) compared to the placebo arm (46%). The majority of patients were Caucasian, reflecting the countries that participated in the trial. The highest enrolling countries were: the US (57%), Poland (16%),

Russia (10%), Germany (6%), Belgium (3%), and Canada (3%). Australia, Italy, Great Britain and the Netherlands enrolled one or two patients each (Table 11).

Table 11: Summary of patient enrollment in Study M2301 by country:

Country	Everolimus		Placebo		Total %	
United States	49	63%	18	46%	67	57%
Poland	10	13%	9	23%	19	16%
Russia	7	9%	5	13%	12	10%
Germany	6	8%	1	3%	7	6%
Belgium	1	1%	2	5%	3	3%
Canada	3	4%	0	0%	3	3%
Australia	1	1%	1	3%	2	2%
Italy	0	0%	2	5%	2	2%
Great Britain	1	1%	0	0%	1	1%
The Netherlands	0	0%	1	3%	1	1%

Table 12 provides a summary of the incidences of major and minor diagnostic criteria of TSC in patients enrolled in Study M2301. For the everolimus arm, the median number of major diagnostic criteria fulfilled was median 7 (range: 2 to 10), and median number of minor diagnostic criteria fulfilled was 1 (range: 0 to 6). For the placebo group, the median number of major diagnostic criteria fulfilled 7 (range: 4 to 9) and the median number of minor diagnostic criteria fulfilled was 1 (range: 0 to 4). At least 2 major TSC diagnostic criteria were present in each patient enrolled in Study M2301; therefore, all patients met the criteria for "definite" diagnosis of TSC, according to the revised Gomez criteria.

Table 12: Summary of baseline TSC diagnostic criteria in patients enrolled in Study M2301

TSC Diagnostic Criteria n (%)	Everolimus N = 78	Placebo N=39
Major features		
Subependymal Giant Cell Astrocytoma	78 (100)	39 (100)
Subependymal nodule	73 (94)	37 (95)
Cortical Tuber	71 (91)	38 (97)
≥3 hypomelanotic macules	70 (90)	36 (92)
Facial angiofibromas or forehead plaque	60 (77)	30 (77)

TSC Diagnostic Criteria n (%)	Everolimus N = 78	Placebo N=39
Cardiac rhabdomyoma, single or multiple	49 (63)	22 (56)
Renal angiomyolipoma	47 (60)	28 (72)
Shagreen patch (connective tissue nevus)	37 (47)	23 (59)
Non-traumatic ungula or periungual fibroma	12 (15)	14 (36)
Multiple retinal nodular hamartomas	11 (14)	9 (23)
Lymphangioleiomyomatosis	1 (1)	0
Minor Features		
Multiple renal cysts	31 (40)	9 (23)
Cerebral white matter radial migration lines	14 (18)	6 (15)
Gingival fibromas	10 (13)	10 (26)
Multiple randomly-distributed pits in dental enamel	10 (13)	6 (15)
Confetti skin lesions	9 (12)	7 (18)
Non-renal hamartoma	6 (8)	4 (10)
Retinal achromic patch	4 (5)	3 (8)
Bone cysts	2 (3)	0
Hamartomatous rectal polyps	0	0

Table 13 summarizes the key baseline characteristics of the SEGA lesions in patients enrolled in Study M2301

Table 13: SEGA characteristics present at baseline in patients enrolled Study M2301

SEGA Characteristics[a] n (%)	Everolimus N = 78	Placebo N=39
Worsening SEGA lesion	66 (85)	34 (87)
Serial growth	63 (81)	32 (82)
New SEGA lesion ≥ 1 cm diameter	7 (9)	5 (13)
New or worsening hydrocephalus	5 (6)	0
Number of target SEGA lesions		
0	2[b] (2.6)	0
1	40 (51)	25 (64)
2	34 (44)	14 (36)
3	1 (1)	0
≥4	1 (1)	0

SEGA Characteristics[a] n (%)	Everolimus N = 78	Placebo N=39
Number of non-target SEGA lesions		
0	46 (59)	20 (51)
1	28 (36)	16 (41)
2	2 (3)	2 (6)
3	2 (3)	1 (3)
SEGA volume[c] (cm^3)		
Mean (standard deviation)	2.8 (3.8)	1.8 (1.7)
Median (range)	1.6 (0.2 to 25.2)	1.3 (0.3 to 9.8)
Bilateral SEGAs	63 (81)	30 (77)
SEGA growth in or into the inferior surface of the ventricle	19 (24)	11 (28)
SEGA growth beyond the subependymal tissue adjacent to the ventricle	8 (10)	3 (8)
Hydrocephalus present	8 (10)	0
Prior surgery	6 (8)	2 (5)

a. As determined by the independent central radiology review.
b. Two patients had a target lesion by local radiology review that was not confirmed by independent central radiology review.
c. Sum of volumes of target SEGA lesions.

According to local radiology reviewer assessments, all patients met the key M2301 eligibility criterion for serial worsening of a SEGA lesion, which required the presence of serial SEGA growth, a new SEGA lesion, or new or worsening hydrocephalus. Because the pre-defined protocol eligibility requirement for documentation of a worsening SEGA lesion was based on local reviewer assessment, all patients enrolled in Study M2301 were eligible for enrollment. However, independent central radiology (IRC) review did not confirm the presence of a worsening SEGA lesion in seventeen patients ([12 (15%) in the everolimus arm and 5 (13%) on the placebo arm]. Table 14 lists the patients who were diagnosed with worsening SEGA lesion at baseline by local investigator review but did not have worsening SEGA by central review. Only one of the 12 patients in the everolimus arm with discrepant eligibility assessments was a responder.

Table 14: Patients with discordant assessments regarding SEGA lesion worsening

Patient Number	Treatment Arm	SEGA Responder?
0352_00001	everolimus	Yes
0500_00003	everolimus	No
0500_00007	everolimus	No
0515_00002	everolimus	No
0515_00008	everolimus	No
0516_00002	everolimus	No
0600_00003	everolimus	No
0600_00004	everolimus	No
0600_00007	everolimus	Not evaluable
0600_00009	everolimus	No
0600_00015	everolimus	No
0600_00019	everolimus	No
0150_00003	placebo	No
0450_00001	placebo	No
0510_00006	placebo	No
0515_00003	placebo	No
0515_00007	placebo	No

Six patients with discordant assessments enrolled in Site 0600 and four enrolled in Site 515.

In addition, the IRC did not confirm the presence of a Target SEGA lesion for two patients: Patient 0500_00006 and Patient 0600_00007. Both patients were randomized to receive everolimus, and were considered not evaluable.

Although used as a stratification factor for randomization, only 15 (19%) patients in the everolimus arm and 7 (18%) patients in the placebo arm reported use of enzyme-inducing antiepileptic use at baseline. Mutations within the TSC2 gene were more commonly observed than mutations in the TSC1 gene (73% versus 12%, respectively). One patient (randomized to the everolimus arm) had mutations in both the TSC1 and TSC2 genes.

6.1.3 Subject Disposition

Study M2301

A total of 117 patients were enrolled in Study M2301 from 24 centers in 10 countries. In accordance with the protocol, patients were randomized on a 2:1 basis to receive everolimus (n=78) or placebo (39), respectively. Table 15 summarizes the disposition of these patients, as of the March 2, 2011 cut-off

date for the primary analysis, and the July 18, 2011 cut-off date used for the 90-day safety update from the safety update.

Table 15: Patient disposition in Study M2301

Patient Disposition	Afinitor	Placebo
No. of patients enrolled	**117**	
No. of patients randomized	**78**	**39**
No. of patient discontinuations during double blind period (March 2, 2011 cut-off)	2	8
Withdrawal of consent	*1*	*1*
Lost to follow-up or administrative Decision	*1*	*1*
Disease progression	*0*	*6*
Total no. of patients remaining on double-blind therapy (at March 2, 2011 cut-off)	**76**	**31**
Additional discontinuations during double-blind period prior to unblinding but after March 2, 2011 cut-off date for primary analysis	0	2
Disease Progression	0	*2*
No. of patients without disease progression who were eligible to enter open label period extension phase after unblinding	76	29
No. of patients entering open label phase after unblinding	76[a]	25[b]
Number entering open label phase after disease progression prior to unblinding	N/A	7
Total no. of patients who received open-label everolimus	**61[c]**	**32[d]**
Discontinuation of open-label treatment	1	0
Number of patients receiving open label everolimus as of July 18, 2011	**60[c]**	**32[d]**

a. At the time of July 18, 2011 data cut-off, 61 patients of the 76 patients randomized to everolimus arm who remained on therapy at the time of unblinding had an evaluation recorded in the open-label period.
b. A total of 4 patients on the placebo arm who were eligible to crossover to everolimus after unblinding did not consent to enter the open-label period. One patient started open label everolimus after the July 18, 2011 cut-off date.
c. 61 of the 76 patients randomized to everolimus had an evaluation recorded for the open label phase prior to July 18, 2012.
d. A total of 31 of 32 patients started open label everolimus prior to the July 18, 2011 cut-off date. The remaining patient commenced everolimus on July 19, 2012.

After reviewing data from the primary analysis of Study M2301, the Study Steering Committee (SSC) recommended unblinding of the study treatment assignments. Accordingly, Study M2301 was unblinded on May 13, 2011. After unblinding, the 29 patients in the placebo arm without evidence of disease progression were eligible to receive open label everolimus; 25 of these 29 patients opted to receive everolimus therapy during the open-label period. Additionally, 7 patients randomized to placebo who exhibited progression of their SEGA lesions received open-label everolimus therapy.

Table 16 provides a listing of patients who discontinued from study-directed therapy during the double-blind period. During the double blind period, a larger percentage of patients prematurely discontinued from study therapy in the placebo arm compared to the everolimus arm. Prior to unblinding of the trial on May 13, 2011, two (2.5%) patients in the everolimus arm prematurely discontinued therapy, compared to 10 (25.6%) patients in the placebo arm.

Table 16: Summary of patient discontinuations from study therapy in Study M2301

Patient ID	Age (years)	Reason for discontinuation	Narrative findings
Everolimus Arm			
0512_00001	5.9	Subject withdrew consent	Patient experienced grade 2 adverse event "aggression/behavioral" and ultimately withdrew consent for study therapy after 5 months of therapy.
0500_00009	15.3	Lost to follow-up	Subject repeatedly failed to show up for scheduled visits and refused phone calls. Patient was discontinued from study therapy

Patient ID	Age (years)	Reason for discontinuation	Narrative findings
			after not showing up for October 2010 visit following receipt of a certified letter.
		Placebo Arm	
0503_00006	7	Subject withdrew consent	
0150_00002	6	Administrative problems	Patient was not compliant with study visits.
0500_00005	21	Disease progression	
0500_00012	1	Disease progression	
0502_00003	7	Disease progression	
0510_00008	5	Disease progression	
0600_00016	5	Disease progression	
0700_00008	6	Disease progression	
0600_00017[a]	11	Disease progression	
0403_00001[a]	2	Disease progression	

[a.] These patients discontinued due to disease progression after the primary analysis cut-off date (March 2, 1011) but prior to unblinding.

During the open-label period, one patient (Patient 0502-0008) discontinued study treatment with everolimus. The caretakers of this 5.9 year old girl, who was randomized to the everolimus arm, withdrew consent for continued therapy after she developed Grade 1 sinusitis on day 423 of study therapy.

Study C2485

Between January 7, 2007 and December 18, 2008, a total of 28 patients with SEGA were enrolled at a single site in Study C2485. Table 17 summarizes the disposition of these patients, as of the December 31, 2010 cut-off date. Twenty-seven (96.4%) patients received the 6-month core therapy, and all decided to continue everolimus in the extension phase of the study. At the time of the data cut-off for the 90-day safety update submitted to NDA 22334 Supplement 6

(March 8, 2010), 25 patients remained on study. Please see Dr. Amir Shahlaee's review of NDA 22334 Supplement 6, dated October 26, 2010 for details.

No patient discontinued study treatment between March 8, 2010 and December 31, 2010. Table 17 provides updated data of the disposition of patients enrolled in Study C2485.

Table 17: Study C2485 patient disposition (data cut-off December 31, 2010)

Disposition		Everolimus (N=28)
Ongoing	n (%)	25 (89)
Discontinued	n (%)	3 (10.7)

A brief summary of the circumstances surrounding everolimus discontinuation is provided below. Adverse events were not cited as the primary reason for discontinuing study therapy for any patient; all patients withdrew consent for continued therapy. However, based on review of patient narratives, it is possible that adverse events contributed to the decision to discontinue everolimus for all three patients.

- Patient 0001/00002 withdrew consent after 4.7 months of treatment. This patient was noncompliant with anti-epileptic medication and developed hyperkinesis prior to completing six months of treatment.
- Patient 0001/00008 discontinued treatment after 17.5 months of therapy. Discontinuation appeared to be due to a combination of factors. This patient was noncompliant with antiseizure medicine and experienced a prolonged seizure requiring hospitalization. The investigator attributed withdrawal to an inability to attend regularly scheduled study visits. The verbatim reason for treatment discontinuation was "hope to reduce incidence of infection."
- Patient 0001/00009 discontinued treatment after 21.5 months of therapy following withdrawal of parental consent. Although this patient's last recorded episode of stomatitis resolved approximately 350 days prior to discontinuing study treatment, stomatitis was listed as a secondary reason for treatment discontinuation.

An additional patient (Patient 001/0011) temporarily discontinued therapy after completing 18 months of therapy. This patient exhibited a 78% reduction in SEGA volume, which met the pre-specified criteria for treatment success (a 75% reduction in SEGA volume). However, after regrowth of the SEGA tumor was demonstrated on follow-up imaging at month 24, she subsequently recommenced therapy due to SEGA regrowth. This patient remains on

everolimus therapy and follow-up imaging on December 1, 2010 demonstrated a 72% reduction of SEGA tumor volume compared to baseline.

As of the December 31, 2010 data cut-off, all 25 patients that remain on study therapy have at least 24 months of exposure to everolimus.

6.1.4 Analysis of Primary Endpoint(s)

Study M2301

The primary efficacy endpoint was SEGA response rate, as determined by independent central radiology review. SEGA response required fulfillment of the following four criteria: (1) a ≥ 50% reduction in SEGA volume relative to baseline (where SEGA volume was the sum of all target SEGA lesion volumes identified at baseline); (2) no unequivocal worsening of non-target SEGA lesions; (3) no new SEGA lesions (≥ 1 cm in longest diameter); and (4) no new or worsening hydrocephalus. SEGA responses were confirmed by central radiology assessment of a follow-up MRI obtained 4-12 weeks after the initial assessment of SEGA response.

Analyses of data from Study M2301 showed that there was a statistically significant difference in the overall SEGA response rate by central radiology review in the treatment arms. A total of 27 of 78 patients (34.6%, 95% CI: 24.2% to 46.2%; p-value: <0.0001) randomized to everolimus exhibited a SEGA response, compared to no patients in the placebo arm. Table 18 summarizes the main efficacy analysis results for SEGA response rate.

Table 18: SEGA response per central radiology review in Study M2301

	Everolimus N = 78	**Placebo N = 39**
Best Overall SEGA Response n (%)		
Response	27 (34.6)	0
Stable Disease	49 (62.8)	36 (92.3)
Progression	0	3 (7.7)
Not Evaluable[a]	2 (2.6)	0
Response Rate (95% CI)	34.6% (24.2%, 46.2%)	0% (0%, 9.0%)
Difference in Response Rate (95% CI)	34.6% (15.1%, 52.3%)	
p-value[b]	< 0.0001	

a. two patients were considered unevaluable because they did not have identified SEGA target lesions by independent central review.

b. p-value was calculated using the one-sided Cochran-Mantel Haenszel test, stratified by protocol randomization stratification factor (EIAED use vs. EIAED non-use).

Reviewer note: As discussed in Section 6.1.2 of this review, independent central radiology (IRC) review did not confirm the presence of a worsening SEGA lesion in seventeen patients [12 (15%) in the everolimus arm and 5 (13%) on the placebo arm]. However, only 1 of the 12 patients with discrepant eligibility assessments in the everolimus arm was a responder. Therefore, it is unlikely that the treatment effect observed in the everolimus arm was substantially obscured by the discrepant interpretation of SEGA worsening.

According to the sponsor's analyses, the median sum of the longest diameter of target SEGA lesions at baseline was 1.6 cm^3 (range: 0.2 to 25.2 cm^3) in the everolimus arm and was 1.3 cm^3 (range: 0.3 to 9.8 cm^3) in the placebo arm. At twelve weeks, the median sum of the longest diameter of the target SEGA lesions was 0.9 cm^3 (range 0.1 cm^3 to 7.4 cm^3) in the everolimus arm, and 1.4 cm^3 (range 0.2 to 10.5 cm^3) in the placebo arm. At 24 weeks, the median sum of the longest diameter of the target SEGA lesions was 0.9 cm^3 (range 0.1 to 6.8 cm^3) in the everolimus arm, and 1.4 cm^3 (range 0.2 cm^3 to 9.7 cm^3) in the placebo arm. The median percentage change from baseline in the sum of the volumes of the target SEGA lesions was -39% (range:-75% to 10%), -48% (range -85% to 22%), and -48% (range:-89% to 0.77%) at Week 12, Week 24, and Week 48, respectively. In the placebo arm, the median percentage change from baseline in the sum of the volumes of the target SEGA lesions in the placebo arm was +0.9% (range:-42% to 69%), +1.6%% (range -58% to 37%), and -6% (range:-38% to 21%) at Week 12, Week 24, and Week 48, respectively.

Consistent with the primary analysis, at Week 12, Week 24, and Week 48, a higher percentage of patients in the everolimus arm exhibited SEGA volume reductions of 30% or greater (Table 19).

Table 19: Summary of percent change in sum of volumes of target SEGA lesions in Study M2301

% Change from Baseline in Sum of Volumes of Target SEGA Lesions[a]	Everolimus N=78			Placebo N=39		
	Week 12 N = 74	Week 24 N=74	Week 48 N=32	Week 12 N=39	Week 24 N=34	Week 48 N=14
≤ - 50%	22 (30)	31 (42)	14 (44)	0	1[b] (3)	0
≤ -30%	54 (73)	58 (78)	26 (81)	3 (8)	5 (15)	2 (14)
< 0%	71 (96)	71 (96)	31 (97)	18 (46)	17 (50)	9 (64)

≥ 0%	3 (4)	3 (4)	1 (3)	21 (54)	17 (50)	5 (36)
≥ 10%	1 (1)	1 (1)	0	11 (28)	8 (24)	3 (21)
≥25%	0	0	0	3 (8)	2 (6)	0

[a.] Calculated relative to the number of patients evaluated at baseline and the corresponding time window.
[b.] Confirmatory scan met criteria for stable disease, so did not meet criteria for SEGA response.

Table 20 lists the key demographic characteristics, maximum percent SEGA volume reduction observed, time to SEGA response, and duration of SETA response for patients randomized to everolimus who exhibited a protocol-defined SEGA response.

Table 20: Patients with SEGA response observed during double-blind period of Study M2301

Patient Number	Gender	Age (years)	Maximum %[a] SEGA volume reduction	Time to Response (days)	Duration of Response[b] (days)
0150_00001	Female	20.1	70	176	160
0251_00001	Male	13.5	68	77	92
0251_00002	Male	6.9	71	84	87
0352_00001	Male	17.3	55	170	81
0352_00002	Female	19.4	60	179	78
0352_00005	Female	12.4	68	93	84
0353_00001	Female	7.5	59	92	85
0500_00001	Female	11.9	66	169	186
0500_00002	Female	10.7	89	91	247
0500_00008	Male	7.6	52	84	85
0501_00004	Male	8.5	74	163	76
0502_00001	Female	11.3	60	169	160
0502_00005	Female	9.8	59	166	169
0502_00007	Female	6.2	68	86	255
0502_00008	Female	4.8	64	85	83
0503_00003	Female	4.6	79	86	250
0503_00005	Female	10.6	73	79	89
0504_00002	Female	8.4	72	87	80
0509_00001	Male	15.3	65	85	176
0509_00002	Female	17.4	61	93	176
0510_00003	Female	3.5	63	83	254
0510_00004	Male	5.2	68	84	255
0510_00011	Male	4.9	71	107	63
0600_00012	Male	2.3	53	88	250
0600_00013	Male	2.9	77	166	179

Patient Number	Gender	Age (years)	Maximum %[a] SEGA volume reduction	Time to Response (days)	Duration of Response[b] (days)
0700_00004	Male	1.6	58	169	174
0700_00005	Male	19.8	55	89	252

a. compared to baseline.
b. censored at the time of data cut-off.

6.1.5 Analysis of Secondary Endpoints(s)

Absolute Change in Seizure Frequency from Baseline to Week 24

The first secondary endpoint tested was the absolute change from baseline in the frequency of seizure events per 24 hours, documented by independent central review of 24-hour video EEG monitoring obtained at baseline and week 24. The statistical analysis plan specified that a last observation carried forward (LOCF) approach be used to analyze the change in seizure frequency from baseline to Week 24. Using the LOCF approach, if the 24 week video EEG was performed before the lower bound of the 24 week time window and after the baseline time window, the seizure frequency at the earlier EEG was used. No change in median seizure frequency was observed from baseline to Week 24 for either treatment arm. Therefore, there was not a statistically significant difference in change in seizure frequency from baseline to Week 24 in the treatment arms (p=0.2004). Table 21, adapted from the Dr. Weishi Yuan's statistical review of this application, provides a summary of the seizure frequency, as documented by 24-hour video EEG.

Table 21: Seizure frequency analysis in Study M2301

Number of Seizures	Everolimus N = 78	Placebo N = 39
Baseline		
Mean (Standard Deviation)	3.41 (8.36)	5.58 (14.98)
Median	0	0
Range	(0, 42.6)	(0, 78.9)
Week 24 (LOCF)		
Mean (Standard Deviation)	2.17 (4.84)	5.33 (15.57)
Median	0	0
Range	(0, 31.6)	(0, 91.5)
Change from baseline to week 24 (LOCF)		
Mean (Standard Deviation)	-1.24 (6.12)	-0.24 (5.70)
Median	0	0
Range	(-34.0, 13.0)	(-15.9, 14.4)
p-value	0.2004	

Dr. Weishi Yuan performed a sensitivity analysis using a non-LOCF approach which used only observed cases without data imputation. The results of this sensitivity analysis were consistent with the results obtained using the LOCF approach.

