CLINICAL AND STATISTICAL REVIEW

Application Type	Efficacy Supplement
Application Number(s)	NDA 22-334/SE1-006
Priority or Standard	Priority
Submit Date(s)	4/30/10
Received Date(s)	4/30/10
PDUFA Goal Date	10/30/10
Division / Office	DDOP/OODP
Reviewer Name(s)	Amir Shahlaee, MD Somesh Chattopadhyay, PhD Shenghui Tang, PhD Ke Liu, MD, PhD (CDTL)
Review Completion Date	10/06/10
Established Name	Everolimus
(Proposed) Trade Name	AFINITOR
Therapeutic Class	m-TOR Inhibitor
Applicant	Novartis
Formulation(s)	2.5 and 5 mg oral tablets
Dosing Regimen	Various
Indication(s)	Subependymal Giant Cell Astrocytoma (SEGA) associated with Tuberous Sclerosis (TS)
Intended Population(s)	Patients with SEGA associated with TS

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

We recommend accelerated approval for everolimus for the indication below:

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.

1.2 Risk Benefit Assessment

This supplemental new drug application (sNDA) was based on the efficacy and safety results from a prospective, single-arm, single-institution study. Study C2485 was conducted in patients with TS who had a radiological diagnosis of SEGA and whose SEGA showed evidence of growth on ≥ 2 serial MRI scans. A total of 28 patients with SEGA with TS were enrolled on this study. Continuous oral dosing of everolimus was started at a dose of 3 mg/m^2/day and titrated to a blood trough level of 5-15 ng/ml. The median duration of treatment was 24.4 months (range 4.7-37.3 months).

The primary endpoint of Study C2485 was the change from baseline in the volume of the primary SEGA lesion at 6 months determined by central radiology review. Twenty-seven of these patients remained on study for the 6 month core phase of the treatment. At 6 months, 9 out of 28 patients (32%, 95% CI: 16% - 52%) had a ≥ 50% reduction in the tumor volume of their largest SEGA lesion. Duration of response for these 9 patients ranged from 97 to 946 days with a median of 266 days. Seven of these 9 patients had an ongoing volumetric reduction of ≥ 50% at the data cutoff.

Four patients had surgical resection of their SEGA lesions with subsequent re-growth prior to receiving AFINITOR treatment. One of 4 patients who had prior surgery experienced a 58% reduction in the tumor volume of their largest SEGA lesion at month 6; 2 additional patients had a volumetric reduction of ≥ 50% on subsequent scans beyond month 6. No patient developed new lesions.

All patients on C2485 experienced an adverse event during therapy. The most common AEs occurring in > 20% of patients included stomatitis (86%), upper respiratory tract infection (82%), sinusitis (39%), otitis media (36%), pyrexia (32%), convulsion (29%), dermatitis acneiform (25%), diarrhoea (25%), cellulitis (21%) and vomiting (21%). Ten patients (36%) had a grade 3 adverse event and 1 patient had a single grade 4 event. There were no deaths on this study and serious adverse events were reported in 4 patients (14%). The toxicity profile observed in C2485 was similar to that described in the current AFINITOR labeling for adult patients with renal cell carcinoma.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

We recommend the following Postmarket Requirements (PMRs):

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).

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).

3. To evaluate the potential for serious risk of adverse long-term effects of AFINITOR 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 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.

4. To evaluate the potential for serious risk of adverse long-term effects of AFINITOR 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 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.

2 Introduction and Regulatory Background

Tuberous sclerosis (TS), an autosomal dominant condition that affects 1 in every 5,000 to 10,000 live births, is characterized by the presence of hamartomatous tumors involving many organ systems including the brain, eyes, heart, lung, liver, kidney and skin.

A consensus conference of experts held in 1998, established specific clinical criteria for the diagnosis of TS. The following criteria were accepted as "major clinical features" of TS:

- Facial angiofibromas or forehead plaques
- Shagreen patch (connective tissue nevus)
- Three or more hypomelanotic macules
- Nontraumatic ungula or periungual fibromas
- Lymphangioleiomyomatosis (also known as lymphangiomyomatosis)
- Renal angiomyolipoma
- Cardiac rhabdomyoma
- Multiple retinal nodular hamartomas
- Cortical tuber
- Subependymal nodules
- Subependymal giant cell astrocytoma (SEGA)

In addition to the major features listed above, the following criteria were listed as minor features of TS:

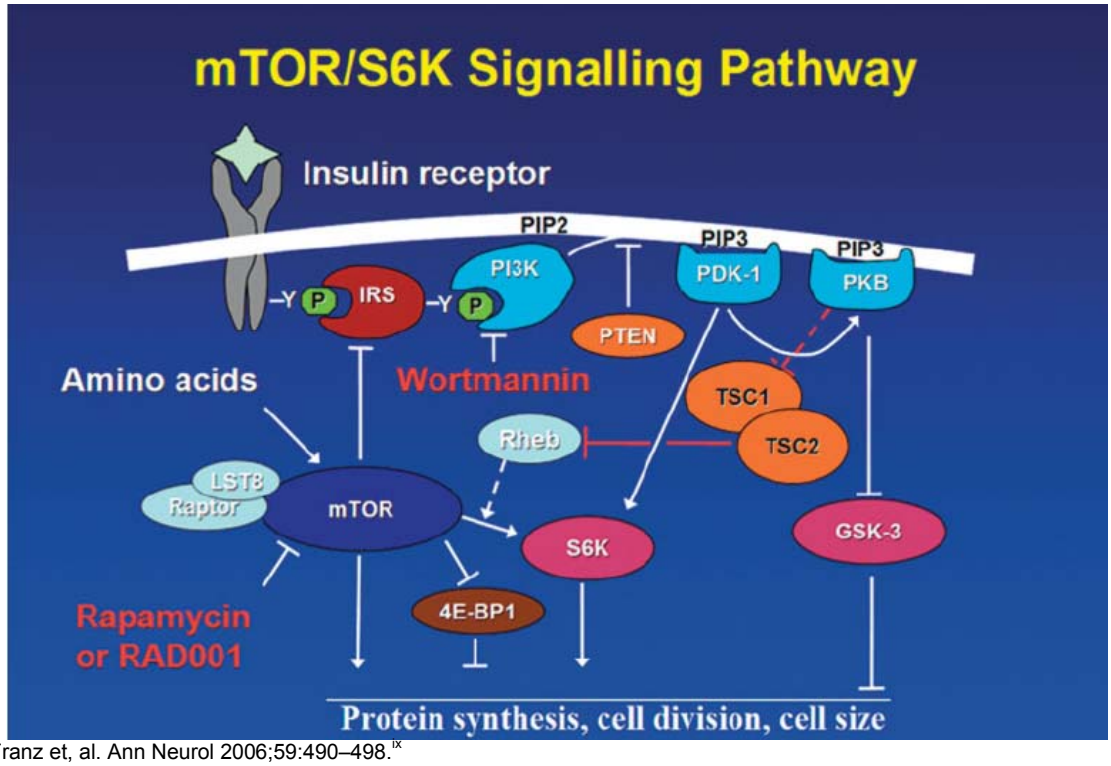
- Confetti skin lesions (multiple 1 to 2 mm hypomelanotic macules)
- Gingival fibromas
- Multiple randomly-distributed pits in dental enamel
- Hamartomatous rectal polyps
- Multiple renal cysts
- Nonrenal hamartomas
- Bone cysts
- Retinal achromic patch
- Cerebral white matter radial migration lines

The diagnosis of definite TS 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 TS-related features and are not considered to have TS. Children with one major plus one minor feature are classified as having probable TS, while those with one major feature only, or two or more minor features but no major features classified as possible TS.[i,ii,iii,iv]

Genetically, TS is an autosomal dominant disorder defined by the presence of mutations in the genes TSC1 and TSC2. TSC1 encodes the protein hamartin while TSC2 encodes tuberin. Hamartin and tuberin form an intracellular, tumor suppressor complex. Through the GTPase activating activity of tuberin, this complex down-regulates the function of Ras homologue enriched in brain (RHEB), a small G protein of the Ras family. When bound to GTP, RHEB is active and stimulates the mammalian target of Rapamycin (mTOR) pathway. mTOR in turn is a major effector of cell growth. Patients with TS have a constitutively activated mTOR pathway due to the dysfunction of the hamartin/tuberin complex and the consequent upregulation of RHEB. mTOR therefore appears to be an ideal therapeutic target in patients with TS.[ii]

SEGAs, one of the major features of TS, can be seen in 6 to 9% of patients with TS. Diagnosis of SEGA is based on clinical and radiological findings. They are typically slow-growing tumors that usually become symptomatic after causing obstructive hydrocephalus. This natural history has led to recommendations that patients with SEGA need periodic radiological evaluations. SEGAs are usually surgically resected if they exhibit progressive growth, cause hydrocephalus and/or other symptoms. Although there currently are no definitive guidelines on optimal timing for surgical intervention for SEGA, most experts agree that early intervention, when progression is documented on serial scans, portends a better outcome. [iii, v, vi, vii, viii]. SEGAs are classified as World Health Organization grade 1 astrocytomas and as such do not respond to chemotherapy or radiation. However, two previous case series have been published reporting response to treatment with rapamycin in at least 8 patients. Interestingly in some patients, stoppage and resumption of therapy directly correlated with the re-growth followed by a second response suggesting direct correlation to rapamycin dosing.[ix,x]

Figure 1 Schematic of mTOR signaling pathway



From Franz et, al. Ann Neurol 2006;59:490–498.[ix]

2.1 Product Information

Drug Established Name:

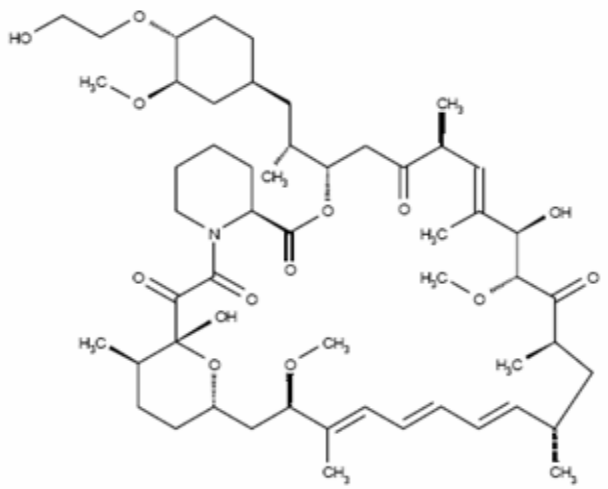
AFINITOR (everolimus), an inhibitor of mTOR, is an antineoplastic agent.

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 2.

Figure 2 Structural formula of everolimus



AFINITOR is supplied as tablets for oral administration containing 2.5 mg, 5 mg and 10 mg of everolimus together with butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone and lactose anhydrous as inactive ingredients.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there are no approved systemic therapies for treating SEGAs.

2.3 Availability of Proposed Active Ingredient in the United States

Everolimus is marketed in the US as AFINITOR® for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. This indication was approved on 3/30/2009 and the labeling revised on 5/13/2010 to account for changes in everolimus absorption as a result of consumption with high fat meals.

Everolimus is also marketed in the US as ZOTRESS® 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 and included a Risk Evaluation and Mitigation Strategy (REMS) consisting of a Medication Guide and a Communication plan. The Zortress REMS is intended to inform:

- Healthcare providers about the following serious risks of wound-healing complications, hyperlipidemia, proteinuria, graft thrombosis, as well as nephrotoxicity when ZORTRESS is co-administered with standard doses of cyclosporine.

- Patients about the serious risks associated with Zortress.

2.4 Important Safety Issues with Consideration to Related Drugs

The safety issues that should be considered with respect to other rapamycin-related drugs are anemia, aphtous stomatitis, lymphopenia, immunosuppression and secondary risk of infection, hyperlipidemia, hyperglycemia, pneumonitis and renal dysfunction.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

2.5.1 Everolimus in other indications:

Everolimus approved under trade name CERTICAN® in 65 countries for prophylaxis after solid organ transplantation.

November 19, 1996: IND 52,003 filed for study of everolimus in transplant patients in US.

March 5, 2003: IND 66,279 for study of everolimus in cancer patients is reasonably safe to proceed.

March 30, 2009: Approved under the trade name AFINITOR®, for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib on 30-Mar-2009 (NDA 22,334).

April 20, 2010: Approved under the trade name ZORTRESS® for prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant. (NDA 21,560)

2.5.2 Everolimus in TS:

Study C2485

November 15, 2004: IND 70,895 for study of everolimus in patients with angiomyolipomata in the setting of TS was safe to proceed.

August 10, 2006: Study of everolimus in patients with SEGA in the setting of TS first submitted to FDA.

January 7, 2007: First patient enrolled.

July 9, 2009: Agency received request for type B meeting from Novartis. Meeting requested to propose change in registration strategy. Request was based upon preliminary review of data from C2485 suggesting responses to therapy at 3 and 6 months post therapy:

- Primary tumor volume reduction ≥ 30%:

56% at 3 months
74% at 6 months

- Total tumor volume response ≥ 30%:
  59% at 3 months
  74% at 6 months

Sponsor proposed to change the primary efficacy endpoint to "change from baseline in the volume of the primary SEGA lesion at 6 months after the start of treatment (or at the last available assessment if a patient ended treatment prior to this time point) as determined by central radiology review".

September 29, 2009: A pre-sNDA meeting was held during which FDA agreed to review data from Study C2485 and consider the sNDA for approval under Subpart H.

FDA requested that

1) additional safety information be submitted with the application
2) patients be followed for at least a year
   a. Safety and efficacy data be provided at the time of submission
3) Sponsor intends to complete recruitment to their Phase 3 trial, M2301, prior to the action date for this supplement
   a. This study is open to patients of any age (expect at least 74 out of 99 subjects will be ≤18 years of age)
4) Sponsor will submit a 3-month update for both efficacy and safety including safety data from M2301

In response to sponsor's proposed endpoint of "change from baseline in the volume of the primary SEGA lesion at 6 months after the start of treatment", FDA requested that:

1. All patients have a minimum of 12 months of efficacy follow up.
2. the sponsor provide*:*
   a. An overview of the evolution of this study's primary endpoints;
   b. Their rationale for primary endpoint-assessment of the change in tumor volume at 6 months; and
   c. An assessment of drug activity using each of these endpoints.

The FDA also requested that ongoing and future studies should use the 1-mg tablet formulation or the proposed pediatric formulation, if available, in patients with SEGA associated with TSC.

November 6, 2009: Novartis submitted a proposal for addressing issues identified by FDA during the pre-sNDA meeting and provided post-meeting questions for FDA consideration. Official meeting minutes were issued by FDA on December 4, 2009 and included responses to the original questions submitted in the pre-sNDA briefing package in addition to the post-meeting questions sent to the Agency on November 6,

2009. In the December 4, 2009 communication FDA agrees to consider review of data for a sNDA SE1-006

December 9, 2009: Cutoff date for data analysis in study. This date represented the 12 month assessment of the last patient.

December 22, 2009: Novartis submitted a prior approval supplement for the 2.5-mg tablet strength to NDA 22-334 (S-005).

February 19, 2010: Novartis submitted a further document to confirm and clarify issues identified in the final meeting minutes.

April 1, 2010: Written Request for study of everolimus in patients with SEGA in the setting of TS issued.

Study M2301

May 31, 2007: End-of-phase II (EoP2) meeting was requested.

October 2, 2007: The EoP2 meeting was held.

October 18, 2007: The official meeting minutes were issued.

- Rationale provided by the sponsor for use of Volumetric Assessment of Tumor Response:

    1. As tumors grow in three dimensions, shrinkage can only be accurately defined as a decrease in tumor volume
    2. RECIST and WHO measurements are essentially surrogates for volume
    3. Planned imaging techniques providing a 3-D information set and computer algorithms, allow for accurate and true tumor measurements using volume rather than only one or two dimensional measurements
    4. Volumetric assessment more accurate, reproducible and objective measure of tumor response

- Central Independent Radiological Review
- All assessments and images will be made available to the Agency

Additionally, the sponsor cited the AACR/FDA Public Workshop on Clinical Trial End Points in Primary Brain Tumors of Jan 20, 2006. They stated that based upon that meeting:

1. Measuring tumor diameter is probably an outdated methodology as small percentage changes in diameter can reflect much larger changes in tumor volume.

2. Both manual and automated segmentation techniques provide more accurate measurements of tumor volume than diameter measurement.
3. Regional distribution of the lesion was considered an important factor; a 1 mm reduction in tumor volume in a certain part of the brain might have a dramatic clinical effect whereas a larger volume reduction elsewhere in the brain might be of less clinical relevance.
4. This may have important implications in evaluation of SEGA lesions, being closely located to the foramen of Munro with the potential risk of hydrocephalus.

The sponsor also stated that no reliable estimates regarding annual incidence of hydrocephalus and SEGA-related surgery are available obviating the use of these outcomes as study endpoints. The sponsor further stated that use of TTP as an endpoint is not practical as SEGA lesions have variable growth rates.

- FDA requested that the sponsor:

    1. Provide criteria for reliable diagnosis of SEGAs.
    2. Provide longer follow-up for toxicity after treatment discontinuation considering risks of long-term treatment and toxicity

- Sponsor proposed

    1. a 50% reduction in tumor volume as defining response
    2. extensions phase of 3 years on drug post completion of therapy in order to supply long-term use data
    3. To capture changes in cognitive function in patients while on therapy using neuropsychometric tools as a secondary endpoint

April 7, 2008: (b) (4)

July 14, 2008: Type A meeting requested to amend study and include patients <3 years of age. This was based on request of European Paediatric Committee.

September 18, 2008: Type A meeting held. FDA agreed to including children <3 years old. FDA requested conduct a relative bioavailability study comparing the pharmacokinetics of the everolimus extemporaneous preparation to that of the whole tablet.

November 10, 2008: In response to FDA request for relative bioavailability study protocol C2121 was submitted.

November 13, 2008: Novartis (b) (4) for Protocol M2301.

March 12, 2009: Protocol M2301 was submitted to FDA along with the Summary of Final Key Results from Study C2121.

May 14, 2009: The Clinical Study Report for Study C2121 was submitted.

August 10, 2009: Study M2301 opened for enrollment (First Patient First Visit [FPFV] occurred on 10-Aug-2009).

August 25, 2009: Amendment 1 to Study M2301 submitted to FDA.

April 16, 2010: Amendment 2 to Study M2301 submitted to FDA.

Study M2301 Summary:

Title: A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with Tuberous Sclerosis Complex (TSC)

Primary Objective:

To compare the SEGA response rate on RAD001 versus placebo in patients with TSC-associated SEGA. SEGA response rate, determined from the Independent Central Radiological review of MRIs, is defined as the proportion of patients with a reduction in SEGA volume of ≥ 50% relative to baseline, where SEGA volume is the sum of the volumes of all target SEGA lesions identified at baseline, and confirmed with a second scan approximately 12 weeks later.

Secondary Objectives:

1. Change from baseline in frequency of epileptiform events.
2. Time to SEGA progression.
3. Skin lesion response rate.
4. Change from baseline in plasma angiogenic molecules, e.g. VEGF, basic FGF, PLGF, soluble VEGF receptor1, and soluble VEGF receptor2.
5. Renal function assessed using calculated creatinine clearance.
6. Safety as assessed by the NCI Common Terminology Criteria for Adverse Events, version 3.0.

Study Design: M2301 is a prospective, double-blind, randomized, parallel group, placebo-controlled, multi-center phase III study evaluating treatment with everolimus versus placebo in 99 patients with TSC-associated SEGA. Randomization is 2 to 1 in favor of everolimus.

Study treatment: Patients will be treated with blinded study treatment until SEGA progression, unacceptable toxicity or discontinuation for any other reason. The starting dose is 4.5 mg/m^2/day. Dose adjustments will be permitted based on safety findings and blood trough measurements (targeting a trough of 10-15 ng/mL). Maximum dose of everolimus permitted is 8.0 mg/m^2/day. Patients who progress on blinded therapy are unblinded and if thought to possibly benefit from everolimus therapy are transitioned to

open label therapy. Study will be closed at 6 months after the last patient is randomized. If study results are positive all patients will have the option of receiving open-label extension therapy and will be followed for 4-5 years.

Eligibility criteria: This study is open to patients with “clinically definite” diagnosis of TS in accordance to the Gomez criterion. Patients however need to have a recent MRI of the brain completed within 3 weeks (21 days) prior to the patient’s randomization that is compared with an MRI of the brain performed at an earlier stage of patient care (pre-baseline) and demonstrates at least one of the following:

- Serial growth, defined as at least a 25% increase in SEGA volume, or
- Presence of a new SEGA lesion ≥ 1 cm in its longest diameter, or
- New or worsening hydrocephalus defined by assessment of ventricular configuration changes, ventricular cap signs (periventricular edema) and qualitative assessment of CSF flow dynamics.

Efficacy assessment: MRI’s of the head will be performed at 12, 24 and 48 weeks and then annually during the extension phase.

Statistical: The primary analysis will be a comparison of the SEGA response rates in the RAD001 and placebo arms using a one-sided exact Cochran-Mantel-Haenszel (CMH) test at the 2.5% level, analyzed in the Full Analysis Set (FAS). The analysis will be performed using a data cut-off defined as 6 months after the last patient is randomized in the trial.
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 RAD001 is hoped to be at least 20%. It is planned to use a one-sided test and a 2.5% significance level. Simulation was used to obtain a sample size of 99 patients (66 randomized to RAD001 and 33 randomized to placebo), which will provide 93% power to detect a treatment difference from 0% on placebo to 20% on RAD001.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Study C2485 was not initially planned to provide clinical data for a regulatory submission. All data was initially captured on "source notes and hospital forms". In June 2009 after discussions with the FDA, the applicant developed a new database and eCRFs and designated investigator staff collected the data from the source documents. The applicant stated that these data were confirmed by an additional member of the investigator staff and then further verified by (b) (4) a CRO working on behalf of the applicant. All eCRFs were finally reviewed by the applicant to identify any additional SAEs. Data were collected up to a planned final analysis cut-off date (12/9/2009) or the date of patient withdrawal from study. These data were subsequently updated and submitted on 4/9/2010 as part of the 3-month data update.

3.2 Compliance with Good Clinical Practices

Study C2485 study report contained a statement that this study was conducted in accordance to the declaration of Helsinki. The study was performed under the oversight of a Data Safety Monitoring Board (DSMB). The original protocol and all amendments were reviewed and approved by the local IRB.