Reviewer note: Because the median number of seizures at baseline was 0, it was unlikely that an improvement in seizure frequency would be detected.

Time to SEGA Progression (TTSP)

Because the null hypothesis was not rejected for the first secondary endpoint tested, absolute change in seizure frequency from baseline to Week 24, the next secondary endpoint, Time to SEGA Progression (TTSP), could not be formally tested.

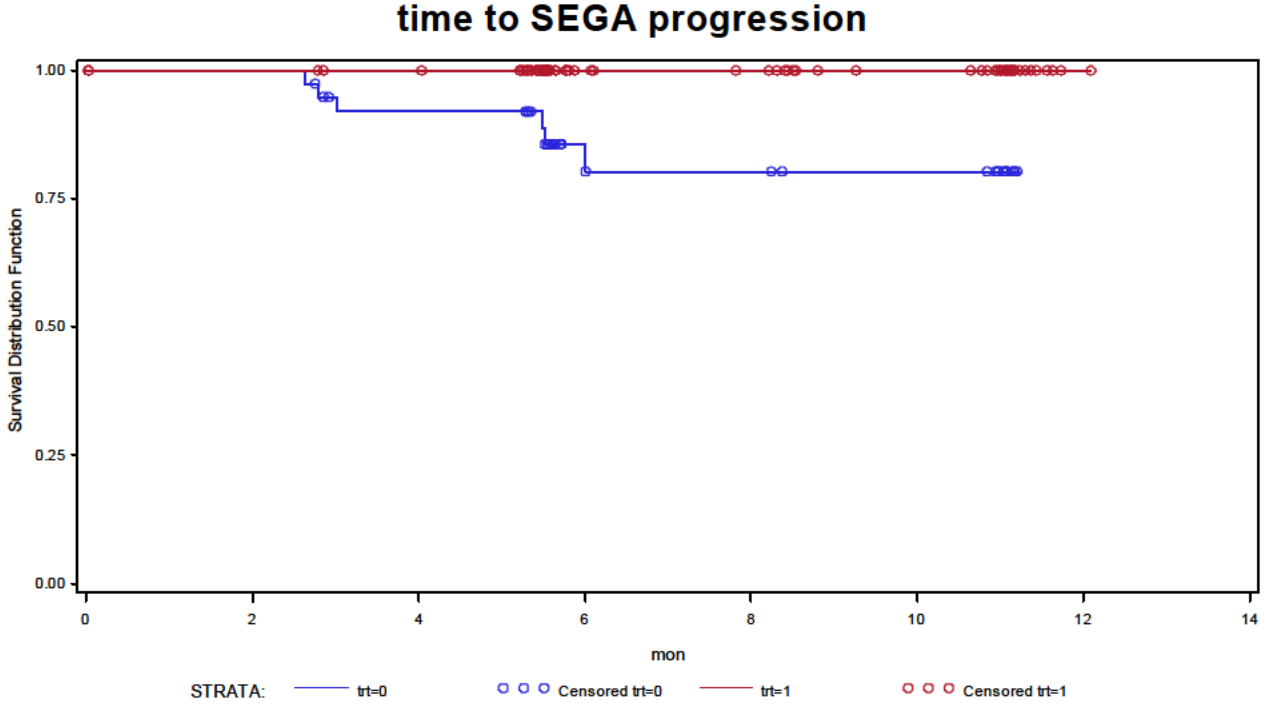
At the time of the primary analysis (data cut-off date of March 2, 2011), SEGA progression was observed in a total of 6 patients in the placebo arm. SEGA progression was not detected in any patient in the everolimus arm. With the caveat that the small number of progressions makes interpretation of results difficult, Table 22 summarizes the results of the TTP analysis for Study M2301.

Table 22: Time to SEGA progression analysis – Study M2301

	Everolimus N = 78	Placebo N = 39
Number of Events (%)	0	6 (15.4)
Median TTSP (95% CI)	NE	NE
Nominal p-value (2-sided)	0.0004	
HR (95% CI)	NE	

Figure 3 shows a Kaplan-Meier plot of TTSP per central radiology review showing the probability of SEGA progression over time in months.

Figure 3: Kaplan-Meier analysis of TTSP per central radiology review



(performed by FDA statistical reviewer Dr. Weishi Yuan)

Skin Lesion Response Rate

Because the null hypothesis was not rejected for the first secondary endpoint tested, absolute change in seizure frequency from baseline to Week 24, the third secondary endpoint, Skin Lesion Response Rate, could not be formally tested.

Table 22 summarizes the analysis of skin lesion response in Study M2301. A partial response, defined as a slight, moderate, or marked improvement in skin lesions using the Physician's Global Assessment of Clinical Condition (PGA), was observed in 30 of 78 (42%) of patients in the everolimus arm and 4 of 38 (11%) patients in the placebo group. Complete absence of skin lesions (a complete response), was not documented in any patient in either arm. Comparison of skin lesion response rates in the everolimus and placebo arms was performed using a CMH test with a one-sided alpha of 2.5%.

Table 23: Skin lesion response in Study M2301

	Everolimus N = 78	**Placebo N = 39**
Best Overall Skin Lesion Response n (%)		
Complete Response	0	0
Partial Response	30 (41.7)	4 (10.5)
Stable Disease	42 (58.3)	33 (86.8)
Progression	0	0
Not Evaluable	0	1 (2.6)
Response Rate (95% CI)	41.7 (30.2, 53.9)	10.5 (2.9, 24.8)
Nominal p-value	0.0004	

6.1.6 Other Endpoints

Duration of SEGA Response

According to the Applicant, all patients who exhibited a SEGA response had ongoing responses at the time of data cut-off for the final analysis. Durations of response ranged from 63+ to 255+ days. Please see Table 20 for a listing of the duration of response for each patient with a SEGA response in Study M2301.

Analysis of efficacy during the open label period of Study M2301

By the time of the primary analysis of study M2301, 5 patients randomized to placebo crossed over to receive open label everolimus after exhibiting progression of their SEGA lesion. Two of these 5 (40%) patients achieved a SEGA response at the time of data cut-off for the primary analysis. Table 24

provides a summary of the key demographic characteristics and treatment outcomes for these patients

Table 24: Patients with SEGA responses during the open label period of Study M2301

Patient number	Age	Gender	Duration of everolimus therapy (days)	Duration of response (days)	Time to response (days)
0502-00003	7	F	377	182+	161
0510-00008	5.4	F	204	114+	85

The remaining 3 patients (0600-00016, 0700-00008, 0500-00005), all male, had a best response that met the criteria for stable disease, but exhibited a ≥ 40% reduction in the SEGA volume compared to baseline while receiving everolimus.

6.1.7 Subpopulations

The relatively small sample size of patients enrolled in Study M2301 limits the utility of subgroup analyses. However, analysis of SEGA response by age, gender, site, and country of enrollment (U.S. versus non U.S) showed that results were generally consistent across subgroups. Table 25, adapted from a table provided by FDA statistical reviewer Weishi Yuan, summarizes SEGA response by subgroup:

Table 25: SEGA response by patient subgroup in Study M2301

Subgroup	Everolimus		Placebo		Difference (95% CI)
	n / N	ORR (95% CI)	n / N	ORR (95% CI)	
Age (years)					
< 3	3 / 13	23.1 (5.0, 53.8)	0 / 7	0 (0, 40.9)	23.1 (-24.1, 63.0)
3 - <18	21 / 55	38.2 (25.4, 52.3)	0 / 26	0 (0, 13.2)	38.2 (15.0, 58.7)
≥ 18	3 / 10	30 (6.7, 65.3)	0 / 6	0 (0, 45.9)	30.0 (-21.2, 72.7)
Gender					
Male	12 / 49	24.5 (13.3, 38.9)	0 / 18	0 (0, 18.5)	24.5 (-2.4, 49.5)
Female	15 / 29	51.7 (32.5, 70.6)	0 / 21	0 (0, 16.1)	51.7 (24.8, 72.9)

Subgroup	Everolimus		Placebo		Difference (95% CI)
	n / N	ORR (95% CI)	n / N	ORR (95% CI)	
Race					
Caucasian	27 / 73	37.0 (26.0, 49.1)	0 / 36	0 (0, 9.7)	37.0 (17.7, 54.7)
Non-Caucasian	0 / 5	0 (0, 52.2)	0 /3	0 (0, 70.8)	NE
Country					
U.S.	16 / 49	32.7 (20.0, 47.5)	0 / 18	0 (0, 18.5)	32.7 (5.8, 56.9)
non-U.S.	11 / 29	37.9 (20.7, 57.7)	0 / 21	0 (0, 16.1)	37.9 (10.2, 61.7)

Abbreviation: NE = not evaluable.

Responders by Gender:

SEGA responses were observed in both male and female patients who received everolimus. A total of 12 of the 49 (24.5%) male patients who received everolimus during the double-blind period of Study M2301 exhibited a SEGA response, compared to 15 of 29 (51.7%) female patients.

Response by Age

SEGA responses were observed in patients < 3 years of age, 3 to < 12 years of age, 12 to < 18 years of age, and > 18 years of age who received everolimus. Table 26 provides a summary of the SEGA response rate by age group.

Table 26: SEGA response in Study M2301 by age group

Best Overall Response n (%)	Everolimus arm N = 78				
	Age Subgroup (years)				
	< 3 n = 13	3 to < 12 n = 38	12 to < 18 n = 17	> 18 n = 10	Total
Response	3 (23)	16 (42)	5 (29)	3 (30)	27 (35)
Stable Disease	10 (77)	20 (53)	12 (71)	7 (70)	49 (63)
Progression	0	0	0	0	0
Not evaluable	0	2 (5)	0	0	2 (2)

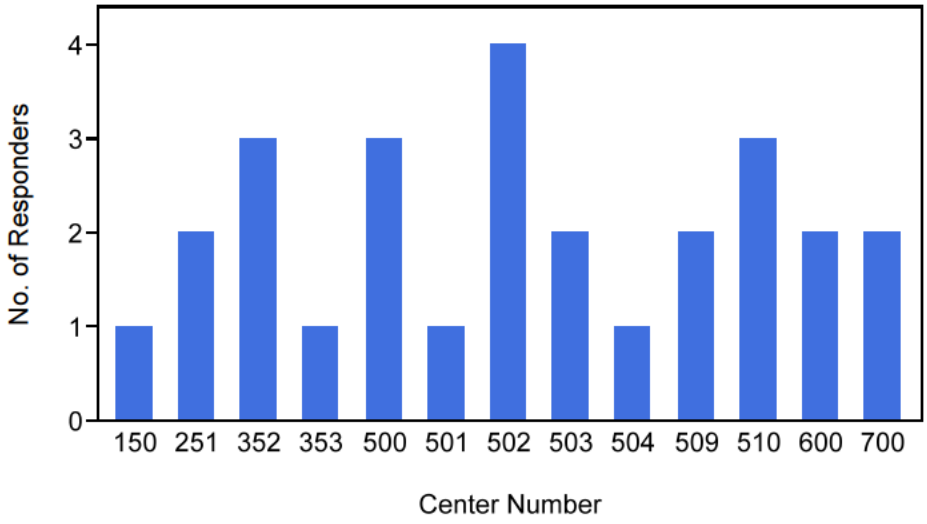
Responders by Site

Patients meeting the primary endpoint for volumetric reduction of sum of target SEGA lesions were enrolled across 13 of the 24 sites (54%) that enrolled at least one patient. Site 502 (University of Alabama at Birmingham, Dr. Bruce Korf, PI) enrolled the largest number of responders. At this site, 4 of 9 (44%) patients enrolled achieved at least a 50% reduction of the sum volumes of the target SEGA lesions. Three responders enrolled at each of the following sites:

- Site 500: Cincinnati Children's Hospital Medical Center
  - PI: Dr. David Franz
  - a total of 15 patients enrolled
  - 20% response rate for the site
- Site 352: University Hospital Heidelberg
  - PI: Dr. Olaf Witt
  - a total of 5 patients enrolled
  - 60% response rate for the site
- Site 510: Texas Scottish Rite Hospital for Children
  - PI: Dr. Steven Sparagana
  - a total of 9 patients enrolled
  - 33% response rate for the site.

Figure 4 provides a graphical summary of the number of patients who exhibited a SEGA response by site in Study M2301.

Figure 4: Number of patients with a SEGA response in each site enrolling patients in Study M2301



Subset of patients who had prior SEGA surgery

Eight patients (7%) enrolled in Study M2301 had undergone surgery for SEGA prior to enrollment in Study M2301 (6 patients (8%) in the everolimus arm and 2 (5%) patients in the placebo arm). Half (3 of 6) of the patients in the everolimus arm with a prior history of SEGA surgery had at least a 50% reduction in the sum of the volumes of their target SEGA lesions during the double blind treatment period. Table 27 lists the patients who underwent surgery for SEGA prior to enrollment in Study M2301. No patient in either of the treatment arms required surgery during Study M2301.

Table 27: Summary of demographic characteristics and outcomes of patients with a history of SEGA surgery prior to enrollment in Study M2301

Patient no.	Age (years)	Gender	Treatment arm	Best overall response	Response duration (days)
0500_00002	10.7	female	everolimus	Response	247
0502_00007	6.2	female	everolimus	Response	255
0503_00003	4.6	female	everolimus	Response	250
0500_00010	11.4	male	everolimus	Stable Disease	N/A
0502_00006	17.3	female	everolimus	Stable Disease	N/A
0600_00009	1.2	male	everolimus	Stable	N/A

Patient no.	Age (years)	Gender	Treatment arm	Best overall response	Response duration (days)
				Disease	
0510_00006	16.1	male	placebo	Stable Disease	N/A
0515_00006	7.1	female	placebo	Stable Disease	N/A

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The clinical pharmacology review of NDA 22334 Supplement 6 stated that the sponsor initially proposed individualized therapeutic drug monitoring for patients with SEGA because it was anticipated that most patients would be on concomitant enzyme-inducing antiepileptic drugs and everolimus is a substrate of CYP3A4. The target everolimus trough range of 5-15 ng/mL was originally identified based on extrapolation from studies of rapamycin in patients with SEGA that used a target trough range of 10-15 ng/mL. This target trough range was subsequently determined to be reasonably safe based on data from Study C2485. The starting dose used in Study C2485, 3 mg/m^2/day, was lower than the starting dose used in Study M2301. For Study M2301, the Applicant increased the starting dose of everolimus based on data from a Phase 1 study identifying a maximum tolerated dose of 5 mg/m^2/day in children with refractory or recurrent solid tumors in order to facilitate attainment of the target trough concentration range in a shorter period of time[17].

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This NDA included updated safety and efficacy data from Study C2485, reflecting an additional year of follow-up of patients enrolled in this trial. The data cut-off for the primary analysis was December 9, 2009, and the data cut-off for the updated analysis was December 31, 2010.

Table 28 provides a listing of the 9 patients who had an ongoing ≥ 50% volumetric reduction of their primary SEGA lesion at 6 months, along with the updated status of SEGA volume reduction as of December 31, 2010. Seven of these 9 patients continued to have an ongoing volumetric reduction of at least 50% as of December 31, 2010.

At the primary analysis 6 months following initiation of treatment of the last patient enrolled in Study C2485 (cut-off 12/9/2009), 9 of 28 patients (32%, 85%

CI: 16 to 52%) had a ≥ 50% reduction of their largest SGA lesion; the median treatment duration was 24 months (range 4.7 to 37.3 months), and the median duration of response was 266 days (range: 97 to 946 days). At the time of the updated analysis (12/31/2010), 7 of the 9 original responders an ongoing volumetric reduction of their primary SEGA tumor of at least 50% ; the median duration of response was 360 days (range 97 to 1191 days) and the median treatment duration was 34 months. Two patients, highlighted in gray, did not have an ongoing ≥ 50% volumetric reduction of their primary SEGA tumor at the time of the updated analysis.

Table 28: Updated status of Study C2485 patients categorized as achieving a > 50% reduction in tumor volume of largest SEGA lesion at 6 months

Patient Number	Gender	Age (years)	Maximum % Reduction in Target SEGA Volume Compared to Baseline	% Reduction in Target SEGA Volume Compared to Baseline Based on Most Recent MRI
0001_00001	Female	25	69%	67%
0001_00004[a]	Male	14	64%	47%
0001_00007	Male	14	64%	64%
0001_00011	Female	12	75%	72%
0001_00013[b]	Female	4	58%	-51%
0001_00025	Male	11	61%	59%
0001_00026	Female	26	65%	53%
0001_00027	Male	8	70%	53%
0001_00028	Male	22	69%	69%

a. Increase over baseline by 51% at December 2010 data cut-off

The median reduction in primary SEGA tumor volume at month 24 was 0.71 cm^3 (range –0.55 to 9.60). At Week 24, 19 of 24 (79%) of patients experienced a reduction of ≥ 30% relative to baseline, and 12 of 24 (50%) experienced reductions 50% or more relative to baseline.

Table 29 summarizes the SEGA volumes by time point according to independent radiology review (sponsor analysis).

Table 29: Summary of changes in volume of primary SEGA lesion over time in Study C2485 (according to independent central radiology review)

	Everolimus							
	Baseline N=28	**Month 3 N=26**	**Month 6 N=27**	**Month 12 N=26**	**Month 18 N=26**	**Week 24 N=24**	**Month 30 N=17**	**Month 36 N=9**
Primary SEGA tumor volume (cm^3)								
Median (range)	1.74 (0.49 to 14.23)	0.84 (0.25 to 8.32)	0.93 (0.31 to 7.98)	0.84 (0.29 to 8.18)	0.81 (0.33 to 5.20)	0.94 (0.20 to 4.63)	1.05 (0.40 to 6.27)	0.97 (0.39 to 2.70)
Median Reduction from baseline (range)		0.63 (-0.12 to 5.91)	0.83 (0.06 to 6.25)	0.85 (0.02 to 6.05)	0.69 (-0.24 to 9.03)	0.71 (-0.55 to 9.60)	1.04 (-0.78 to 7.96)	1.34 (0.15 to 4.75)
Percentage reduction in primary SEGA tumor volume from baseline n (%)								
≥ 50%		10 (39)	9 (33)	9 (35)	11 (42)	12 (50)	7 (41)	5 (56)
≥ 30%		17 (65)	21 (78)	20(77)	18 (69)	19 (79)	11 (65)	7 (78)
≥ 0%		25 (96)	27 (100)	26 (100)	24 (92)	23 (96)	15 (88)	9 (100)
No change		0	0	0	1 (4)	0	0	0
Increase		1 (4)	0	0	1 (4)	1 (4)	2 (12)	0

Two patients who experienced at least a best overall response of at least a 30% reduction in primary SEGA tumor volume subsequently experienced progression of their SEGA lesion (an increase from nadir of at least 25% to a value greater than to baseline) while receiving everolimus. The median time from first response to progression or censoring was 23.8 months (range >0 to 39 months).

Study C2485 and Study M2301 are still ongoing. To fulfill the postmarketing requirements issued at the time of the 2010 accelerated approval for SEGA, the Applicant will provide long-term (at least 5 years) follow-up efficacy and safety data from Study C2485. According to the specifications of the PMR, the final study report and datasets for Study C2485 will be submitted in November 2014. Similarly, the Applicant is required to submit the final study report and datasets that include a minimum of 4 years of follow-up patients enrolled in Study M2301 by March 2015.

6.1.10 Additional Efficacy Issues/Analyses

Angiomyolipoma responses were also analyzed in Study M2301. In order to qualify as a response, fulfillment of the following criteria were was required:

- Reduction in angiomyolipoma volume of ≥ 50% relative to baseline (angiomyolipoma volume was the sum of the volumes of all target angiomyolipomas identified at baseline)
- No new angiomyolipomas ≥1 cm in longest diameter
- No increases in kidney volume > 20% from nadir
- No angiomyolipoma-related ≥ Grade 2 bleeding.

Angiomyolipoma responses were confirmed with a second scan performed 8-12 weeks following original detection of the response).

Angiomyolipoma responses were observed in the everolimus arm only. A total of 16 of 30 (53%) patients in the everolimus arm and with angiomyolipoma at baseline exhibited a response (all partial responses). Angiomyolipoma progression was detected in 3 of 14 (21%) patients in the placebo arm with angiomyolipoma identified at baseline. Angiomyolipoma progression was not observed in the everolimus arm.

No additional efficacy issues or analyses are pertinent to this application. When the long-term efficacy data and final clinical study reports from Study C2485 and Study M2301 are submitted to fulfill the outstanding postmarketing requirements, FDA will conduct additional analyses to determine whether conversion from accelerated to full approval is warranted.

7 Review of Safety

Safety Summary

In general, at the proposed dose and schedule, the safety profile of everolimus in children and adult patients with SEGA enrolled in Study C2485 and Study M2301 was generally similar to that previously described in the approved label for Afinitor. The most common adverse event in both studies was stomatitis. In both studies, the rate of patient discontinuations was low and there were no patient deaths reported for either study.

In Study M2301, no adverse reactions resulted in treatment discontinuation of everolimus during the double-blind treatment period. Dose interruptions or reductions due to adverse reactions occurred in 56% of everolimus-treated patients. The most common adverse reaction leading to dose adjustment was stomatitis. The most common adverse reactions reported for everolimus (incidence ≥ 20%) were: stomatitis (62%); pyrexia (23%); anxiety, aggression, or other behavioral disturbance (21%); and rash (21%). The most common Grade 3-4 adverse reactions (incidence ≥ 2%) were stomatitis (9%, all Grade 3), pyrexia (6%, all Grade 3), pneumonia (3%), gastroenteritis (4%), aggression (3%), agitation (3%), and amenorrhea (3%). The most common key laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia and elevated partial thromboplastin time. The most common Grade 3-4 laboratory abnormality (incidence ≥ 3%) was neutropenia (9%). Serious adverse events (SAEs) were reported for 19 (24%) of patients in the everolimus group and 5 (13%) patients in the placebo group during the double blind treatment period. Infections were the most common type of serious adverse event.

7.1 Methods

The clinical review of safety focused on the results of the randomized trial, Study M2301, which provided more robust data due to the greater number of patients enrolled and the presence of a placebo control group. Additionally, clinical review of follow-up safety data from Study C2485 were reviewed to examine for consistency with the toxicity profile evident from Study M2301, with a focus on analysis of severe adverse events, serious adverse events, and adverse events leading to discontinuation of everolimus.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The databases used to evaluate safety reflected adverse events collected from 107 patients with Tuberous Sclerosis for the treatment of SEGA in Study M2301 (n=79) and Study C2485 (n=28). All data for Study C2485 reported to in this

NDA included additional data collected between December 9, 209 and the cut-off date of December 31, 2010.

In the integrated summary of safety included in this submission, the Applicant included listings, tabular summaries by preferred term and system organ class, and narratives of serious adverse events from ongoing studies of everolimus. In addition the most recent Periodic Safety Update Report for Afinitor was included. These reports were examined to look for additional safety signals relevant to the SEGA population that were not evident from analyses of data from studies M2301 and C2485.

7.1.2 Categorization of Adverse Events

Medical Dictionary for Regulatory Activities (MedDRA) version 13.1 was used to code all adverse events in Study M2301 and Study C2485. The coding of verbatim to preferred terms was appropriate.

Adverse events were assessed using the National Cancer Institute's (NCI) Common Toxicity Criteria for Adverse events version 3.0. For adverse events without available CTCAE grading, grade 1 was assigned for adverse events considered to be mild, grade 2 was assigned to adverse events considered to be moderate, grade 3 was assigned to adverse events considered to be severe, and grade 4 was assigned to adverse events considered to be life-threatening.

For Study C2485, adverse events were captured for all adverse events reported prior to data cut-off. However, only adverse events beginning on or after the first day of study therapy until 28 days after study treatment discontinuation were considered treatment emergent.

For Study M2301, there were two types of safety summaries and listings provided, one based on assessments collected during the double-blind phase of the study, and the other based on assessments collected during the open-label phase of the study. The former provided the primary basis for analysis of safety in this application. All safety assessments collected no later than 28 days after the date of the last double-blind study drug administration and before the start of open-label everolimus were included in the double-blind analysis. The analysis of adverse events during the open-label phase of Study M2301 included adverse events defined as open-label baseline or collected after the start of open-label everolimus and no later than 28 days after the date of last everolimus administration. For both the double-blind and open-label periods, adverse events occurring either prior to initiation of everolimus therapy or those occurring more than 28 days after the last everolimus treatment were recorded but not flagged as treatment emergent.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No pooling of data across studies was performed.

Reviewer comment: given the small number of patients enrolled in Study C2485 and the differences in starting dosage regimen and target everolimus trough concentration used in both clinical studies, I consider this acceptable.

7.2 Adequacy of Safety Assessments

Overall, the safety assessments performed in Study M2301 and Study C2485 were of adequate quality and breadth to permit an appropriate assessment of safety of the use of everolimus in patients with worsening SEGA lesions that are not surgically resectable. The long term safety of everolimus in this patient population has not been well established, but the outstanding postmarketing requirements for continued collection of safety data (including information regarding the impact of everolimus on growth, and physical maturation and development, and attainment of developmental milestones) will address this issue.

Please refer to Dr. Amir Shahlaee's clinical review of sNDA 22334, Supplement 6 dated October 26, 2010 for details regarding the safety assessments performed in Study C2485.

For Study M2301, safety assessments included monitoring and documenting all treatment-emergent adverse events, serious adverse events, and other significant adverse events. Patients were queried for the occurrence of adverse events through non-directive questioning at each study visit, and when volunteered by the patient during or between scheduled visits, through physical examination, laboratory test results, or other assessments. Adverse events were recorded in case report forms from the time of starting study treatment up until 28 days after the last dose (until the follow-up visit). All serious adverse events occurring within 28 days of study treatment discontinuation, irrespective of causality were documented in case report forms. Serious adverse events for which everolimus was suspected to play a role in causality were captured for an additional 8 weeks after the follow-up visit for a total of 12 weeks after treatment discontinuation. Endocrine testing was performed annually until the patient's 10^{th} birthday, and every 12 weeks thereafter. Blood samples for assessment of pharmacokinetic, hematology, and chemistry parameters were collected at each study visit. Please refer to the schedule of assessments for Study M2301 in Table 8 of Section 5.3.1.7 of this review for additional details regarding the routine assessments performed during Study M2301.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure

Overall, exposure to everolimus was sufficient to permit an adequate assessment of safety in the target population of patients. The number and demographic composition of patients studied in Study M2301 and C485 were appropriate given the given epidemiology of subependymal giant cell astrocytoma associated with tuberous sclerosis. In both studies, patients received treatment with study drug until SEGA progression, occurrence of unacceptable toxicity, or the investigator or patient decided to discontinue study therapy.

Study M2301

In Study M2301, a total of 79 patients were exposed to everolimus and 39 patients were exposed to placebo during the double-blind period. Table 30 provides a summary of the duration of exposure during the double blind period for Study M2301.

Table 30: Summary of treatment exposure during the double blind period in Study M2301

Treatment Arm	Number of Weeks				
	Mean	Std Dev	Median	Min	Max
Everolimus	54.5	15.0	52.2	24.0	89.1
Placebo	49.5	19.1	46.6	13.9	87.6

A total of 47 patients in the everolimus arm (60.3%) received study treatment for a period of at least 48 weeks. Total patient year exposure for this study was 81.4 patient-years for everolimus and 37 patient-years for placebo. Table 31 provides a breakdown of patient exposure to everolimus in weeks.

Table 31: Duration of treatment exposure during the double blind period in Study M2301

Exposure by Duration Category n (%)	Everolimus N=78	Placebo N=39
Less than 12 weeks	0	0
12 to < 24 weeks	0	4 (10)
24 to < 36 weeks	3 (4)	4 (10)
36 to < 48 weeks	28 (36)	13 (33)
≥ 48 weeks	47 (60)	18 (46)

Table 32 summarizes the cumulative dose and dose intensity by treatment group for Study M2301. The median daily dose of everolimus was 6 mg/m^2/day (range, 2.3 mg/m^2/day to 12.4 mg/m^2/day).

Table 32: Cumulative dose and dose intensity during the double blind period in Study M2301

	Everolimus N=78	Placebo N=39
Cumulative Dose (mg/m^2)	0	0
Mean (std dev)	2374 (993)	1780 (871)
Median (range)	2231 (613 to 4724)	1565 (428 to 3513)
Dose intensity (mg/m^2/day)		
Mean (std dev)	6.3 (2.1)	18 (46)
Median (range)	6.0 (2.3 to 12.4)	5.1 (2.6 to 9.4)

Table 33 summarizes duration of treatment exposure, cumulative dose, and dose intensity by age subgroup for Study M2301. Overall, patients in each age subgroup had adequate exposure to everolimus to enable an assessment of efficacy and safety of everolimus for the treatment of SEGA in each age group. However, there are not enough patients in each subgroup to draw definitive conclusions regarding differences in exposure among age subgroups.

Table 33: Exposure by patient age during the double blind period in Study M2301

	Everolimus N=78			Placebo N=39		
	< 3 years n = 13	**3-18 years n = 55**	**> 18 years n = 16**	**< 3 years n = 7**	**3-18 years n = 26**	**> 18 years n = 6**
Exposure Duration (weeks)						
Mean (std dev)	60.6 (16.0)	53.8 (15.2)	49.9 (11.3)	41.7 (8.3)	50.8 (21.5)	53.1 (16.5)
Median (range)	63.4 (36.1 to 82.6)	51.7 (24.0 to 89.1)	46.9 (37.4 to 71.1)	45.3 (26.0 to 50.6)	48.3 (13.9 to 87.6)	58.4 (27.4 to 73.0)
Cumulative Dose (mg/m^2)						
Mean (std dev)	2121.0 (823.2)	2548.3 (1044.2)	1745.2 (533.2)	1221.9 (357.9)	1858.8 (958.2)	2087.1 (664.4)
Median (range)	2116 (1040.7 to 3542.3)	2548.0 (612.9 to 4724.0)	1723.0 (912.7 to 2448.5)	1135.2 (881.8 to 1887.8)	1668.5 (427.7 to 3513.2)	2199.9 (1107.5 to 3007.4)
Dose intensity (mg/m^2/day)						
Mean (std dev)	5.1 (1.9)	6.7 (2.1)	5.0 (1.4)	4.3 (1.3)	5.2 (1.4)	5.8 (1.5)
Median (range)	4.3 (2.3 to 7.8)	6.5 (2.6 to 12.4)	4.7 (2.8 to 7.2)	3.4 (3.2 to 6.2)	5.2 (2.6 to 9.4)	5.8 (3.7 to 7.5)

Table 34 summarizes patient exposure, cumulative dose, and dose intensity by gender for Study M2301. Overall, the exposure to everolimus appeared comparable in males and females. Median duration of exposure was longer in females (56.3 weeks) compared to males (51.7 weeks). In contrast, median cumulative dose and dose-intensity was higher in males (2251.1mg/m^2 and 6.5 mg/m^2/day, respectively) compared to females (1986.6 1mg/m^2 and 5.4 mg/m^2/day, respectively). However, the small number of patients in each subgroup precludes making definitive conclusions regarding differences in exposure among males and females in Study M2301.

Table 34: Patient exposure during the double blind period by gender and treatment group for Study M2301 (July 18, 2011 cut-off)

	Everolimus N=78		Placebo N=39	
	Male n = 49	**Female n = 29**	**Male n = 18**	**Female n = 21**
Exposure Duration (weeks)				
Mean (std dev)	51.7 (12.9)	59.2 (17.3)	46.1 (18.5)	52.5 (19.6)
Median (range)	51.7 (24.0 to 75.6)	56.3 (35.3 to 89.1)	44.1 (20.1 to 85.4)	50.6 (13.9 to 87.6)
Cumulative Dose (mg/m^2)				
Mean (std dev)	2380.7 (947.7)	2363.0 (1084.2)	1694.7 (872.6)	1852.3 (884.7)
Median (range)	2251.1 (612.9 to 4724.0)	1986.6 (1040.7 to 4475.1)	1558.7 (710.5 to 3440.0)	1598.3 (427.7 to 3513.2)
Dose intensity (mg/m^2/day)				
Mean (std dev)	6.6 (2.1)	5.7 (2.0)	5.3 (1.7)	5.0 (1.2)
Median (range)	6.5 (2.8 to 12.4)	5.4 (2.3 to 10.8)	5.5 (2.6 to 9.4)	4.6 (3.4 to 7.5)

For details regarding attainment of therapeutic drug levels, please see the Dr. Jian Wang's clinical pharmacology review of this NDA. Following an initial starting dose of 4.5 mg/m^2/day and subsequent dose adjustments, the median C_{min} was 3.7 ng/mL at Week 2 and Week 4. The median C_{min} ranged from 4.9 to 7.1 ng/mL from Weeks 6 to 48.

Study C2485
In Study C2485, Novartis supplied everolimus as 2.5 mg and 5 mg immediate release tablets for investigational use. Everolimus was administered at a starting dose of 3 mg/m^2/day or every other day to achieve target trough concentrations of 5-15 mg/ml. Patients unable to tolerate everolimus had their doses held or reduced by 25% with the goal of achieving trough concentrations of 5-10 ng/mL.

Alternatively, dose escalations of 25% were permitted if current dosing was unable to achieve target trough levels. Dosing was monitored and adjusted during the core 6 month and the extension phase. A total of 28 patients were exposed to everolimus in Study C2485.

Achievement of the target trough concentrations of 5-15 ng/mL appeared to be variable; the median everolimus trough concentrations at month 24 and 36 were 4.8 ng/mL (range: 1.6 to 10.1 ng/ml) and 4.2 ng/mL (range 1.2 to 9.4 ng/mL), respectively.

Total patient-year exposure for Study C2485 was 75.6 patient-years, as of the December 30, 2010 data cut-off for the updated analysis submitted with this NDA. The median duration of everolimus exposure was 34.2 months (range 4.7 to 47.1 months), and all patients who remained on therapy at data cut-off had been exposed to everolimus for a minimum of 2 years. The median daily dose of everolimus was 5.3 mg/m^2 (range: 2.1 to 12.3 mg/m^2), and the median cumulative dose was 5206.4 mg/m^2 (range: 597.4 to 12871.1 mg/m^2).
Dose Modification for Study M2301

Dose Modifications in Study M2301

Dose modifications (dose interruptions or reductions) occurred more frequently in the everolimus group compared to the placebo group during the double-blind period (Table 35). Dose reductions occurred in a similar proportion of patients in the two treatment groups (46.2% of patients in the everolimus group compared to 48.7% of patients in the placebo group), but dose interruptions occurred more commonly in the everolimus group (60.3% of patients in the everolimus group compared to 20.5% of patients in the placebo group). Adverse events were the most common reason for dose modification in the everolimus group.

Table 35: Incidence of dose modifications in Study M2301

	Everolimus N=78 n (%)	Placebo N=39 n (%)
Any Dose Modification		
No. of Patients requiring dose interruption and/or reduction	60 (77)	23 (59)
1 dose modification	20 (26)	15 (39)
≥ 2 dose modifications	40 (51)	8 (21)
Reason for Dose Modification		
Adverse event	44 (56)	4 (10)
Protocol-directed	29 (37)	18 (46)
Scheduling conflict	11 (14)	3 (8)
Dosing error	11 (14)	4 (10)
Laboratory test abnormality	2 (3)	0
Change in body surface area	2 (3)	0
Dose Interruptions		
No. of Patients requiring dose interruption	47 (60)	8 (21)
1 dose interruption	18 (23)	2 (5)
≥ 2 dose interruptions	29 (37)	6 (15)
Reason for Dose Interruption		
Adverse event	39 (50)	4 (10)
Scheduling conflict	11 (14)	2 (5)
Dosing error	9 (12)	3 (8)
Laboratory test abnormality	2 (3)	0
Dose Reductions		
No. of Patients requiring dose interruption	36 (46)	19 (49)
1 dose reduction	21(27)	16 (41)
≥ 2 dose reductions	15 (19)	3 (8)
Reason for Dose Reduction		
Protocol-directed	29 (37)	18 (46)
Adverse event	8 (10)	0
Dosing error	2 (3)	1 (3)
Change in body surface area	2 (3)	0
Scheduling conflict	1 (1)	1(3)
Laboratory test abnormality		

Dose Modifications in Study C2485

Dose modifications, consisting of dose interruption or dose reduction, were required by most (27 of 28, or 96%) patients enrolled in Study C2485. The majority (24 of 28, or 86%) of patients required at least two dose interruptions or dose reductions. A total of 24 of 28 patients (86%) required a dose interruption due to an adverse event. Most patients required dose reductions that were protocol-directed (16 of 28, or 57%) or following an adverse event (12 of 28, or 42.9%).

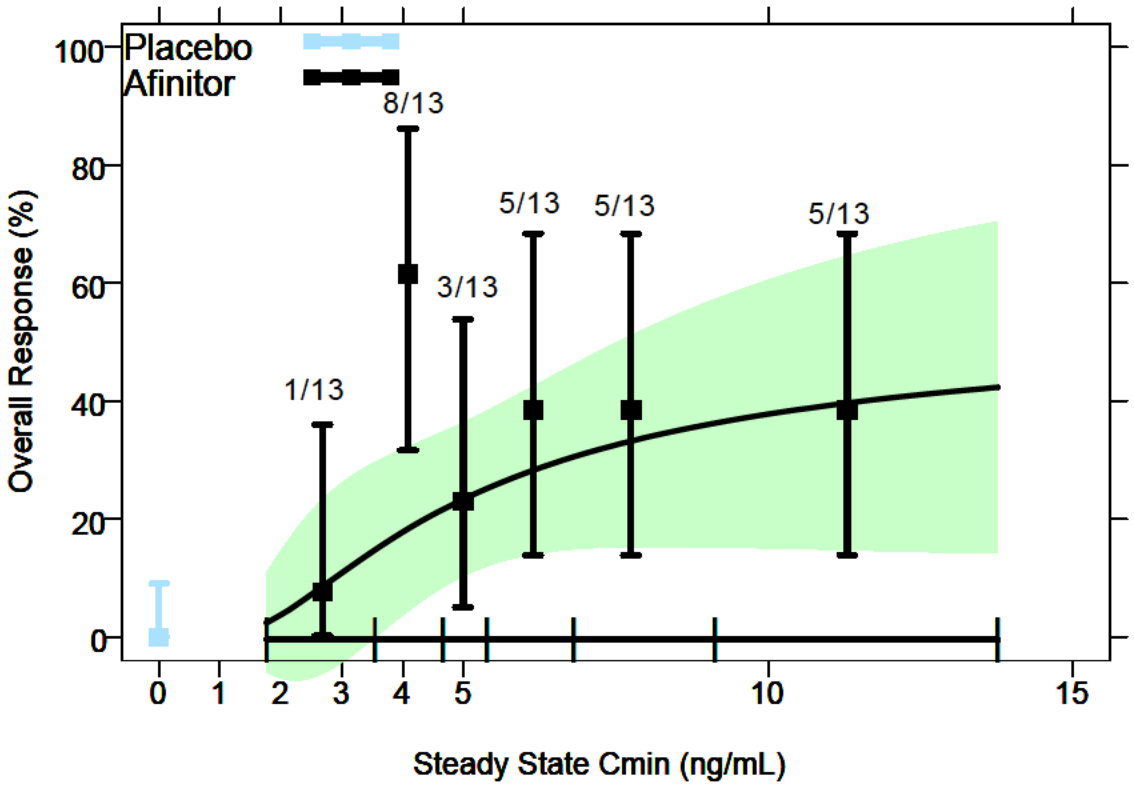
All 28 patients required at least one dose increase to attain the everolimus target trough concentration, and 26 of 28 (93%) patients required two or more dose increases.

7.2.2 Explorations for Dose Response

During the review of sNDA 22334 Supplement 6 that led to accelerated approval of Afinitor in patients with SEGA, FDA concluded that analysis of the data from the 28 patients enrolled in Study C2485 demonstrated an increased response with increased average $C_{min,}$ but there appeared to be no additional benefit with achievement of C_{min} ≥3 ng/ml. No dose response relationship for safety was apparent.

The FDA clinical pharmacology review team conducted analyses of dose-response from pharmacokinetic data obtained in Study M2301. Their analyses were consistent with the analyses of pharmacokinetic data from Study C2485. [See Figure 5, copied from a slide from Dr. Jian Wang, FDA Office of Clinical Pharmacology].

Figure 5: Exposure-response analysis – Study M2301



(provided by Jian Wang PhD, FDA Office of Clinical Pharmacology

Although SEGA responses were observed in patients with average Steady State C_{mins} of less than 5 ng/mL, the Clinical and Clinical Pharmacology Review teams proposed that the target trough concentration range be 5 – 15 ng/mL for the following reasons:

1. The dose-response relationship appeared to be stable at C_{min} levels ≥ 5 ng/mL.
2. Additional analyses of dose-response using continuous data conducted by Dr. Wang showed a consistent SEGA response for C_{mins} ≥5 ng/mL (See Dr. Jian Wang's review of this NDA for details).
3. The target trough levels for Study M2301 were between 5 – 15 ng/mL. Even with this target trough level, the average C_{min} was below 5 in a substantial proportion of patients (approximately 44%). If a target level below 5 ng/mL was included in labeling, it appears that a significant portion of patients would have levels below 3 ng/mL.
4. There does not appear to be an incremental safety risk at the 5-15 ng/mL trough range.

The upper limit of the everolimus target trough concentration range, 15 ng/mL, was selected for several reasons. First, an exposure-response relationship for safety was not evident from analysis of data from Study C2485 and study M2301. Additionally, 10 of 78 patients enrolled in Study M2301 had everolimus trough levels between 10-15 ng/mL; incidence of serious adverse events in this group of patients was similar to those of patients with lower trough levels. Additionally, a target range between 5 and 15 ng/mL is achievable with the current dose strengths available for Afinitor and Afinitor Disperz and will require fewer dose adjustments to maintain a therapeutic level compared to a narrower target range.

The relationship between serum everolimus levels to adverse events is further discussed in 7.5.1 (Dose Dependency for Adverse Events.)

7.2.3 Special Animal and/or In Vitro Testing

No new pharmacology-toxicology animal or in vitro data were included in this NDA. Dr Shahlaee's clinical review of sNDA 22334 Supplement 6 includes the following statement:

> In juvenile rat toxicity studies, dose-related delayed attainment of developmental landmarks including delayed eye-opening, delayed reproductive developments in males and females and increased latency time during the learning and memory phases were observed at doses as low as 0.15 mg/kg/day.

For further information, refer to the pharmacological toxicology review of sNDA 22334, Supplement 6.

Reviewer comment: Data from Study M2301 and Study C2485 are not mature enough at this time to permit an adequate clinical assessment of the extent to which long term use everolimus impacts growth and development of patients with tuberous sclerosis complex. The Applicant will submit long term data and analyses of development to fulfill outstanding postmarketing requirements negotiated during the review of sNDA 22334 Supplement 6.

7.2.4 Routine Clinical Testing

Please refer to Table 8 for details regarding the planned routine clinical testing performed in Study M2301. Details regarding the planned routine clinical testing for Study C2485 can be found in the clinical review of sNDA 22334, Supplement 6 (dated October 26, 2010) by Dr. Amir Shahlaee.

7.2.5 Metabolic, Clearance, and Interaction Workup

This NDA included a report of Study 1000720, entitled "Brain distribution of RAD001 in rats after oral administration of 3 mg/kg RAD001 with and without oral co-administration of 10 mg cyclosporine." The results of this study were finalized on January 18, 2012.

Table 36, copied from the Applicant's submission, summarizes the PK parameters measured following oral administration of 3 mg/kg RAD001 with and without oral pre-treatment with 10 mg/kg cyclosporine (a P-gp inhibitor).

Table 36: Results of Study 1000720 (copied from Applicant submission)

RAD001, Group 2

Parameter	Blood	Brain cortex	CSF
Tmax (h)	1	24	24
Cmax (ng/mL)	54.5	8.65 [a]	2.07
AUClast (h·ng/mL)	505	180 [a]	34.7
AUC ratio (tissue/blood)	1.00	0.356	0.0688

RAD001 & Cyclosporine, Group 3

Parameter	Blood	Brain cortex	CSF
Tmax (h)	1	24	4
Cmax (ng/mL)	62.9	28.1 [a]	2.07
AUClast (h·ng/mL)	741	471 [a]	29.8
AUC ratio (tissue/blood)	1.00	0.636	0.0402

a: For brain cortex units are ng/g for Cmax and h·ng/g for AUClast

The Applicant concluded that co-administration of cyclosporine enhanced brain concentrations of RAD001, but had a lesser effect on RAD001 concentrations in the blood and little or no impact on RAD001 concentrations in the CSF.