FDA's Division of Scientific Investigation (DSI) inspected the single study site of C2485 on 9/27/10. Assessment of data integrity from this inspection revealed that although some regulatory violations were noted, they were relatively few, random and isolated instances. The noted protocol violations for the most part, occurred outside the core period of the study during the extension phase. The regulatory violations observed were not related to the integrity of the core study data, and the data is acceptable in support of the pending application.

3.3 Financial Disclosures

The applicant (Novartis) certifies that none of the 14 investigators or sub-investigators were full or part-time employees of Novartis. Additionally, based on the study site's 'Policy on Financial Conflicts of Interest in Research' none of the investigators or subinvestigators had any financial interests in Novartis.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

No issues. For further relevant details please see 2.1 Product Information

4.2 Preclinical Pharmacology/Toxicology

Please see pharmacology/toxicology review for further details.

The following is taken from pharmacology/toxicology review.

"There is no pharmacology and toxicology study submitted in this efficacy supplement. However, pharmacology and toxicology studies were submitted under NDAs 21-560 and 22-334 and reviewed and documented in DARRTS previously. Juvenile toxicity studies were conducted in rats and monkeys previously and are specifically relevant to this supplement because of the indicated pediatric population. In the rat juvenile toxicity study, dose-related systemic toxicities including decreased body weight gain and food consumption, and delayed attainment of some developmental landmarks were observed at doses as low as 0.15 mg/kg/day but with full or partial recovery after cessation of dosing for 26 weeks. In addition, dose-dependent, irreversible bilateral lenticular alterations including zones of discontinuity and focal cataracts were observed. No significant toxicity was observed in monkeys at doses up to 0.5 mg/kg/day; however, developmental parameters were not evaluated in this monkey study."

4.3 Clinical Pharmacology

Please see clinical pharmacology review for further details.

The following is excerpted from the clinical pharmacology review.
"The sponsor proposed individualized dosing with TDM (b) (4) . TDM is proposed for this indication since most of the patients will be on concomitant enzyme-inducing antiepileptic drugs and everolimus is a substrate of CYP3A4. (b) (4)

The exposure-efficacy analysis supported the lower limit of the target range of 5 ng/ml. The upper limit of (b) (4) was not justified because there was no additional reduction in tumor volume with trough concentrations >3 ng/ml and >90% of the observed data

were below 10 ng/ml in the core treatment phase. Thus, a target range of 5–10 ng/ml for TDM is recommended.

Some of the patients exhibited tumor re-growth during the follow-up phase. Analysis relating tumor re-growth with exposures does not indicate that lower exposures are responsible for this phenomenon.

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

In healthy volunteer studies, everolimus exposures were significantly increased when Afinitor was taken with moderate CYP3A4 or PgP inhibitors (reviewed in the original NDA). The sponsor has proposed a 50% lower starting dose for patients taking moderate CYP3A4 or PgP inhibitors. For patient with BSA <1.2 m^2, starting dose reduction is not possible due to the unavailability of lower dose strengths. Pharmacokinetic simulations support alternate-day dosing for these patients."

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1 provides a summary of all studies that were submitted in this sNDA.

Efficacy claim is based on one, single-arm, single-center, and open-label investigator-initiated study, C2485, conducted under a research IND.

C2121, a comparative bioavailability and bioequivalence study compared the systemic exposure to everolimus when intact tablets were taken as opposed to when tablets were suspended in water prior to intake. This study is reviewed in detail by the clinical pharmacology reviewer.

Safety data summary from study B351 is provided. This study was performed in pediatric solid organ transplant patients. Neither CSRs, tabular summary of data or CRFs from B351 were provided for review. In addition, blinded tabular summaries of SAEs from two ongoing studies, M2301 and M2302 are provided.

5.2 Review Strategy

The focus of the clinical review was on the efficacy and safety data of study C2485. Safety data from the solid organ transplant B251 and SAE tabulations from M2301 and M2302 were also reviewed. The electronic submission, with the CSRs, and other relevant portions of study C2485 were reviewed and analyzed. The key review materials and activities are outlined below:

- Electronic submission of the NDA;
- Relevant published literature;
- Relevant submissions in response to medical officer's questions;
- Sponsor presentation to FDA on June 21, 2010 and
- Major efficacy and safety analyses reproduced or audited using the SAS datasets.

Table 1 Clinical Trials Submitted to sNDA 22-334, SE1/006

Study ID	Design and population	Regimen	# of subjects
C2485	Single-arm, open-label, single-center study in patients with SEGA in the setting of TS	Everolimus started at 3.0 mg/m^2/day and dose titrated to achieve a serum level of 5-15 ng/mL	28
(Trial submitted to support safety)			
B351	International, multicenter, open-label, single-arm trial in pediatric *de novo* renal transplant recipients	Everolimus in combination with cyclosporine and corticosteroids	37
M2301	Randomized, double-blind, placebo-controlled study in the treatment of SEGA in the setting of TS	Everolimus monotherapy	Planned 99
M2302	Randomized, double-blind, placebo-controlled study in the treatment of angiomyolipoma in patients with either TS or sporadic lymphangioleiomyomatosis (LAM)	Everolimus monotherapy	Planned 99

5.3 Discussion of C2485

Study Title: Everolimus (RAD 001) therapy of giant cell astrocytomas in patients with tuberous sclerosis complex

Objectives:

Primary objective

To evaluate the safety and potential side effects of everolimus in TS patients with SEGA

Secondary objectives

To evaluate whether:

- Everolimus therapy in TS patients with SEGA results in decreased tumor size
- Everolimus has beneficial activity separate from effects on SEGA
- mTOR inhibition by everolimus *in vivo* correlates with clinical outcome

Reviewer's note: When study C2485 was originally designed (7/25/2006), the primary objective of the study was:

To evaluate the clinical effectiveness of everolimus to reduce the size of giant cell astrocytoma burden in patients with TS.

Based upon feedback from the CCHMC IRB/DSMB (1/19/2007) the primary objective of this study was changed to:

To evaluate the safety and potential side effects of everolimus therapy in patients with TS.

The sponsor, however, stated that "efficacy was always the intended primary objective".

Study design:

Single-arm, prospective, open-label

Eligibility:

Inclusion criteria:

Patients who met the following criteria were eligible:

- Age ≥ 3 years
- If female and of child-bearing potential, documentation of negative pregnancy test prior to enrollment
- Presence of giant cell astrocytoma as defined by imaging characteristics and serial increase in size of lesion on ≥ 2 MRI scans
- Adequate renal function (creatinine < 1.5 mg/dL)
- Clinically definite diagnosis of TS (per modified Gomez criteria or positive genetic test)

Exclusion criteria:

Patients who met the following criteria were ineligible:

- Serious intercurrent medical illness or other uncontrolled medical disease which could compromise participation in the study (i.e., uncontrolled diabetes, uncontrolled hypertension, severe malnutrition, significant cardiac disease, chronic liver or renal disease, gastrointestinal disease that could significantly alter the absorption of everolimus, human immunodeficiency virus [HIV] positivity, or chronic treatment with systemic steroids or another immunosuppressive agent). Patients with uncontrolled epilepsy were not excluded.
- Significant hematologic or hepatic abnormality:
    - transaminase levels > 3 x upper limit of normal (ULN)
    - serum albumin < 3 g/dL
    - hematocrit (HCT) < 30%

  - platelets < 80,000 /mm^3
  - absolute neutrophil count (ANC) < 1,000/mm^3
  - total white blood cell (WBC) count < 3,000/mm^3

- Continuous requirement for supplemental oxygen
- Intercurrent infection at initiation of everolimus
- Embolization of angiomyolipoma within 1 month of initiation of everolimus;
- Any other recent surgery within 2 months
- Pregnant or lactating women
- Inadequate contraception. Patients who were fertile had to maintain adequate contraception throughout the trial and for 3 months after stopping study drug. Acceptable contraceptive measures included non estrogen-containing birth control regimen, prior hysterectomy, tubal ligation, complete abstinence, barrier methods that included both a cervical diaphragm and spermicidal jelly, intrauterine devices, progesterone-based contraceptives, or vasectomy in partner.
- Use of an investigational drug within the past 30 days
- Not adequately recovered from the acute toxicities of any prior therapy
- Clinical evidence of impending herniation or focal neurologic deficit related to the patient's astrocytoma

Treatment plan:

Everolimus was administered orally at a starting dose of 3.0 mg/m^2/day (once-daily or on an alternate day regimen) and subsequently titrated, subject to tolerability, to attain whole blood trough concentrations of 5-15 ng/mL.

The core treatment phase was to last for a period of 6 months. Patients subsequently transitioned to a long-term extension phase, where treatment was to continue for as long as therapeutic benefit was evident without significant adverse effect or risk to the patient. If a patient were to achieve a 75% volume reduction in their SEGA, they would be discontinued and followed with serial imaging. Additionally, if a patient had no regression of his/her tumor or slowing of the tumor growth velocity after 6 months of therapy with documented therapeutic serum everolimus levels, they would be discontinued from study.

Reviewer's note:

1. The targeted everolimus levels in study C2485 was based on previous experience with rapamycin at Cincinnati Children's Hospital Medical Center.[ix] However no data appears to suggest that a trough range of 5-15 ng/mL of everolimus is optimal for safety or efficacy. Furthermore, originally this study used a target trough of 10-15 ng/mL. This was changed to the current target levels as part of amendment 4 to the clinical protocol. Trough levels above 10 were difficult to achieve presumably due to concomitant use of enzyme inducing anti-epileptic drugs (EIAEDs) and some patients were noted to have responses at trough levels below 5 ng/mL.

2. In addition to questions regarding appropriate trough levels, no clear cut data is available supporting length of therapy. All previous experience with everolimus has either been for shorter durations (renal cell carcinoma) or at lower doses as part of multi-drug regimens (renal transplant).

Monitoring:

Core 6-month treatment phase:

- Clinic visits at monthly intervals
  - Physical examination
  - Blood collection
    - routine laboratory tests
    - urinalysis
    - evaluation of everolimus trough concentrations.

  Patients were required to have a follow-up visit 1 month after completing the core study phase.
- Volumetric assessment of SEGA volume based on magnetic resonance imaging (MRI)
  - Baseline, Month 3 and Month 6
- Seizure frequency reporting
  - Each study visit
- 24-hour video electroencephalograms (EEGs)
  - In patients reporting > 1 seizure over the preceding 6 months
  - Baseline and were repeated at Month 6
- Quality of life questionnaires (Quality of Life in Children with Epilepsy [QOLCE])
  - Baseline, Month 3 and Month 6
- Neuropsychological assessments
  - Baseline and Month 6 only
- Adverse events (AEs)

Assessed on an ongoing basis and laboratory parameters were evaluated at each clinic visit. For more details please see Table 2.

Extension phase:

- Study visits
  Every 6 months with
  A 3-month visit considered optional
  A telephone interview will be conducted at the 3-month time point if the patient is unable to attend the clinic
- Laboratory tests
  Every 3 months
- Brain MRIs
  Every 6 months or more frequently, if indicated.
- Monitoring for safety (AEs) on ongoing basis

The monitoring schedule in the Extension phase is summarized in Table 3.

Table 2 Core phase: monthly evaluation and visit schedule

Event	Baseline	Month 1 [a]	Month 2 [a]	Month 3 [a]	Month 4 [a]	Month 5 [a]	Month 6 [a]	Follow-up [b]
Informed consent [c]	X							
History and physical	X	X	X	X			X	X
Liver and renal profiles, blood glucose	X	X	X	X	X	X	X	X
Documentation of skin exam [d]	X						X	
Fasting lipid profile	X	X	X	X	X	X	X	X
CBC, differential	X	X	X	X	X	X	X	X
Everolimus blood concentration		X	X	X	X	X	X	
Urinalysis [e]	X	X	X	X			X	X
Urine pregnancy test [f]	X	X	X	X			X	X
Brain MRI/MRS	X			X			X	
QoL questionnaire	X			X			X	
Neuropsychology	X						X	
Neurotelemetry (video-EEG)	X						X	
Saved serum and plasma [g]	X	X	X	X			X	X

CBC Complete blood count; EEG Electroencephalogram; MRI/MRS Magnetic resonance imaging/MR spectroscopy; QoL Quality of life

[a] Visit window ± 1 week
[b] Follow-up visit 1 month (± 1 week) after completion of core phase
[c] Provided by patient or guardian
[d] Included photograph of patients with angiofibromas and other skin lesions at baseline and 6 months, as well as other times as needed
[e] Urinalysis was optional since it could be difficult to obtain urine specimens from some patients in this population
[f] If female and of child-bearing potential
[g] Serum and plasma was used in the analysis of MRS data

Adapted from Table 9-1, CSR page 47 for study C2485.

Table 3 Extension phase: evaluation and visit schedule

Event	On-treatment schedule – repeat until off-study				
	Every 3 months [a]	Every 6 months [a]	Every 9 months [a]	Every 12 months [a]	Off-study follow-up [b]
Medical history	X	X	X	X	X
Physical exam		X		X	X
Telephone contact	X		X		
Liver and renal profile, blood glucose	X	X	X	X	X
Fasting lipid profile	X	X	X	X	X
CBC, differential	X	X	X	X	X
Everolimus blood concentration	X	X	X	X	
Urinalysis [c]	X	X	X	X	X
Urine pregnancy test [d]	X	X	X	X	X
Brain MRI/MRS		X		X	
QoL questionnaire		X		X	
Saved serum and plasma [e]	X	X	X	X	X

CBC Complete blood count; MRI/MRS Magnetic resonance imaging/spectroscopy; QoL Quality of life

[a] Visit window ± 2 weeks
[b] Follow-up visit 1 month (±1 week) after extension phase completion
[c] Urinalysis is optional since it can be difficult to obtain urine specimens from some patients in this population
[d] If female and of child-bearing potential
[e] Saved serum and plasma is required only if it is a visit at the site
Adapted from Table 9-2, CSR page 47 for study C2485.

Endpoints:

Primary

To evaluate the incidence of reported and observed adverse side effects as a percentage of patients enrolled in the study and treated with everolimus.

Secondary

1. Assessment of SEGA tumor size reduction as determined by MRI volume measurement before therapy and at Months 3 and 6

2. Assessment of Seizure frequency, as assessed by 24-hour video-EEG monitoring at baseline and Month 6

3. Assessment of Quality of life (QoL), as assessed by a standardized QOLCE questionnaire

4. Assessment of Neuropsychometric functioning, as assessed by a battery of age-appropriate tests at baseline and Month 6

5. Assessment of response of facial angiofibromas, as assessed by digital photography

6. To measure reduction in choline and myoinositol peaks using magnetic resonance spectroscopy (MRS)

Reviewer's note: Original primary endpoint at the time of first IRB submission was SEGA tumor size reduction as determined by MRI volume measurement before therapy and at months 3 and 6. As per IRB request, however, the primary endpoint was changed to assessment of safety and the efficacy endpoint became the secondary endpoint (January 19, 2007).

A primary SEGA lesion was identified for each patient, representing the largest SEGA tumor seen in that patient. For patients to be eligible for study, lesions had to have demonstrated serial growth on ≥ 2 MRI scans pre-baseline. Tumor response was subsequently assessed at 3 months and 6 months post therapy.

Based upon their analysis of local results of study C2485 a decision was made by the applicant in June 2009 to use these results as the basis for accelerated approval. Changes were then made to the planned analysis as part of the applicant's registration plan. The changes to the planned evaluation are summarized in Table 4 and Table 5. *Response was originally assessed by local radiologists based on changes in tumor volume.[xi] This was performed using a Vitrea 2® workstation based on 1-mm coronal reformatted images from volume acquisitions either post-contrast sagittal 3-D SPGR (1.5-tesla GE MRI [GE Medical Systems, Milwaukee, WI] and 1.5-tesla Siemens MRI [Siemens Medical Systems, South Iselin, NJ]), or T-1 MPRAGE (3.0-tesla Siemens MRI). All measurements and volume determinations are performed by the same radiologist. After decision by Novartis to use this data for this sNDA all data were reassessed by an independent neuroradiologist who reviewed all scans on each patient in accordance to a detailed radiological review charter.*

Minor changes were also made to exploratory and secondary endpoints.

Table 4 Evolution of safety endpoints on C2485

Objectives	Endpoints / variables / outcome measures		Planned Novartis presentation of data	Rationale for Novartis approach
	CCHMC	Novartis		
To evaluate the safety and potential side effects of everolimus in TS patients with SEGA	**Incidence of reported or observed adverse side effects (primary outcome measures)**	Safety and potential side effects • AEs/ adverse drug reactions • laboratory evaluations (including urinalysis) • vital signs	Frequency of events by • system organ class • preferred term • maximum severity (grade) • relationship to study drug Laboratory evaluations and vital signs by • mean changes from baseline • values deviating from reference range • marked outliers	Adverse events will be presented according to accepted regulatory standards, including the percentage of patients with AEs rather than AEs as a percentage of total AEs.

Adapted from Table 9-6, page 61 of clinical study report for C2485.

Table 5 Evolution of efficacy endpoints of C2485

Objectives	Endpoints / variables / outcome measures		Planned Novartis presentation of data	Rationale for Novartis approach
	CCHMC	Novartis		
To evaluate whether everolimus in TS patients with SEGA tumors results in decreased SEGA tumor size	Reduction in SEGA tumor volume at 3 and 6 mo (as determined by local investigator assessment)	**Change from baseline in volume of primary SEGA lesion at 6 mo (as determined by central radiology review) (primary efficacy endpoint)**	Mean and median change (and mean and median percentage change) from baseline, with 95% CI and p-value (one-sample Wilcoxon signed rank test)	Rather than incorporating a multiplicity adjustment and simultaneously analyzing reductions from baseline in SEGA volume at both 3 and 6 months, the 6-month endpoint was selected to be primary, on the basis that a sustained reduction in SEGA volume at 6 months (as opposed to 3 months) would be of greater clinical relevance. As the clinical cut-off date was 12 months after the last patient commenced therapy, all patients could have had a 6-month MRI. Those that discontinued before the 6-month MRI will be included in the primary analysis using their 3-month MRI (i.e., a last observation carried forward approach). Consistent with how the study investigators conducted the trial, focus was on the primary lesion (i.e., that with the greatest volume).
		Change in volume of primary SEGA lesion at 3 mo (central radiology review)	As above	
		Change in volume of primary SEGA lesion at 3 and 6 mo (local investigator assessment)	As above	
		Change in volume of total SEGA lesions at 3 and 6 mo (central radiology review and local investigator assessment)	As above	
		SEGA response rate (≥ 30% and ≥ 50% reduction relative to baseline) at 3 and 6 mo (central radiology review and local investigator assessment)	Response rate	

Adapted from Table 9-6, page 62 of clinical study report for C2485.

Reviewer's note:

1. The Applicant made the decision to use volume change at 6 months as the primary endpoint for the purpose of supplemental NDA (sNDA) filing. Although this had been part of the original study design, this change in primary endpoint was first discussed with FDA after all 28 patients were already on therapy (7/9/09) in preparation for the pre-sNDA meeting.

2. The use of reduction of tumor volume as a regulatory endpoint in oncology drug approval is novel. Therefore, it remains unclear if reduction of SEGA tumor volume in an otherwise asymptomatic patient with a small and resectable tumor represents a clinical benefit. This is in part due to lack of active agents in the past and hence lack of any large prospective studies utilizing systemic therapy in this disease. Review of published literature on SEGAs however reveals that no single convention has been previously utilized for measuring and reporting study methods with some studies using largest diameter [v,vii, viii] while others reported 2 or 3 dimensional assessments [iii, x]. The applicant and PI originally presented their plans for use of volumetric assessment of SEGA lesions during EOP2 planning meeting for study M2301 with the FDA on 10/2/07. The applicant argued that volumetric assessment is the most accurate means of assessing tumor shrinkage and that RECIST and WHO measurements are essentially surrogates for volume. Furthermore the applicant stated that pre-planned imaging techniques providing a 3 dimensional information set to be assessed by computer algorithms allow for accurate volumetric measurements.

The applicant specifically stressed that the regional distribution of the lesion near the foramen of Monroe must be considered as an important factor with a 1 ml reduction in tumor volume having a dramatic clinical effect whereas a larger volume reduction elsewhere in the brain might be of less clinical relevance. Depending on location, small

changes in SEGA volume may produce CSF obstruction at the foramen of Monroe resulting in hydrocephalus and urgent surgical intervention.
Additionally the applicant cited the AACR/FDA Public Workshop on Clinical Trial End Points in Primary Brain Tumors on 1/20/06 were a discussant supported the use of volumetric measurements. Furthermore, the applicant presented published experience for use of volume reduction as an endpoint in other oncologic processes. [xi]

The FDA expressed concerns regarding this endpoint and proposed consideration of alternative measures of demonstrating clinical benefit such as decreases in number of patients who experience hydrocephalus. The applicant however states that hydrocephalus is too infrequent to allow powering a trial to reduce the incidence and no reliable estimates regarding the annual incidence of hydrocephalous are available. In addition the applicant states that there is no agreement among experts on what represents a progression or worsening that necessitates surgical intervention.

Additional communication was held between the applicant and the FDA during the pre-NDA meeting on 9/29/09. The FDA agreed to consider the results of volumetric assessment as part of the review. This is in part due to the fact that in patients with unresectable or previously treated lesion that are now showing evidence of regrowth volumetric reduction in tumor size may represent a potential benefit as larger SEGA size is generally associated with more morbidity and mortality.

Statistical Analysis Plan:

Original plan: C2485 was designed to evaluate the primary outcome of reported incidence and observed adverse side effects as a percentage of total number of patients. The secondary outcome of measure was “overall reduction in SEGA tumor volume”. Change in tumor volume as a result of therapy was to be measured and compared with the baseline using paired t test or Wilcoxon Signed Rank, depending on whether data were normally distributed. The protocol stated that a “treatment efficacy as 30% or more reduction in SEGA tumor size from baseline” as a result of therapy with everolimus, based on previously published results with rapamycin. Sample size was set at 20 with 100% power, at alpha .05 to detect statistical significance. Descriptive statistics were to be used for evaluating the outcomes of other secondary and exploratory endpoints.

After a decision was made to use this study as the basis for a regulatory submission, given the sample size of the study and feedback from FDA, the applicant chose a non-parametric one-sided Wilcoxon signed rank test as the statistical test for the primary analysis.

The hypothesis being tested was that the median change from baseline in the primary SEGA volume was ≥ 0:

H0: $\Delta \geq 0$ versus Ha: $\Delta < 0$

where H0 is the null hypothesis, Ha is the alternative hypothesis, and Δ is the median change at 6 months from baseline in primary SEGA volume. The analysis was conducted on the Full Analysis Set which included all 28 treated patients.