This NDA included data and a population PK study report entitled "Study CRAD001M2301: Population pharmacokinetics of everolimus in the treatment of patients with tuberous sclerosis complex who have subependymal giant cell astrocytomas – Modeling Report." Based on the modeling conducted by the Applicant, the Applicant concluded that "body surface area was a significant covariate for clearance and volume" and that "age was not significant after adjusting for BSA." Furthermore, the Applicant concluded that "the use of cytochrome P450 3A (CYP3A) and/or P-glycoprotein (PgP) enzyme inducers was a significant covariate for clearance." The Applicant noted that "Patients taking CYP3A or PgP inducers may require an increased dose to attain trough concentrations within the proposed target range….".

Please see the clinical pharmacology review by Jian Wang, PhD, for a detailed review of this PK study report. Dr. Wang noted that in patients with SEGA, the geometric mean C_{min} values normalized to mg/m^2 dose in patients aged < 10 years and 10 to 18 years were lower by 54% and 40% respectively, than those observed in adults (> 18 years of age), suggesting that everolimus clearance normalized to body surface area was higher in pediatric patients as compared to adults.

Reviewer note: The clinical impact of potential differences in clearance of everolimus between pediatric and adult patients with SEGA is mitigated by the dose adjustments based on upon therapeutic drug monitoring. Proposed labeling includes instructions for avoidance of strong CYP3A4 inducers if alternative therapy is available. Proposed labeling also includes a recommendation to double the dose of Afinitor or Afinitor Disperz in patients with SEGA who require treatment with a strong CYP3A4 inducer, with subsequent dose adjustment based on therapeutic drug monitoring.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Everolimus is an inhibitor of the mammalian target of rapamycin (mTOR). Other members of this class of agents include sirolimus and temsirolimus.

Temsirolimus (Torisel) is indicated for advanced renal cell carcinoma. The most common adverse reactions (incidence ≥ 30%) are rash, asthenia, mucositis, nausea, edema, and anorexia. The most common laboratory abnormalities (incidence ≥30%) are anemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, elevated alkaline phosphatase, elevated serum creatinine, lymphopenia, hypophosphatemia, thrombocytopenia, elevated AST, and leukopenia. Rare but significant adverse reactions include hypersensitivity reactions, infections from immunosuppression, interstitial lung disease, bowel perforation, and renal failure.

Sirolimus is approved for the prophylaxis of organ rejection in patients ≥ 13 years of age receiving renal transplants. The most common (incidence ≥ 30%) adverse reactions are: peripheral edema, hypertriglyceridemia, hypertension, hypercholesterolemia, increased creatinine, abdominal pain, diarrhea, headache, fever, urinary tract infection, anemia, nausea, arthralgia, pain, and thrombocytopenia. Rare but significant adverse reactions include hypersensitivity reactions, angioedema, delayed wound healing, interstitial lung disease, and renal failure. Development of lymphoma and other malignancies, particularly of the skin, have been reported in patients treated with sirolimus. There have also been reports of activation of latent viral infections such as BK-virus associated-

nephropathy and progressive multifocal leukoencephalopathy (PML) associated with sirolimus.

7.3 Major Safety Results

7.3.1 Deaths

No patients enrolled in either Study C2485 or Study M2301 died on study or within 30 days of study therapy.

7.3.2 Nonfatal Serious Adverse Events

Adverse events were designated Serious Adverse Events (SAEs) if they met one of the following criteria:

- resulted in death
- was life-threatening (an event in which the subject was at risk of death at the time of the event)
- required inpatient hospitalization or prolongation of existing hospitalization
- resulted in persistent or significant disability or incapacity
- was a congenital anomaly or birth defect.

This definition of SAE is in accordance with ICH E6 Good Clinical Practice Guidelines. SAEs, regardless of causality assessment, were collected for 28 days following study drug discontinuation. Serious adverse events that were judged by the investigator to be related to study treatment were to be collected for an additional 8 weeks (56 days) after the follow-up visit (to a total of 12 weeks or 84 days after treatment discontinuation).

Serious Adverse Events – Study M2301 (Double-Blind period)

Based on the 120-day safety update (with a data cut-off of July 18, 2011), serious adverse events (SAEs) were reported for 19 (24%) of patients in the everolimus group and 5 (13%) patients in the placebo group during the double blind treatment period. Overall, the incidence of specific SAEs was low, with a less than 5% difference in per-patient incidence between the treatment and control group.

Table 37 provides a summary of serious adverse events that occurred during the double blind period, by system organ class and treatment group for patients enrolled in study M2301. The majority of serious adverse events in the everolimus group belonged to the infections and infestations system organ class.

Table 37: Serious adverse events occurring during the double blind period by System Organ Class in Study M2301

System Organ Class	Everolimus N = 78		Placebo N = 39	
	No. of patients	%	No. of patients	%
Infections and infestations	12	15%	3	8%
Nervous system disorders	5	6%	2	5%
Gastrointestinal disorders	3	4%	0	0%
General disorders and administration site conditions	3	4%	1	3%
Immune system disorders	1	1%	0	0%
Metabolism and nutrition disorders	1	1%	0	0%
Musculoskeletal and connective tissue disorders	1	1%	0	0%
Psychiatric disorders	1	1%	0	0%
Respiratory, thoracic and mediastinal disorders	1	1%	0	0%
Vascular disorders	0	0%	1	3%

Table 38 lists serious adverse events that occurred during the double blind period, by preferred term and treatment group for patients enrolled in study M2301. Adverse events that occurred in a higher percentage of patients in the Afinitor group are shaded in light grey.

Table 38: Serious adverse events occurring during the double blind period by Preferred Term in Study M2301

Preferred Term	Everolimus N = 78		Placebo N = 39	
	No. of patients	%	No. of patients	%
Convulsion	3	4%	2	5%
Pyrexia	3	4%	1	3%
Bronchitis	2	3%	1	3%
Gastroenteritis	2	3%	0	0%
Gastroenteritis viral	2	3%	0	0%
Pneumonia	2	3%	1	3%

Preferred Term	Everolimus N = 78		Placebo N = 39	
	No. of patients	%	No. of patients	%
Status epilepticus	2	3%	0	0%
Upper respiratory tract infection	2	3%	1	3%
Abdominal pain	1	1%	0	0%
Adenovirus infection	1	1%	0	0%
Agitation	1	1%	0	0%
Bronchopneumonia	1	1%	0	0%
Dehydration	1	1%	0	0%
Dysphagia	1	1%	0	0%
Ear infection bacterial	1	1%	0	0%
Febrile infection	1	1%	0	0%
Foreign body aspiration	1	1%	0	0%
Gastrointestinal infection	1	1%	0	0%
Grand mal convulsion	1	1%	0	0%
Hypersensitivity	1	1%	0	0%
Influenza	1	1%	0	0%
Otitis media	1	1%	0	0%
Patellofemoral pain syndrome	1	1%	0	0%
Respiratory tract infection viral	1	1%	0	0%
Tendon disorder	1	1%	0	0%
Umbilical hernia	1	1%	0	0%
Urinary tract infection	1	1%	0	0%
Raynaud's phenomenon	0	0%	1	3%

The preferred terms with the largest difference (+3%) between the Afinitor group and Placebo group were: gastroenteritis, viral gastroenteritis, and status epilepticus; each of these adverse events were reported by two patients in the Afinitor group and no patients in the placebo group.

Reviewer note: gastroenteritis, including viral gastroenteritis, is listed as a common adverse event in Section 6.5 (Clinical Study Experience in Subependymal Giant Cell Astrocytoma with TSC) of the proposed Afinitor label Of note, the incidence of the preferred term "convulsion" was comparable

between the two treatment arms. A total of 21 of 78 (27%) patients in the everolimus group experienced at least one convulsion, compared to 11 of 39 (28%) patients in the placebo group. The incidences of Grade 2 convulsions was similar (5%) in both treatment groups There were two patients who experienced status epilepticus while being treated with everolimus (Patient 0515-00002 and Patient 0502-00008). These cases are confounded by comorbid medical conditions and concomitant medications, and the investigators did not suspect that the status epilepticus was causally related to everolimus. Patient 0515-00002 experienced Grade 3 status epilepticus four days following initiation of azithromycin; this patient's valproic acid level was subsequently discovered to be at the low therapeutic range of 51.4. Patient 0502-00008 had a history of infantile spasms and complex partial seizures treated with multiple anticonvulsants; she experienced Grade 3 status epilepticus associated with a urinary tract infection. Both patients remained on everolimus after recovering from status epilepticus.

Table 39 provides a summary of serious adverse events occurring during the double-blind period that were suspected to be related to everolimus by the investigating physician.

Table 39: Serious adverse events attributed to everolimus during the double-blind period in Study M2301

Subject ID Number	Age (years)	Preferred Term	CTCAE Grade	Study Day Start of AE	AE duration (days)	Action Taken
0353_00002	2.5	Pyrexia	2	80	5	Dose interruption and/or modification, concomitant medication given
		Pyrexia	3	102	13	concomitant medication given
		Gastroenteritis viral	3	103	12	Dose interruption and/or modification, concomitant medication given, hospitalization*
		Broncho-pneumonia	3	105	11	Concomitant medication given
		Pyrexia	2	126	6	Concomitant medication given
		Upper respiratory tract infection	3	126	15	Concomitant medication given
		Febrile infection	3	156	13	Dose interruption and/or modification, concomitant medication given
		Influenza	2	213	9	concomitant medication given, hospitalization*
0502_00007	6.2	Pneumonia	3	404	7	Dose interruption and/or modification, concomitant medication given, hospitalization*
0509_00003	18.2	Dehydration	3	123	4	Dose interruption and/or modification, concomitant

Subject ID Number	Age (years)	Preferred Term	CTCAE Grade	Study Day Start of AE	AE duration (days)	Action Taken
						medication given, hospitalization*
		Gastroenteritis viral	3	123	4	Dose interruption and/or modification, concomitant medication given, hospitalization*
0516_00002	1.3	Ear infection bacterial	3	256	56	Dose interruption and/or modification, concomitant medication given, non-drug therapy administered, hospitalization*

* or prolonged hospitalization

A total of four patients (5.1%) in the everolimus group experienced serious adverse events that were suspected by the investigator to be related to study drug.

Notably, none of the patients who experienced a serious adverse event permanently discontinued everolimus due to an SAE.

Serious Adverse Events – Study M2301 (Open-Label Period)
Based on the 120-day safety update (with a data cut-off of July 18, 2011), 5 patients (5.4%) experienced serious adverse events during the open-label period of the study.

Table 40 provides a summary of the serious adverse events that occurred during the open label period of Study M2301. Events shaded in gray were attributed to everolimus by the investigator.

Table 40: Serious adverse events occurring during the open label treatment period in Study M2301

Patient ID Number	Age (years)	Preferred Term	CTCAE Grade	Study Day Start of AE	AE duration (days)	Action Taken
0500_00003	19.8	Parainfluenza virus infection	3	39	7	Dose interruption and/or modification, concomitant medication given, hospitalization*
0502_00003	7.0	Headache	2	112	4	Concomitant medication given, hospitalization*
0502_00003	7.0	Tooth abscess	2	484	16	Dose interruption and/or modification, concomitant medication given, hospitalization*
0510_00002	12.6	Gastroenteritis viral	3	43	6	Concomitant medication given, hospitalization*
0511_00003	13.0	Complex partial seizures	3	19	2	Concomitant medication given, hospitalization*
0700_00004	1.6	Pneumonia	3	61	Ongoing at cut-off	Dose interruption and/or modification, concomitant medication given, hospitalization*

* or prolonged hospitalization

Serious Adverse Events – Study C2485

At the time of the 90-day safety update during review of sNDA 22334, Supplement 6 (data cut-off of March 8, 2010), nonfatal serious adverse events occurred in a total of 4 of 28 (14%) patients. At the time of data cut-off for the updated analysis of Study C2485 (December 31, 2010) serious adverse events were reported for an additional 2 patients; overall, 6 patients (21.4%) reported a total of 9 non-fatal serious adverse events during or within 28-days following treatment with everolimus. Table 41 provides a summary of the serious adverse events that occurred in subjects receiving everolimus in Study C2485. Events shaded in gray were attributed to everolimus by the investigator.

Table 41: Serious adverse events – updated analysis of Study C2485

Pt. ID No.	Age (years)	Preferred Term	CTCAE Grade	Study Day Start of AE	AE duration (days)	Action Taken
2	3	Convulsion	2	65	1	Concomitant medication given, hospitalization[b]
3	3	Pneumonia	3	733	20	Dose interruption and/or modification, concomitant medication given, hospitalization[b]
6[a]	15	Abscess limb	3	1007	20	Dose interruption and/or modification, concomitant medication given, hospitalization[b]
14	5	Gastroenteritis	3	271	3	Dose interruption and/or modification, concomitant medication given, hospitalization[b]
		Bronchitis viral	3	43	14	Dose interruption and/or modification, non-drug therapy given, hospitalization[b]
15	34	Convulsion	4	651	1	Concomitant medication given, hospitalization[b]
22[a]	5	Leukocytosis	1	775	5	Dose interruption and/or modification, concomitant medication given, hospitalization[b]
		Petechiae	1	775	5	Dose interruption and/or modification, concomitant medication given, hospitalization[b]
		Post lumbar puncture syndrome	3	775	8	Concomitant medication and non-drug therapy given, hospitalization[b]

[a] serious adverse event (s) not previously reported – occurring between March 8, 2010 and December 31, 2010.
[b] or prolonged hospitalization

Dr. Amir Shahlaee's clinical review of sNDA 22334, Supplement 6 dated October 26, 2010, contains additional information regarding the serious adverse events experienced by Subject 2, Subject 3, Subject 14, and Subject 15.

Patient 6 developed an abscess of his right leg on day 1007 of treatment. Everolimus treatment was temporarily held, and the patient was hospitalized and treated with intravenous antibiotics.

Patient 22 presented with grade 1 leukocytosis, grade 1 petechiae, and grade 3 post lumbar puncture syndrome on Day 775 of therapy, Everolimus was temporarily stopped and the patient was hospitalized. The patient received treatment with intravenous fluids and antibiotics, and the leukocytosis and petechiae resolved four days later.

7.3.3 Dropouts and/or Discontinuations

Please see section 6.1.3 (Subject Disposition) for information regarding discontinuations of patients enrolled in Study M2301 and Study C2485.

During the open-label period of Study M2301, one patient (Patient 0502-0008) discontinued study treatment with everolimus due to an adverse event. This 5.9 year old girl was randomized to receive everolimus. She experienced Grade 3 status epilepticus on Day 175 of everolimus therapy, which required hospitalization and temporary discontinuation of study therapy. Status epilepticus resolved on the same day (Day 175). On Day 176, she developed a Grade 1 urinary tract infection that was treated with multiple antibiotics and resolved on Day 179. Everolimus was restarted at the same dose on Day 195 of therapy. On day 423 (June 11, 2011), the patient developed a Grade 1 sinus infection, withdrew consent for continued therapy with everolimus. *Reviewer comment: This patient exhibited a SEGA response during everolimus therapy (>50% reduction in sum of volumes of target SEGA lesions).*

7.3.4 Significant Adverse Events

Adverse event leading to permanent discontinuation of study drug during the open label period in Study M2301

The 90-day safety update included a single non-serious adverse event, Grade 1 sinusitis, leading to permanent discontinuation of everolimus. This adverse event occurred in 4 year old girl (Patient 0502_00008) on day 423 of treatment. This patient also previously required temporary interruption of everolimus due to a serious adverse event, Grade 3 status epilepticus, that occurred on Day 175 of therapy.

Note: This discontinuation, reported in the safety update submitted by the Applicant on May 4, 2012, occurred during the open label period of treatment after Study M2301 was unblinded.

Adverse events leading to dose interruption or modification

Table 42 summarizes the per-patient incidence of adverse events requiring dose interruption or dose modification in Study M2301. A higher percentage of patients required dose interruption or dose modification due to adverse events in the everolimus arm (55%) compared to the placebo arm (13%). The most commonly reported adverse that required dose adjustment of everolimus and that also occurred with at least a 5% higher per-patient incidence in the everolimus group were: stomatitis (+15%), mouth ulceration (+9%), and upper respiratory tract infection(+5%).

Table 42: Per-patient incidence of adverse events requiring dose interruption or modification in Study M2301

Preferred Term	Everolimus N = 78		Placebo N = 39	
	n	%	n	%
Stomatitis	14	18%	1	3%
Mouth ulceration	7	9%	0	0%
Pyrexia	5	6%	1	3%
Pneumonia	4	5%	1	3%
Upper respiratory tract infection	4	5%	0	0%
Neutropenia	3	4%	1	3%
Bronchitis	2	3%	0	0%
Gastroenteritis	2	3%	0	0%
Gastroenteritis viral	2	3%	0	0%
Nasopharyngitis	2	3%	0	0%
Pharyngitis	2	3%	1	3%
Pharyngitis streptococcal	2	3%	0	0%
Viral infection	2	3%	0	0%
Abdominal pain	1	1%	0	0%
Aggression	1	1%	0	0%
Anemia	1	1%	0	0%
Blast cells present[a]	1	1%	0	0%
Blood alkaline phosphatase increased	1	1%	1	3%
Clavicle fracture	1	1%	0	0%

Preferred Term	Everolimus N = 78		Placebo N = 39	
	n	%	n	%
Constipation	1	1%	0	0%
Convulsion	1	1%	0	0%
Cough	1	1%	0	0%
Dehydration	1	1%	0	0%
Diarrhea	1	1%	0	0%
Ear infection	1	1%	0	0%
Ear infection bacterial	1	1%	0	0%
Enteritis	1	1%	0	0%
Febrile infection	1	1%	0	0%
Foreign body aspiration	1	1%	0	0%
Gingivitis	1	1%	0	0%
Hypersensitivity	1	1%	0	0%
Impaired healing	1	1%	0	0%
Impetigo	1	1%	0	0%
Influenza	1	1%	0	0%
Influenza like illness	1	1%	0	0%
Nausea	1	1%	0	0%
Neutrophil count decreased	1	1%	0	0%
Oral pain	1	1%	0	0%
Otitis media	1	1%	0	0%
Periorbital cellulitis	1	1%	0	0%
Pneumonitis	1	1%	0	0%
Postoperative wound infection	1	1%	0	0%
Rash maculo-papular	1	1%	0	0%
Respiratory tract infection	1	1%	0	0%
Respiratory tract infection viral	1	1%	0	0%
Sinusitis	1	1%	0	0%
Status epilepticus	1	1%	0	0%
Umbilical hernia	1	1%	0	0%
Vomiting	1	1%	0	0%
Blood fibrinogen decreased	0	0%	1	3%

a. this adverse event occurred in the context of iron deficiency anemia, resolved after 15 days and was not considered to be related to everolimus by the

investigator. This patient resumed everolimus after resolution of the adverse event.
b. this adverse event was reported in error. The patient's white blood cell count was normal at the time of the reported adverse event.

Adverse Events Requiring Additional Therapy – Study M2301

Adverse events requiring addition of concomitant medication or non-drug therapy occurred more frequently in the everolimus arm (96%) compared to the placebo arm (80%). The most commonly reported adverse that required additional therapy and that also occurred with at least a 5% higher per-patient incidence in patients treated with everolimus were: mouth ulceration (+22%), stomatitis (+17%), acne (+9%), rash (+6%), respiratory tract infection (+6%), rhinitis (+6%), viral respiratory tract infection (+5%), and insomnia (+5%).

7.3.5 Submission Specific Primary Safety Concerns

The NDA included specific analyses of the following adverse events reported in Study M2301, which were identified as "clinically notable adverse events" by the Applicant. These adverse events are all listed in the current Afinitor label.

- Infections and infestations
- Stomatitis and related events
- Rash and related adverse events
- Cytopenias
- Hemorrhages
- Amenorrhea
- Hypersensitivity reactions (anaphylactic reactions)
- Non-infectious pneumonitis
- Hyperglycemia/new-onset diabetes
- Thromboembolism

<u>Infections and infestations</u>
Consistent with the known adverse event profile of everolimus, the per-patient incidence of infections was higher in the everolimus arm (76%) compared to the placebo arm (69%). Most infections were mild (Grade 1 or Grade 2). Please see Section 7.4.1 for a listing of the common infectious adverse events. Infections of Grade-3 or grade0-4 severity occurred in 13% of patients in the everolimus arm and 5% of patients in the placebo arm. The following Grade 3 infectious adverse events occurred most frequently:

- Bronchitis (4% in the everolimus arm and 3% in the placebo arm)

- Gastroenteritis viral (3% in the everolimus arm and 0% in the placebo arm)
- Pneumonia (3% in the everolimus arm and 0% in the placebo arm)
- Otitis Media (1 in the everolimus arm and 3% in the placebo arm).

Reviewer note: The risk of infections is currently listed in the Warnings and Precautions section of the Afinitor label. Additionally, respiratory tract infections, pneumonia and gastroenteritis are included in Section 6.5 of the proposed labeling for Afinitor and Afinitor Disperz.

Stomatitis and related adverse events

Consistent with the known toxicity profile of everolimus, stomatitis and related events (mouth ulceration, lip ulceration) were reported more commonly in the everolimus group (62%) compared to the placebo group (26%). A total of 7 patients (9%) treated with everolimus experienced Grade 3 stomatitis or mouth ulceration, compared to 1 patient (3%) in the placebo group. No patient in either treatment group experienced a Grade 4 stomatitis-related event.

Reviewer note: *The risk of stomatitis is currently listed in the Warnings and Precautions section of the Afinitor label. Additionally, stomatitis is listed in Section 6.5 of the proposed labeling for Afinitor and Afinitor Disperz.*

Rash and related adverse events

Consistent with the known toxicity profile of everolimus, the incidence of rash (including the preferred terms rash, rash generalized, rash macular, rash maculo-papular, rash papular, dermatitis allergic, and urticaria) was more common among everolimus-treated patients (21%) compared to placebo-treated patients (8%). All of these rash-related adverse events were mild (Grade 1 or Grade 2 severity).

Reviewer note: Rash is listed in Section 6.5 of the proposed labeling for Afinitor and Afinitor Disperz.

Cytopenias

Consistent with the known toxicity profile of everolimus, the incidence of cytopenias (including the preferred terms neutrophil count decreased, neutropenia, lymphocyte count decreased, monocyte count decreased, platelet count decreased, white blood cell count decreased, and leukopenia) was more common among everolimus-treated patients (17%) compared to placebo-treated patients (3%). The most frequently occurring cytopenia continued to be decreased neutrophil count (8%) and neutropenia (6%). Grade 3 cytopenias occurred in 4 everolimus-treated patients (4%) and one placebo-treated patient (3%). These adverse events required dose interruption or dose modification.