Analysis population:

- The Full Analysis Set (FAS) is the primary population for efficacy analysis (equivalent of the intent to treat population) and represents all patients that received a dose of therapy
- The Safety Analysis set was all patients who received a dose of therapy and had at least one post baseline safety assessment
- The Per-protocol Population consisted of all patients from the FAS without any major protocol deviation, who were evaluable for efficacy, and who have completed a minimum exposure requirement (i.e., no cumulative interruptions of > 6 weeks in the first 12 weeks since start of study treatment)

Protocol Amendments:

The protocol was amended seven times. All patients had been enrolled before Amendment 7 took effect.

Table 6 Protocol Amendments

Amendment	Date	Patients enrolled (n)	Major changes
1	1/19/07	0	• Optimize serum trough sampling
2	5/17/07	5	• Addition of blood draw at Months 4 and 5 to monitor clinical laboratory tests (including urinalysis and study drug levels) • Addition of Quality of Life in Childhood Epilepsy questionnaire to be performed at baseline, and Months 3 and 6 • Addition of Visit windows to schedule of events • Use of NCI CTCAE for grading adverse events • Per DSMB recommendations, the statement that 'all infections would be attributed to at least possibly related to study drug" was added
3	2/11/08	14	• Provision made to replace patients who withdrew before completing 3 months of treatment to ensure enrollment of at least 20 evaluable patients. • Requirement for measuring trough study drug levels after every dose modification removed
4	6/17/08	19	• Change sample size from 20 to 25 evaluable patients • Eliminated study drug dose ceiling of 6.5 mg/m^2/day • Changed target trough levels to 5-15 ng/mL • Allow for additional days of study treatment if patient missed > 10 consecutive doses so that total duration was 6 months • Added an open-label extension phase with tabular presentation of study visits. • Introduced instructions for resumption of study therapy in a patient who has experienced an SAE
5	9/24/08	23	• Minor changes to follow up schedule
6	11/19/08	26	• Increased enrollment goal from 25 to 27 patients
7	2/10/10	28	• Added genetic testing for the diagnosis of TS and consenting for providing the information to health authorities

6 Review of Efficacy

Efficacy Summary

C2485 was conducted in a single US site in patients with SEGA associated with TS. The primary endpoint was reduction in primary SEGA volume from baseline to Month 6 by independent central review. In total, 28 patients received treatment with everolimus; 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 everolimus treatment. After the core treatment phase, patients could continue to receive everolimus treatment as part of an extension treatment phase where SEGA volume was assessed every 6 months.

At 6 months, 9 out of 28 patients (32%, 95 CI: 16% - 52%) had a ≥ 50% reduction in the tumor volume of their largest SEGA lesion. Duration of response for these 9 patients ranged from 97 to 946 days with a median of 266 days. Seven of these 9 patients had an ongoing volumetric reduction of ≥ 50% at the data cutoff.

One of 4 patients who had prior surgery experienced a 58% reduction in the tumor volume of their largest SEGA lesion at month 6; 2 additional patients had a volumetric reduction of ≥ 50% on subsequent scans beyond month 6.

Overall, 19 patients experienced a BOR of ≥ 50% reduction in the tumor volume of their largest SEGA lesion at some point in therapy although not all were able to retain this response at time of data cutoff.

No patients experienced a CR; however, no patients developed new lesions.

No further efficacy conclusions regarding seizure rates could be reached as the study was not blinded, the patients did not have significant enough change in seizure rates and other anti-epileptic medications had also been dose adjusted.

6.1 Indication

Treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS).

6.2 Methods

Refer to section 5 of this review.

6.3 Demographics

Table 7 summarizes the demographic characteristics of 28 patients treated on C2485. The mean age was 12.5 years (SD=7.53). Most patients carried the diagnosis of TS for

their entire life with mean number of years since diagnosis of 12.1 years (SD=7.7). Seventeen (61%) of the patients were male and 11 (39%) female. Four (14%) patients were >21 years of age. The majority (86%) of the patients were Caucasian.

Table 7 Demographic Characteristics of patients on C2485

Demographic characteristic	Everolimus N=28 n (%)	
Age (years)		
n	28	
Mean (standard deviation)	12.5	(7.53)
Median	11.0	
Range	3 to 34	
Age group (years) (n [%])		
3 to < 12	16	(57.1)
> 12 to < 18	6	(21.4)
≥ 18	6	(21.4)
Sex (n [%])		
Male	17	(60.7)
Female	11	(39.3)
Race (n [%])		
Caucasian/White	24	(85.7)
Black	2	(7.1)
Other [a]	2	(7.1)
Weight (kg)		
N	28	
Mean (standard deviation)	52.0	(30.60)
Median	48.2	
Range	13.1 to 132.6	
Height (cm)		
n	28	
Mean (standard deviation)	145.7	(27.09)
Median	141.0	
Range	91.5 to 187.0	
Body mass index (kg/m^2)		
n	28	
Mean (standard deviation)	22.3	(6.79)
Median	20.3	
Range	13.9 to 39.4	
Body surface area (m^2) [b]		
n	28	
Mean (standard deviation)	1.42	(0.54)
Median	1.38	
Range	0.6 to 2.6	

[a] 2 patients were of mixed race (0001/00002 - ¼ black / ¾ white and 0001/00019 - black/white)
[b] Body surface area = √([height (cm) x weight (kg)]/3600)

Twenty-seven patients were non-Hispanic/Latino (0001/00002 was of unknown mixed ethnicity)

Adapted from Study C2485 CSR, Table 10-4, page 71.

6.4 Patient Baseline Characteristics

6.4.1 TS diagnosis and SEGA lesions

All 28 patients had TS diagnosis according to the modified Gomez criteria and confirmed by central review. All patients had ≥ 2 major criteria (in addition to SEGA) as needed for clinical diagnosis of "definite TS". Table 8 lists the number of TS major criteria seen in each patient. The patients had a median of 7 (range: 4,10) major features.

Reviewer's note:

The presence of at least 3 major criteria for TS in addition to presence of SEGA in every patient is supportive of the correct diagnosis of "definite TS" in all patients.

Table 8 Characteristics of TS diagnosis in patients on C2485

Patient #	# of major criterion	# of minor criterion	Age	Years since diagnosis
1	8	4	25	25.2
2	5	0	3	2.9
3	7	4	3	2.9
4	6	0	14	14.5
5	6	0	11	6.9
6	7	2	15	14.9
7	7	0	14	14.2
8	7	1	25	23.3
9	8	1	9	9.1
10	7	1	6	4.9
11	7	2	12	12.0
12	4	2	17	17.1
13	4	0	4	0.7
14	7	0	5	5.6
15	7	2	34	33.8
16	6	0	9	8.7
17	8	1	17	16.3
18	9	1	9	9.2
19	7	2	8	7.3
20	7	1	7	6.6
21	10	2	11	11.0
22	6	0	5	6.1
23	8	3	19	19.1
24	5	0	18	17.4
25	5	0	11	10.7
26	7	1	8	8.2
27	8	0	8	8.4
28	8	0	22	22.3

Source: *CSR, CRFs and ATSD.xpt.*

The three most common major diagnostic criteria for TS see in the C2485 patient population were subependymal nodules, SEGA and cortical tubers. All three of these CNS findings were seen in all patients. With respect to the number of SEGA lesions based on central radiological review, 15 (54%) of the patients had only one measureable SEGA lesion and 13 (46%) had two lesions. Twelve (43%) had bilateral SEGA. Only 6 (21%) patients had hydrocephalus at baseline. Table 9 describes the frequency of reported major TS criteria and Table 10 summarizes the baseline SEGA lesions.

Table 9 Frequency of Tuberous Sclerosis Complex major diagnostic criteria in C2485 Patients

Major TSC criteria	# of patients (n=28)	% of patients
Lymphangioleiomyomatosis	0	0
Multiple retinal nodular hamartomas	4	14
Nontraumatic ungual or periungual fibroma	6	21
Shagreen patch (connective tissue nevus)	9	32
Cardiac rhabdomyoma, single or multiple	17	61
Renal angiomyolipoma	22	79
Hypomelanotic macules (three or more)	24	86
Facial angiofibromas or forehead plaque	25	89
Cortical tuber	28	100
SEGA	28	100
Subependymal nodule	28	100

Table 10 Baseline SEGA Lesions in C2485 Patients

PT #	# of measured SEGA Lesions		Bilateral lesions	Inferior Growth	Parenchymal Invasion	Hydrocephalus	Pre-baseline growth
	Local Review	Central Review					
1	1	1	-	-	Superficial	-	Y
2	1	2	Y	-	Superficial	-	Y
3	1	1	-	-	Superficial	-	Y
4	2	2	Y	-	Deep	-	Y
5	1	1	-	-	Superficial	-	?
6	1	1	-	-	Superficial	-	?
7	1	1	-	-	Superficial	Y	Y
8	1	2	Y	-	Superficial	-	Y
9	1	2	Y	-	Superficial	-	Y
10	1	1	-	-	Superficial	-	Y
11	1	1	-	-	None	-	Y
12	1	1	-	-	Superficial	Y	Y
13	1	1	-	-	Superficial	-	Y
14	1	2	Y	-	Superficial	-	Y
15	1	1	-	-	Deep	Y	Y
16	1	2	Y	-	Superficial	-	?
17	1	1	-	-	Superficial	Y	Y
18	1	1	-	-	Superficial	-	Y
19	1	1	-	-	Superficial	-	Y
20	1	2	Y	-	Superficial	Y	Y
21	1	2	Y	-	Superficial	-	Y
22	1	2	Y	-	Superficial	-	Y
23	1	1	-	-	Superficial	-	Y
24	1	2	-	-	Superficial	-	Y
25	2	2	Y	-	Superficial	Y	?
26	1	2	Y	-	Superficial	-	Y
27	1	1	-	-	Superficial	-	?
28	2	2	Y	-	Superficial	-	?

Derived from atscles.xpt
? reflects lack of definitive evidence of primary SEGA growth on pre-therapy MRI scans.

There was 100% concordance in the selection of the primary SEGA lesion between the independent radiologist and local radiologist, although 8 patients were reported to have an additional secondary measureable lesion by the independent radiology reviewer (Table 10).

Reviewer's Note: Patient's # 9, 17 and 24 had non-contrast MRI's used as part of their pre-baseline follow up. Patient #23 had a screening MRI that was non-contrast based on local read but with contrast based on central read. The use of different radiological methods for assessing tumor burden may be a source of inaccuracy and bias.

6.4.2 Prior therapy

Five patients had a total of 14 previous neurosurgical procedures. Four of these patients had a total of 7 procedures for resection of their targeted SEGA lesions. Two patients, including one with a history of SEGA resection, had received prior rapamycin treatment (Table 11).

Table 11 Previous SEGA Therapy for Patients in C2485

Patient #	Type of therapy	Date of initiation	Date of termination	Date of RAD001 initiation
12	SEGA Resection	Jan, 1991	-	Dec 19, 2007
	Rapamycin	May 09, 2005	Aug 01, 2007	Dec 19, 2007
13	SEGA Resection	May 02, 2007	-	Feb 06, 2008
15	Craniotomy with SEGA Resection	Jan 09, 1992	-	Feb 13, 2008
	Craniotomy with SEGA Resection (#2)	May 28, 1992	-	
	Radiosurgery of SEGA	Jul 24, 2001	-	
19	Rapamycin	Jul, 2005	Jun, 2007	Mar 12, 2008
24	SEGA Resection	Jul 26, 2002	-	Sep 30, 2008
	SEGA Resection	Jul 11, 2008	-	

Derived from acnd.xpt and atrt.xpt.

6.5 Protocol violations and Deviations

Three categories of protocol violations/deviations discussed below are:
1) Questionable tumor size progression prior to enrollment;
2) Concomitant treatment with CYP 3A inducers and inhibitors; and
3) Dosing errors

Table 12 Protocol Deviations (Applicant's Table)

Protocol deviation	Everolimus N=28 n (%)	
Number of patients with at least 1 deviation	**17**	**(60.7)**
Nature of protocol deviation [a]		
Prohibited medication deviations	14	(50.0)
Coadministration of medication affecting CYP3A	14	(50.0)
Eligibility criteria deviations	7	(25.0)
Written informed consent partially incomplete [b]	6	(21.4)
Inadequate renal function (Cr ≥ 1.5 mg/dL)	1	(3.6)
Study medication deviations	2	(7.1)
Incorrect dosing	2	(7.1)
Other deviations	1	(3.6)
Lesion assessment performed with CT-scan	1	(3.6)

Cr Serum creatinine

[a] Not mutually exclusive
[b] Applies only to informed consent for protocol amendments effective after initial study entry

Five patients (#5, #16, #25, #27 and # 28) had their pre-baseline and baseline scan measurements for SEGA lesions that were discrepant with the protocol defined eligibility (Table 13).

Table 13 Patients with Questionable Eligibility Based on Baseline scans

Patient #	Scan status	Scan Dates	Measurements by central IR (cm^3)	Comments
5	Pre-BL		0.53	Pre-baseline scans were reviewed by independent radiology in Day 90 safety update. The increase of 0.03 cm^3 is questionable specially when considering the previous decrease in tumor size between 2 pre-baseline scans.
	Pre-BL		0.46	
	Baseline	18 Apr 07	0.49	
6	Pre-BL	13 Nov 06	0.64	The increase in lesion volume between pre-BL and BL scans is only 0.02 cm^3. There is also a significant discrepancy in the volume assessment of the baseline scan between local (0.95 cm^3) and independent review.
	Baseline	06 Jun 07	0.66	
16	Pre-BL #1	26 Jul 06	0.89	Tumor volume appears to have decreased in size in time period between 2 pre-BL scans. Reason for decrease is unexplained.
	Pre-BL #2	05 Nov 07	0.7	
	Baseline	18 Feb 08	0.83 (0.76 + 0.06)	
	Pre-BL #2	14 Sep 07	Unavailable	
	Baseline	16 Jun 08	0.71 (0.57 + 0.14)	
23	Pre-BL	25 Aug 05	1.82	The local radiologist labeled baseline MRI scan as non-contrast while the independent reviewer labeled it as with contrast. All other scans with contrast. Effect of contrast on measurements unclear.
	Baseline	07 Jul 08	2.77	
24	Pre-BL #1	21 Oct 04	3.34 (2.57 + 0.77)	Both pre-baseline MRI scans were without contrast. Effect on interpretation of results is unclear.
	Pre-BL #2	13 Jul 08	2.85 (1.68 + 1.17)	
	Baseline	29 Sep 08	3.32 (2.03 + 1.29)	
25	Pre-BL #1	11 Jul 07	4.25 (2.14 + 2.11)	Tumor volume appears

Patient #	Scan status	Scan Dates	Measurements by central IR (cm^3)	Comments
	Pre-BL #2	15 Jul 08	5.47 (3.11 + 2.35)	to have decreased in size in time period between pre-BL #2 and baseline scans. Reason for decrease is not explained. Additionally there is a significant discrepancy between local (3.3 + 2.2= 5.5 cm^3) and central measurement of baseline scan.
	Baseline	20 Oct 08	3.66 (2.18 + 1.48)	
27	Pre-BL #1	27 Dec 04	0.97	Tumor volume appears to have decreased in size in time period between pre-BL #2 and baseline scans. Reason for decrease is unexplained. Additionally BL scan was performed 83 days prior to initiation of study treatment.
	Pre-BL #2	26 Jun 08	2.75	
	Baseline	19 Sep 08	2.20	
28	Pre-BL #1	25 Sep 07	4.45 (2.3 + 2.15)	The total volume of SEGAs appears to have been decreasing prior to therapy initiation. Additionally there is a significant discrepancy between local (2.6 + 2.8 = 5.4 cm^3) and central measurement of baseline scan.
	Pre-BL #2	18 Apr 08	4.26 (2.09 + 2.17)	
	Baseline	23 Oct 08	4.11 (2.26 + 1.85)	

Derived from atscles.xpt

We inquired the sponsor regarding above discrepancies. The sponsor responded that most patient's pre-baseline scans were performed in outside hospitals without standard methodology which could have led to measurement discrepancies. For patients # 25, 27 and 28 the lesions were considered as progressing based on original growth on scans.

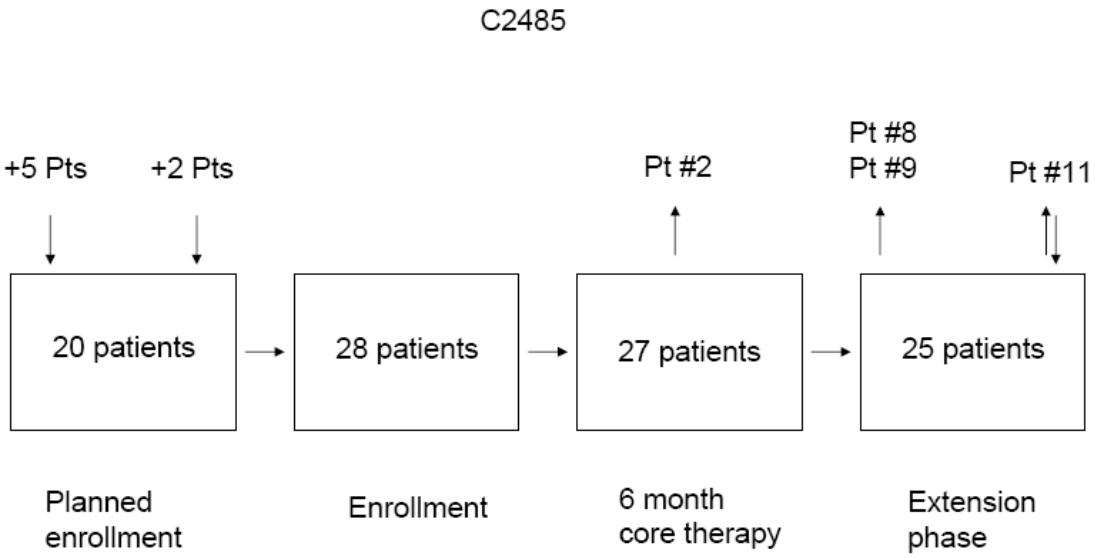
6.6 Subject Disposition

Twenty-eight patients with SEGA in the setting of TS were screened and all found eligible and enrolled on study between January 2007 and December 2008. Twenty-seven (96.4%) received the 6 month core therapy and all elected to continue on

extension phase of study. All 27 have received ≥ 12 months of therapy. Twenty five patients still remain on study at the time of data cutoff.
Reviewer note: In this submission the applicant refers to the data from the 28 (100%) of patients who were enrolled on study as the "Full Analysis Set". This same data set is used for evaluation of the safety profile (Safety population). The 27 (96%) patients who actually completed 6 months of therapy are referred to as the "Per-protocol population".

Reviewer note: Per-protocol population included 27 patients who completed 6 months of therapy.

Figure 3 Patient Disposition



One patient, Patient #2, withdrew from study during the 6 month core phase.

Patients # 8 withdrew 17.5 months into therapy with everolimus while patient #9 withdrew after 21.5 months.

One additional patient, patient #11, was removed from study after 18 months of therapy due to meeting off therapy requirements (>75% reduction in SEGA volume) with subsequent re-enrollment due to progression.

There were no patients who were lost to follow up. All patients who received a dose of therapy were included in efficacy analysis.

Reviewer's note: There has not been any change to patient disposition at time of 90 day update (Cut off date of March 8, 2010) with 25 patients remaining on study.

6.7 Analysis of Primary Endpoint

6.7.1 Change from baseline in volume of primary SEGA lesion at 6 months (as determined by central radiology review)

Table 14 Response of primary SEGA lesion to everolimus therapy - Full Analysis Set (Applicant's Table)

SEGA volume (cm^3)	Independent central review	
	Baseline N=28	Month 6 N=28
Mean (standard deviation)	2.45 (2.813)	1.30 (1.476)
Median	1.74	0.93
Range	0.49 to 14.23	0.31 to 7.98
Reduction from baseline		
Mean (standard deviation)	1.15 (1.421)	
Median	0.80	
Range	0.06 to 6.25	
Primary analysis		
p-value [a]	<0.001	
95% CI for median [b]	0.4 to 1.2	
Percentage reduction from baseline, n (%)		
≥ 50%	9	(32.1)
≥ 30%	21	(75.0)
> 0%	28	(100.0)
No change	0	
% increase	0	

The applicant reports that of the 28 patients enrolled on study C2485, 21 (75%) had a reduction of ≥ 30% in volume of their primary tumor while 9 patients (32%) had a reduction of ≥ 50% on their 6 month evaluation as determined by independent radiology review (IR). Twenty-seven of these patients remained on study for at least 6 months while one patient, patient #2 was withdrawn from study by parents at 4.7 months (Day 135) into study. All patients on study, including patient #2, were reported to have some response to therapy.

Based on independent radiology review, the mean primary SEGA volume at baseline was 2.45 cm^3 (SD= 2.81) with a median of 1.74 (0.49, 14.23). At the 6 month time point the mean primary SEGA volume was 1.30 cm^3 (SD=1.48) with a median of 0.93 cm^3 (0.31, 7.98). The mean and median for the Per-Protocol Population were very similar to the Full Analysis Set. The median change in volume at 6 months for the Full Analysis

Set was 0.80 cm^3 (0.06, 6.25) with a mean of 1.15 cm^3 (SD=1.42). The applicant considers this finding to be clinically and statistically significant with p <0.001.

Reviewer's comment: due to the small number of patients, the applicant's analysis can be only considered as exploratory.
We performed an analysis of primary SEGA response to everolimus therapy at 6 months for each patient. The results of this can be found in Table 15 and Table 16.

Table 15 Categories of primary SEGA Tumor Size on C2485 (Based on IR)

Tumor size category	# of patients (n=28)			
	Baseline	**6 Months**	**Nadir**	**Last scan**
<1 cm^3	10 (36%)	15 (54%)	19 (69%)	18 (64%)
1 cm^3 to <2 cm^3	6 (21%)	8 (29%)	7 (25%)	6 (21%)
2 cm^3 to <5 cm^3	9 (32%)	4 (14%)	2 (7%)	4 (14%)
≥5 cm^3	3 (11%)	1 (4%)	0	0

Eighteen of the 28 patients (64%) had a baseline tumor volume of > 1 cm^3. At month 6, the number of patients with such a volume became 13 (46%). This represented a mean tumor response of 47% (SD=13%) with a median of 48% (18%, 65%). These findings are highly suggestive of activity of everolimus in patients with larger tumors, particularly tumors > 2 cm^3 in diameter (Table 15).

Table 16 Primary Tumor response by IR Review at 6 months

Pt #	Baseline 1° SEGA Volume (cm^3)	6 Month 1° SEGA Volume (cm^3)	Change in SEGA Volume (cm^3)		Days on therapy
1	5.82	2.23	3.59	62%	186
2	0.68	0.58	0.10	15%	135
3	1.68	0.85	0.83	49%	173
4	2.95	1.07	1.88	64%	199
5	0.49	0.41	0.08	16%	180
6	0.66	0.34	0.32	48%	179
7	7.45	2.96	4.49	60%	170
8	2.90	2.04	0.86	30%	178
9	0.86	0.55	0.31	36%	208
10	0.80	0.49	0.31	39%	167
11	1.85	0.65	1.20	65%	195
12	4.39	2.54	1.85	42%	173
13	1.54	0.65	0.89	58%	182
14	0.54	0.35	0.19	35%	180
15	14.23	7.98	6.25	44%	180
16	0.76	0.70	0.06	8%	173
17	2.27	1.35	0.92	41%	182
18	1.52	1.25	0.27	18%	194
19	1.69	0.93	0.76	45%	175
20	1.79	1.18	0.61	34%	187
21	0.98	0.71	0.27	28%	195
22	0.57	0.31	0.26	46%	194
23	2.77	1.49	1.28	46%	191
24	2.03	1.47	0.56	28%	194
25	2.18	0.93	1.25	57%	187
26	0.85	0.37	0.48	56%	187
27	2.20	1.04	1.16	53%	179
28	2.26	1.11	1.15	51%	180

Reviewer's Comments: We identified the following issues during our review:

1) *Single-arm, single-center, open-label trial with small number of patients.*
2) *Evolving trial endpoints: changing from safety evaluation to tumor responses by volume*
3) *Retrospecitve data collection and analysis with inherent bias*
4) *Changing the sample size of the trial from 20 to 25 then to 27 with a final sample size of 28.*
5) *Eligibility issues as described in Table 13.*

Despite these issues, We verified the tumor responses in each patient. *The mean volume change as a result of therapy in the 8 patients enrolled after study amendments was 0.80 (SD=0.45) with a median of 0.86 (0.26, 1.28). The mean percent decline in*

SEGA volume was 46% (SD=12%) with a median of 49% (28%, 57%). These numbers appear to be in line with the overall changes seen in the entire patient population. The change in volume for the last 3 patients, all enrolled after amendment 6, however is in excess of 50%.

6.7.2 Concordance of independent review and local review

To evaluate the reliability of volumetric measurements performed in this study we compared the baseline and 6 month measurements of primary tumor size by the local and independent radiologists. When comparing independent radiology and local review of primary SEGA size, 19 (69%) patients had a baseline evaluation that was larger based upon local radiology review. In addition, scans from 18 (64%) patients were read as having a larger tumor at the 6 month evaluation by local review. Fifteen (53%) patients were considered to have larger primary tumors on both scans as read by LR. These results are summarized in Table 17.

Table 17 Volumetric Measurement Discrepancies between IR and LR

Pt #	Discrepancy in BL volume (cm^3)	Discrepancy in 6M volume (cm^3)	Reduction in tumor volume at 6M by IR (cm^3)	Reduction in tumor volume at 6M by LR (cm^3)	Discrepancy in reduction in tumor volume at 6M (cm^3)
1	-1.28	-0.07	3.59	4.8	-1.21
2	0.01	0.04	0.1	0.13	-0.03
3	-0.62	-0.25	0.83	1.2	-0.37
4	-0.45	-0.23	1.88	2.1	-0.22
5	-0.18	-0.05	0.08	0.21	-0.13
6	-0.29	-0.42	0.32	0.19	0.13
7	0.85	-0.44	4.49	3.2	1.29
8	-0.2	-0.96	0.86	0.1	0.76
9	-0.24	0.27	0.31	0.82	-0.51
10	-0.6	-0.19	0.31	0.72	-0.41
11	0.05	-0.21	1.2	0.94	0.26
12	0.59	0.24	1.85	1.5	0.35
13	0.04	0.04	0.89	0.89	0
14	-0.02	-0.03	0.19	0.18	0.01
15	10.83	4.68	6.25	0.1	6.15
16	-0.14	-0.02	0.06	0.18	-0.12
17	-0.43	-0.05	0.92	1.3	-0.38
18	0.32	0.15	0.27	0.1	0.17
19	-0.51	-0.07	0.76	1.2	-0.44
20	-0.01	0.32	0.61	0.94	-0.33
21	0.63	0.52	0.27	0.16	0.11
22	0.19	-0.05	0.26	0.02	0.24
23	-0.23	-0.21	1.28	1.3	-0.02
24	-0.57	0.07	0.56	1.2	-0.64
25	-1.12	-0.77	1.25	1.6	-0.35
26	-0.25	-0.13	0.48	0.6	-0.12
27	-0.1	0.12	1.16	1.38	-0.22
28	-0.54	-0.49	1.15	1.2	-0.05

Figure 4 Concordance of Response Evaluations between Independent and Local Review

Independent review

Local Review	>50%	<50%
>50%	6	5
<50%	3	14

	>30%	<30%
>30%	17	4
<30%	4	3

Figure 4 shows that in 20 patients, the concordance between IR and LR was 100% regardless whether 50% or 30% volumetric reduction was used as response criteria..

6.7.3 Tumor response by other evaluation criteria

To further define, quantify and validate the degree of volumetric response seen in patients on study C2485, we requested the applicant to submit the tumor response data according to Response Criteria In Solid Tumors (RECIST) or World Health Organization (WHO) tumor response criteria.

Two Dimensional Assessment of Tumor Response

WHO criteria define a best overall response (BOR) of >50% of the area of the perpendicular diameters at any time point during the course of therapy as long as this is not preceded by progressive disease (tumor growth of >25%) in one or more lesions. Additionally, all measureable lesions are used in determination of response using WHO criteria. All responses need to be confirmed by repeat tumor assessment within 4 weeks from the date of initial assessment suggesting response. Confirmatory scans were however, not performed in the current study.

Eight patients had a response of > 50% according to WHO. Only 7 (25%) of these patients however were considered to have partial response (95% CI of 11% to 45%. One patient (#11) had progressive disease on prior staging scans, a response assessment of No Change (NC). (Table 18).

Table 18 Total SEGA Tumor Response according to WHO Criteria

Pt #	Baseline (cm^2)	6 months		Nadir		Last	
		cm^2	% Response	cm^2	% Response	cm^2	% Response
1	3.81	1.82	52	1.80	53	1.80	53
2	0.90	0.89	1	0.89	1	0.89	1
3	1.62	1.03	37	0.91	44	1.36	16
4	3.26	1.83	44	1.83	44	2.12	35
5	0.70	0.66	6	0.46	34	0.51	28
6	0.95	0.67	30	0.50	47	0.50	47
7	5.47	2.76	50*	2.76	50*	3.42	37
8	3.48	2.97	15	1.90	45	3.26	6
9	0.83	0.63	24	0.56	33	0.75	10
10	0.86	0.58	33	0.58	33	0.59	32
11	1.61	0.88	46	0.67	58	1.69	-5
12	4.51	2.68	41	2.43	46	2.43	46
13	3.17	1.23	61	0.84	74	2.41	24
14	0.86	0.70	19	0.63	27	1.28	-48
15	10.56	7.92	25	5.14	51	5.14	51
16	1.10	0.96	13	0.91	17	1.01	8
17	2.40	1.92	20	1.31	45	1.39	42
18	3.81	2.81	26	2.59	32	2.59	32
19	2.03	1.02	50*	0.85	58	1.21	40
20	3.11	2.35	24	1.64	47	1.64	47
21	1.84	1.41	24	1.41	24	1.86	-1
22	0.78	0.62	20	0.62	20	0.80	-3
23	2.87	1.59	45	1.25	57	1.25	57
24	4.10	2.64	36	2.64	36	3.93	4
25	5.23	3.14	40	3.14	40	3.19	39
26	1.27	0.59	54	0.59	54	0.77	39
27	2.07	1.62	22	1.15	44	1.15	44
28	4.49	2.69	40	1.97	56	1.97	56

**Result rounded up: patient not considered a responder.*
Patients who were considered responders are listed in red.

Reviewer's note: One of the 7 responders was a patient whose eligibility was questionable (#28). This patient also maintained the response at the end of therapy.

In addition, the response of the primary SEGA lesion at 6 months, at BOR and at end of therapy was assessed and is presented in Table 19. Nine patients had a BOR in primary SEGA of > 50%. Seven (25%) of these patients qualified as having PR with 4 (14%) retaining their PR status at time of last scan. These results are similar to BOR of all SEGA lesions according to WHO criteria.

Table 19 Primary SEGA lesion Response according to WHO criteria

Pt #	Baseline (cm^2)	6 months		Nadir		Last	
		cm^2	% Response	cm^2	% Response	cm^2	% Response
1	3.812	1.816	52	1.797	53	1.797	53
2	0.803	0.774	4	0.774	4	0.774	4
3	1.620	1.025	37	0.914	44	1.359	16
4	2.818	1.643	42	1.643	42	1.709	39
5	0.701	0.661	6	0.462	34	0.506	28
6	0.954	0.668	30	0.502	47	0.502	47
7	5.474	2.757	50*	2.757	50*	3.424	37
8	2.765	2.444	12	1.339	52	2.656	4
9	0.551	0.341	38	0.341	38	0.483	12
10	0.861	0.580	33	0.580	33	0.586	32
11	1.612	0.877	46	0.669	58	1.689	-5
12	4.511	2.682	41	2.425	46	2.425	46
13	3.167	1.234	61	0.839	74	2.411	24
14	0.727	0.568	22	0.540	26	1.150	-58
15	10.559	7.915	25	5.140	51	5.140	51
16	0.941	0.828	12	0.693	26	0.815	13
17	2.402	1.917	20	1.313	45	1.385	42
18	3.811	2.810	26	2.588	32	2.588	32
19	2.030	1.024	50*	0.849	58	1.209	40
20	2.150	1.740	19	1.085	50*	1.085	50
21	1.342	1.109	17	1.109	17	1.593	-19
22	0.595	0.513	14	0.513	14	0.647	-9
23	2.871	1.590	45	1.247	57	1.247	57
24	2.480	1.645	34	1.645	34	2.726	-10
25	2.824	1.550	45	1.488	47	1.488	47
26	0.903	0.300	67	0.300	67	0.522	42
27	2.068	1.616	22	1.152	44	1.152	44
28	2.430	1.541	37	1.164	52	1.164	52

**Result rounded up: patient not considered a responder.*
Patients who were considered responders are listed in red.

One Dimensional Assessment of Tumor Response

RECIST 1.1 criteria are based upon the sum of the longest diameter of all target lesions. These criteria were retrospectively applied to all scans from study C2485. These criteria, much like the WHO criteria, are based upon the BOR at any point during therapy. Furthermore all responses need to be confirmed within 4 weeks. Seven patients had BOR of PR (95% CI: 11% to 45%) according to RECIST 1.1 criteria (Table 20).

Table 20 Response according to RECIST criteria

Pt #	Baseline (cm)	6 months		Nadir		Last	
		cm	% Response	cm	% Response	cm	% Response
1	2.33	1.57	33	1.57	33	1.64	30*
2	1.44	1.46	-1	1.46	-1	1.46	-1
3	1.39	1.08	22	1.01	27	1.30	6
4	2.65	2.00	25	1.97	26	2.21	17
5	1.04	0.89	14	0.77	26	0.87	16
6	1.14	0.98	14	0.74	35	0.74	35
7	2.86	1.99	30	1.99	30	2.04	29
8	3.17	2.99	6	2.65	16	3.37	-6
9	2.02	1.79	11	1.31	35	1.80	11
10	1.14	0.89	22	0.89	22	1.03	10
11	1.60	1.32	18	1.05	34	1.63	-2
12	2.42	2.13	12	1.93	20	2.01	17
13	2.36	1.72	27	1.63	31	1.98	16
14	1.51	1.48	2	1.33	12	2.01	-33
15	3.70	3.31	11	3.31	11	2.72	26
16	1.48	1.44	3	1.39	6	1.55	-5
17	1.69	1.60	5	1.24	27	1.36	20
18	2.32	1.68	28	1.68	28	2.30	1
19	1.76	1.08	39	1.08	39	1.32	25
20	3.03	2.45	19	2.13	30*	2.13	30*
21	2.58	2.12	18	2.12	18	2.31	10
22	1.33	1.11	17	1.11	17	1.27	5
23	1.88	1.43	24	1.42	24	1.42	24
24	3.63	3.01	17	3.01	17	3.48	4
25	3.83	3.02	21	3.02	21	3.20	16
26	1.82	1.48	19	1.33	27	1.78	2
27	1.57	1.41	10	1.24	21	1.35	14
28	3.42	2.60	24	2.40	30*	2.40	30*

** Result rounded up: patient not considered a responder.*
Patients who were considered responders are listed in red.

Reviewer's comments:

Lesions <10 mm in diameter are not considered evaluable based upon RECIST 1.1. Thus, patient #22 would not have been evaluable as both of the patients SEGA lesions were < 10mm in diameter. Additionally 8 of the 13 patients with secondary lesions would have had secondary lesions that are not evaluable. If this criterion was applied strictly, patient #26 would also have a BOR that was considered a PR and as a result 8 of 27 patients (30%) would be considered responders.

It also has to be noted that 1 of the patients who was considered a responder (patient #6) by RECIST, had questionable eligibility criteria.

When evaluating last documented scans based on RECIST, 23 (82%) had some evidence of tumor growth compared to BOR. Five (18%) patients had a tumor that was bigger than baseline with 4 patients meeting criteria for PD. Only 1 patient (#6) still meets criteria for partial response at end of therapy.

Table 21 provides a comparison of the response rates based upon volumetric, one-dimensional (RECIST) and two-dimensional (WHO) criteria. As can be noted a PR as assessed by WHO criteria does not necessarily equate to a PR by RECIST criteria or visa versa; nor do PRs by either criterion translate to a 50% volumetric reduction. Only 3 patients were considered PRs by RECIST and WHO and a ≥ 50% responder by volumetric criteria. However, 9 patients who had > 50% volumetric reduction at 6 months (# 1, 4, 7, 11, 13, 25, 26, 27, and 28) showed either partial response (PR) or stable disease (SD) according to RECIST criteria. Similarly, these 9 patients showed either PR or no changes according to WHO criteria.

Table 21 Comparison of Response by volumetric reduction, RECIST and WHO criteria

Patient	BOR primary SEGA volume	BOR SEGA diameter (RECIST 1.1)	BOR SEGA area (WHO)
1	≥ 50%	PR	PR
13	≥ 50%	PR	PR
19	≥ 50%	PR	PR
7	≥ 50%	PR	NC
9	≥ 50%	PR	NC
11	≥ 50%	PR	NC
15	≥ 50%	SD	PR
26	≥ 50%	SD	PR
28	≥ 50%	SD	PR
3	≥ 50%	SD	NC
4	≥ 50%	SD	NC
10	≥ 50%	SD	NC
12	≥ 50%	SD	NC
17	≥ 50%	SD	NC
20	≥ 50%	SD	NC
22	≥ 50%	SD	NC
25	≥ 50%	SD	NC
27	≥ 50%	SD	NC
6	≥ 30%	PR	NC
23	≥ 30%	SD	PR
5	≥ 30%	SD	NC
8	≥ 30%	SD	NC
14	≥ 30%	SD	NC
16	≥ 30%	SD	NC
21	≥ 0%	SD	NC
24	≥ 0%	SD	NC
2	≥ 0%	SD	NC
18	≥ 0%	SD	NC

BOR: Best overall response; NC: No change; PR: Partial response; RECIST: Response evaluation criteria in solid tumors; SD: Stable disease; SEGA: Subependymal giant cell astrocytoma; WHO: World Health Organization

Adapted from Table 2-2, Response to FDA Information Request 6, submitted 8/6/10.

6.7.4 Summary of SEGA responses (volumetric reduction) to everolimus treatment

Although there is no correlation of the percentage in volumetric reduction of the SEGA to the clinical outcome, we used a 50% volume reduction as the threshold for SEGA response based on the following:

a. There was a high concordance between IR and LR readings when 50% was used as the threshold

b. SEGAs showing 50% volume reduction at 6 months also demonstrated either PR or SD or NC according to RECIST and WHO criteria

c. The applicant's confirmation trial, M2301, uses 50% SEGA volume reduction at 6 months as primary endpoint

Using this response criteria, 9 patients (#s 1, 4, 7, 11, 13, 25, 26, 27, and 28) out of 28 (32%, 95% CI: 16% - 52%) had a ≥ 50% reduction in the tumor volume of their largest SEGA lesion at 6 months. One of 4 patients who had prior surgery experienced a 58% reduction in the tumor volume of their largest SEGA lesion at month 6 (# 13); 2 additional patients had a volumetric reduction of ≥ 50% on subsequent scans beyond month 6 (#s 12 and 15). No patient developed new lesions.

6.7.5 Durability of response of primary tumor

All patients enrolled in C2485 were reported by the applicant as experiencing some degree of response to treatment with everolimus at 6 months as described in the previous section.

Based upon data provided at the 90-day update, 19 patients experienced a tumor volume reduction of > 50% at some point during therapy. The eligibility of three of these patients (#25, #27 and #28) was questionable as discussed in section 6.1.2 and Table 13*. Removing these three patients from analysis did not alter our results. Additionally, only 15 patients had response of > 50% by local review. This excluded patients #7, #17, #22 and #25 who were not considered > 50% responders by local review.*

For the patients with a documented response of > 50% mean time to response was 243 days (SD = 200 days) with a median of 118 days (82, 565). The mean duration of response (patients censored at time of last available scan documenting a response of > 50%) for the responders was 297 days (SD = 300) with a median of 183 (0, 945). Patients 9, 10, 20, 22 and 23 each had only a single documented scan with > 50% volume reduction in primary SEGA lesion per independent radiologist review. The duration of response for these patients was censored to be 0. Additionally, for patients with mild fluctuations in scan results below 50% response, the date of the final scan documenting >50% response was used as date of censoring. (Table 22).

Evaluating the last available scan on each patient reveals that 16 (57%) of the patients demonstrated a tumor re-growth of ≥ 5% compared to the best documented response to therapy. This included 13 (54%) of the 24 patients who had a best documented response of greater than 30% and 9 out of the 19 (47%) patients with a previous response of > 50%. Two (3.6%) patients, #13 and #18, had a growth of the primary tumor to levels higher than documented at baseline as assessed by independent radiology. Local radiology review however also considered patient #14 as having progressed at the time of last scan in addition to patients # 13 and 18. Patient # 18 however responded to further therapy with everolimus with decrease in tumor size at time of last scan. Additionally, patient #11 had a response of >75% based on LR at 18

months (day 554) and was removed from study. This patient's tumor re-grew by day 694 and therapy had to be resumed with good response.

These findings are summarized in Table 23.

Table 22 Duration of Response in Patients with >50% Volume Reduction in Primary SEGA

Pt #	1st Response		Last Response			Loss of response		
	Day	%	Day	%	Duration	Day	%	Duration
1	95	51	1040	69	945	-	-	-
3	82	52	733	57	651	914	38%	832
4	101	59	906	50	805	-	-	-
7	92	53	738	51	646	-	-	-
9	84	53	-	-	0	208	36	124
10	400	64	-	-	0	554	18	154
11	195	65	813	55	618	694	29%	-
12	537	53	726	55	189	-	-	-
13	182	58	349	57	167	545	19	363
15	565	63	733	67	168	-	-	-
17	502	55	685	51	183	-	-	-
19	84	57	560	54	476	-	-	-
20	561	58	-	-	0	-	-	-
22	118	56	-	-	0	194	46	76
23	561	67	-	-	0	-	-	-
25	105	60	356	61	251	-	-	-
26	91	65	187	56	96	385	5	294
27	90	68	355	70	265	-	-	-
28	180	51	356	62	176	-	-	-

Table 23 Durability of Response to everolimus in C2485

Pt #	Baseline volume (cm^3)	Best response				Final			
		Volume (cm^3)	Response		Day	Volume (cm^3)	Response		Day
1	5.82	1.83	3.99	69%	1040	1.83	3.99	69%	1040
2	0.68	0.58	0.1	15%	135	0.58	0.1	15%	135
3	1.68	0.62	1.06	63%	355	0.97	0.71	42%	1090
4	2.95	1.07	1.88	64%	199	1.48	1.47	50%*	906
5	0.49	0.33	0.16	33%	544	0.40	0.09	18%	915
6	0.66	0.34	0.32	48%	179	0.47	0.19	29%	923
7	7.45	2.96	4.49	60%	170	3.66	3.79	51%	738
8	2.90	1.46	1.44	50%*	357	2.33	0.57	20%	531
9	0.86	0.40	0.46	53%	84	0.61	0.25	29%	545
10	0.80	0.29	0.51	64%	400	0.42	0.38	48%	729
11	1.85	0.47	1.38	75%	554	0.83	1.02	55%	813
12	4.39	1.96	2.43	55%	726	1.96	2.43	55%	726
13	1.54	0.65	0.89	58%	182	2.09	-0.55	-36%	733
14	0.54	0.35	0.19	35%	180	0.42	0.12	22%	643
15	14.23	4.63	9.60	67%	733	4.63	9.60	67%	733
16	0.76	0.47	0.29	38%	364	0.50	0.26	34%	735
17	2.27	1.02	1.25	55%	502	1.11	1.16	51%	685
18	1.52	1.25	0.27	18%	194	1.37	0.15	10%	728
19	1.69	0.73	0.96	57%	84	0.78	0.91	54%	560
20	1.79	0.76	1.03	58%	561	0.76	1.03	58%	561
21	0.98	0.71	0.27	28%	195	0.82	0.16	16%	554
22	0.57	0.25	0.32	56%	118	0.36	0.21	37%	538
23	2.77	0.92	1.85	67%	561	0.92	1.85	67%	561
24	2.03	1.47	0.56	28%	194	1.82	0.21	10%	413
25	2.18	0.86	1.32	61%	356	0.86	1.32	61%	356
26	0.85	0.30	0.55	65%	91	0.81	0.04	5%	385
27	2.20	0.67	1.53	70%	355	0.67	1.53	70%	355
28	2.26	0.86	1.4	62%	356	0.86	1.4	62%	356

** Result rounded up: patient not considered a responder.*
Patients who were considered responders are listed in red.

The mean final documented primary SEGA volume in C2485 was 1.23 cm^3 (SD=1.00) with a median of 0.85 cm^3 (0.36, 4.63). When compared to the results at 6 months, most patients continue to respond with further volumetric reduction. Some patients however have eventual regrowth despite continued therapy after experiencing BOR. Seven of the patients who had a BOR of ≥ 50% had a decrease in their volumetric reduction to < 50% by the data cutoff. Nonetheless, most patients continue to have an improvement when compared to baseline values, especially for those patients who had larger volume of primary SEGA (Table 15 *and* Table 23).
In summary, duration of response for 9 patients whose primary SEGA lesion showed >50% volume reduction ranged from 97 to 946 days with a median of 266 days. Seven of these 9 patients had an ongoing volumetric reduction of ≥ 50% at the data cutoff.