Reviewer note: Neutropenia and anemia are listed in Section 6.5 of the proposed Afinitor labeling.

Hemorrhages

Consistent with the known toxicity profile of everolimus, hemorrhage (epistaxis, blood in the urine menorrhagia, metrorrhagia, vessel puncture site hematoma, and gingival bleeding) were slightly more common in the everolimus group (9%) compared to the placebo group (5%). With the exception of epistaxis, which occurred in 4 patients receiving everolimus, all bleeding events occurred in a single patient. No Grade 3 or Grade 4 bleeding events were reported.

Reviewer comment: epistaxis, menorrhagia, and metrorrhagia are included in Section 6.5 of the proposed Afinitor labeling.

Amenorrhea

Current Afinitor labeling lists amenorrhea as an adverse reaction associated with Afinitor in patients with TSC and renal angiomyolipoma. In Study M2301, there were 3 cases of amenorrhea in 18 females (17%) between the ages of 10 to 55 in the everolimus group and no cases in the placebo group. All cases were initially recorded as Grade 1 in severity, and two of the cases became Grade 3 in severity due to their duration. All cases were considered to be secondary amenorrhea because they occurred in patients who previously had normal menses. Two patients received medication (Depo-Provera and Loestrin 24 for one patient and one patient received Prometrium) prior to resolution of amenorrhea.

Reviewer comment: amenorrhea, menstrual irregularity, menorrhagia, and metrorrhagia are included in Section 6.5 of the proposed Afinitor labeling. The Applicant is currently conducting long term follow-up of patients continuing to receive everolimus through the extension phases of Study C2485 and Study M2301. Patients will be evaluated for growth and development milestones, including attainment of menarche in females and adrenarche in males, and Tanner Stage progression; additionally, luteinizing and follicle stimulating hormones (LH, FSH), and testosterone levels in boys and LH, FSH and estradiol levels in girls will be evaluated to better understand the impact of long term use of everolimus on growth and development.

Hypersensitivity reactions

Hypersensitivity reactions occurred in 2 (3%) Afinitor-treated patients. Both hypersensitivity reactions were Grade 1 severity. No cases of anaphylaxis were reported.

Reviewer comment: It is unlikely that everolimus played a role in the hypersensitivity reaction for either patient. Both patients were retreated with

everolimus following a brief interruption of therapy without recurrence of allergic symptoms.

Non-infectious pneumonitis

One case of non-infectious pneumonitis (Grade 2) occurred in a patient in the everolimus group. The everolimus dose was reduced from 8-mg to 6-mg in this patient, and the pneumonitis resolved after 8 weeks without additional intervention.

Reviewer comment: Non-infectious pneumonitis is listed in the Warnings and Precautions section of the Afinitor label.

Hyperglycemia/new onset diabetes mellitus

No patients in the everolimus group experienced adverse events of hyperglycemia or new onset diabetes mellitus during the double-blind portion of Study M2301.

Reviewer comment: Based on analysis of laboratory parameters, increased serum glucose occurred in 4 (5%) of patients in the everolimus group and 4 (10%) of patients in the placebo group. All elevated glucose levels were of mild severity.

Renal events

Renal events (one episode of Grade 1 renal impairment, one episode of Grade 1 proteinuria, and one episode of Grade 1 urinary protein increased) were reported in 3 patients (4%) in the everolimus group and no patients in the placebo group. Everolimus was not interrupted or adjusted due to these adverse events.

Thromboembolic events

No thromboembolic events occurred in patients in the either treatment group of Study M2301.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study M2301

The majority of patients in both treatment groups experienced an adverse event. A total of 76 of 78 (97%) of patients in the Afinitor group experienced an adverse event, compared to 36 of 39 (92%) of patients in the Placebo group.

As described in Table 43, The Gastrointestinal Disorders System Organ Class (SOC) had the highest incidence of treatment-emergent adverse events in the everolimus group (77%). The following SOCs had the greatest difference in incidence of adverse events in the everolimus group relative to the placebo group:

- Gastrointestinal disorders (+25.6%; primarily mouth ulceration and stomatitis)
- Skin and subcutaneous tissue disorders (+23.1, primarily rashes and acne)
- Psychiatric disorders (+20.5%, including aggression, agitation, anxiety, and behavioral disturbances)

Table 43: Per-patient incidence of adverse events during double blind period of Study M2301 by System Organ Class

System Organ Class	Everolimus N = 78		Placebo N = 39	
	n	%	n	%
Gastrointestinal disorders	60	77%	20	51%
Infections and infestations	59	76%	27	69%
Nervous system disorders	34	44%	18	46%
General disorders and administration site conditions	32	41%	13	33%
Skin and subcutaneous tissue disorders	30	38%	6	15%
Respiratory, thoracic and mediastinal disorders	27	35%	9	23%
Psychiatric disorders	24	31%	4	10%
Investigations	18	23%	7	18%
Metabolism and nutrition disorders	17	22%	8	21%
Injury, poisoning and procedural complications	15	19%	7	18%

System Organ Class	Everolimus N = 78		Placebo N = 39	
	n	%	n	%
Musculoskeletal and connective tissue disorders	13	17%	0	0%
Blood and lymphatic system disorders	9	12%	1	3%
Reproductive system and breast disorders	8	10%	1	3%
Eye disorders	4	5%	1	3%
Renal and urinary disorders	4	5%	0	0%
Vascular disorders	3	4%	2	5%
Ear and labyrinth disorders	2	3%	2	5%
Immune system disorders	2	3%	1	3%
Cardiac disorders	1	1%	1	3%
Endocrine disorders	0	0%	1	3%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0%	4	10%

Table 44 lists the treatment-emergent adverse reactions occurring during the double-blind period of Study M2301 with a reported per-patient incidence of at least 5%, in addition to all treatment emergent adverse reactions of Grade 3 or Grade 4 severity. The preferred terms shaded in gray are listed in Section 6.5 of the proposed Afinitor labeling.

A higher percentage of patients in the Afinitor group experienced adverse events of Grade 3 or 4 severity. In the Afinitor group, 28 of 78 patients (36%) experienced at least one adverse event of maximal Grade 3 severity, compared to 9 of 39 (23%) of patients in the placebo group. Grade 4 adverse events were relatively rare in both groups, 2 of 78 (3%) patients experienced a Grade 4 adverse event in the Afinitor group, compared to 1 of 39 patients (3%) in the placebo group.

Table 44: Per-patient incidence of treatment emergent adverse reactions during the double blind period of Study M2301 by Preferred Term

Preferred Term	Everolimus N = 78				Placebo N = 39			
	All Grades		Grade 3 or 4		All Grades		Grade 3 or 4	
	n	%	n	%	n	%	n	%
Mouth ulceration[a]	26	33%	1	1%	2	5%	0	0%
Stomatitis[a]	25	32%	6	8%	8	21%	1	3%
Convulsion	21	27%	4	5%	11	28%	2	5%
Pyrexia	18	23%	5	6%	7	18%	1	3%
Vomiting	17	22%	1	1%	5	13%	0	0%
Nasopharyngitis	15	19%	1	1%	10	26%	0	0%
Upper respiratory tract infection[b]	14	18%	1	1%	9	23%	0	0%
Diarrhea	13	17%	0	0%	2	5%	0	0%
Cough	12	15%	0	0%	5	13%	0	0%
Fatigue	11	14%	0	0%	1	3%	0	0%
Pharyngitis	9	12%	0	0%	2	5%	0	0%
Bronchitis	8	10%	3	4%	4	10%	1	3%
Otitis media	8	10%	1	1%	3	8%	1	3%
Constipation	8	10%	0	0%	1	3%	0	0%
Pharyngitis streptococcal	8	10%	0	0%	1	3%	0	0%
Acne	8	10%	0	0%	2	5%	0	0%
Rash[c]	8	10%	0	0%	1	3%	0	0%
Ear infection	7	9%	1	1%	2	5%	0	0%
Sinusitis	7	9%	0	0%	3	8%	0	0%
Decreased appetite	7	9%	0	0%	2	5%	0	0%
Headache	7	9%	0	0%	3	8%	0	0%
Aggression[d]	6	8%	2	3%	1	3%	0	0%
Neutrophil count decreased	6	8%	1	1%	0	0%	0	0%
Nausea	6	8%	0	0%	0	0%	0	0%
Rhinitis	6	8%	0	0%	2	5%	0	0%
Pain in extremity	6	8%	0	0%	0	0%	0	0%
Neutropenia	5	6%	3	4%	1	3%	1	3%
Pneumonia	5	6%	2	3%	2	5%	0	0%
Respiratory tract infection viral[b]	5	6%	1	1%	0	0%	0	0%
Respiratory tract infection[b]	5	6%	0	0%	1	3%	0	0%

Preferred Term	Everolimus N = 78				Placebo N = 39			
	All Grades		Grade 3 or 4		All Grades		Grade 3 or 4	
	n	%	n	%	n	%	n	%
Blood cholesterol increased	5	6%	0	0%	1	3%	0	0%
Blood lactate dehydrogenase increased	5	6%	0	0%	0	0%	0	0%
Hypercholesterolaemia	5	6%	0	0%	1	3%	0	0%
Insomnia	5	6%	0	0%	0	0%	0	0%
Gastroenteritis viral[e]	4	5%	2	3%	1	3%	0	0%
Gastroenteritis[e]	4	5%	1	1%	0	0%	0	0%
Viral infection	4	5%	1	1%	2	5%	0	0%
Anemia	4	5%	0	0%	0	0%	0	0%
Abdominal pain	4	5%	0	0%	1	3%	0	0%
Oral pain	4	5%	0	0%	0	0%	0	0%
Irritability	4	5%	0	0%	1	3%	0	0%
Low density lipoprotein increased	4	5%	0	0%	1	3%	0	0%
Dizziness	4	5%	0	0%	2	5%	0	0%
Epistaxis	4	5%	0	0%	1	3%	0	0%
Agitation[d]	3	4%	2	3%	0	0%	0	0%
Amenorrhea	3	4%	2	3%	0	0%	0	0%
Status epilepticus	2	3%	2	3%	0	0%	0	0%
Gastrointestinal infection[e]	2	3%	1	1%	0	0%	0	0%
Clavicle fracture	2	3%	1	1%	0	0%	0	0%
Fall	2	3%	1	1%	2	5%	0	0%
Deafness	1	1%	1	1%	0	0%	0	0%
Bronchopneumonia	1	1%	1	1%	0	0%	0	0%
Ear infection bacterial	1	1%	1	1%	0	0%	0	0%
Febrile infection	1	1%	1	1%	0	0%	0	0%
Blast cells present	1	1%	1	1%	0	0%	0	0%
Blood alkaline phosphatase increased	1	1%	1	1%	1	3%	1	3%
Dehydration	1	1%	1	1%	3	8%	0	0%
Grand mal convulsion	1	1%	1	1%	0	0%	0	0%
Postictal psychosis	1	1%	1	1%	0	0%	0	0%

a. In the proposed label, the incidence of stomatitis (62% in the Afinitor group and 26% in the placebo group) includes the preferred terms stomatitis, mouth ulceration, and lip ulceration.

b. In the proposed label, the incidence of respiratory tract infection (31% in the Afinitor group and 23% in the placebo group) includes the preferred terms respiratory tract infection, upper respiratory tract infection and viral respiratory tract infection.
c. In the proposed label, the incidence of rash (21% in the Afinitor group and 8% in the placebo group) includes the preferred terms rash, rash generalized, rash macular, rash maculo-papular, rash papular, dermatitis allergic, and urticaria.
d. In the proposed label, the preferred terms agitation, anxiety, panic attack, aggression, abnormal behavior and obsessive compulsive disorder are combined and listed as "Anxiety, aggression, or other behavioral disturbance." (incidence 21% in the Afinitor group and 3% in the placebo group).
e. In the proposed label, the incidence of gastroenteritis (10% in the Afinitor group and 3% in the placebo group) includes the preferred terms gastroenteritis, gastroenteritis viral, and gastrointestinal infection.

Because of the increased incidence of adverse events occurring in the Psychiatric Disorders SOC in the everolimus group, additional analyses of adverse events reported for this SOC were conducted. Table 45 summarizes the per-patient incidence of adverse events within the Psychiatric Disorders SOC reported during the double blind period of Study M2301. Preferred terms included in Section 6.5 of the proposed label are shaded in grey.

Table 45: PPI of treatment-emergent adverse events within the Psychiatric Disorders SOC reported for the double blind period of Study M2301

Preferred Term	Everolimus		Placebo	
	n	%	n	%
Aggression	6	8%	1	3%
Insomnia	5	6%	0	0%
Abnormal behavior	3	4%	0	0%
Agitation	3	4%	0	0%
Anxiety	3	4%	1	3%
Affect lability	1	1%	0	0%
Anger	1	1%	0	0%
Emotional disorder	1	1%	0	0%
Hallucination	1	1%	0	0%
Impulsive behavior	1	1%	0	0%
Intentional[a] self-injury	1	1%	0	0%
Obsessive-compulsive disorder	1	1%	0	0%
Panic attack	1	1%	0	0%

Preferred Term	Everolimus		Placebo	
	n	%	n	%
Personality disorder	1	1%	0	0%
Postictal psychosis	1	1%	0	0%
Restlessness	1	1%	0	0%
Transient psychosis	1	1%	0	0%
Dysthymic disorder	0	0%	1	3%
Sleep disorder	0	0%	2	5%

a. This adverse event consisted of Grade 1 head banging in a 10 year old with pre-existing signs consistent with an autistic spectrum disorder. She was taking multiple other medications, including lamictal. This patient did not require dose modification secondary to this event, which resolved.

The majority of psychiatric adverse events were mild; there were two Grade 2 adverse events of agitation, and one Grade 3 adverse event of post-ictal psychosis. Because the clinical presentation of agitation, anxiety, abnormal behavior, panic attack, and aggression can be similar in pediatric patients, this clinical reviewer recommended combining these preferred terms into a heading entitled "anxiety, aggression, or other behavioral disturbance" in the adverse event table in Section 6.5 the proposed package insert. When combining these terms, the per-patient incidence of anxiety, aggression, or other behavioral disorders was 21% (16 of 78 patients) in the everolimus arm and 3% (1 of 39 patients) in the placebo arm.

Study C2485

Table 46 lists the treatment-emergent adverse reactions with a reported incidence of at least 10% in addition to all treatment emergent adverse reactions of Grade 3 or Grade 4 severity for patients enrolled in Study C2485.

All 28 patients enrolled in study C2485 experienced an adverse event during study treatment. However, the majority of adverse events were non-serious adverse events of Grade 1 or Grade 2 severity.

In general, the type and incidences of adverse events reported for Study C2485 using the new data cut-off date are similar to the type and incidences of adverse events reported using the data cut-off for the primary analysis used to support the 2010 accelerated approval for SEGA. Additionally, the types and incidences of adverse reactions commonly reported in study C2485 are comparable to those reported for Study M2301, and those included in the adverse reaction sections for other indications in the current Afinitor label. The adverse events shaded in

light grey are those treatment emergent adverse events with a per-patient incidence of at least 10% that were not included in the adverse event section for SEGA in current labeling.

Table 46: Per-patient incidence of treatment emergent adverse reactions for Study C2485 by MedDRA System Organ Class and Preferred Term

Study C2485 N = 28					
System Organ Class	Preferred Term	All Grades		Grade 3 and Above	
		n	%	n	%
Gastrointestinal disorders	Stomatitis	24	86%	2	7%
Infections and infestations	Upper respiratory tract infection	24	86%	0	0%
Infections and infestations	Sinusitis	13	46%	1	4%
Infections and infestations	Otitis media	10	36%	0	0%
Gastrointestinal disorders	Diarrhea	9	32%	0	0%
General disorders and administration site conditions	Pyrexia	9	32%	0	0%
Nervous system disorders	Convulsion	8	29%	3	11%
Infections and infestations	Gastroenteritis	8	29%	1	4%
Infections and infestations	Cellulitis	8	29%	0	0%
Respiratory, thoracic and mediastinal disorders	Rhinitis allergic	8	29%	0	0%
Gastrointestinal disorders	Vomiting	7	25%	0	0%
Infections and infestations	Pharyngitis	7	25%	0	0%
Skin and subcutaneous tissue disorders	Dermatitis acneiform	7	25%	0	0%
Infections and infestations	Otitis externa	6	21%	0	0%
Infections and infestations	Skin infection	6	21%	0	0%
Injury, poisoning and procedural complications	Excoriation	6	21%	0	0%
Psychiatric disorders	Abnormal behavior	6	21%	0	0%

Study C2485 N = 28					
System Organ Class	Preferred Term	All Grades		Grade 3 and Above	
		n	%	n	%
Respiratory, thoracic and mediastinal disorders	Cough	6	21%	0	0%
Skin and subcutaneous tissue disorders	Dry skin	6	21%	0	0%
Infections and infestations	Body tinea	5	18%	0	0%
Nervous system disorders	Headache	5	18%	0	0%
Psychiatric disorders	Personality change	5	18%	0	0%
Respiratory, thoracic and mediastinal disorders	Nasal congestion	5	18%	0	0%
Skin and subcutaneous tissue disorders	Dermatitis contact	5	18%	0	0%
Skin and subcutaneous tissue disorders	Rash	5	18%	0	0%
Investigations	Neutrophil count decreased	4	14%	2	7%
Infections and infestations	Pneumonia	4	14%	1	4%
Nervous system disorders	Dizziness	4	14%	1	4%
Gastrointestinal disorders	Abdominal pain	4	14%	0	0%
Gastrointestinal disorders	Mouth ulceration	4	14%	0	0%
Infections and infestations	Gastric infection	4	14%	0	0%
Infections and infestations	Urinary tract infection	4	14%	0	0%
Investigations	Blood cholesterol increased	4	14%	0	0%
Investigations	Blood triglycerides increased	4	14%	0	0%
Skin and subcutaneous tissue disorders	Acne	4	14%	0	0%
Eye disorders	Conjunctivitis	3	11%	0	0%
Gastrointestinal disorders	Constipation	3	11%	0	0%

Study C2485 N = 28					
System Organ Class	Preferred Term	All Grades		Grade 3 and Above	
		n	%	n	%
Gastrointestinal disorders	Dental caries	3	11%	0	0%
General disorders and administration site conditions	Fatigue	3	11%	0	0%
Infections and infestations	Furuncle	3	11%	0	0%
Infections and infestations	Nasopharyngitis	3	11%	0	0%
Injury, poisoning and procedural complications	Contusion	3	11%	0	0%
Injury, poisoning and procedural complications	Laceration	3	11%	0	0%
Investigations	Blood alkaline phosphatase increased	3	11%	0	0%
Metabolism and nutrition disorders	Hypertriglyceridemia	3	11%	0	0%
Musculoskeletal and connective tissue disorders	Back pain	3	11%	0	0%
Blood and lymphatic system disorders	Cyclic neutropenia	1	4%	1	4%
Infections and infestations	Abscess limb	1	4%	1	4%
Infections and infestations	Bronchitis viral	1	4%	1	4%
Injury, poisoning and procedural complications	Post lumbar puncture syndrome	1	4%	1	4%
Respiratory, thoracic and mediastinal disorders	Aspiration	1	4%	1	4%
Respiratory, thoracic and mediastinal disorders	Sleep apnea syndrome	1	4%	1	4%

(Data cut-off December 31, 2010)

A number of the shaded adverse events (conjunctivitis, dental caries, furuncle, nasopharyngitis, contusion, laceration, blood alkaline phosphatase increase, back pain) are not recommended for inclusion in current labeling either because the cases are small in number, confounded, or because data from Study M2301

does not support their inclusion. The remaining preferred terms (abnormal behavior and fatigue) are listed in the proposed Afinitor label.

7.4.2 Laboratory Findings

This clinical review focused the review of laboratory findings primarily on Study M2301, because the presence of a placebo arm permitted a comparative analysis to aid in an assessment of causality.

Hematology Findings

Overall, hematology laboratory abnormalities occurred more frequently during the double-blind study period in everolimus-treated patients compared to patients treated with placebo. Increased partial thromboplastin time (+28.2%) and decreased hemoglobin (+20.5%) occurred more frequently in the everolimus arm.

No grade 4 hematological abnormalities occurred in either treatment group. By the time of the data cut-off date for the safety update (July 18, 2011), all cases of Grade 3 hematological abnormalities had resolved.

Decreased Leukocyte Count

The percentage of patients with low white blood cells was comparable between the two treatment arms. There were no reports of Grade 3 or 4 leukopenia in either arm.

A total of 30 (38%) of patients in the everolimus arm experienced Grade 1 leukopenia, compared to 14 (36%) of patients in the treatment group. One patient experienced Grade 2 leukopenia in the placebo group, and all leucopenia was Grade 1 severity in the treatment group.

Decreased Neutrophil Count

The per-patient incidence of neutropenia was comparable in the two groups. Clinically significant (Grade 3) neutropenia occurred more frequently in the everolimus group, but Grade 4 neutropenia was not reported in either treatment group.

A total of 36 patients (46%) in the everolimus group had neutrophil counts that were below the lower limit of normal, compared to 16 patients (41%) in the placebo group. Maximal neutropenia was Grade 1 severity in 12 (15%) patients in the everolimus group and 8 (20%) patients in the control group.
Grade 2 neutropenia: 17 (22%) of patients in the treatment arm had neutrophil counts less than 1500 but at least 1000. Seven (18%) patients in the placebo arm had neutrophil counts less than 1500 but at least 1000.

Grade 3 neutropenia: 7 patients (9%) in the treatment arm had ANC between 500 and 1000. One patient (3%) in the placebo group (0600_00016, ANC 0.98) had an ANC less than 1000.

Hemoglobin Analysis

A total of 32 (41%) patients in the everolimus group had hemoglobin levels below normal at least once during the double blind treatment period. A total of 8 (21%) patients in the placebo group had hemoglobin levels below the lower limit of normal.

Grade 2 anemia occurred in 6 patients (7%) in the everolimus group and in 1 patient (3%) in the placebo group. Grade 3 or Grade 4 anemia was not reported in either treatment group.

One patient (0700_00001) had an elevated hemoglobin at baseline that decreased to normal levels during therapy:

Lymphocyte Analysis

One patient in the placebo group (0503_00002) had lymphopenia intermittently during the study period (ranging from Grade 1 to 2), and one patient in the everolimus group (0509_00003) had transient lymphopenia (Grade 3) on Visit 8, which resolved within 2 weeks.