6.8 Analysis of Secondary Endpoints

6.8.1 Change from baseline in volume of primary SEGA lesion at 6 months (as determined by local radiology review)

The mean primary SEGA tumor volume at baseline as assessed by local radiology review (LR) was 2.25 cm^3 (SD=1.66) with a median of 2.00 (0.35, 7.10). LR review of scans at 6 months of therapy showed a mean primary SEGA volume of 1.34 cm3 (S=1.01) with a median of 0.96 (0.19, 3.40).

Reviewer's note: The mean primary target volume at 6 months as presented in the CSR is 1.24 (SD=0.897). This discrepancy is due to the 6 month evaluations of patients number 2 and 14. The values used by the applicant for this evaluation were based on scans done on day 68 (pt #2) and day 280 (pt #14). The values used in We's analyses were based on scans on day 135 and 180 respectively.

The mean change in volume (Full Analysis Set) at 6 months for primary tumor based on LR was 1.01 cm3 (1.04) with a median of 0.92 (0.02, 4.80). These values were identical regardless of which 6 months scan sets are used. Further comparison between the results of IR and LR data sets are discussed in section 6.7.2 Concordance of independent review and local review.

Reviewer's note: Analysis of 90-day update data did not affect the results of response at month 6 based on local review. When evaluating long-term outcome as assessed by local review, however, patients #13, 14 and 18 had shown evidence of increase beyond baseline tumor volume. This assessment is consistent with the results of independent review that also suggested that patients #13 and 18 had both showed evidence of tumor growth beyond size at baseline. Patient #14 was also assessed as having evidence of growth by independent review although not in excess of baseline size. It does need to be mentioned that the primary lesion in patient # 14 was smaller than 1 cm^3 and significant inter-observer discrepancies had been noted in these lesions based on previous assessment. Regardless, these results do not disagree with or alter the risk to benefit ratio as assessed by independent review above.

Table 24 Primary Tumor Response Based on Local Radiology Review at 6 Months

Pt #	Baseline 1° SEGA Volume (cm^3)	6 Month 1° SEGA Volume (cm^3)	Change in SEGA Volume (cm^3)	
1	7.10	2.30	4.8	68%
2	0.67	0.43	0.24	36%
3	2.30	1.10	1.2	52%
4	3.40	1.30	2.1	62%
5	0.67	0.46	0.21	31%
6	0.95	0.76	0.19	20%
7	6.60	3.40	3.2	48%
8	3.10	3.00	0.1	3%
9	1.10	0.28	0.82	75%
10	1.40	0.68	0.72	51%
11	1.80	0.86	0.94	52%
12	3.80	2.30	1.5	39%
13	1.50	0.61	0.89	59%
14	0.56	0.51	0.05	9%
15	3.40	3.30	0.1	3%
16	0.90	0.72	0.18	20%
17	2.70	1.40	1.3	48%
18	1.20	1.10	0.1	8%
19	2.20	1.00	1.2	55%
20	1.80	0.86	0.94	52%
21	0.35	0.19	0.16	46%
22	0.38	0.36	0.02	5%
23	3.00	1.70	1.3	43%
24	2.60	1.40	1.2	46%
25	3.30	1.70	1.6	48%
26	1.10	0.50	0.6	55%
27	2.30	0.92	1.38	60%
28	2.80	1.60	1.2	43%

2. Change from baseline in overall volume of SEGA lesions at 6 months (as determined by independent radiology and local review)

Based on the review by the independent radiologist, 13 (46%) of the patients on this study had a secondary SEGA lesion. Only 3 (11%) patients had a secondary lesion >1 cm^3 in size. At the 6 month time point only 1 (4%) patient had a secondary SEGA lesion greater than >1 cm^3 in size. The mean total SEGA volume at 6 months based on IR was 1.45 cm^3 (SD=1.49) with a median of 0.99 (0.34, 7.98). This represented an average decline of 1.27 cm^3 (SD=1.42) with a median of 0.9 (0.07, 6.25) from the baseline values.

Table 25 Tumor Response in Patients with Secondary SEGA Lesions at 6 month by IR

Pt #	Baseline Volume (cm^3)		6 Month Volume (cm^3)		Change in overall SEGA Volume (cm^3)	
	1° SEGA	2° SEGA	1° SEGA	2° SEGA		
2	0.68	0.04	0.58	0.05	0.09	12%
4	2.95	0.34	1.07	0.08	2.14	65%
8	2.90	0.56	2.04	0.36	1.07	31%
9	0.86	0.31	0.55	0.21	0.42	36%
14	0.54	0.06	0.35	0.06	0.2	33%
16	0.76	0.06	0.70	0.06	0.07	8%
20	1.79	0.89	1.18	0.58	0.91	34%
21	0.98	0.22	0.71	0.10	0.39	32%
22	0.57	0.14	0.31	0.04	0.36	51%
24	2.03	1.29	1.47	0.80	1.04	31%
25	2.18	1.48	0.93	0.66	2.07	57%
26	0.85	0.22	0.37	0.13	0.57	53%
28	2.26	1.85	1.11	1.07	1.93	47%

Only 3 of the patients identified by the independent reviewer as having a measureable secondary lesion at baseline were also identified by the local reviewer. Patients # 20 and 24 both had SEGA lesions in excess of 0.5 cm^3 but were not reported by local reviewer as having secondary lesions (Table 26).

Table 26 Patients with Secondary SEGA lesions and 6 Month Response to Therapy Based on LR

Pt #	Baseline Volume (cm^3)		6 Month Volume (cm^3)		Change in overall SEGA Volume (cm^3)	
	1° SEGA	2° SEGA	1° SEGA	2° SEGA		
4	3.40	0.64	1.30	0.22	2.52	62%
25	3.30	2.20	1.70	1.20	2.6	47%
28	2.80	2.60	1.60	1.60	2.2	41%

The mean total SEGA volume based on local radiology review at 6 months was 1.35 cm^3 (SD=1.01) with a median of 0.96 (0.19, 3.40). The mean change in volume was 1.10 (SD=1.12) with a median of 0.92 (0.02, 4.80).

Reviewer's note: Only 4 of the patients with 2 lesions had new scans provided as part of the 90 day update. All patients maintained response beyond the 6 month timeline with out any significant re-growth of the lesions.

Overall, results from LR were consistent with those according to IR.

6.8.2 Seizure frequency

A large percentage of patients with TS suffer from chronic seizure disorders. In order to evaluate effect of treatment with everolimus on seizure frequency in study C2485, 24-hour video-EEGs were performed in all patients with uncontrolled seizures, defined as >1 seizure/month at baseline. According to the protocol, video EEGs were performed

using the "10/20 international system of electrode placement." EEG/video monitoring was to be performed at baseline and then again at end of core treatment phase of 6 months. Both bipolar and referential montages were to be reviewed. In addition "Interictal EEG segments and all ictal EEG and video segments" were to be "analyzed by a trained epileptologist." EEG data was to be quantified regarding absolute frequency of epileptiform events and characterized with regard to character and type of epileptiform abnormalities.

Data from 24-hour video-EEG studies performed on 18 patients were provided. All except patient #2 who was withdrawn from study at day 135 had a follow up study. In one patient, patient #3, baseline study was <18 hours (17.7) long and hence not considered adequate by the applicant. Baseline study was on average performed 3 days (SD = 5) prior to start of therapy with a median of 1 day prior (0, 20). Follow up study was on average performed 196 days (SD = 33) into study with a median of 188 days (168, 285). Table 27 summarizes the breakdown of seizure subtypes and response as documented on 24-hour video-EEG.

Reviewer's note: Patients 1, 2, 9, 11, 18 and 27 did not meet criteria of >1 seizure per month as specified by protocol based on caregiver reports at baseline.

Table 27 Response to Everolimus as Documented on Video EEG

	Baseline			6 month			Change		
	n	Mean	Median	n	Mean	Median	n	Mean	Median
Total # of Seizures (per 24 hours)									
Partial and Generalized	17	6.30 (7.88)	1.00 (0.0, 25.0)	17	2.75 (8.65)	0.00 (0.0, 35.8)	16	-2.65 (6.09)	-0.99 (-17.0, 10.8)
Clinical seizures (per 24 hours)									
Partial	17	0.53 (1.07)	0.00 (0.0, 3.0)	17	0.11 (0.32)	0.00 (0.0, 1.0)	16	-0.44 (0.97)	0.00 (-3.0, 0.0)
Generalized	17	1.53 (5.36)	0.00 (0.0, 22.0)	17 (1)	2.10	0.00 (0.0, 35.8)	16	0.61 (3.65)	0.00 (-4.0, 13.8)
Subclinical seizures (per 24 hours)									
Partial	17	3.48 (5.37)	0.98 (0.0, 18.0)	17	0.53 (1.58)	0.00 (0.0, 6.0)	16	-2.01 (2.99)	-0.49 (-10.0, 0.0)
Generalized	17	0.76 (3.15)	0.00 (0.0, 13.0)	17	0.00 (0.00)	0.00 (0.0, 0.0)	16	-0.81 (3.25)	0.00 (-13.0, 0.0)
Interictal epileptiform abnormalities									
Awake (1st 15 min)	18	9.33 (16.54)	0.00 (0.0, 66.0)	17	8.47 (22.34)	0.00 (0.0, 96.0)	17	0.35 (30.28)	0.00 (-66.0, 96.0)
Stg-II Sleep (1st 15 min)	18	117.33 (149.55)	59.50 (3.0, 632.0)	17	102.35 (143.90)	36.00 (0.0, 494.0)	17	-20.65 (85.47)	-20.0 (-227, 201)

Reviewer's note: It is important to note that the only category of seizures that had a statistically significant improvement at month 6 was the overall # of seizures. This was based on before and after EEGs on 16 (57%) patients, only 12 (43%) of whom had seizures documented on their baseline video-EEG. The number of patients with each seizure subtype at baseline and 6 months is summarized in Table 28. The interictal abnormalities were not counted as part of total seizure number.

Table 28 Number of patients with evidence of improvement on video-EEG

	Baseline (n=16)	**6 Months (n=16)**
Clinical seizures		
Partial	4 (25%)	2 (13%)
Generalized	2 (13%)	1 (6%)
Subclinical seizures		
Partial	8 (50%)	2 (13%)
Generalized	1 (6%)	0
Total seizures	11 (69%)	5 (31%)
Interictal epileptiform abnormalities		
Awake	7 (41%)	7 (41%)
Stage 2 sleep	17 (100%)	14 (88%)

Reviewer's note: Nine (32%) patients showed evidence of improvement in total number of seizures. In 3 of these patients (# 1, 10 and 14) this represented an improvement of a single seizure. In all 3 patients, the patient had a single subclinical, partial seizure that was not seen in follow up. Two (# 27 and 28) of these patients had questionable eligibility at baseline as their tumors appeared to be shrinking in size prior to enrollment. In addition, 6 of these patients appeared to have an escalation in their anti-epileptic meds between the two studies although the applicant states that these patients did not have increases in their blood antiepileptic levels. No data however is provided to support this. These results are summarized Table 29.

One (6%) patient, patients #7, had a worsening of his seizure status after 6 months of everolimus therapy.

Reviewer's note: The 90 day update did not contain any new video EEG data.

Table 29 Patients with improvement in total number of seizures

Pt #	Baseline		6 Months	
	Total Seizure #	AEDs	Total Seizure #	AEDs
1	1	Clonazepam 0.5 mg Oxcarbazepine 900 mg	0	Clonazepam 1 mg Oxcarbazepine 1500 mg
8	13	Topiramate 350 mg Zonisamide 200 mg	1	Topiramate 350 mg Zonisamide 800 mg
9	7	Lamotrigine 75 mg	3	Lamotrigine 100 mg
10	1	Diazepam 15 mg Levetiracetam 1000 mg Lamotrigine 175 mg Topiramate 100 mg	0	Diazepam 17.5 mg Levetiracetam 1000 mg Lamotrigine 200 mg Topiramate 100 mg
11	5	Diazepam 15 mg Lamotrigine 200 mg	0	Valproic acid 750 mg Diazepam 17.5 mg Lamotrigine 250 mg
14	1	Clonazepam 0.5 mg Valproic acid 800 mg Diazepam 5 mg	0	Valproic acid 1450 mg Diazepam 5 mg
20	13	Oxcarbazepine 300 mg	6	Oxcarbazepine 300 mg
27	6	Valproic acid 500 mg	0	Valproic acid 500 mg
28	17	Carbamazepine 500 mg Levetiracetam 1000 mg Lamotrigine 300 mg Lorazepam 0.5 mg Topiramate 375 mg	0	Carbamazepine 200 mg Valproic acid 500 mg Lamotrigine 350 mg Lorazepam 0.5 mg

In addition to the 24-hour video-EEG monitoring, the number and frequency of seizures based upon caregiver observation were documented. These results were categorized as summarized in Table 30. There appears to be an increase in number of patients who did not experience a seizure in ≥ 6 months since last seizure or no seizure since last visit with a decrease in proportion of patients who experienced ≥1 seizure per day on everolimus therapy.

Table 30 Frequency of Seizures as Reported by the Caregiver

	Baseline N=26 n (%)	Month 3 N=23 n (%)	Month 6 N=25 n (%)	Month 12 N=25 n (%)	*Month 18 N=21 n (%)*	*Month 24 N=15 n (%)*
≥ 6 months since last seizure or no seizure since last visit	10 (38.5)	10 (43.5)	12 (48.0)	15 (60.0)	*15 (71.4)*	*9 (60.0)*
≥ 1 seizure since last visit but < 1 per month	4 (15.4)	4 (17.4)	4 (16.0)	4 (16.0)	*2 (9.5)*	*1 (6.7)*
≥ 1 seizure per month but < 1 per week	1 (3.8)	4 (17.4)	2 (8.0)	2 (8.0)	*0*	*2 (13.3)*
≥ 1 seizure per week but < 1 per day	4 (15.4)	3 (13.0)	5 (20.0)	3 (12.0)	*3 (14.3)*	*0*
≥ 1 seizure per day	7 (26.9)	2 (8.7)	2 (8.0)	1 (4.0)	*1 (4.8)*	*3 (20.0)*

Data outputs for Months 18 and 24 changed during the 90-day period after the initial cut-off date. Data changes are noted in italicized text.

Assessments were assigned to time windows based on the evaluation date (constructed around the scheduled assessment time)
If 2 assessments were to occur within the same time window, that closest to the scheduled time of assessment was used in the analysis

Adapted from CSR 90 day update, Table 11-9, Page 98.

Reported improvements in seizure frequency for each patient were analyzed. Thirteen of 24 patients with baseline and 6 month reports had an improvement in seizure frequency as summarized in Table 31.

Table 31 Patients with caretaker reported improvement in seizure frequency

Pt#	Baseline Sz Frequency	12 M Seizure Frequency
1	≥1 Sz since last visit but <1/month	≥6M since last Sz or none since last visit
9		
18		
8	≥1 Sz/week but <1 Sz/day	≥1 Sz/month but <1 Sz/week
20		≥1 Sz since last visit but <1/month
10		≥6M since last Sz or none since last visit
26		
14	≥1 Sz/day	≥1 Sz/week but <1 Sz/day
21		
25		
28		≥1 Sz/month but <1 Sz/week
16		≥1 Sz since last visit but <1/month
3		≥6M since last Sz or none since last visit

Reviewer's note: Patient's 1, 8, 9, 10, 20 and 28 had a caregiver reported improvement and an improvement in the 24-hour video-EEG.

Reviewer's note (90 day update):

1. *Only 6 patients (patients 1, 3, 14, 18, 20 and 28) in* Table 31 *did not have a worsening of the seizure frequency noted at 12 months. . Patient's # 14 and 18 both had evidence of progression of their primary SEGA volume on therapy although they maintained their seizure frequency improvement.*

2. *As per Table 30 there was an increase in number of patients with > 1 seizure/day by the 18 and 24 month time points. This is primarily due to data from patients # 7 and 11 each of whom had a one time report of more than 1 seizure/day. No definitive conclusions can be reached from this data due to small sample size.*

3. *DDOP requested consultation from the Division of Neurology Products (DNP) to evaluate above findings. DNP has identified the deficiencies listed below. These deficiencies make the results of the seizure findings unreliable. Additional studies will need to be performed to definitively assess the effects of everolimus on seizures in the TS patient population.*

    a. *number of patients evaluated is too small*
    b. *Typically, patients must also be shown to have at least 3-4 seizures per month at baseline to demonstrate an efficacious effect in studies of anti-epileptic drugs. In the current study patients with greater than 1 seizure per month at baseline were included and in fact 6 of the patients included did not meet this criterion.*
    c. *Six of the patients appeared to have had some increase in the baseline AEDs and another patient to have had a substitution in the baseline AEDs, and AED levels were not reported*
    d. *There was no control arm which can bias seizure reporting by caregivers.*

6.8.3 Quality of Life

The Quality of Life in Epilepsy Patient Inventory (QOLCE questionnaire) was to be completed by all patients or their caregivers at baseline, at the 3 month and at the 6 month visit. Twenty six patients completed this questionnaire at baseline and 6 months while only 25 completed it at 3 months. The overall quality of life score was associated with an improvement over time. Additionally, there was an improvement in the 'stigmata item' over time. An apparent improvement in 'social interactions' and decrease in 'memory' was noted. Both changes were <10%.

6.8.4 Neuropsychological assessments

Neurological and cognitive effects were assessed using a battery of tests administered by a trained neuropsychologist at baseline and then again at the 6 month visit. This battery of tests consisted of WPPSI-III (core subtests), Bracken Preschool Screening, Beery VMI, NEPSY Phonological Processing, NEPSY Arrows, Purdue Pegboard Test, Grooved Pegboard Test, BASC Parent, BRIEF Parent, WISC-IV, WRAT-III, JLO, Conners CPT, WCST, WAISIII, SCL-90, and the Frontal Systems Behavior Scale.

Four patients were cognitively and behaviorally impaired to such an extent that standardized assessment was not possible. Testing was performed for the remaining 24 patients. No deleterious effects were observed in any of the neuropsychological or intelligence measures. Specifically no changes were observed in the 'Behavioral adjustment', 'Intelligence', 'Academic achievement' or 'Visual spatial and visual motor integration' categories based on the sponsor's analysis.

Reviewer's note: DDOP requested a consultation from the DNP to evaluate above data. DNP offered the following interpretation of this data:

'With regard to the use of Quality of Life assessments and neuropsychometric testing, it is usually not possible to use these measures as efficacy measures although they can offer safety information. Quality of Life assessments have been used in epilepsy studies as a safety measure but never as an efficacy measure. A fundamental problem is that these tests are not normed for special populations such as the tuberous sclerosis population where many if not most of the patients have significant cognitive and behavioral impairments at baseline that interfere with the administration and interpretation of the testing. It is not clear how sensitive or insensitive the scales used would be for the positive or negative changes effected by the treatment.

In summary, the Quality of Life assessments and neuropsychometric testing provide some reassurance with regard to safety but have no efficacy endpoint value.

6.9 Subpopulations

Due to the small sample size of this study, lack of a definitive definition for response and the variable length of exposure to the drugs, the following subpopulation analyses remain exploratory and no conclusions could be made as to whether there was a difference in response in each subpopulation analyzed.

6.9.1 Age

Table 32 Response of Primary SEGA Lesion at 6 months Grouped by Age

Age (years)	3 - <12	12 - <18	≥18
Volumetric Response in cm^3			
Mean (SD)	0.49 (0.383)	1.78 (1.454)	2.28 (2.224)
Median	0.31	1.53	1.21
Range	0.06-1.25	0.32-4.49	0.56-6.25
Percentage reduction from baseline, n (%)			
≥ 50%	4 (25)	3 (50)	2 (33)
≥ 30%	11 (69)	6 (100)	4 (67)
≥ 0%	16 (100)	6 (100)	6 (100)

6.9.2 Gender

Table 33 Response of Primary SEGA Lesion to at 6 Months Grouped by Gender

Gender	Male (n=17)	Female (n=11)
Volumetric Response in cm^3		
Mean (SD)	1.29 (1.641)	0.93 (1.026)
Median	0.83	0.48
Range	0.06-6.25	0.10-3.59
Percentage reduction from baseline, n (%)		
≥ 50%	5 (29)	4 (36)
≥ 30%	13 (77)	8 (73)
≥ 0%	17 (100.0)	11 (100.0)

6.9.3 Race

Majority of patients on this study were Caucasian with only 2 patients listed as Black and 2 as "other" race. No further detail was provided on race of two patients listed as other by sponsor. One patient, patient #2, withdrew from study at 4.7 months. She was listed under race category of "other". Only 1 patient (# 19) with race listed as "other" experienced a response of >50% by 6 months while one patient (# 20) with race listed as Black had a best overall response of > 50%. Both patients retained the response at time of last scan. Small sample size precludes any other conclusions regarding this subgroup.

6.10 Analysis of Clinical Information Relevant to Dosing Recommendations

In this study everolimus was administered at a starting dose of 3 mg/m^2/day or every other day with titration to achieve trough serum levels of 5-15 ng/ml. Dosing was monitored and adjusted during the core 6 month and the extension phase. The targeted therapeutic levels in this study were based upon empirical observations made with use of sirolimus in the treatment of SEGA.

There is evidence of an exposure response relationship for efficacy in this study. Analysis of the data on the 28 patients in this study demonstrated an increased response with increased average C_{min} with no additional benefit at C_{min} ≥3 ng/ml. No dose response relationship for safety however could be demonstrated. The relationship of serum everolimus levels to adverse events is further discussed in 7.5.1 Dose Dependency for Adverse Events.