The incidence of lymphocytosis in the treatment group and placebo group was comparable. Lymphocytosis occurred in 21 patients (27%) in the everolimus and in 9 patients in the placebo group (24%). Lymphocytosis tended to occur in younger patients. Median age of patients experiencing lymphocytosis was 2.7 years (range: 1 year to 17 years) in the everolimus group and 1.6 years (range 0.8 years to 5.5 years) in the placebo group. .

Median maximum ALC was 6.3X 10^9/L (range 4.1 X 10^9/L to 17.5 X 10^9/L) in the everolimus group and 6.01 X 10^9/L (range 4.2 X 10^9/L to 11.0 X 10^9/L) in the placebo group.

Eosinophilia

The incidence of eosinophilia in the treatment group and placebo group was comparable. Eosinophilia was reported at least once in 10 (13%) of patients in the everolimus group and 5 (13%) of patients in the placebo group. Median maximum absolute eosinophil count was 0.76 X10^9/L (range: 0.56 – 2.76) in the everolimus group and 0.86 X 10^9/L (range 0.82-3.45) in the placebo group.

Low eosinophil count occurred in 34 (43%) of everolimus patients and 15 (39%) of placebo patients.

Platelet Count

Thrombocytopenia occurred in 5 (6%) of patients in the everolimus group and 4 (13%) patients in the placebo group. With the exception of one patient in the everolimus group (patient 0511_00002) who experienced transient Grade 2 thrombocytopenia (see below), thrombocytopenia was limited to Grade 1.

There was a higher incidence of thrombocytosis in the everolimus group (22 patients, or 28%) compared to the placebo group (6 patients, or 15%). Four patients in the everolimus group experienced mild thrombocytosis ranging from 505 to 673 X 10^9/L.

Prothrombin Time (INR)

The per-patient incidence of increased prothrombin time or INR was comparable in the treatment groups. A total of 25 of 78 (32%) patients had at least one episode of increased INR in the everolimus group, compared to 15 of 39 (39%) patients in the placebo group. Prolonged PT/INR of Grade 3 severity occurred in 6% and 5% of patients in the everolimus and placebo groups, respectively.

Partial Thromboplastin time (PTT)

Increased PTT of any Grade occurred in 56 of 78 (72%) patients in the everolimus group and 17 of 39 (44%) patients in the placebo group. However, Grade 3 PTT prolongation occurred in a higher percentage of patients in the placebo arm (5% in the placebo group and 3% in the everolimus group).

Reviewer comment: Elevated PTT is listed as an adverse event in the proposed label. However, the clinical significance of the PTT elevation in the patients enrolled in Study M2301 is uncertain; the PTT elevation tended to be relatively mild in severity and no patient had bleeding related to PTT abnormalities.

Biochemistry Parameters

Elevations in cholesterol (+42%), serum glutamic oxaloacetic transaminase (SGOT) (+33%), serum glutamic pyruvic transaminase (SGPT) (+15%) and serum triglycerides (12%) occurred more frequently in the everolimus group compared to the placebo group. Additionally, decreased serum bicarbonate occurred more frequently in the everolimus group (+22%). Table 47 provides a summary of the per-patient incidence of laboratory abnormalities reported in Study M301.

Table 47: Per-patient incidence of abnormal biochemistry laboratory values in Study M2301

Abnormal laboratory value	Everolimus N = 78				Placebo N = 39			
	All Grades		Grade 3/4		All Grades		Grade 3/4	
	n	%	n	%	n	%	n	%
Decreased bicarbonate	67	86	1	1	25	64	0	0
Increased total cholesterol	63	81	0	0	15	39	0	0
Decreased fibrinogen	33	42	0	0	30	77	1	3
Increased AST (SGOT)	26	33	0	0	0	0	0	0
Increased triglycerides	21	27	0	0	6	15	0	0
Increased ALT (SGPT)	14	18	0	0	1	3	0	0
Increased alkaline phosphatase	10	13	1	1	7	18	2	5
Decreased glucose	9	12	0	0	2	5	0	0
Decreased phosphate	7	9	1	1	1	3	0	0
Increased calcium	7	9	0	0	8	21	0	0
Decreased potassium	7	9	0	0	1	3	0	0
Increased glucose	4	5	0	0	4	10	0	0
Increased magnesium	3	4	0	0	0	1	3	0
Increased creatinine	3	4	0	0	0	0	0	0
Increased sodium	3	4	1	1	0	0	0	0
Decreased calcium	2	3	0	0	1	3	0	0
Decreased sodium	2	3	0	0	1	3	0	0
Increased total bilirubin	1	1	0	0	1	3	0	0
Decreased magnesium	0	0	0	0	1	3	0	0
Increased potassium	0	0	0	0	1	3	0	0

The vast majority of laboratory abnormalities were transient and of mild (Grade 1 or 2) severity. One patient experienced a Grade 4 sodium elevation (from 143 mmol/L at baseline to 162 mmol/L on Day 92 of therapy). Sodium levels decreased to 141 mmol/L by Day 122.

A review of laboratory abnormalities did not uncover any Hy's Law cases in Study M2301 or Study C2485.

Measures of endocrine function
Abnormal luteinizing hormone (LH) levels were the most common abnormality in the everolimus group relating to endocrine function. A total of 14 of 78 (18%) of patients in the everolimus arm and 2 of 39 (5.1%) of patients in the placebo arm had at least one LH level above the normal range. The distribution of male and female patients with above-normal levels was relatively similar in the everolimus and placebo groups.

Reviewer note: A total of 4 of 78 (5%) of everolimus-treated patients had at least one LH level above 15 IU/L, compared to 1 of 39 (3%) if patients in the placebo group. Due to the limited duration of follow-up of patients enrolled in Study M2301 to date, It is unclear what the clinical implications of these abnormalities in LH are at this time. The Applicant will submit comprehensive assessments of endocrine function, physical development, and pubertal development as part of the follow-up data required to fulfill the outstanding postmarketing requirements.

7.4.3 Vital Signs

Although more than 70% of patients in both treatment groups experienced at least one abnormal vital sign parameter, no clear differences in the incidence of abnormal systolic blood pressure, diastolic blood pressure, and pulse rate were evident in everolimus- and placebo- treated patients. Similarly, examination of changes in body weight, temperature, and respiratory rate failed to uncover any trends indicating a difference between the treatment groups.

7.4.4 Electrocardiograms (ECGs)

In Study M2301, electrocardiograms (ECGs) were performed at screening/baseline and again at the end of treatment in Study M2301. Because most patients remained on study at the end of data cut-off, there were very few post-treatment ECGs performed. In the limited number of samples, no clinically important post-treatment ECG changes were evident.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies or clinical trials were submitted to this NDA. The ongoing PMRs address the need for long-term data to examine the long term use of everolimus in patients with SEGA and TSC.

7.4.6 Immunogenicity

Immunogenicity studies were not performed in Study M2301 or Study C2485.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The Applicant performed an analysis of the relationship between time-normalized C_{min} values and the per patient incidence of cytopenia, hemorrhage, hypersensitivity reactions (anaphylactic reaction), infections and infestations, non infectious pneumonitis, rash, renal events, stomatitis (including stomatitis, oral mucositis, and ulcers), and amenorrhea. This analysis is depicted in Table 48 (adapted from the Applicant's submission).

Table 48: Applicant-conducted analysis of per-patient incidence of adverse events by time-normalized C_{min}

Adverse Event Type	Time-normalized C_{min} (ng/mL)*		
	< 5 ng/mL N=34	5-10 ng/mL N=35	> 10 ng/mL N=9
	n (%)		
Cytopenia	3 (9)	7 (20)	2 (22)
Hemorrhages	2 (6)	3 (9)	2 (22)
Hypersensitivity Reactions	1 (3)	1 (3)	0
Infections and Infestations	27 (79)	23 (66)	6 (67)
Non infectious pneumonitis	0	1 (3)	0
Rashes	9 (27)	3 (9)	1 (11)
Renal events	0	0	1 (11)
Stomatitis	20 (59)	21 (60)	5 (56)
Amenorrhea	1 (3)	0 (0)	2 (22)

*The Applicant calculated the time-normalized C_{min} for each patient as an area under the concentration-curve over the entire study period, divided by the study treatment period.
Source: Adapted from Applicant's submission

The Applicant performed an additional analysis of the relationship between time-normalized C_{2h} values and the per patient incidence of cytopenia, hemorrhage, hypersensitivity reactions (anaphylactic reaction), infections and infestations, non infectious pneumonitis, rash, renal events, stomatitis (including stomatitis, oral mucositis, and ulcers), an amenorrhea. This analysis is depicted in Table 49 (adapted from the Applicant's submission).

Table 49: Applicant-conducted analysis of per-patient incidence of adverse events by time-normalized C_{2h}

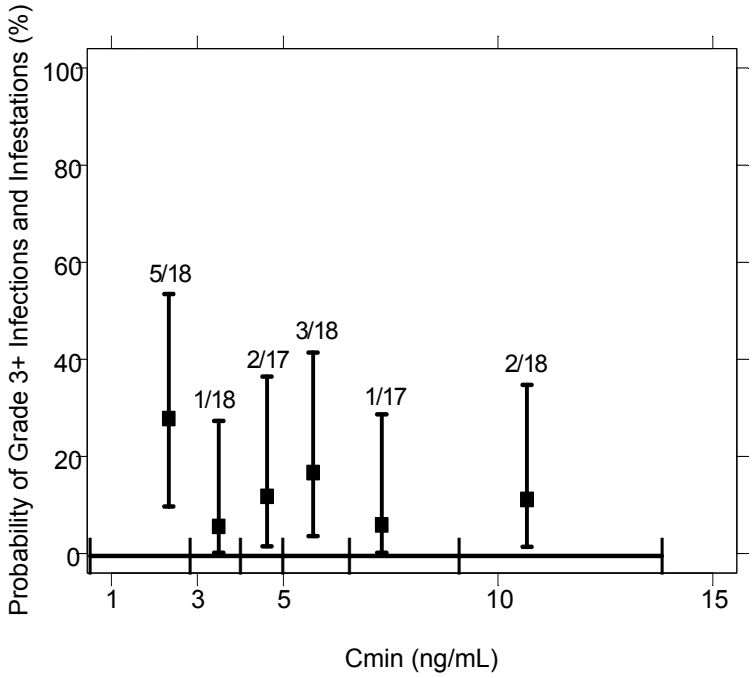
Adverse Event Type	Time-normalized C_{2h}(ng/mL)*		
	< 20 ng/mL N=16	20-50 ng/mL N=55	> 50 ng/mL N=5
	n (%)		
Cytopenia	2 (13)	10 (18)	0
Hemorrhages	2 (13)	3 (6)	1 (20)
Hypersensitivity Reactions	1 (6)	1 (2)	0
Infections and Infestations	12 (75)	38 (70)	4 (80)
Non infectious pneumonitis	0	1 (2)	0
Rashes	3 (19)	8 (15)	1 (20)
Renal events	0	1 (2)	0
Stomatitis	8 (50)	35 (64)	1 (20)
Amenorrhea	1 (6)	2 (4)	0

*The Applicant calculated the time-normalized C_{2h} for each patient as an area under the concentration-curve over the entire study period, divided by the study treatment period. Patients who did not have C_{2h} values recorded in the confirmed PK sample set were excluded from this analysis.
Source: Adapted from Applicant's submission

Although the number of patients in each C_{min} and C_{2h} subgroup is small, these analyses suggests that higher exposures within the target C_{min} range of 5-15 ng/mL and at C_{2h} levels up to 63.4 ng/mL did not confer a higher risk of adverse events in patients enrolled in Study M2301.

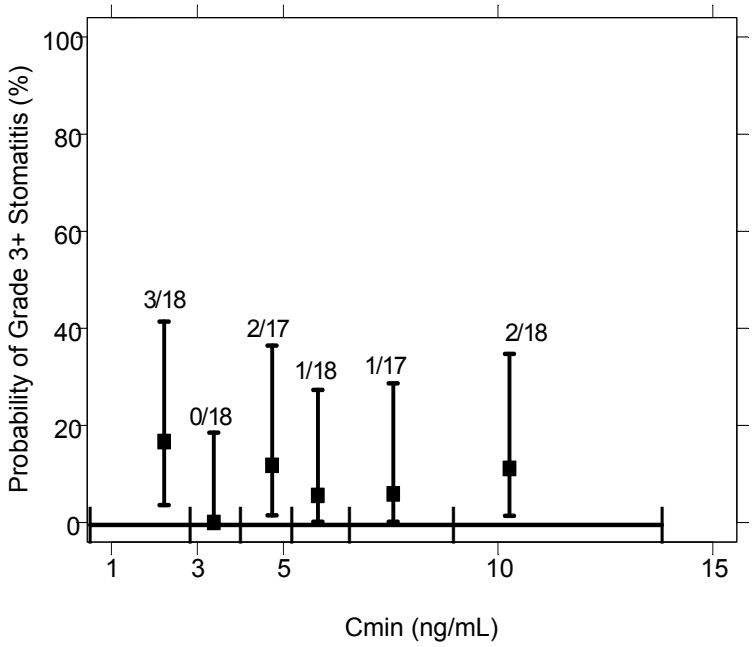
FDA clinical pharmacology reviewer Dr. Jian Wang performed additional analyses looking for an exposure-response relationship for infectious and stomatitis adverse events using combined adverse event data from everolimus-treated patients in Study M2301 (N=78) and Study C2485 (N=28). As Figure 6 and Figure 7 illustrate, there does not appear to be a relationship between everolimus C_{min} and the probability of developing Grade 3 or 4 infection or stomatitis.

Figure 6: Analysis of incidence of severe infections by everolimus C_{min} levels in Study M2301 and Study C2485



(provided by Jian Wang, PhD, FDA Office of Clinical Pharmacology)

Figure 7: Analysis of incidence of severe stomatitis by everolimus C_{min} levels in Study M2301 and Study C2485

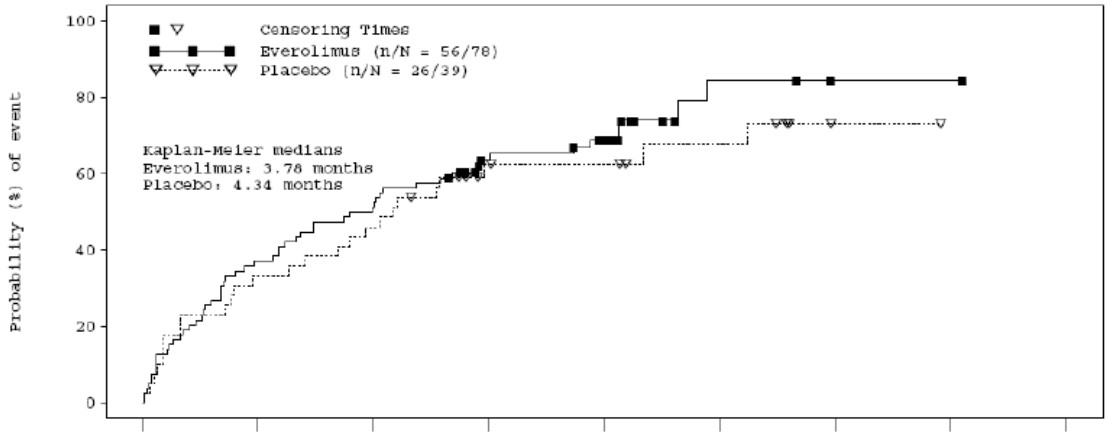


(provided by Jian Wang, PhD, FDA Office of Clinical Pharmacology)

7.5.2 Time Dependency for Adverse Events

The Applicant conducted an analysis of comparing the time to first occurrence of infections in the everolimus and placebo groups. This analysis by the Applicant demonstrated that the time to first occurrence of infection was slightly shorter in the everolimus group compared to the placebo-group (Figure 8, below). This analysis indicated that the median time to occurrence of a first infection was slightly shorter in the everolimus group (3.8 months) compared to the placebo group (4.3 months).

Figure 8: Applicant-conducted analysis comparing the time to first occurrence of infection in the everolimus and placebo groups in Study M2301



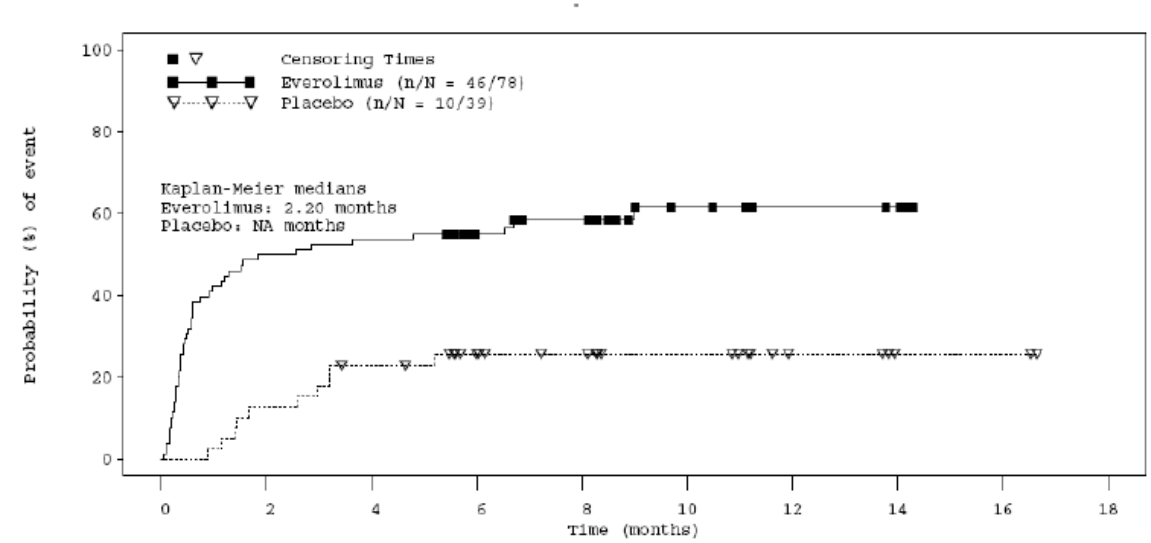
No. of patients still at risk

Time (months)	0	2	4	6	8	10	12	14	16
Everolimus	78	49	38	21	15	3	1	1	0
Placebo	39	26	21	11	10	6	1	0	0

(copied from NDA submission)

The Applicant also conducted an analysis comparing the time to first occurrence of mucositis (including the preferred terms stomatitis, oral mucositis and ulcer). The median time to occurrence of stomatitis, 2.2 months, was shorter in the everolimus group compared to the placebo group, where the median was not reached (Figure 9, below).

Figure 9: Applicant-conducted analysis comparing the time to first occurrence of stomatitis in the everolimus and placebo groups in Study M2301



No. of patients still at risk

Time (months)	0	2	4	6	8	10	12	14	16	18
Everolimus	78	39	36	27	22	10	6	5	0	0
Placebo	39	34	29	19	15	11	5	2	2	0

(copied from NDA submission)

7.5.3 Drug-Demographic Interactions

The patient population enrolled in Study C2485 and Study M2301 was relatively homogeneous with respect to race; a total of 109 of 117 (93%) patients and 24 of 28 (86%) patients enrolled in Study M2301 were Caucasian. Therefore, it is not possible to conduct a meaningful analysis of adverse events by race.

Subgroup analyses of adverse events reported in Study M2301 generally indicated that the risk of adverse events did not vary with age or gender, except that adverse events within the Infections and Infestations system organ class were reported more frequently in younger patients. All patients less than three years of age in both treatment group had had an infectious adverse event, compared to 69% and 65% of patients aged 3 to < 18 in the everolimus and placebo groups, respectively. Furthermore, in patients 18 years of age and older, infections were reported in 50% and 33% of patients in everolimus and placebo groups, respectively.

Gender

Table 50 summarizes the breakdown of adverse events by gender for Study M2301

Table 50: Per-patient incidence of adverse events occurring during the double-blind period of Study M2301 by gender

Preferred Term	Adverse Events – All Grades					
	Everolimus N = 78			Placebo n = 39		
	Male n = 49	Female n = 29	Total	Male n = 18	Female n = 21	Total
Mouth ulceration	31%	38%	33%	0%	10%	5%
Stomatitis	37%	24%	32%	22%	19%	21%
Convulsion	27%	28%	27%	28%	29%	28%
Pyrexia	27%	17%	23%	11%	24%	18%
Vomiting	20%	24%	22%	11%	14%	13%
Nasopharyngitis	16%	24%	19%	11%	38%	26%
Upper respiratory tract infection	20%	14%	18%	22%	24%	23%
Diarrhea	22%	7%	17%	6%	5%	5%
Cough	8%	28%	15%	11%	14%	13%
Fatigue	10%	21%	14%	0%	5%	3%
Pharyngitis	10%	14%	12%	6%	5%	5%
Acne	12%	7%	10%	6%	5%	5%
Bronchitis	8%	14%	10%	11%	10%	10%
Constipation	6%	17%	10%	0%	5%	3%
Otitis media	8%	14%	10%	6%	10%	8%
Pharyngitis streptococcal	10%	10%	10%	6%	0%	3%
Rash	12%	7%	10%	0%	5%	3%

Adverse events occurred in the majority of patients in both treatment groups, with 76 of 78 patients experiencing an adverse event in the everolimus group. A total of 28 of 29 females and 48 of 49 males experienced an adverse event in the everolimus group.

Serious adverse events appeared to occur more commonly in males compared to females. Serious adverse events occurred in 15 of 49 (30%) male patients in the everolimus group and 4 of 29 (14%) female patients in the everolimus group.

Serious adverse events occurred in 2 of 18 (11%) males in the placebo group and 3 of 21 (14%) of females in the placebo group.

Reviewer comment: Based upon this analysis, males appear to have a higher incidence of serious adverse events overall compared to females. However, definitive conclusions cannot be made regarding the relationship between SAEs and gender due to the relatively small sample size and small number serious adverse events. The relationship between gender and the incidence of adverse events will be reexamined

when the Applicant submits updated safety data from Study M2301 and Study C2485 to fulfill the outstanding PMRs.

Age
Table 51 illustrates that a higher proportion of patients experienced at least one serious adverse event in the youngest age subgroup (less than three years of age) in both treatment groups. However, overall, regardless of age subgroup, a higher percentage of patients experienced at least one serious adverse event in the everolimus group compared to the placebo group.

Table 51: Proportion of patients experiencing serious adverse events by age subgroup - Study M2301

Age Subgroup (years)	Everolimus (N = 78)	Placebo (N = 39)
0 - < 3	7 of 13 (54%)	2 of 7 (29%)
3 to < 18	10 of 55 (18%)	3 of 26 (12%)
> 18	2 of 10 (20%)	0 of 6 (0%)

Table 52 and Table 53 summarize the per-patient incidence of serious adverse events reported during the double-blind period of Study M2301 for each age subgroup by System Organ Class and Preferred Term, respectively. 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.
.

Table 52: Per-patient incidence of serious adverse events by System Organ Class (SOC) and age subgroup – Study M2301

SOC	Total				Less than 3 years				3 years to < 18 years				> 18			
	Everolimus (N = 78)		Placebo (N=39)		Everolimus (N = 13)		Placebo (N=7)		Everolimus (N = 55)		Placebo (N=26)		Everolimus (N = 10)		Placebo (N=6)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Infections and infestations	12	15%	3	8%	6	46%	2	29%	5	9%	1	4%	1	10%	0	0
Nervous system disorders	5	6%	2	5%	1	8%	1	14%	4	7%	1	4%	0	0	0	0
Gastrointestinal disorders	3	4%	0	0%	1	8%	0	0%	2	4%	0	0%	0	0	0	0
General disorders and administration site conditions	3	4%	1	3%	2	15%	1	14%	1	2%	0	0%	0	0	0	0
Immune system disorders	1	1%	0	0%	0	0	0	0	1	2%	0	0%	0	0	0	0
Metabolism and nutrition disorders	1	1%	0	0%	0	0	0	0	0	0	0	0	1	10%	0	0
Musculoskeletal and connective tissue disorders	1	1%	0	0%	0	0	0	0	0	0	0	0	1	10%	0	0
Psychiatric disorders	1	1%	0	0%	0	0	0	0	1	2%	0	0%	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1	1%	0	0%	0	0	0	0	1	2%	0	0%	0	0	0	0
Vascular disorders	0	0%	1	3%	0	0	0	0	0	0%	1	4%				

Table 53: Serious adverse events with a per-patient Incidence of at least 10% in the everolimus group by Preferred Term and age subgroup - Study M2301

Preferred Term	Everolimus N = 78					Placebo N = 39				
	Age Subgroup (years)					Age Subgroup (years)				
	< 3 n = 13	3-<12 n = 38	12 - < 18 n = 17	≥18 n= 10	Total	< 3 n = 7	3 to < 12 n = 16	12 to < 18 n = 10	18 and older n = 6	Total
Mouth ulceration	0%	53%	24%	20%	33%	0%	6%	10%	0%	5%
Stomatitis	69%	21%	24%	40%	32%	43%	19%	10%	17%	21%
Convulsion	15%	34%	29%	10%	27%	14%	38%	30%	17%	28%
Pyrexia	38%	24%	24%	0%	23%	43%	19%	10%	0%	18%
Vomiting	15%	32%	6%	20%	22%	0%	19%	10%	17%	13%
Nasopharyngitis	31%	21%	6%	20%	19%	43%	19%	40%	0%	26%
Upper respiratory tract infection	23%	21%	18%	0%	18%	43%	19%	20%	17%	23%
Diarrhea	15%	21%	12%	10%	17%	14%	6%	0%	0%	5%
Cough	23%	18%	6%	10%	15%	14%	19%	0%	17%	13%
Fatigue	0%	13%	18%	30%	14%	0%	0%	0%	17%	3%
Pharyngitis	46%	5%	0%	10%	12%	0%	13%	0%	0%	5%
Acne	0%	0%	35%	20%	10%	0%	6%	0%	17%	5%
Bronchitis	23%	8%	12%	0%	10%	29%	13%	0%	0%	10%
Constipation	15%	11%	6%	10%	10%	0%	0%	10%	0%	3%
Otitis media	23%	11%	6%	0%	10%	14%	13%	0%	0%	8%
Pharyngitis streptococcal	0%	16%	6%	10%	10%	0%	0%	10%	0%	3%
Rash	0%	16%	6%	10%	10%	14%	0%	0%	0%	3%

7.5.4 Drug-Disease Interactions

There was no new information on drug-disease interactions in this NDA.

No studies of the impact of impaired hepatic function on everolimus exposure have been conducted in pediatric patients. However, the safety, tolerability and pharmacokinetics of everolimus were evaluated in a single oral dose study of everolimus in adult subjects with impaired hepatic function relative to adult subjects with normal hepatic function. Exposure was increased in patients with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment. Compared to normal subjects (N=13), there was a 1.8-fold, 3.2-fold, and 3.6-fold increase in exposure (AUC) for subjects with mild (Child-Pugh class A, N=6), moderate (Child-Pugh class B, N=9), and severe (Child-Pugh class C, N=6) hepatic impairment, respectively. In another study, the average AUC of everolimus in eight subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in eight subjects with normal hepatic function.

Current labeling states that patients with SEGA who have mild (Child Pugh class A) or moderate (Child Pugh class B) hepatic impairment may not require dose reduction. In addition, labeling includes instructions for monitoring or everolimus trough concentrations approximately two weeks after commencing treatment, dose modification, or a change in hepatic function. *Reviewer comment: This approach to dosing of SEGA patients with mild and moderate hepatic impairment is reasonable because of the wide target therapeutic range (everolimus trough concentrations 5-15 ng/mL), lack of apparent relationship between toxicity and everolimus exposure at doses of everolimus administered in Study C2485 and Study M2301, and the opportunity for dose reduction based on therapeutic drug monitoring in this patient population.*

Prior labeling stated that patients with SEGA patients who have Child-Pugh class C hepatic impairment should not receive Afinitor. This recommendation was inconsistent with the recommendation for a 75% dose reduction in adult patients with progressive neuroendocrine tumors of pancreatic origin (PNET), renal cell carcinoma (RCC), and renal angiomyolipoma and tuberous sclerosis complex (TSC). For the same reasons that reduction of the starting dose is considered unnecessary in patients with mild and moderate hepatic impairment (outlined in the paragraph above), the clinical and clinical pharmacology reviewers recommended that Afinitor labeling be changed to include instructions for a 50% dose reduction of everolimus in patients with severe hepatic impairment for whom everolimus therapy is indicated.

No clinical studies were conducted with everolimus in patients with decreased renal function. However, renal impairment is not expected to influence drug exposure;

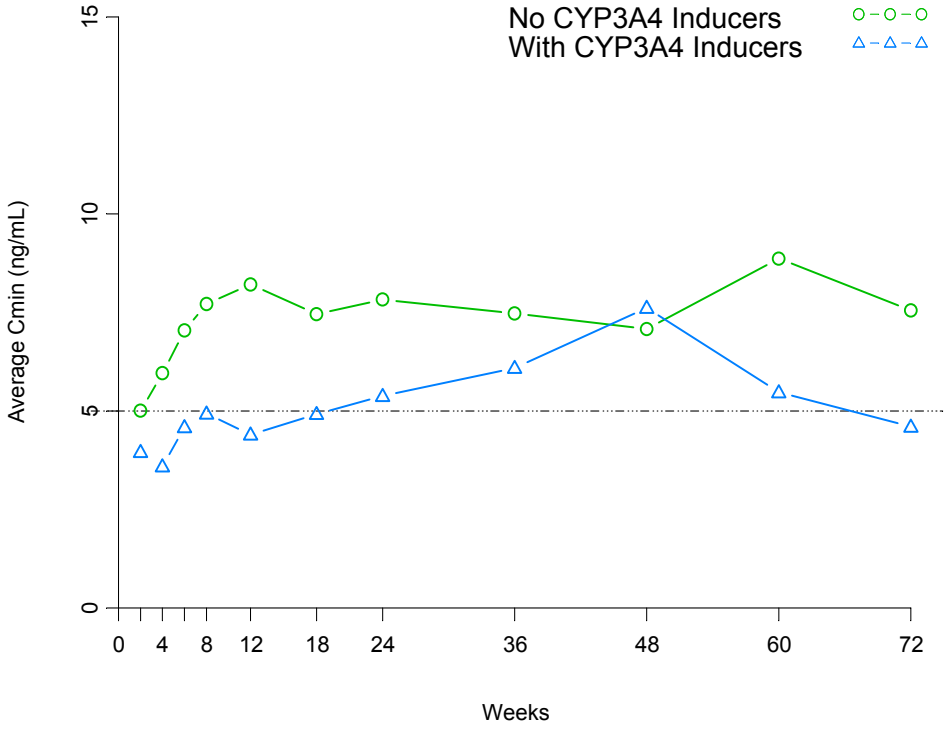
therefore, no dosage adjustment of everolimus is recommended in patients with renal impairment.

7.5.5 Drug-Drug Interactions

In Study M2301 and Study C2485, the use of enzyme-inducing anti-epileptic drugs (EIAEDs), considered to be strong inducers of CYP3A4, was allowed. The starting dose was not adjusted in patients who received concomitant EIAEDs; however, dose was subsequently titrated based on therapeutic drug monitoring that occurred throughout the study. As shown in Figure 10, adapted provided by FDA clinical pharmacology reviewer Dr. Jian Wang, patients receiving concomitant CYP3A4 inducers tended to take longer to attain an average everolimus C_{min} within the target range.

Reviewer comment: Proposed labeling includes instructions for patients who receive strong CYP3A4 inducers to double the dose of Afinitor Tablets or Afinitor Disperz and assess everolimus trough concentrations two weeks later. Proposed labeling also includes instructions for patients to return to the previous dose used if the strong CYP3A4 inducer is discontinued. Proposed labeling also includes instructions to assess everolimus trough concentrations two weeks following any dose adjustment, initiation of a CYP3A4 inducer, or discontinuation of a CYP3A4 inducer.

Figure 10: Average everolimus Cmin with and without concomitant CYP3A4 inducers



(provided by Jian Wang, PhD, FDA Office of Clinical Pharmacology)

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new human carcinogenicity studies were submitted to this NDA. No cases of secondary malignancy have been reported in patients enrolled in Study M2301 and Study C2485. Please see Dr. Amir Shahlaee's review of sNDA 22334 SE1-006, dated October 26, 2010, for an analysis of the risk of secondary malignancies with the use of everolimus in cancer patients and in the post-solid organ transplant setting. Dr. Shahlaee concluded that

> *The data provided by the Applicant suggest lower rates of secondary malignancies in patients receiving monotherapy with everolimus or other mTOR inhibitors when compared to transplant patients who are on*

prolonged, multi-drug regimens. However, this analysis does not entirely rule out a higher risk in patients with TS who are exposed to mTOR inhibitor therapy. It is however suggested that the antiproliferative characteristics of mTOR inhibitors do decrease the inherent risks associated with immunosuppressive characteristics.

Reviewer comment: Continued pharmacovigilance is warranted to better determine if there is a risk of secondary malignancy with the long term use of everolimus in patients with SEGA. FDA review of the long term safety and efficacy data submitted to fulfill the outstanding postmarketing requirements will include an assessment of serious adverse events, which would capture secondary malignancies if they occur in this patient population.

7.6.2 Human Reproduction and Pregnancy Data

No new information regarding human reproduction and pregnancy was contained in this NDA. The findings of secondary amenorrhea are discussed in Section 7.3.5 of this review. Everolimus is considered a pregnancy category D drug. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures for SEGA patients.

Reviewer comment: Section 17.9 of the proposed Afinitor label refers patients and caregivers to the FDA-approved Instructions for Use. The proposed Instructions for Use contains instructions that Afinitor Disperz should not be prepared by a woman who is pregnant or intends to become pregnant. In addition, the Instructions for Use pamphlet contains precautions for safe handling and preparation of Afinitor Disperz to decrease the likelihood of inadvertent exposure to everolimus.

7.6.3 Pediatrics and Assessment of Effects on Growth

A meaningful analysis of the effects of everolimus on growth is not yet possible due to the short period of follow up of patients in Study M2301 and Study C2485. A preliminary analysis of changes in body mass index, weight, and height of patients enrolled in study M2301 did not show any clear trend in differences in growth between the everolimus and placebo groups.

A formal analysis of the effects of long-term use of everolimus on growth and development of patients enrolled in Study C2485 and Study M2301 will be submitted to fulfill the outstanding postmarketing requirements (due in 2014 and 2015).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The label states that single doses up to 70 mg have been administered and that the acute toxicity profile observed with the 70 mg dose was consistent with that of the 10 mg dose.

There are no reports of everolimus being used as a drug of abuse. Based upon its mechanism of action, side effect profile, and approved indications, it is unlikely that this agent will be intentionally misused or abused.

The Applicant has not provided any data regarding the risks of withdrawal or rebound effects with the use of everolimus.

7.7 Additional Submissions / Safety Issues

Information contained in the safety updated submitted on May 4, 2012 was incorporated into the safety analyses in this review.

8 Postmarket Experience

As of April 27, 2012, Afinitor is approved in over 80 countries for the treatment of patients with advanced renal cell carcinoma, in over 40 countries for the treatment of patients with SEGA and TSC and patients with advanced neuroendocrine tumors, two countries outside of the US for treatment of advanced breast cancer, and in two countries (including the US) for the treatment of patients with renal angiomyolipoma and TSC. Additionally, On July 20, 2012 FDA approved Afinitor for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole.

The most recent periodic safety report (covering the reporting period from January 1, 2012 through March 31, 2012) stated that approximately (b) (4) Afinitor prescriptions were sold in the U.S. during the reporting period. The Applicant estimated that approximately (b) (4) U.S. patients used Afinitor during the three month-period.

FDA conducts surveillance of postmarketing safety data for everolimus on an ongoing basis, in addition reviewing the periodic safety reports submitted by the Applicant. No new information has emerged based on review of postmarketing data from usage of Afinitor that would substantially alter the known safety profile of everolimus in the oncology setting, or the risk-benefit analysis for its use in the SEGA population. The Applicant continues to systematically collect the long-term safety data from ongoing studies that are required to fulfill the postmarketing requirements established at the time of the 2010 accelerated approval of everolimus for the treatment of SEGA.

9 Appendices

9.1 Literature Review/References

During the course of review of this NDA, a review of pertinent literature on the following topics was performed: the pathophysiology and epidemiology of tuberous sclerosis and SEGA; the natural history of SEGA; approaches to treatment of SEGA; timing of intervention for the treatment of SEGA; published studies and literature reports describing clinical experience with use of everolimus in the treatment of SEGA. This literature review did not uncover any additional information that would substantially alter the risk/benefit profile of everolimus in the treatment of patients SEGA.

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10. Jiang T, Jia G, Ma Z et al. *The diagnosis and treatment of subependymal giant cell astrocytoma combined with tuberous sclerosis*. Child Nerv Syst. 2011; 27:55-62.

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15. Rapamune package insert. Accessed at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails in August 3, 2012.

16. Torisel package insert. Accessed at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo on August 3, 2012.

17. Fouladi M, Laningham F, Wu J, et al. *Phase I study of everolimus in pediatric patients with refractory solid tumors.* J Clin Oncol. 2007 Oct 20; 25(30):4806-4812.

9.2 Labeling Recommendations

Please refer to the FDA-approved labeling for AFINITOR and AFINITOR DISPERZ.

Labeling negotiations are ongoing at the time of this review. Proposed wording for the key clinical sections of the package insert for Afinitor and Afinitor Disperz that are affected by this NDA are listed below in italics. This wording is subject to change.

Section 1.5 (Indications and Usage):

AFINITOR® and AFINITOR® DISPERZ are indicated in pediatric and adult patients with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.

Effectiveness is based on demonstration of durable objective response, as evidenced by reduction in SEGA tumor volume. Improvement in disease-related symptoms and overall survival in patients with SEGA and TSC have not been demonstrated.

Section 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.

Section 2.3 (Recommended Dose in Subependymal Giant Cell Astrocytoma with TSC):

The recommended starting dose is 4.5 mg/m2, 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.

Section 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.*

Section 2.5 (Dose Modifications in Subependymal Giant Cell Astrocytoma with TSC)

Adverse Reactions
Reduce dose or withhold AFINITOR Tablets or AFINITOR DISPERZ for severe or intolerable adverse reactions [see Warnings and Precautions (5)].

Reduce the dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately 50%. If dose reduction is required for patients receiving the lowest available strength, administer every other day [see Table 1 in Dosage and Administration (2.2)].

Hepatic Impairment

- *Reduce the starting dose of AFINITOR Tablets or AFINITOR DISPERZ by approximately* (b) (4) *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.

Section 2.7 (Administration and Preparation of AFINITOR DISPERZ (everolimus tablets for oral suspension*)*

Do not combine the two formulations (AFINITOR Tablets and AFINITOR DISPERZ) to achieve the desired dose. Use one formulation or the otherAdminister AFINITOR DISPERZ (everolimus tablets for oral suspension) as a suspension only.

Administer AFINITOR DISPERZ orally once daily at the same time every day. Administer either consistently with food or consistently without food [see Clinical Pharmacology (12.3)].

Administer suspension immediately after preparation. Discard suspension 60 minutes after preparation.

Prepare suspension only in water.

Using an oral syringe:

- *Place the prescribed dose of AFINITOR DISPERZ into a 10-mL syringe. Do not exceed a total of 10 mg per syringe. If higher doses are required, prepare an additional syringe. Do not break or crush tablets.*
- *Draw approximately 5 mL of water and 4 mL of air into the syringe.*
- *Place the filled syringe into a container (tip up) for 3 minutes, until the AFINITOR DISPERZ tablets are in suspension.*
- *Gently invert the syringe 5 times immediately prior to administration.*

- *After administration of the prepared suspension, draw approximately 5 mL of water and 4 mL of air into the same syringe, and swirl the contents to suspend remaining particles. Administer the entire contents of the syringe.*
- *Using a small drinking glass:*
- *Place the prescribed dose of AFINITOR DISPERZ into a small drinking glass (maximum size 100 mL) containing approximately 25 mL of water. Do not exceed a total of 10 mg of AFINITOR DISPERZ per glass. If higher doses are required, prepare an additional glass. Do not break or crush tablets.*
- *Allow 3 minutes for suspension to occur.*
- *Stir the contents gently with a spoon, immediately prior to drinking.*
- *After administration of the prepared suspension, add 25 mL of water and stir with the same spoon to re-suspend remaining particles. Administer the entire contents of the glass*

Section 6.5 (Clinical Study Experience in Subependymal Giant Cell Astrocytoma with TSC)

The data described below are based on a randomized (2:1), double-blind, placebo-controlled trial (Study 1) of AFINITOR in 117 patients with SEGA and TSC. The median age of patients was 9.5 years (range 0.8 to 26 years), 93% were Caucasian, and 57% were male. The median duration of blinded study treatment was 52 weeks (range 24 to 89 weeks) for patients receiving AFINITOR and 47 weeks (range 14 to 88 weeks) for those receiving placebo.
The most common adverse reaction reported for AFINITOR (incidence ≥ 30%) was stomatitis. The most common Grade 3-4 adverse reactions (incidence ≥ 2%) were stomatitis, pyrexia, pneumonia, viral gastroenteritis, aggression, agitation, and amenorrhea. The most common key laboratory abnormalities (incidence ≥ 50%) were hypercholesterolemia and elevated partial thromboplastin time. The most common Grade 3-4 laboratory abnormality (incidence ≥ 3%) was neutropenia.
There were no adverse reactions resulting in permanent discontinuation. Dose adjustments (interruptions or reductions) due to adverse reactions occurred in 55% of AFINITOR-treated patients. The most common adverse reaction leading to AFINITOR dose adjustment was stomatitis.
Table 10 compares the incidence of adverse reactions reported with an incidence of ≥ 10% for patients receiving AFINITOR and occurring more frequently with AFINITOR than with placebo. Laboratory abnormalities are described separately in Table 11.

Table 10: Adverse Reactions Reported in ≥10% of AFINITOR-treated Patients with SEGA in Study 1

	AFINITOR N=78			*Placebo N=39*		
	All grades	*Grade 3*	*Grade 4*	*All grades*	*Grade 3*	*Grade 4*
	%	*%*	*%*	*%*	*%*	*%*
Any adverse reaction	***97***	***36***	***3***	***92***	***23***	***3***
Gastrointestinal disorders						
Stomatitis[a]	*62*	*9*	*0*	*26*	*3*	*0*
Vomiting	*22*	*1*	*0*	*13*	*0*	*0*
Diarrhea	*17*	*0*	*0*	*5*	*0*	*0*
Constipation	*10*	*0*	*0*	*3*	*0*	*0*
General disorders and administration site conditions						
Pyrexia	*23*	*6*	*0*	*18*	*3*	*0*
Fatigue	*14*	*0*	*0*	*3*	*0*	*0*
Psychiatric and behavioral disorder						
Anxiety, aggression or other behavioral disturbance[b]	*21*	*5*	*0*	*3*	*0*	*0*
Skin and subcutaneous tissue disorders						
Rash[c]	*21*	*0*	*0*	*8*	*0*	*0*
Acne	*10*	*0*	*0*	*5*	*0*	*0*
Infections and infestations						
Gastroenteritis[d]	*10*	*4*	*1*	*3*	*0*	*0*
Pharyngitis streptococcal	*10*	*0*	*0*	*3*	*0*	*0*

Grading according to CTCAE Version 3.0

[a] *Includes mouth ulceration, stomatitis, and lip ulceration*

[b] *Includes agitation, anxiety, panic attack, aggression, abnormal behavior, and obsessive compulsive disorder*

[c] *Includes rash, rash generalized, rash macular, rash maculo-papular, rash papular, dermatitis allergic, and urticaria*

[d] *Includes gastroenteritis, gastroenteritis viral, and gastrointestinal infection*

Amenorrhea occurred in 17% of AFINITOR-treated females aged 10 to 55 years (3 of 18) and none of the females in the placebo group. For this same group of AFINITOR-treated females, the following menstrual abnormalities were reported: dysmenorrhea (6%), menorrhagia (6%), metrorrhagia (6%), and unspecified menstrual irregularity (6%).

The following additional adverse reactions occurred in AFINITOR-treated patients: nausea (8%), pain in extremity (8%), insomnia (6%), pneumonia (6%), epistaxis (5%), hypersensitivity (3%), and pneumonitis (1%).