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

Table 34 Dosing Regimen Proposed by the Applicant

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

Reviewer's note: The applicant's proposed dosing regimen appears acceptable. Refer to Clinical Pharmacology review for details.

6.11 Discussion of Persistence of Efficacy and/or Tolerance Effects

All patients enrolled in C2485 were reported by the applicant as experiencing some degree of response to treatment with everolimus at 6 months as described in the previous sections. Based upon data provided at the 90 day update 19 patients experienced a tumor volume reduction of >50% during therapy. The eligibility of three of these patients (#25, 27 and 28) was questionable as discussed in section 6.1.2 and Table 13*. Sensitivity analysis by removing these patients did not alter the overall results. For patients with a documented response of >50% mean time to response was 243 days (SD = 200 days) with a median of 118 days (82, 565). The mean duration of response (patients censored at time of last available scan documenting a response of > 50%) for the responders was 297 days (SD = 300) with a median of 183 (0, 945). Patients 9, 10, 20, 22 and 23 each had only a single documented scan with > 50% volume reduction in primary SEGA lesion per independent radiologist review. The duration of response for these patients was considered to be 0 during the analysis. Additionally, patients with mild fluctuations in scan results below 50% response were censored at the date of the final scan documenting >50% response* (Table 22)*.*

Evaluating the last available scan on each patient reveals that 16 (57%) of the patients demonstrated a tumor re-growth of ≥5% compared to the best documented response to therapy. This increase was seen in 13 of the 24 patients (54%) who had a best documented response of > 30% and 9 out of the 19 patients (47%) with a previous response of > 50%. Two (7%) patients, #13 and #18, had a growth of the primary tumor to levels higher than documented at baseline as assessed by independent radiology. Local radiology review however also considered patient #14 as having progressed at time of last scan in addition to patients # 13 and 18. Patient # 18 however responded to further therapy with everolimus with decrease in tumor size at time of last scan. Additionally, patient #11 had a response of >75% based on LR at 18 months (day 554) and was removed from study. This patient's tumor re-grew by day 694 and therapy had to be resumed with good response (Table 23).

6.12 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety review included a review of the data submitted in the 90-day update (the data cutoff as of 08-Mar-2010) to study 2845. This was agreed upon by the FDA during the pre-sNDA meeting.

Safety Summary

Everolimus is approved in the US and several other countries for the treatment of advanced RCC and also for prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant. With the current supplement, the applicant is seeking accelerated approval for the indication of treating patients with SEGA in the setting of TS. This indication differs from previous indications by primarily affecting a pediatric patient population. The safety review of this supplement primarily consisted of review of the data from study C2485. Twenty two (79%) of these patients were between the ages of 3 and 18 years. Only 5 (18%) patients had received previous therapy for their SEGA including 4 who had a surgical resection with subsequent tumor re-growth.

A confirmatory randomized, double blind, placebo-controlled study, M2301, is currently ongoing and has recently finished enrollment. Blinded tabulations of serious adverse events (SAEs) reported on these studies were submitted as part of this sNDA. Additionally, safety data from the primary study in pediatric renal transplant, B351, were submitted. Studies M2301 and M2302 are expected to enroll 99 patients each in a 2 to 1 randomization while B351 enrolled 37 patients (Table 1).

In study C2485 the starting dose of everolimus was at 3.0 mg/m^2/day titrated to maintain a serum drug level of 5-15 ng/ml. Therapy modifications for toxicity included temporary interruption and or dose reductions. Twenty-five patients (89%) on this study experienced either a dose reduction or a dose interruption while on study with 22 patients (79%) having an adverse event (AE) as the underlying cause. Three (11%) patients withdrew from this study and although all cited toxicity as part of their reason for withdrawal, none were discontinued due to an adverse event. All patients on this study had ≥ 1 adverse event although only 10 patients (36%) had a grade 3 adverse event and 1 patient a single grade 4 event. There were no deaths on this study and only 4 (14%) of patients experienced an SAE.

The main safety findings on this study are:

Infections: Twenty-five (89%) patients enrolled on C2485 were reported to have an infectious AE. This was further complicated by the immunosuppressive effects of everolimus including the presence of leucopenia in more than 50% of patients. More than 80% of the patients on C2485 were reported to have an “upper respiratory infection” with more than 30% who developed “sinusitis” and/or “otitis media”. The majority of these events, however, were grade 1 or grade 2 events and were treated on an outpatient basis. There were reports of patients with pneumonia both in the SEGA

population and in the solid organ transplant population although it was difficult to distinguish the pulmonary symptoms from the non-infectious pneumonitis that is known to be associated with mTOR inhibitors.

Stomatitis: More than 80% of the patients on study C2485 were reported to have an episode of stomatitis. All of these patients were grade 1 or 2 episodes with the exception of 1 grade 3 event. This is a well known side effect of everolimus and other mTOR inhibitors that may be of extra concern in pediatric age patients due to potential effects on food intake.

Non-infectious pneumonitis: Non-infectious pneumonitis has been reported in up to 14% of patients with RCC who were treated with everolimus. Although no patients on C2485 were reported to experience pneumonitis, there were reports of infectious lower respiratory processes that necessitated treatment stoppage. The occurrence of pulmonary symptoms needs to be closely monitored in patients treated with everolimus.

Endocrine and metabolism: The occurrence of triglyceride, cholesterol and glucose abnormalities in patients treated with mTOR inhibitors is well documented. This often requires treatment with concomitant medications. This is particularly concerning as cases of new onset diabetes mellitus have been reported in association with everolimus therapy including one patient on C2485. The development of these abnormalities in pediatric age patients with an anticipated prolonged survival is concerning and needs to be closely monitored.

Neuropsychological development: Patients with TS have baseline cognitive neurological and cognitive abnormalities. There have been reports of psychiatric and behavorial changes in association with everolimus. Additionally, there have been reports of developmental delays in juvenile preclinical studies. The neuropsychological tests performed in the small patient population on C2485 did not reveal any safety concerns. This issue however must be evaluated in more detail in a randomized fashion.

Physical development: The effects of prolonged therapy with mTOR inhibitors on physical growth and maturation of pediatric patients is undefined. No evidence of adverse effects on growth were noted on C2485, although the data were not collected systemically to evaluate the growth. This is particularly concerning as cases of low testosterone concentrations associated with high levels of follicle-stimulating hormone have been reported in association with everolimus in other trials. No evidence of hypogonadism in this SEGA patient population was noted but no specific evaluations were conducted. Formal testing of effects on height, weight, tanner stage and other developmental parameters needs to be performed for patients with expected prolonged life expectancy and need for therapy with everolimus.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The current application is intended for the treatment of SEGA in the setting of TS. This indication is primarily in pediatric patients. The primary source of safety data in this patient population was generated is the single-arm, single-institution study, C2485. The Full Analysis Set (FAS) of C2485 was used to generate the primary safety data for this supplemental NDA. The safety assessment schedule is summarized in Table 2 and Table 3. The occurrence of treatment-emergent adverse events (TEAEs) including serious adverse events (SAEs) were monitored by "non-directive questioning of the patients and their parents/legal guardian at each clinic visit" and then recorded. In addition TEAEs volunteered by patients/care givers or "detected by physical examination, laboratory test results" and "other safety assessments" were documented.

A waiver was sought by the applicant and granted by the FDA for an integrated summary of safety (ISS) at the time of the pre-NDA meeting. However, FDA requested that the safety data from C2485 be supplemented with the following:

- Long-term pediatric data from a phase-III trial in *de novo* renal transplant recipients (B351). Data sets and CSRs are not provided from B351.
- Line listings of all SAEs reported on ongoing oncology studies collected between 8/16/08 and 2/26/10
- Blinded tabular summary of SAEs from randomized study of everolimus for SEGA in the setting of TS (M2301) using cut-off of 4/12/10
- Blinded tabular summary of SAEs from randomized study of everolimus for angiomyolipomas in setting of TS (M2302) using cut-off date of 4/12/10

Reviewer's note: Study B351 was an international, multicenter, open-label, single-arm trial. Patients received everolimus at a fixed dose of 0.8 mg/m^2 (max dose 1.5 mg) BID in combination with cyclosporine and corticosteroids in pediatric (≤ 16 years) de novo renal transplant recipients. Nineteen patients were treated (Cohort 1) before this study was amended to lower cyclosporine doses due to concerns regarding renal toxicity of the combination. Subsequent to this amendment, 18 patients (Cohort 2) were enrolled on the study. In Cohort 2 everolimus trough concentrations of ≥ 3 ng/ml were targeted.

Data from single-dose PK studies conducted in pediatric transplant recipients (B257 and B258) were not provided.

7.1.2 Categorization of Adverse Events

All AEs were captured and reported for patients enrolled on C2485 as long as they occurred between the day of start of therapy and day 28 after cessation of therapy. For study B351 AEs were collected up to 7 days after everolimus cessation. Additionally, AEs on C2485 were graded using CTCAE criteria while events on B351 were graded as mild, moderate or severe. AEs were then reported and coded using MedDRA version 12.0.
SAEs were identified using standard criteria:

- Death

- Life-threatening event
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Cancer (applicable to Study C2485)
- Drug overdose (applicable to Study C2485)

In C2485 SAEs occurring > 4 weeks after study discontinuation were only reported if a relationship to the everolimus was suspected. Adverse events, whether serious or non-serious, were to be followed until resolution regardless of whether the subjects were still participating in the study.

Reviewer's note: *The use of NCI CTCAE to grade adverse events was only implemented at the time of amendment # 2 for C2845 (5/17/07). It is unclear how adverse events were graded prior to this amendment to the study. Five patients (18%) had been enrolled at the time of this amendment. None of these patients had been enrolled for more than 4 months. Although the protocol did not state which version of the NCI CTCAE criteria was used, the audit documentation submitted by the applicant stated that NCI CTCAE version 3.0 was utilized.*

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

No pooling of data was performed.

7.2 Adequacy of Safety Assessments

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

In this study everolimus was administered at a starting dose of 3 mg/m^2/day or every other day with titration to achieve trough serum everolimus levels of 5-15 ng/ml. Patients unable to tolerate their 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 levels. Dosing was monitored and adjusted during the core 6 month and the extension phase.

Reviewer's note:

1. *This study was amended on 6/17/08 (amendment #4) to change the target therapeutic level from 10-15 ng/ml to 5-15 ng/ml.*
2. *This study was originally designed for a total treatment period of 6 months. If a subject missed more than 10 consecutive everolimus doses additional replacement days of everolimus therapy where added at the end. The study was later amended (amendment #4) to include an extension phase following the 6*

month core therapy phase. Patients will remain on study indefinitely as long as they continue to respond to therapy.

All patients enrolled on study received everolimus therapy. Seventeen (61%) patients received therapy for a period longer than 21 months. Total patient-year exposure for this study was 55.2 patient-years. Further details regarding the patient's calculated everolimus exposure can be found in Table 35.

Table 35 Exposure to everolimus on C2485

	Duration of exposure (months)	Cumulative dose (mg/m^2)	Dose intensity (mg/m^2/day)
Mean (SD)	23.6 (7.64)	3735.4 (2049.08)	5.18 (2.207)
Median	24.4	3349.4	5.31
Range	(4.7, 37.3)	(597.4, 9085.8)	(1.8, 12.2)

The median daily dose of everolimus was 4.66 mg/m^2 (0.0 to 7.8) at 3 months and 5.63 mg/m^2 (1.5 to 10.5) at 6 months. For details of therapeutic drug levels please see clinical pharmacology review.
Reviewer's note: There were a total of 37 patients enrolled on B351. These patients were between 1 and 16 years of age. Twenty-two (59%) of these patients were male and 15 (41%) female. Three (8%) were categorized as "Black", 2 (5%) as "Oriental" and 9 (24%) as other. The remaining 23 (62%) patients were Caucasian. Patients on B351 had duration of exposure ranging from 0.1 to 66.2 months when combining both cohorts. Even though patients on B351 received lower doses than the SEGA patients, potentiation due to cyclosporine effects raised their trough everolimus levels to levels equivalent to the SEGA patients.

Discontinuations

Patients were allowed to discontinue therapy if they had a documented reduction of ≥ 75% in the volume of their primary SEGA. Alternatively if a patient did not experience any response after 6 months of everolimus therapy with adequate therapeutic levels, they were removed from study.

Reviewer's note: One patient, #11, achieved a response of 75% by local review and was subsequently removed from study. This patient however experienced re-growth of his primary SEGA lesion and therapy was resumed. This patient is further discussed in 6.6 Subject Disposition.

Discontinuations were also allowed due to adverse events. Reason listed for dose discontinuation in the protocol included

1. Serious infections
2. Interstitial pneumonitis.
3. Significant hematologic abnormality
   - Hct < 20%

- ANC < 500
- WBC < 1,000
- Plts < 40,000

Overall 3 patients had everolimus therapy discontinued for reasons other than efficacy. This included patients #2, 8 and 9. Although none of the discontinuations were directly due to a single occurrence of an adverse event, the verbatim reports of reason for withdrawal referenced adverse events in all of these patients. Specifically, patient #8 cited "increased infections" while patient #9 cited multiple episodes of stomatitis as reasons for withdrawal of consent.
These are discussed in more detail in 6.6 Subject Disposition.

Reviewer's note: Nine (24%) patients on B351 discontinued therapy. Four of these patients withdrew from study due to adverse events. Seven adverse events were noted as contributing to discontinuation of therapy. These included 1 report each of Postoperative complications NOS, Procedural pain, Epstein-Barr virus infection, Blood creatinine increased, Generalized edema, Dehydration and Lymphoproliferative disorder. These AEs all are distinctive for routinely happening in renal transplant populations. Only AE of concern for this supplement is the presence of the single patient with post-transplant lymphoproliferative disease. This topic will be reviewed separately and is thought to reflect the effect of cyclosporine rather than everolimus. Regardless appropriate safety measures including close surveillance are essential for patients receiving everolimus monotherapy.

Dose reductions/interruptions

In addition to the patients who withdrew from study, 23 patients (82%) had at least one temporary dose interruption. Twenty one (75%) of these patients had more than one interruption with median of 3 (Range: 1, 25) and mean of 5.4 (SD = 5.6) interruptions. The mean total days of therapy interruption was 45.4 days (SD = 69.4) with median of 18 days (range: 1, 262).

Most common reason for dose interruptions was adverse events with 22 (79%) of the patients having a dose interruption due to adverse events. In the cohort of patients that experienced an AE associated interruption, the mean number of interruptions was 4.7 (SD=4.1) with a median of 3 (range: 1, 15). Mean length of a dose interruption due to adverse events was 8.8 (SD= 12.2) days with a median of 5 days (range: 0, 74). The median total # of days of dose interruption due to adverse events was 17 days (range: 3, 255).

One patient, #11, had a per protocol dose interruption due to tumor response of >75% as assessed by local review.

Reviewer's note: Subjects #14 and #7 had therapeutic interruptions due to AEs totaling 204 and 255 days respectively. These patients had been on study for 760 and 867 days respectively.

Dose reductions or temporary hold were also permitted in C2485 if a patient experienced “non life-threatening and treatable conditions” such as hyperlipidemia (cholesterol > 200, triglycerides > 400) or hematologic abnormalities (i.e. Hct < 30%, ANC < 1,000, total WBC < 3,000, platelets < 80,000, total WBC <3,000) or metabolic abnormalities (transaminases >3 times normal, serum albumin <3.0 mg/dl). Additionally serum trough levels > 15 ng/ml would prompt a dose reduction.
If everolimus was held less than 7 days or SAE likely unrelated or only possibly related to everolimus, the study drug had to be resumed at 75-100% of previous tolerated dose (or initial dose). For patients in which everolimus was held for greater than 7 days or SAE likely related or definitely related to everolimus, the decision to resume and the rate of adjustments was determined on case by case basis, depending on SAE and patient co morbidities. In general, subject had to resume therapy at 50-75% of previous tolerated dose (or initial dose). Everolimus dose could be increased to previous tolerated dose 2 weeks later, with further dose escalation/adjustment per study protocol.
At the time of data cutoff 19 (68%) patients on study C2485 have experienced at least 1 dose reduction with 14 (50%) experiencing more than 1. The patients who experienced dose reductions on average had 2.5 (SD = 1.4) dose reductions with a median of 2 episodes (range: 1, 6). The most common reason for dose reductions was reported as “per protocol“ by the applicant with 15 (54%) patients experiencing per protocol dose reductions. Twelve (43%) of patients had a dose reduction due to an adverse event. One patient, # 17, had a dose reduction due to a lab abnormality. It is not clear what the lab abnormality was.

Reviewer’s note: Overall 25 (89%) patients had to have a dose interruption or a dose reduction. Twenty-two (79%) patients had dose reductions/interruptions due to adverse events while in 15 (54%) patients these were done per protocol. It is unclear what the per protocol reasons for dose reductions or interruptions were in each case.

A total of 565 AEs were reported in study C2485. One hundred and forty-four (25%) of these AEs led to dose reduction/interruptions in the 22 patients discussed above. In these 22 patients mean number of AEs causing dose reduction/interruption was 6.5 (SD = 5.8) with a median of 5 (range: 1, 23). The AEs causing dose interruptions/reductions in > 1 patient are listed in order of frequency in Table 36*.*

Table 36 Adverse Events Causing Dose Interruption/Reduction in >1 patient on C2485

AE by MedDRA PT	# of patients (n=28)
Upper respiratory tract infection	16 (57%)
Sinusitis	9 (32%)
Otitis media	8 (29%)
Stomatitis	5 (18%)
Cough	4 (14%)
Pyrexia	4 (14%)
Cellulitis	3 (11%)
Diarrhoea	3 (11%)
White blood cell count decreased	3 (11%)
Dermatitis contact	2 (7%)
Gastroenteritis	2 (7%)
Otitis externa	2 (7%)
Personality change	2 (7%)
Pneumonia	2 (7%)
Urinary tract infection	2 (7%)
Vomiting	2 (7%)

AEs leading to dose reductions/interruptions were most commonly seen in the Infections and infestations (20 patients, 71%), Gastrointestinal disorders (9 patients, 32%), General disorders and administration site conditions (6 patients, 21%) Respiratory, thoracic and mediastinal disorders (6 patients, 21%), Psychiatric disorders (4 patients, 14%) and Investigations (4 patients, 14%). System Organ Classifications.

Ninety-nine of these AEs were grade 2 (69%) with 37 (26%) grade 1 and 8 (6%) grade 3. The majority of these AE's (82%) were attributed to the drug.

No data for temporary dose changes from B351 was provided.

Dose increases

Patients on C2485 had a starting everolimus dose of 3 mg/m2/day. Doses were further increased with the goal of achieving a trough serum level of 5-10 ng/ml. All (100%) patients on C2485 had to receive dose increases with 25 (89%) patients having more than one dose increase. The reason for dose increases in 27 (96%) patients was reported as per protocol.

Demographics

The small size of Study C2485 limits any accurate subgroup analysis of patients enrolled. Table 37, Table 38 and Table 39 breakdown the exposure of patients on this study by sex, gender and race.

Table 37 Exposure to everolimus on C2485 by gender

	Duration of exposure (months)		Cumulative dose (mg/m^2)		Dose intensity (mg/m^2/day)	
Gender	M (n = 17)	F (n = 11)	M (n = 17)	F (n = 11)	M (n = 17)	F (n = 11)
Mean (SD)	23.5 (7.4)	23.1 (8.0)	4106 (2373)	3163 (1316)	5.7 (2.6)	4.7 (1.6)
Median	23.5	24.2	3628	3242	5.8	4.7
Range	14.5, 36.2	5.1, 37.0	1240, 9086	597, 5021	1.9, 12.4	2.7, 6.9

Table 38 Exposure to everolimus on C2485 by age

	Duration of exposure (months)			Cumulative dose (mg/m^2)		
Age in years	3 to < 12 (n = 16)	12 to 18 (n = 6)	≥ 18 (n = 6)	3 to < 12 (n = 16)	12 to 18 (n = 6)	≥ 18 (n = 6)
Mean (SD)	21.9 (7.4)	29.1 (4.5)	21.4 (8.3)	3963 (2235)	4261 (2100)	2603 (1112)
Median	22.4	27.4	18.0	3519	3534	2671
Range	5.1, 35.9	24.2, 36.2	14.5, 37.0	597, 9086	2451, 6998	1240, 4223

Table 39 Exposure to everolimus on C2485 by race

	Duration of exposure (months)			Cumulative dose (mg/m^2)		
Race	Caucasian (n = 24)	Black (n = 2)	other (n = 2)	Caucasian (n = 24)	Black (n = 2)	other (n = 2)
Mean (SD)	24.5 (7.0)	18.5 (2.2)	14.3 (13.0)	3823 (2082)	4251 (1768)	2172 (2227)
Median	24.1	18.5	14.3	3349	4251	2172
Range	14.5, 37.0	17, 20.1	5.1, 23.5	1241, 9086	3002, 5501	597, 3747

7.2.2 Explorations for Dose Response

There is evidence of an exposure response relationship for efficacy in this study. Analysis of the data on the 28 patients in this study demonstrated an increased response with increased average C_{min} with no additional benefit at C_{min} ≥3 ng/ml. No dose response relationship for safety however could be demonstrated. The relationship of serum everolimus levels to adverse events is further discussed in 7.5.1 Dose Dependency for Adverse Events.

Reviewer's note: The C_{min} of 3 ng/ml is below the lower level of the therapeutic target in this study. This suggests that potentially patients may be able to respond and maintain response at lower doses of everolimus. For further details please see clinical pharmacology review.

7.2.3 Special Animal and/or In Vitro Testing

Juvenile rat and monkey studies were performed to support this supplement. 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.

Reviewer's note: The juvenile studies were considered adequate based on the pharmacological toxicology team evaluation. There have also been reports in literature suggesting some improvement in the learning and behavioral deficits rodent TS models who received m-TOR inhibitors.[xii] There are currently no clinical data available on this subject. For further details please see pharmacological toxicology review.

7.2.4 Routine Clinical Testing

For detailed listing of planned clinical testing please see Table 3.

Additionally serum everolimus levels were followed at every visit and 2 weeks after every dose change.

Reviewer's note: The frequency of the visits, laboratory tests and MRI scans appear to be adequate. Exceptions include:

a) Baseline imaging studies were often performed more than a month prior to patient enrollment on study. Ideally baseline scans should be within 2 weeks of therapy commencement.

b) Repeat EEG testing and neuropsychology monitoring could help document any changes that may occur with prolonged everolimus therapy.

c) There was no attempt to document any therapeutic anti-epileptic drug levels. This has made the assessment of any beneficial effects of everolimus on seizures difficult.

d) There were no attempts to document any changes in the growth and development patterns of patients treated with everolimus.
These should be addressed as part of the confirmatory study, M2301.

7.2.5 Metabolic, Clearance, and Interaction Workup

Reviewer's note: No new data were provided by the applicant.

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, temsirolimus and radeferolimus.

Sirolimus is approved for the prophylaxis of organ rejection in patients aged ≥13 years receiving renal transplants in the US.

- The most common (> 30%) adverse reactions are: peripheral edema, hypertriglyceridemia, hypertension, hypercholesterolemia, creatinine increased, abdominal pain, diarrhea, headache, fever, urinary tract infection, anemia, nausea, arthralgia, pain, and thrombocytopenia.

- There have been reports of activation of latent viral infections, such as BK virus associated-nephropathy and progressive multifocal leukoencephalopathy (PML) in association with sirolimus.

- Interstitial lung disease (ILD) has been reported in association with sirolimus.

Temsirolimus is approved for the treatment of advanced renal cell cancer in the US.

- The most common adverse reactions (incidence ≥ 30%) were rash, asthenia, mucositis, nausea, edema, and anorexia. The most common laboratory abnormalities (incidence ≥ 30%) were anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, elevated alkaline phosphatase, elevated serum creatinine, lymphopenia, hypophosphatemia, thrombocytopenia, elevated AST, and leukopenia.

- The most common grade 3/4 adverse reactions (incidence ≥ 5%) included asthenia, dyspnea, rash, and pain. The most common grade 3/4 laboratory abnormalities (incidence ≥ 5%) included hypertriglyceridemia, anemia, hypophosphatemia, hyperglycemia, lymphopenia, and neutropenia.

- Rare serious adverse reactions associated with temsirolimus included interstitial lung disease, bowel perforation, and acute renal failure.

Radeferolimus remains an experimental agent and the safety profile of this agent has not been fully evaluated.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths on study C2485 or study B351.

7.3.2 Nonfatal Serious Adverse Events

Four (14%) of the patients enrolled on C2485 experienced a non-fatal SAE. One (4%) of these patients experienced >1 SAE while 2 (7%) experienced an SAE that was attributed to everolimus therapy. These are summarized in Table 40.

Narrative summaries:

Patient #2: Patient had seizures on subsequent days (days 64 and 65) of therapy that led to hospital admission. Following her admission for seizure activity patient # 2 (3 year old female) was withdrawn from study by parents (day 135) prior to completion of core 6 month therapy. This was attributed to non-compliance with AEDs and development of hyperkinesis.

Patient #3 (3 year old male) developed a right lower lobe pneumonia unresponsive to oral antibiotics and β_2-agonists on day 733 of therapy. He was discharged from hospital after a 3 day admission on IV antibiotics and temporary cessation of study drug therapy. This was attributed to everolimus and may have been secondary to everolimus associated pneumonitis.

Patient #14 (5 year old male) had an extensive medical history of previous upper respiratory and pulmonary disease. On day 43 of therapy this patient presented with "viral bronchitis" necessitating a 2 day hospital admission. Patient improved on oral antibiotics after stoppage of study therapy which was resumed 2 months later. This presentation may also be consistent with everolimus associated pneumonitis. This patient also had an SAE of severe vomiting leading to hospitalization at day 271. These AEs led to 73 and 14 days of withholding therapy respectively.

Patient #15 had history of multiple SEGA related surgeries and seizures. After having a seizure he responded to antiepileptic therapy. At 35 years of age, he represented the only subject experiencing an SAE that was older than 5 years old. This seizure was not attributed to everolimus therapy.

Reviewer's note: 90-day safety update is included in review of SAEs. There were no new SAEs.

Table 40 Patients Experiencing an SAE on Study C2485

Pt #	Grade	Attribution	SAE	Day of Onset	Length of SAE
2	2	-	Convulsion	65	1
3	3	Yes	Pneumonia	733	20
14	3	Yes	Bronchitis viral	43	14
14	3	-	Vomiting	271	3
15	4	-	Convulsion	651	1

Reviewer's note: In cohort 1 of study B351, 10 (52.6%) of 19 patients at 12 months, 11 (73.3%) of 15 at 36 months and 9 (90%) of 10 at 60 months had experienced an SAE. In cohort 2, 10 (55.6%) of 18 had an SAE by 12 months. Most SAEs in this patient population were related to the underlying disease process such as urinary tract infection and pyelonephritis. Reported SAEs of concern however include pneumonia which was reported in 2 patients at 36 months and then again at 60 months. It is unclear if these events occurred in the same patients or 2 patients at two different time points or 4

patients. Additionally, 1 patient was reported to experience sepsis at month 36 and one patient at month 60. No further data is available on these patients.

In addition to the SAE reports from B351, tabulated, blinded SAE reports from M2301 and M2302 were also provided. These SAEs are tabulated in Table 41*. As these were blinded studies it is unclear if these patients received everolimus or not. The primary SAEs of concern are the episodes of edema or peripheral edema noted in M2302. This however may be related to underlying renal angiomyolipomas. In addition, other patients are noted with bone and joint issues including gout. These numbers however are too small to make any significant conclusions.*

Table 41 SAEs on M2301 and M 2302

Study M2301	
Case number	**MedDRA Preferred Term**
PHHO2009PL12029	Endotracheal intubation
	Laryngeal oedema
PHHO2010PL01927	Pyrexia
	Pharyngitis
	Convulsion
	Neutropenia
	Upper respiratory tract infection
PHHO2010PL03378	Pyrexia
	Infection
	Otitis media
	Convulsion
PHHO2010RU05109	Pyrexia
	Pneumonia
Study M2302	
Case number	**MedDRA Preferred Term**
PHHO2009US15664	Vulvovaginal pruritus
	Vaginal swelling
PHHO2010CA03580	Delusion
	Hallucination
	Psychotic disorder
	Obsessive-compulsive disorder
PHHO2010DE01992	Bone oedema
	Joint stabilisation
	Arthralgia
	Joint effusion
	Deep vein thrombosis
	Complex regional pain syndrome
	Bone disorder
	Osteopenia
PHHO2010DE03404	Oedema
	Renal failure acute
	Hyperkalaemia
PHHO2010US02552	Urine abnormality
	Urine odour abnormal
	Flank pain
	Pollakiuria
	Pyrexia
	Disease progression
	Pyelonephritis
PHHO2010DE06384	Joint effusion
	Oedema peripheral
PHHO2010DE07483	Gout
	Local swelling
	Oedema peripheral

One patient on M2301 developed delusion, hallucination, psychotic disorder and obsessive-compulsive disorder. Five (18%) patients in C2485 were also reported as having personality change. However, due to the limited data that were not collected systemically, no definitive conclusions can be made as to whether everolimus could

cause psychiatric/psychological problems. M2301 and M2302 will provide additional data that are collected systemically to evaluate the actual rate of behavorial and psychiatric changes in the TS population.

7.3.3 Dropouts and/or Discontinuations

Patients # 2, 8 and 9 all withdrew consent from this study. Only 1 (4%) patient, patient # 2, withdrew from study prior to finishing core 6 month phase. None of the withdrawals was due to a single AE although cumulative AEs did contribute to at least 2 of the cases.

Patient #2 was a 3 year old patient whose family elected to withdraw from study due to noncompliance with anti-epileptic medications and worsening hyperkinesis 4.7 months into therapy. Patient was reported as withdrawing due to side effects in CRF.

Reviewer's Note: Patient had 13 reported adverse events while on study. Eight of these AEs were grade 2 and 5 grade 1. Patient did appear to have some neurological side effects such as sleepiness, agitation, irritability and seizures. The seizures were SAEs. It is unclear whether these neurological symptoms/signs were due to AED or the effects from everolimus.

Patients # 8 and 9 withdrew from therapy during the extension phase.
Patient #8 was a 25 year old patient who was on study for 17.5 months but then withdrew due to what appears to have beencumulative adverse events. Specifically, the patient was noted to be noncompliant with antiepileptic medications and experienced a prolonged seizure. At the time of hospital admission patient was also noted to have a pulmonary infiltrate vs. atelectasis. Patient reported withdrawing from study with "hope to reduce incidence of infection".

Reviewer's note: The pulmonary findings in this patient may be attributable to everolimus associated pneumonitis.
Patient had 14 infectious AEs while on study. All were considered grade 2 events.

Patient #9 was a nine year old patient who remained on study for a total of 21.5 months. Parents cited 4 separate episodes of stomatitis as reason for withdrawal of consent.

One additional patient, patient #11, was removed from study after 18 months of therapy according the study protocol (>75% reduction in SEGA volume). Therapy was however resumed after observation of re-growth of tumor 4.5 months after cessation of therapy.

There were no patients who were lost to follow up. All patients who received a dose of therapy were included in efficacy analysis.

Reviewer's note: Number of patients withdrawing from study remained unchanged at the time of 90 day update.

Reviewer's note: Nine (24%) patients on B351 discontinued therapy. Four of these patients withdrew from study due to adverse events. Seven adverse events were noted as contributing to discontinuation of therapy. These included 1 report each of Postoperative complications NOS, Procedural pain, Epstein-Barr virus infection, Blood creatinine increased, Generalized edema, Dehydration and Lymphoproliferative disorder. These AEs all are distinctive for routinely happening in renal transplant populations. Only AE of concern for this supplement is the presence of the single patient with post-transplant lymphoproliferative disease. This topic will be reviewed separately and is thought to reflect the effect of cyclosporine rather than everolimus. Regardless appropriate safety measures including close surveillance are essential for patients receiving everolimus monotherapy.

7.3.4 Significant Adverse Events

Stomatitis

One hundred and seventeen episodes of stomatitis were reported in 24 (86%) patients on study C2485. These patients had a median of 4 (range: 1, 15) episodes per patient with a mean of 4 episodes (SD = 3.9). All events were grade 1 or 2 episodes with the exception of 1 grade 3 event. Median time to first onset of stomatitis/oral mucositis among patients with an event was 39.5 days (range: 6 to 697). Median duration of stomatitis events was 10.5 day (range: 3, 384) with all but 12 cases requiring concomitant treatment. All episodes were reported as resolved with the exception of 9 episodes in 8 patients. Seven of these events were grade 1 with 2 reported as grade 2. Fifteen episodes in 5 (18%) patients (# 5, 7, 9 15 and 18) lead to temporary interruption or dose reduction of everolimus therapy.

Reviewer's note: Patient #18 was reported to have a total of 4 episodes of stomatitis lasting 159 days. This patient also was reported as experiencing possible progression on one set of scans. Additionally patient #9 who experienced 2 episodes of stomatitis over 46 days reported recurrent episodes of stomatitis as a reason for study withdrawal. In addition to the cases reported as stomatitis, 2 patients had reports of 3 episodes of oral/oropharyngeal pain. Both of these patients, #15 and #23, were reported as experiencing grade 1 stomatitis. The reports of stomatitis in this patient population appear to be consistent with the previously reported events in adult studies.

Infections

Twenty-five (89%) patients enrolled on C2485 were reported to have an AE classified in the Infections and infestations MedDRA SOC. A total of 174 infectious AEs were reported in these patients with an average of 6.9 (SD = 5.6) and a median of 4 (range: 1, 20) AEs. There were 15 grade 1, 154 grade 2 and 4 grade 3 AEs. These AEs are summarized in Table 42. Only two of these AEs were considered to be SAEs. These included one episode of pneumonia and one episode of viral bronchitis.

One hundred and forty-three (82%) of these AEs required the administration of a concomitant medication. This included all 4 patients with grade 3, 127 patients with grade 2 and 12 with grade 1 AEs. Seventy-nine of these AEs also required a dose reduction or temporary interruption of everolimus therapy. This included 71 grade 2 in addition to 4 grade 1 and all 4 grade 3 AEs. Although no patient had to be discontinued as a result of a specific AE, patient #8 did state increase in rate of infections as a reason for study withdrawal.

The mean duration of these AEs was 16.6 (SD = 16.7) days with median of 11 (range: 2, 106) days. The median duration of the AE for the patients with grade 1 AEs was 10 (range: 2, 85), for grade two 11 (range: 2, 106) and for grade three, 17 (range: 7, 51) days.

Complete resolution was documented for all but 12 of the reported infectious AEs. Eleven of these AEs were grade 2 and one was a grade 1 AE. This included 3 cases of skin infection, 2 cases each of furuncle, rhinitis and upper respiratory tract infection and 1 each of otitis externa, otitis media and sinusitis.

Reviewer's note: In order to better define the organ systems primarily affected by infectious processes, all infectious AEs were grouped by MedDRA Higher Level Term (HLT). The most common HLTs were upper respiratory tract infections (78, 45%), ear infections (38, 22%), abdominal and gastrointestinal infections (10, 6%), bacterial infections NEC (9, 5%), skin structures and soft tissue infections (9, 5%), lower respiratory tract and lung infections (7, 4%), Tinea infections (6, 3%), eye and eyelid infections (4, 2%) infections NEC (3, 2%), urinary tract infections (3, 2%), viral infections NEC (2, 1%), dental and oral soft tissue infections (1, < 1%), ectoparasitic infestations (1, < 1%), fungal infections NEC (1, < 1%) and Helicobacter infections (1, < 1%).

Table 42 Infections on C2485 by MedDRA PT

AE by MedDRA PT	Grade 1-3 AEs		Grade 3 AEs	
	n=28	%	n=28	%
Upper respiratory tract infection	23	82	0	0
Sinusitis	11	39	1	4
Otitis media	10	36	0	0
Cellulitis	6	21	0	0
Body tinea	5	18	0	0
Gastroenteritis	5	18	0	0
Skin infection	5	18	0	0
Gastric infection	4	14	0	0
Otitis externa	4	14	0	0
Pharyngitis	3	11	0	0
Conjunctivitis infective	2	7	0	0
Furuncle	2	7	0	0
Infection	2	7	0	0
Pneumonia	2	7	1	4
Rhinitis	2	7	0	0
Urinary tract infection	2	7	0	0
Acarodermatitis	1	4	0	0
Bronchitis	1	4	0	0
Bronchitis viral	1	4	1	4
Catheter site cellulitis	1	4	0	0
Eyelid infection	1	4	0	0
Gastroenteritis viral	1	4	0	0
Helicobacter infection	1	4	0	0
Hordeolum	1	4	0	0
Impetigo	1	4	0	0
Laryngitis	1	4	0	0
Lymph gland infection	1	4	0	0
Nasopharyngitis	1	4	0	0
Tooth infection	1	4	1	4
Vulvovaginal mycotic infection	1	4	0	0

Myelosuppression

In order to identify all cases of hematological toxicity that were reported on C2485, We performed a search using the MedDRA “Blood and Lymphatic Disorders” and “Investigations” SOCs.
Five patients had an AE reported that classified under the Blood and Lymphatic Disorders SOC. These included 2 cases of Iron deficiency anemia (# 10 and # 11), 1 case of anemia (# 26), 1 case of “cyclic neutropenia” (# 18) and 1 case of submandibular lymphadenopathy. All of these AEs were considered grade 1 events with the exception of the event of cyclic neutropenia which was a grade 3 event. The event

of cyclic neutropenia lasted 29 days and did lead to a dose adjustment and administration of concomitant medications.
Seven patients had a total of 13 hematologically related AEs reported under the MedDRA Investigations SOC. These included the AEs of White blood cell count decreased (#14, #17 and #19), Neutrophil count decreased (#14 and # 27), Platelet count decreased (# 14), Haemoglobin decreased (#25), International normalized ratio increased (#15) and Mean cell volume decreased (#13). The majority of events were grade 1 or 2 with exception of 3 events of grade 3 White blood cell count decreased and 1 of Neutrophil count decreased all in patient #14. These events of White blood count decreased lasted 2, 50 and 92 days respectively.

Reviewer's note: Patient # 14 experienced the highest number of AEs of any patients on this study. In addition this patient missed a substantial portion of the first 3 months of therapy due to AEs. This patient was receiving a CYP3A4 inhibitor (fluconazole) and valproic acid which is known to suppress the bone marrow.
Please see 7.4.2 Laboratory Findings *for additional details on laboratory abnormalities that were detected based on results communicated but not reported as an AE by the applicant.*

Metabolic events

A total of 6 patients with metabolic abnormalities were identified by review of data from the Investigations and the Metabolism and nutrition disorders SOC. These AEs included Hypertriglyceridemia/Blood triglycerides increased (#2, #5, #9, #15, #23), Hypercholesterolaemia/ Blood cholesterol Increased (#1, #15,) and Hyperglycemia/Type 2 diabetes mellitus (#2, #6).
All events were grade 1 except a CTCAE grade 2 event of hyperglycemia in patient #2. This event lasted 2 days and required everolimus dose adjustment.

Reviewer's note: Patients #23 (Blood triglycerides increased), #15 (Hypercholesterolaemia, Hypertriglyceridemia) and 6 (Type 2 diabetes mellitus) all required treatment with concomitant medications.

Dermatologic AEs

In order to evaluate potential skin manifestations of everolimus associated toxicity all AEs classified under the Skin and subcutaneous tissue disorders SOC were reviewed. Nineteen patients enrolled on C2485 were reported to have experienced "Dermatitis", "Acne", "Dermatitis contact", "Rash", "Dry skin" or "Dermatitis acneiform". Eleven of these patients experienced at least one grade 2 event with the rest only experiencing grade 1 events. Three patients had a dose adjustment, while 15 had to receive concomitant drug therapy. An additional 4 patients had the the AE of "Excoriation" reported under the Injury, poisoning and procedural complication SOC. All of these events were CTCAE grade 1 events.

Hepatic events

There was a single grade 1 adverse event of "Aspartate aminotransferase increased" reported on patient #11. It did not require everolimus dose adjustment nor did it require concomitant therapy. It is however reported as having a prolonged course of 330 days.

Reviewer's note: The majority of episodes of transaminase or bilirubin elevation were not reported as AEs by the investigator and applicant. These however were identified by screening of the laboratory investigations results.
These are summarized in 7.4.2 Laboratory Findings

There were no cases of Hy's Law detected in the 28 patients on this study.

Renal events

The AEs classified under the MedDRA SOCs Renal and urinary disorders and Investigations were evaluated for any possible renal toxicities. Six patients were identified have to have hematuria (#10 and #13), proteinuria (#18 and #23), urinary incontinence (#11), renal cyst (#4) and pollakiuria (#10). All events were grade 1 events except for one episode of proteinuria in patient #23. No dose adjustments were made in everolimus as a result of any of these AEs. The episodes of proteinuria and the episode of hematuria were attributed to everolimus therapy by the applicant. No additional AEs reported under investigations SOC.

Reviewer's note: Many episodes of proteinuria and renal function changes were not reported as AEs by the investigator and applicant. These however were identified by screening of the laboratory investigations results. These are summarized in 7.4.2 Laboratory Findings. *Most AEs were grade 1 or 2.*

Pulmonary events

Interstitial lung disease and pneumonitis are well known complications of everolimus therapy in adults. In order to identify any potential cases all AEs classified under the Infections and infestations SOC and the Respiratory, thoracic and mediastinal disorders SOC were reviewed closely. Three subjects (#3, #11 and #14) had episodes of Pneumonia, Bronchitis or Bronchitis viral. Two of these episodes in patients #3 and #14 were considered SAEs due to need for hospitalization. These two patients were reported to have multiple episodes of pulmonary AEs that are suspicious for being everolimus related. All episodes needed adjustment of everolimus dosing and administration of concomitant medications. All episodes were grade 2 except for the 2 SAEs which were considered grade 3 events.

Reviewer's note: The 3 subjects who had events suspicious for being pulmonary toxicity from everolimus all were on CYP3A4 inhibitors which may prolong everolimus metabolism. Patient #3 was also reported as having an AE of "Chest X-ray abnormal". All 3 of these patients however did recover from their pulmonary AE.

Cardiac Events

Three patients (#4, #6, #10) had one adverse event each under the MedDRA Cardiac SOC. These were two events of palpitations and 1 event of sinus tachycardia. All events were grade 1 and with recovery. Only the event of sinus tachycardia in patient #10 was attributed to everolimus by the applicant. Two patients (#6 and # 10) did require administration of concomitant medications. Patient #10 received "slow iron with calcium" as concomitant medication based on CRF.

Reviewer's note: The event of sinus tachycardia was a prolonged event lasting 231 days.

7.3.5 Submission Specific Primary Safety Concerns

None

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Reviewer's note: All patients on C2485 experienced at least on AE. The majority of these adverse events were low grade with only one NCI CTCAE grade 4 adverse event. These adverse events are summarized in Table 44. At the time of the original submission with data cut off as of 09 December 2009, 519 AEs were reported. This number had increased to 565 AEs by the time of the 90 day update with cutoff date as of March 8, 2010. The most common adverse events reported in this study included stomatitis, upper respiratory tract infection, sinusitis, otitis media, and pyrexia. Most of these events were grade 1 and 2 events. These are summarized in Table 46. The only grade 3/4 AE that occurred in more than on patient was convulsions. This however was in patients who had an underlying seizure disorder and was considered unrelated to the everolimus therapy by the applicant. Additionally, Table 45 summarizes all AEs that were attributed to everolimus. The most frequently reported AEs attributed to everolimus were stomatitis, upper respiratory tract infection, sinusitis, otitis media, pyrexia, and acneiform dermatitis, similar to the overall pattern of AEs.

No new SAEs or deaths were reported in 6 month time interval between the original submission and the 90 day update.

The adverse events were also categorized based on MedDRA system order classification (SOC) with AEs in Infections and infestations, Gastrointestinal disorders, Respiratory disorders, Skin and subcutaneous tissue disorders, Investigations and General disorders and administration site conditions all affecting more than 50% of subjects enrolled on study. This is summarized in Table 43.

Reviewer's note: In the renal transplant population, ≥ 50% of patients experienced AEs coded in the 'infections and infestations', 'gastrointestinal disorders', 'general disorders and administration site conditions', 'vascular disorders', and 'respiratory, thoracic and mediastinal disorders' MedDRA SOCs. The MedDRA PT's with ≥ 30% of patients having an AE that codes to them included hirsutism, Cushingoid, gingival hyperplasia, hypertension, pyrexia, upper respiratory tract infection, rhinorrhea, urinary tract infection, constipation, cough, vomiting, and peripheral edema. The AE pattern seen in these patients appeared to be distinctly related to their underlying disease process and no new safety concerns were identified that may affect this supplement.