Table 11: Key Laboratory Abnormalities Reported in AFINITOR-treated Patients with SEGA in Study 1

	AFINITOR N=78			*Placebo N=39*		
	All grades %	***Grade 3 %***	***Grade 4 %***	***All grades %***	***Grade 3 %***	***Grade 4 %***
Hematology						
Elevated partial thromboplastin time	*72*	*3*	*0*	*44*	*5*	*0*
Neutropenia	*46*	*9*	*0*	*41*	*3*	*0*
Anemia	*41*	*0*	*0*	*21*	*0*	*0*
Hypercholesterolemia	*81*	*0*	*0*	*39*	*0*	*0*
Elevated aspartate transaminase (AST)	*33*	*0*	*0*	*0*	*0*	*0*
Hypertriglyceridemia	*27*	*0*	*0*	*15*	*0*	*0*
Elevated alanine transaminase (ALT)	*18*	*0*	*0*	*3*	*0*	*0*
Hypophosphatemia	*9*	*1*	*0*	*3*	*0*	*0*

Grading according to CTCAE Version 3.0

Longer-term follow-up of 34.2 months (range 4.7 to 47.1 months) from a non-randomized, open-label, 28-patient trial resulted in the following additional notable adverse reactions and key laboratory abnormalities: cellulitis (29%), hyperglycemia (25%), and elevated creatinine (14%).

Section 8.4 (Pediatric Use)

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

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

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

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

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

Section 14.5 (Subependymal Giant Cell Astrocytoma with Tuberous Sclerosis Complex)

Study 1 was a randomized (2:1), double-blind, placebo-controlled trial of AFINITOR Tablets conducted in 117 pediatric and adult patients with Subependymal Giant Cell Astrocytoma (SEGA) and Tuberous Sclerosis Complex (TSC). Eligible patients had at least one SEGA lesion ≥ 1.0 cm in longest diameter on MRI based on local radiology assessment and one or more of the following: serial radiological evidence of SEGA growth, a new SEGA lesion ≥ 1 cm in longest diameter, or new or worsening hydrocephalus. Patients randomized to the treatment arm received AFINITOR Tablets at a starting dose of 4.5 mg/m^2 daily, with subsequent dose adjustments as needed to achieve and maintain everolimus trough concentrations of 5 to 15 ng/mL as tolerated. AFINITOR/matched placebo treatment continued until disease progression or unacceptable toxicity. MRI scans for disease assessment were obtained at baseline, 12, 24, and 48 weeks, and annually thereafter.

The primary efficacy outcome measure was SEGA response rate based on independent central radiology review. SEGA response was defined as a ≥ 50% reduction in the sum of SEGA volume relative to baseline, in the absence of unequivocal worsening of non-target SEGA lesions, a new SEGA lesion ≥ 1 cm, and new or worsening hydrocephalus. Secondary efficacy outcome measures were absolute change in frequency of total seizure events per 24-hour video-EEG, time to SEGA progression, and skin lesion response rate. Analyses of efficacy outcome measures were limited to the blinded treatment period which ended 6 months after the last patient was randomized. The analysis of SEGA response rate was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomization (yes/no).

Of the 117 patients enrolled, 78 were randomized to AFINITOR and 39 to placebo. The median age was 9.5 years (range 0.8 to 26 years; 69% were 3 to < 18 years at enrollment; 17% were < 3 years at enrollment), 57% were male, and 93% were Caucasian. At baseline, 18% of patients were receiving EIAEDs. Based on central

radiology review at baseline, 98% of patients had at least one SEGA lesion ≥ 1.0 cm in longest diameter, 79% had bilateral SEGAs, 43% had ≥ 2 target SEGA lesions, 26% had growth in or into the inferior surface of the ventricle, 9% had evidence of growth beyond the subependymal tissue adjacent to the ventricle, and 7% had radiographic evidence of hydrocephalus. The median values for the sum of all target SEGA lesions at baseline were 1.63 cm^3 (range 0.18 to 25.15 cm^3) and 1.30 cm^3 (range 0.32 to 9.75 cm^3) in the AFINITOR and placebo arms respectively. Eight (7%) patients had prior SEGA-related surgery. The median duration of follow-up was 8.4 months.

The SEGA response rate was statistically significantly higher in AFINITOR-treated patients. There were 27 (35%) patients with SEGA responses in the AFINITOR arm and no SEGA responses in the placebo arm. Results are displayed in Table 16. At the time of the primary efficacy analysis, the median duration of response was 5.3 months (range 2.1 to 8.4 months) and all SEGA responses were ongoing. No patient in either treatment arm required surgical intervention during the course of Study 1.

Table 16: SEGA response

	AFINITOR N=78	***Placebo N=39***	***p-value***
Primary analysis			
SEGA response rate[a] - (%)	***35***	***0***	***<0.0001***
95% CI	*24, 46*	*0, 9*	

[a] *Per independent central radiology review*

(b) (4)

With a median follow-up of 8.4 months, SEGA progression was detected in 6 of 39 (15.4%) patients randomized to receive placebo and none of the 78 patients randomized to receive AFINITOR.

Study 2 was an open-label, single-arm trial conducted to evaluate the safety and efficacy of AFINITOR in patients with SEGA and TSC. Serial radiological evidence of SEGA growth was required for entry. Change in SEGA volume at the end of the core 6-month treatment phase was assessed via independent central radiology review. In total, 28 patients received treatment with AFINITOR; median age was 11 years (range 3-34), 61% male, 86% Caucasian. Four patients had surgical resection of their SEGA lesions with subsequent re-growth prior to receiving AFINITOR treatment. After the core treatment phase, patients could continue to receive AFINITOR treatment as part of an extension treatment phase where SEGA volume was assessed every 6 months. The median duration of treatment was 34.2 months (range 4.7-47.1 months).

At 6 months, 9 out of 28 patients (32%, 95% CI: 16% to 52%) had a ≥ 50% reduction in the tumor volume of their largest SEGA lesion. The median duration of response for

these 9 patients was 360 days (range 97 to 1191 days). Seven of these 9 patients had an ongoing volumetric reduction of ≥ 50% at the data cut-off.

Three of 4 patients who had prior surgery experienced a ≥ 50% reduction in the tumor volume of their largest SEGA lesion. One of these three patients responded by month 6. No patient developed new lesions.

Section 17.9 (Safe Handling Practices for AFINITOR DISPERZ)
Advise patients and their caregivers to read and carefully follow the FDA approved AFINITOR DISPERZ "Instructions for Use" to minimize unintended exposure to AFINITOR.

Section 17.10 (Dosing Instructions)
(b) (4)

9.3 Advisory Committee Meeting

The Division of Oncology Products 2 of the Office of Oncology Drug Products decided that advice from the Oncology Drugs Advisory Committee (ODAC) was not necessary in order to render a regulatory decision for this NDA. During review of the supplemental NDA that culminated in the 2010 accelerated approval of Afinitor for the treatment of SEGA, FDA consulted three special government employees (SGEs) with expertise in

the treatment of patients with SEGA and one SGE with expertise in neuroradiology. For details regarding the consensus opinion provided by these experts, please refer to Dr. Amir Shahlaee's review of sNDA 22334 SE1-006, dated October 26, 2010.

9.4 Pediatric Exclusivity Determination

This NDA included outstanding analyses and data required to fulfill the terms of the Written Request issued by FDA on April 1, 2010 and a Request for Pediatric Exclusivity Determination by the Applicant. Table 54, adapted from the sponsor's submission, outlines the items contained in the written request, along with the information and responses submitted by the Applicant. Based on review of the data submitted, the clinical, clinical pharmacology, and statistical reviewers concluded that the Applicant fulfilled the requirements of the Written Request. On July 10, 2012, the review team met with the FDA Pediatric Exclusivity Board and formally recommended that pediatric exclusivity be awarded to the Applicant. After reviewing the terms of the Pediatric Written Request and a summary of the contents of NDA 203985, the Pediatric Exclusivity Board concurred with this recommendation.

Table 54: Pediatric exclusivity determination template for Afinitor Written Request (adapted from the Applicant's submission)

Written Request Items	Information Submitted / Applicant's Response
Type of studies: • **Study 1:** A non-randomized, open-label phase 2 study of everolimus for the treatment of patients with SEGA associated with tuberous sclerosis complex (TSC) • **Study 2:** A randomized, double-blind, placebo-controlled phase 3 study of everolimus for the treatment of patients with SEGA associated with TSC	**Type of studies:** • **Study 1:** Single-center, non-randomized, open-label, phase 2 study of everolimus for the treatment of patients with SEGA associated with tuberous sclerosis complex (TSC) *[Study C2485]* • **Study 2:** Multi-center randomized, double-blind, placebo-controlled phase 3 study of everolimus for the treatment of patients with SEGA associated with TSC *[Study M2301]*
Indication to be studied: Treatment of patients with SEGA associated with TSC	**Indication to be studied:** Treatment of patients with SEGA associated with TSC [proposed] Of note, the wording of the proposed indication ('treatment of patients with TSC who have SEGA and require therapeutic intervention but are not likely to be cured by surgery') more closely reflects the population enrolled across Study 1 and Study 2.

Age group in which studies will be performed:
• **Study 1:** 3 years and older
• **Study 2:** Any age
	Age group in which studies will be performed:
	• **Study 1:** 3 years and older [Study C2485]
	  • The study enrolled patients aged 3 to 34 years
	• **Study 2:** Any age [Study M2301]
	  • The study enrolled patients aged 0.8 to 26.6 years

Number of patients to be studied: • **Study 1:** At least 28 patients. A minimum of 22 patients must be less than 18 years of age.	**Number of patients to be studied:** • **Study 1:** The study enrolled 28 patients in the everolimus arm; 22 were < 18 years of age [Study C2485]. • Enrolled patients aged 3 to 34 years were distributed among the following age groups (n [%]): 3 to < 12 years (16 [57.1%]), > 12 to < 18 years (6 [21.4%]), and ≥ 18 years (6 [21.4%])

Written Request Items	Information Submitted / Applicant's Response
• **Study 2:** At least 99 patients. At least 74 patients from birth to less than 18 years.	• **Study 2:** The study enrolled 117 patients, 78 were randomized to the everolimus arm and 39 to the placebo arm; 101 patients were < 18 years of age [Study M2301]. • Enrolled patients aged 0.8 to 26.6 years were distributed among the following age groups (n [%]): < 3 years (20 [17.1%]), 3 to < 18 years (81 [69.2%]), and ≥ 18 years (16 [13.7%])
Study endpoints: • **Study 1:** The primary efficacy endpoint is reduction in SEGA tumor volume. The duration of response is also to be measured. Additional endpoints include safety and potential side effects, and the effect of everolimus on frequency of epileptiform events (in a subgroup of patients), and hydrocephalus. • **Study 2:** The primary efficacy endpoint is SEGA response rate determined by the Independent Central Radiological Review of MRIs in the core treatment phase, obtained up to 6 months after the last patient is enrolled. Additional endpoints include absolute change from baseline in frequency of epileptiform events per 24 hours, time to SEGA progression, skin lesion response rate, change from baseline in angiogenesis markers, exposure of everolimus in treated patients, duration of SEGA response, time to SEGA response, and safety.	**Study endpoints:** • **Study 1:** The primary efficacy endpoint was reduction in SEGA tumor volume [Study C2485]. The duration of response was also measured [Study C2485]. Additional endpoints included safety and potential side effects [Study C2485], and the effect of everolimus on frequency of epileptiform events (in a subgroup of patients) [Study C2485], and hydrocephalus [Study C2485]. • **Study 2:** The primary efficacy endpoint was SEGA response rate determined by the Independent Central Radiological Review of MRIs in the core treatment phase, obtained up to 6 months after the last patient was enrolled [Study M2301]. Additional endpoints included absolute change from baseline in frequency of epileptiform events per 24 hours, time to SEGA progression, skin lesion response], change from baseline in angiogenesis markers, exposure of everolimus in treated patients, duration of SEGA response, time to SEGA response, and safety.

Drug information:
• **Study 1:**
  • *Dosage form:* 2.5 mg and 5 mg tablets
  • *Route of administration*: Oral
  • *Regimen:* An initial everolimus dose of 3 mg/m^2/day is to be administered as a daily or alternate day regimen, with dose titration to achieve a therapeutic pre-dose trough concentration range (5-15 ng/mL), subject to tolerability
	Drug information:
	• **Study 1:**
	  • *Dosage form:* 2.5 mg and 5 mg tablets
	  • *Route of administration*: Oral
	  • *Regimen:* An initial everolimus dose of 3 mg/m^2/day was administered as a daily or alternate day regimen. The dose was titrated to achieve a therapeutic pre-dose trough concentration range (5-15 ng/mL), subject to tolerability [Study C2485]

Written Request Items	Information Submitted / Applicant's Response

• **Study 2:**
  • *Dosage form:* 1 mg tablets
  • *Route of administration:* Oral
  • *Regimen:* An initial everolimus dose of 4.5mg/m^2 taken once daily, with dose titration to achieve a therapeutic pre-dose trough concentration range (5-15 ng/mL), subject to tolerability
	• **Study 2:**
	  • *Dosage form:* 1 mg tablets [Study M2301]
	  • *Route of administration:* Oral [Study M2301]
	  • *Regimen:* An initial everolimus dose of 4.5mg/m^2 was taken once daily. The dose was subsequently titrated to achieve a therapeutic pre-dose trough concentration range (5-15 ng/mL), subject to tolerability [Study M2301]

Use an age-appropriate formulation in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.	The 2.5-mg tablet used in Study 1 is FDA approved for the treatment of patients with TSC who have SEGA. The 1-mg tablet used in Study 2 is a clinical supply formulation and was used as a flexible and easy way to allow blinding of the treatment groups (everolimus vs. placebo); however, data from Study 2 show that there is (b) (4) Instead, Novartis is seeking marketing approval for an enhanced pediatric-appropriate formulation of 2 mg, 3 mg, and 5 mg dispersible tablets. This formulation has been developed to facilitate dosing in pediatric patients and provides advantages in terms of improved dispersion properties and shorter disintegration time. Furthermore, the dispersible tablets can be dispersed in as little as 5 mL of water and yields a suspension within 3 minutes. These characteristics allow for easier administration, including the possibility of direct administration via an oral syringe into the mouths of children or patients who are unable or have difficulties swallowing intact tablets. Additionally, these strengths will allow dosing from 2 mg upwards with only one or two tablets used for most of the doses.
If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under Section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice reflecting the fact that the approved pediatric formulation has not been marketed, in accordance with Section 505A(e)(2).	Not applicable

Written Request Items	Information Submitted / Applicant's Response
If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.	Not applicable
Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.	Relative bioavailability studies comparing the formulation used in Studies 1 and 2 and the proposed pediatric appropriate dispersible formulation were conducted [Study X2105], [Study X2106].
Drug specific safety concerns: The most common adverse events suspected as related to treatment with everolimus are hypogonadism, stomatitis, rash, anemia, fatigue, asthenia, diarrhea, anorexia, nausea, hypercholesterolemia, mucosal inflammation, vomiting, hypertriglyceridemia, cough, peripheral edema, dry skin, epistaxis, pruritus, and dyspnea. The most common Grade 3 or 4 adverse events suspected to be related to treatment are anemia, infections, hyperglycemia, stomatitis, fatigue, lymphopenia, hypercholesterolemia, pneumonitis, and elevated gamma-glutamyl transferase concentrations.	• **Study 1:** Information submitted was a comprehensive assessment of safety [Study C2485-Section 12]. The subjects were monitored for adverse events during the study period. The subjects were instructed to inform the study physician and/or study nurse-coordinator of any adverse events that occurred at any time during the study. Blood pressure, pulse, respiration and temperature were monitored at the initial visit and at every visit during the study. Periodic laboratory tests were performed to evaluate potential side effects of everolimus. The following assessments were made at every visit: liver and renal profiles (including gamma-glutamyl transferase); fasting lipid profile; complete blood count with differential; hormone levels (endocrine hormone levels were performed annually for patients younger than 10 years, but at every visit for patients age 10 and older); urinalysis (when possible); and urine pregnancy test (in females of child-bearing potential). Any adverse events or serious adverse events were reported with their severity and relationship to

Written Request Items	Information Submitted / Applicant's Response
	study drug. • **Study 2:** Information submitted was a comprehensive assessment of safety [Study M2301-Section 12]. Safety tests included monitoring and recording of all adverse events and serious adverse events at every visit, and monitoring of vital signs, physical condition, and body height (using a stadiometer) and weight. Laboratory assessments including hematology and blood chemistry (including serum creatinine, calculated creatinine clearance, and liver enzymes/liver function tests) were done every two weeks for the first 8 weeks, at weeks 12, 18 and 24, and every 12 weeks thereafter. Additional laboratory assessments including, coagulation and lipid profile were conducted at screening/baseline and every 12 weeks thereafter. For all patients, pre-baseline height and weight was collected in order to adequately represent the patient's rate of growth prior to starting the study. All patients had additional blood samples collected during screening and annually thereafter until their 10th birthday and every 12 weeks thereafter for endocrine hormonal assessments. These assessments include: follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, and estradiol (female patients). In addition, to assess overall sexual development, all patients were evaluated using Tanner Staging at screening/baseline and then annually thereafter. Growth and development milestones; age of thelarche (females), age of adrenarche (males), date of menarche (females) were captured. Chest CT and/or pulmonary function testing were to be performed per the investigator's clinical judgment when non-infectious pneumonitis was suspected. Patients will be followed for safety until at least 28 days after study treatment discontinuation. Following these 28 days, any serious adverse events that are suspected to be related to the study drug and occur within the next 8 weeks (56 days) are to also be collected. All adverse events were reported.
Statistical information, including power of studies and statistical assessments: • **Study 1:** Provide summaries of demographic, safety, efficacy, and PK data. The sample size of 28, assuming a standard deviation of 1.33,	**Statistical information, including power of studies and statistical assessments:** • **Study 1:** Summaries of demographic, safety, efficacy, and PK data were provided. The sample size of 28, assuming a standard deviation

Written Request Items	Information Submitted / Applicant's Response
would have at least 90% power to detect a mean reduction in SEGA volume, from baseline of at least 1cm^3, based on a one-sided t-test with α = 0.025. The non-parametric Wilcoxon signed rank test would also have approximately 90% power to detect a median reduction of 1cm^3.	of 1.33, had at least 90% power to detect a mean reduction in SEGA volume, from baseline of at least 1cm^3, based on a one-sided t-test with α = 0.025. The non-parametric Wilcoxon signed rank test also had approximately 90% power to detect a median reduction of 1cm^3 [Study C2485].
• **Study 2:** The primary analysis compares SEGA response rate between the two treatment arms using an exact Cochran-Mantel-Haenszel test. The patients will be randomized in a 2:1 ratio between everolimus and placebo. As there are no reported cases of tumor regression in patients with SEGA, the response rate on placebo is expected to be close to 0%. The SEGA response rate on everolimus is expected to be at least 20%. The sample size of 99 patients will provide at least 90% power to detect a difference of SEGA response rate, assuming a binomial distribution, between everolimus and placebo arms at a one-sided significance level of 0.025. Summaries of demographic, safety, and efficacy, data must be provided.	• **Study 2:** The primary analysis compared SEGA response rate between the two treatment arms using an exact Cochran-Mantel-Haenszel test [Study M2301]. The patients were be randomized in a 2:1 ratio between everolimus and placebo. As there were no reported cases of tumor regression in patients with SEGA, the response rate on placebo was expected to be close to 0%. The SEGA response rate on everolimus was expected to be at least 20%. The sample size of 99 patients would provide at least 90% power to detect a difference of SEGA response rate, assuming a binomial distribution, between everolimus and placebo arms at a one-sided significance level of 0.025. Summaries of demographic, safety, and efficacy, data were provided.
• **All studies:** Everolimus pharmacokinetics must be summarized using descriptive statistics. Relationships between dose; efficacy endpoints, safety endpoints and exposure must be explored and presented for all patients. In addition, relationships between use of enzyme inducing antiepileptic drugs and response and pharmacokinetic endpoints should be explored. If data from Study 1 and Study 2 allow, a PK-PD model should be developed to describe the relationships between dose and exposure and between exposure and efficacy and safety parameters.	• **All studies:** Everolimus pharmacokinetics were summarized using descriptive statistics. Relationships between dose, efficacy endpoints, safety endpoints and exposure were explored and presented for all patients. In addition, relationships between use of enzyme inducing antiepileptic drugs and response and pharmacokinetic endpoints were explored. • To satisfy the requirement of a PK-PD model, a population PK report based on Study 2, describing the dose-exposure relationship, and a PK-PD model report also based on Study 2 [RAD001M2301 exposure-response modeling], describing the exposure-efficacy relationship in patients were generated. Limitations in Study 1 did not allow for its inclusion in the PK-PD model (details provided in [expert-statement]). Within the everolimus exposures observed in Studies 1 and 2, no apparent relationship was seen between time-averaged Cmin and the incidence of clinically notable AEs, suggesting that higher Cmin was not associated with an increased safety risk. These AEs were believed

Written Request Items	Information Submitted / Applicant's Response
	to have occurred at the lower end of the exposure-safety relationship thus would not allow a PK-PD model. However, information on the relationship between exposure and safety parameters are provided in the Summary of Clinical Pharmacology for Study1 and Study 2.
Labeling that may result from the studies: You must submit proposed pediatric labeling to incorporate the findings of the studies. Under Section 505A(j) of the Act, regardless of whether the studies demonstrate that everolimus is safe and effective, or whether such study results are inconclusive in the studied pediatric populations or subpopulations, the labeling must include information about the results of the studies. Under Section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.	**Labeling that may result from the studies:** Novartis submitted proposed labeling incorporating findings from Studies M2301 and C2485 [proposed], [annotated].
Format and types of reports to be submitted: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement. Under Section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.	**Format and types of reports to be submitted:** Full study reports not previously submitted to the Agency including full analysis, assessment, and interpretation of the data were submitted for Study 1 [Study C2485] and Study 2 [Study M2301]. The reports include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies were categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, one of the following designations was used: Hispanic/Latino or Not Hispanic/Latino. All postmarketing adverse event reports up to 31-Dec-2011 were submitted as narrative and tabular reports.

Written Request Items	Information Submitted / Applicant's Response
Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.	Study data was not submitted according to the Study Data Tabulation (SDTM) standard published by Clinical Data Interchange Standards Consortium (CDISC) but in accordance with standard Novartis practices which have been deemed acceptable.
Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before June 30, 2013. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.	**Timeframe for submitting reports of the studies:** Novartis submitted the reports for the studies required to fulfill the terms of the Written Request on February 29, 2012.

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

/s/

MARTHA B DONOGHUE
08/05/2012

SUZANNE G DEMKO
08/05/2012