Table 43 Adverse Events Categorized Based on MedDRA SOC for Patients on C2485

MeDDRA SOC	# of AEs		# of patients with AE	
	(n=565)	%	(n=28)	%
Infections and infestations	173	31	25	89
Gastrointestinal disorders	167	30	27	96
Respiratory, thoracic and mediastinal disorders	32	6	14	50
Skin and subcutaneous tissue disorders	32	6	20	71
Nervous system disorders	28	5	13	46
Investigations	25	4	15	54
General disorders and administration site conditions	24	4	14	50
Psychiatric disorders	17	3	12	43
Injury, poisoning and procedural complications	13	2	12	43
Metabolism and nutrition disorders	10	2	8	29
Musculoskeletal and connective tissue disorders	10	2	5	18
Renal and urinary disorders	8	1	6	21
Eye disorders	6	1	4	14
Blood and lymphatic system disorders	5	1	5	18
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	1	4	14
Cardiac disorders	3	1	3	11
Immune system disorders	2	< 1	2	7
Reproductive system and breast disorders	2	< 1	2	7
Vascular disorders	2	< 1	2	7
Ear and labyrinth disorders	1	< 1	1	4
Endocrine disorders	1	< 1	1	4

Table 44 Most Common Adverse Events (>5% of patients) on C2485

Adverse Event	Grade 1-4		Grade 3-4	
	n=28	%	n=28	%
Stomatitis	24	86	1	4
Upper respiratory tract infection	23	82	0	0
Sinusitis	11	39	1	4
Otitis media	10	36	0	0
Pyrexia	9	32	0	0
Convulsion	8	29	3	11
Diarrhoea	7	25	0	0
Dermatitis acneiform	7	25	0	0
Vomiting	6	21	1	4
Cellulitis	6	21	0	0
Cough	6	21	0	0
Body tinea	5	18	0	0
Gastroenteritis	5	18	0	0
Skin infection	5	18	0	0
Headache	5	18	0	0
Personality change	5	18	0	0
Dry skin	5	18	0	0
Rash	5	18	0	0
Gastric infection	4	14	0	0
Otitis externa	4	14	0	0
Excoriation	4	14	0	0
Dizziness	4	14	1	4
Nasal congestion	4	14	0	0
Rhinitis allergic	4	14	0	0
Dermatitis contact	4	14	0	0
Abdominal pain	3	11	0	0
Constipation	3	11	0	0
Pharyngitis	3	11	0	0
White blood cell count decreased	3	11	1	4
Hypertriglyceridaemia	3	11	0	0
Acne	3	11	0	0
Iron deficiency anaemia	2	7	0	0
Palpitations	2	7	0	0
Dental caries	2	7	0	0
Gastritis	2	7	0	0
Fatigue	2	7	0	0
Gait disturbance	2	7	0	0
Injection site haematoma	2	7	0	0
Irritability	2	7	0	0
Conjunctivitis infective	2	7	0	0
Furuncle	2	7	0	0
Infection	2	7	0	0

Adverse Event	Grade 1-4		Grade 3-4	
	n=28	%	n=28	%
Pneumonia	2	7	1	4
Rhinitis	2	7	0	0
Urinary tract infection	2	7	0	0
Fall	2	7	0	0
Medical device complication	2	7	0	0
Blood immunoglobulin G decreased	2	7	0	0
Blood triglycerides increased	2	7	0	0
Neutrophil count decreased	2	7	1	4
Back pain	2	7	0	0
Somnolence	2	7	0	0
Abnormal behaviour	2	7	0	0
Anxiety	2	7	0	0
Haematuria	2	7	0	0
Proteinuria	2	7	0	0
Menstruation irregular	2	7	0	0
Epistaxis	2	7	0	0
Pharyngeal inflammation	2	7	0	0
Rhinorrhoea	2	7	0	0

Table 45 Most Common AEs Attributed to everolimus in >5% of patients on C2485

Adverse event	Grade 1-3		Grade 3	
	n=28	%	N=28	%
Stomatitis	24	86	1	4
Upper respiratory tract infection	23	82	0	0
Sinusitis	11	39	1	4
Otitis media	10	36	0	0
Pyrexia	7	25	0	0
Dermatitis acneiform	7	25	0	0
Diarrhoea	6	21	0	0
Cellulitis	6	21	0	0
Gastroenteritis	5	18	0	0
Body tinea	4	14	0	0
Gastric infection	4	14	0	0
Otitis externa	4	14	0	0
Skin infection	4	14	0	0
Pharyngitis	3	11	0	0
White blood cell count decreased	3	11	1	4
Hypertriglyceridaemia	3	11	0	0
Cough	3	11	0	0
Acne	3	11	0	0
Gastritis	2	7	0	0
Vomiting	2	7	0	0
Furuncle	2	7	0	0
Infection	2	7	0	0
Pneumonia	2	7	1	4
Urinary tract infection	2	7	0	0
Blood immunoglobulin G decreased	2	7	0	0
Blood triglycerides increased	2	7	0	0
Proteinuria	2	7	0	0
Pharyngeal inflammation	2	7	0	0

Table 46 Grade 3 and 4 AEs on C2485

Pt #	AE	Day of onset	Length of AE (days)	Grade	Attribution
3	Pneumonia	733	20	3	Yes
5	Tooth infection	48	7	3	Yes
7	Sinusitis	281	51	3	Yes
8	Convulsion	385	2	3	-
8	Convulsion	491	2	3	-
11	Dizziness	91	106	3	-
14	Aspiration	215	2	3	-
14	White blood cell count decreased	47	2	3	Yes
14	White blood cell count decreased	363	50	3	-
14	White blood cell count decreased	461	92	3	-
14	Neutrophil count decreased	461	92	3	-
14	Bronchitis viral	43	14	3	Yes
14	Vomiting	271	3	3	-
15	Convulsion	651	1	4	-
17	Stomatitis	54	11	3	Yes
18	Cyclic neutropenia	35	29	3	-
23	Sleep apnoea syndrome	94	.	3	-
26	Convulsion	57	1	3	-

Reviewer's note: The AEs on B351 were not coded using CTCAE criteria. This made any comparison to the safety data generated from the analysis of study C2485 difficult. The only AEs that were considered severe in nature and affected more than one patient in B351 were pneumonia, pyrexia, urinary tract infection and hypertension.

7.4.2 Laboratory Findings

The xpt file alrs was reviewed for all laboratory values provided for the 28 patients enrolled on C2485. These laboratory results were confirmed in the case report forms. Additionally the reports of adverse events related to laboratory abnormalities and or classified under the MedDRA SOC investigations in aaev.xpt were reviewed for confirmation. Our findings were then compared to results presented in the clinical study report and the 90 day update.

The reported laboratory findings were classified under 3 broad groups of Biochemistry, Hematology and Urinary measurements. These are separately analyzed below.

Hematology

Three-hundred and forty-eight complete blood count (CBC) results were submitted on the 28 patients enrolled on C2485. CBCs should have been performed monthly for the first 6 months and every 3 months afterwards. The mean number of CBCs performed on

patients enrolled was 12.4 (SD = 3.0) with a median of 13 (range: 5, 19). Our analysis of the following parameters will be based on these results.

WBC

Fifteen (54%) patients on C2485 had a WBC count less than the lower limit of normal (< LLN). In 5 patients (#s 15, 17, 18, 20 and 24) the baseline level was < LLN and they did not have any decline from baseline while receiving therapy. The low baseline levels in these patients most likely represented a normal variation. In the other 10 (36%) patients WBC counts declined with subsequent recovery. In 8 of these patients WBC count did not drop lower than 3.0 x 10^9/L and hence was considered CTCAE level 1 toxicity. In 2 patients, #11 and # 18, WBC count dropped to 2.9 x 10^9/L which represents a CTCAE grade 2 toxicity. Both of these episodes were not at baseline and all patients demonstrated recovery in subsequently documented CBCs.

Reviewer's note: Leukopenia is an established side effect of everolimus. The drops in WBC noted in C2485 however were primarily grade one and recovery was noted in follow up CBCs.

Seven patients on C2485 had a WBC count > ULN. In 6 patients this appeared to be a one or two time fluctuation. In patient # 22, the WBC was elevated above the ULN on 7 separate occasions. The mean value during these intervals was 14.4 (SD = 1.8) with a median of 14.5 (range: 11.8, 16.4).

Reviewer's note: The elevated WBC levels do not appear to be clinically significant. It is unlikely that these are related to everolimus therapy.

Absolute Neutrophil Count (ANC)

Neutrophil counts were only provided on 25 patients and only 3 patients had > 3 separate ANC levels reported. Nine ANCs were reported in 6 patients that were lower than the LLN. In patient # 20, an ANC of .94 x 10^9/L which represents a CTCAE level 3 toxicity. Three patients had a CTCAE level 2 toxicity as their worst ANC drop while the other 2 patients had a level 1 toxicity as there lowest reported ANC.

An ANC > ULN was reported in one patient, #6, one occasion. This was an ANC of 7100 and not considered a clinically significant finding as patient subsequently had normal counts.

Reviewer's note: The number of patients who had an ANC performed is inadequate to reach any conclusions. Decreased WBC with secondary decrease in ANC is a well known side effect of everolimus as seen in the RCC and renal transplant studies.

Hemoglobin (Hgb)

Hemoglobin levels < LLN were reported on 12 (43%) patients on study C2485. One of these patients (#17) had a low hemoglobin level at baseline. Although below the LLN none of these Hgb levels was below 10 g/dl hence all were considered CTCAE grade 1. The mean Hgb value for these levels was 11.9 (SD = 1.0) with a median of 11.6 (range: 10.2, 13.7). In all of these cases the Hgb levels recovered to > LLN or were not clinically significant.

Four patients had Hgb levels reported that were above the upper limit of normal (ULN). In one patient, #20, the ULN cutoffs appear to be incorrect. In two of the patients, #3 and #13, the levels were slightly > ULN and subsequently fell within range. In one patient, # 4, Hgb levels at baseline appeared to be high normal and stayed elevated through the course of therapy, drifting above ULN for the majority of the study. This patient's baseline Hgb level was 15.7 g/dl with a mean value of 16.2 (SD = 0.75) and a median of 16.2 (range: 14.7, 17.4). In all of these cases with the exception of one level obtained on patient 4, the rise above ULN was less than 2 g/dl and hence CTCAE grade 1.

Reviewer's note: Patient Hgb levels do not appear to be significantly affected by everolimus therapy.

Platelets (plt)

Twelve platelet levels < LLN were reported in 6 (21%) patients enrolled on C2485. All had normal baseline platelet counts. Two platelet levels (57 x 10^3/µl and 73 x 10^3/µl) documented in patient #11 were considered CTCAE toxicity level 2 and the remainder CTCAE level 1. In this patient platelet counts eventually did recover although this patient was thrombocytopenic for close to 10 months. Only 2 patients had a low platelet count as their last documented count (patient #1 had a platelet count of 123 x 10^3/µl and patient # 28 had a last count of 133 x 10^3/µl). Both were CTCAE grade 1 toxicities.

Reviewer's note: The prolonged thrombocytopenia in patient #11 is concerning even though this patient's platelet counts eventually recovered. Eight patients had 27 platelet counts that were > ULN. The range of these counts was from 345 x 10^3/µl to 767 x 10^3/µl. These elevated platelet counts are not clinically significant findings.

Reviewer's note: The hematology data from B351 were reviewed and were similar to experience in SEGA patients.

Biochemistry

Three-hundred and fifty-one blood chemistry results were documented in the 28 patients enrolled on C2485. The mean number of chemistries performed on these patients was 12.5 (SD = 2.7) with a median of 13 (range: 5, 17).

ALT

Thirty-six elevated ALT levels were reported on 14 (50%) patients enrolled on C2485. Two patients (#1 and #17) had CTCAE grade 1 levels at baseline that did not worsen. Thirty seven of these levels in 10 (36%) patients were CTCAE grade 1 with two patients, #10 and #11, having a single level that was considered CTCAE grade 2.

Reviewer's note: Multiple different upper limits of normal for ALT levels were listed in the provided data tables suggesting multiple different source laboratories. Two additional patients, patient #23 and # 6, had ALT levels that depending upon the cut off for ULN could be approaching 3 x ULN. Patient #6 had an increasing ALT which persisted for 3 months at time of last laboratory check.

AST

One hundred and fifty-seven AST levels in 26 patients were reported to be > ULN. Only patient #11 however was noted to have an AST level that was considered a CTCAE grade 3 elevation with the rest considered grade 1 events.

Reviewer's note: Fifteen of these patients had AST levels that were elevated at baseline.

Indirect Bilirubin

Twenty one abnormally elevated indirect bilirubin levels were reported on 4 (14%) patients enrolled on study. Ten of these increases were CTCAE grade 1, 9 were grade 2 and 2 grade 3. Both grade 3 events were in patient #15. The maximum toxicity level in 3 patients was grade 2 in 3 patients (4, 5 and 27) and grade 3 in one patient (#15). Only patient #4 had elevated levels at baseline.

Reviewer's note: In all of these cases the pattern of rise in indirect bilirubin levels did not appear to be consistent with drug injury and may have been a function of what was considered to be the ULN at different laboratories. None of these patients had elevated transaminases and hence did not qualify as Hy's law candidates.

Direct Bilirubin

There was a single report of an elevated direct bilirubin level in patient #5. This laboratory finding was resolved at time of follow up testing.

Reviewer's note: All prior and subsequent direct bilirubin levels were within normal limits and the patient did not meet the criteria for Hy's law.

Triglycerides

If using CTCAE criteria, 16 patients (57%) had a level greater than 150 mg/dl which is the cutoff for grade 1 hypertriglyceridemia. However only 12 (43%) of these patients had a level that was considered greater than the ULN based on local lab. In 12 of these patients (43%) the baseline value was normal. Eight (29%) patients had a rise to CTCAE level 1 hypertriglyceridemia and 5 (18%) had a rise to level 2. One patient (#15) with an increase to level 2 had a baseline level 1 elevation.

Reviewer's note: In 4 patients the elevated triglyceride levels did not normalize (#s 1, 5, 8 and 15). All of these patients had documented CTCAE grade 2 elevations. Two of these patients had a grade 1 hypertriglyceridemia at baseline (#s 2 and 15). Patient # 9 also had grade 1 hypertriglyceridemia at baseline that normalized.

HDL

Eleven HDL levels that were higher than the ULN were reported in 5 patients. All of these levels were sporadic with subsequently documented normalization.

LDL

Reviewer's note: One hundred and ninety four LDL levels were considered higher than the ULN in 26 patients. Close review of the data on these patients however suggests that only 12 of these patients showed a trend suggestive of increase in levels during therapy. The mean baseline LDL level was 97 (SD = 32) with a median of 87 (range: 48, 184). At time of 1 month follow-up the mean level was 110 (SD = 35) with a median of 101 (range: 71, 243). At time of 12 month follow-up, mean LDL level was at 114 (SD = 30) with a median of 108 (range: 73, 188). These numbers suggest a therapy associated increase in LDL levels but the data subset is too small to be conclusive.

Cholesterol

Ninety-six cholesterol levels that were higher than the ULN were reported in 19 (68%) patients on C2485. Only 2 levels in patient #1 were CTCAE grade 2 with the remainder of the levels considered CTCAE grade 1 events. Patient #1 had baseline CTCAE level 1 hypercholesterolemia.

Reviewer's note: Five patients had elevated levels at baseline although in 7 patients the levels appeared to rise due to everolimus exposure. Mean baseline cholesterol level in C2485 was 163.7 (SD = 33.7) with a median of 157 mg/dl (range: 121, 261). At one month the mean cholesterol level was 185.6 (SD = 37.7) with a median of 181 (range: 133, 312). At 12 months the mean was 185.9 (SD = 30.0) with a median of 184 (range: 137, 259).

Creatinine

Twelve creatinine levels above the upper limit of normal were reported in 3 patients enrolled on C2485. These changes were in patients # 10, # 23 and # 26 and all increases were considered to be CTCAE level 1. In patient # 10 there was a one time increase of 0.1 mg/dl with subsequent return to within normal limits. In the other two patients creatinine was > ULN at baseline but no subsequent rises were documented and levels remained stable.

Reviewer's note: In this study there does not appear to be any effects on rise in creatinine levels although this has been a concern in studies with adult patients and in the renal transplant setting. The enrollment of patient #23 was considered to be a protocol deviation as the baseline creatinine was higher than 1.5mg/dL.

BUN

Ten BUN values above > ULN were reported in 7 (25%) patients. In 5 patients the BUN elevation was an isolated finding with a normal creatinine documented at same time (#s 1, 2, 8, 10 and 25) and in the other 2 (#s 23 and 25) the highest value was at baseline with follow up levels being stable or improved. The BUN elevations when assessed using the CTCAE criteria for "Investigations, other" would best classify under grade 1 or in one case of patient # 25 as grade 2.

Reviewer's note: The mildly elevated BUN values were not suggestive of renal toxicity.

Sodium

Twenty-three elevated sodium levels were reported in 13 (46%) patients enrolled on C2485. Only one sodium level was considered a CTCAE level 2 toxicity (# 27). All these levels were temporary with other documented normal levels.

Six low sodium levels were also reported in 5 patients. All subsequently improved and were CTCAE level 1 events.

Potassium

Fourteen episodes of low potassium levels were documented in 10 patients. All episodes where CTCAE level 1. In 1 patient, #7, the last 3 documented potassium levels were < LLN.

Eighteen potassium levels > ULN were also reported in 9 patients. All episodes were CTCAE level 1 with the exception of a single episode in patient # 25 that classified as CTCAE grade 2 toxicity.

Reviewer's note: The potassium abnormalities were all mild and the pattern was not suggestive of any relationship to everolimus exposure.

Glucose

Nineteen episodes of Glucose levels < LLN were reported in 10 patients. Two patients (#13 and # 21) experienced a single CTCAE grade 2 episode with the remainder of the episodes being grade 1 episodes. Two patients had an abnormal level at baseline: #26 had a baseline low glucose that was CTCAE level 1 and #27 had a baseline level that was CTCAE level 2.

Fourteen Glucose levels > ULN were also reported in 7 patients on C2485. All were CTCAE level 1. The pattern of elevated Glucose levels was only concerning in 1 patient, #6, who had multiple elevated levels in the latter half of his therapy. All of these patients had normal baseline glucose levels.

Calcium

Ninety-one calcium levels were documented on 25 patients enrolled on C2485. There were only 6 calcium levels that were outside of the normal range in 6 patients. All levels classified as CTCAE level 1 with 2 being < LLN and 4 levels > ULN.

Reviewer's note: Due to limited amount of data reported no conclusions can be reached.

Bicarbonate

No bicarbonate levels were reported on patients on C2485.

Albumin

Two patients (#11 and #14) were reported to have a one time albumin level that was < LLN. Both of these results were isolated lab reports with remainder of the albumin levels within the parameters set as normal by the respective laboratories.

Six Albumin levels > ULN were reported in 5 patients. All of these levels were only mildly elevated. Only patient # 10 had 2 albumin levels that were > ULN. All of these patients had multiple other levels within the range specified as normal by the respective laboratories.

Reviewer's note: There does not appear to be any adverse effects on albumin levels in patients on C2485.

Alkaline Phosphatase

Forty two elevated alkaline phosphatase levels were reported in 15 (54%) patients enrolled on C2485. Four alkaline phosphatase levels in one patient (#16) were considered as CTCAE grade 2 abnormalities while the rest were grade 1. No obvious trends were apparent suggesting a sudden rise in alkaline phosphatase levels as a result of everolimus therapy. In most cases the levels were stable through out therapy

however depending on the laboratory performing the tests, the limits of the normal range appeared to change.

Reviewer's note: There does not appear to be any relationship between everolimus exposure and increases in alkaline phosphatase in C2485.

Urine Protein

Two hundred and fifty-six urine protein levels were submitted on 28 patients. Majority of the results were either negative or trace. Seventeen patients had a result (52 results) that indicated some degree of proteinuria. Positive results included + (1 pt), 1+ (2 pts), 2+ (2 pts), 3+ (1 pt), ≥ 300 mg/dl (1 pt), 30 mg/dl (14 pts), 50 mg/dl (1 pt) and 100 mg/dl (4 pts). Six patients (#1, 5, 17, 18, 21 and 23) had a negative result at baseline but then had urine analysis positive for protein. Additionally patient #8 had a baseline urine protein of 30 but subsequently had consistent levels above baseline.

Reviewer's note: Proteinuria is a known side effect of everolimus and 7 (25%) of the patients on this study have a pattern suggestive of development/worsening of proteinuria on therapy. It however has to be pointed out that none of these patients appear to have developed hypoalbuminemia or clinical symptoms consistent with nephrotic syndrome.

7.4.3 Vital Signs

All vital signs including temperature, pulse, respirations, blood pressure, height and weight evaluated. To ensure uniform analysis values were compared from baseline to 12 month time point which is the last documented clinic visit for patients with shortest documented follow up.

Temperature

Two hundred and three body temperatures were reported on the 28 patients enrolled on C2485. No temperatures above 37.9° were reported in any of these patients with a minimum temperature of 32.9°. The mean body temperature was 36.2° (SD = 0.66) with a median of 36.3°. There did not appear to be any trends towards changes in temperatures although 25% of patients had previously been reported to have experienced pyrexia.

Reviewer's note: There is no association between everolimus therapy and changes in basal body temperatures although patients have an increased incidence of infections and may experience pyrexia in association with that.

Pulse rate (PR):

Two hundred and eighteen pulse rates were reported on the 28 patients enrolled on C2485. Twenty one patients had both a documented baseline and one a documented

one year PR. The mean baseline PR was 70.1 (SD = 8.8) with a median of 69 (range: 55, 86). At the 12 month visit the mean PR was 74.0 (SD = 9.9) with a median of 73 (range: 63, 99). There are only 2 pulse rates of > 100 both in patient # 17. Only 13 patients had a PR of < 60 reported and in 12 of these patients this was an isolated event. Patient #3 however did have 5 documented PRs of < 60. This patients PR appeared to have minimal fluctuations although no baseline value was provided.

Reviewer's note: There does not appear to be any relationship between treatment with everolimus and heart changes as all documented fluctuations appear to be within range of normal physiologic changes.

Systolic Blood Pressure (SBP)

Twenty one patients had a documented SBP at baseline and then again at 12 months. The mean baseline SBP was 113.5 (SD = 10.9) with a median of 114 (range: 93, 137). For this same group of patient the mean SBP at 12 months was 123 (SD = 12) with a median of 122 (range: 105, 146). This suggests a ~10 point increase in mean SBP from baseline to 12 months. Additionally, for all patients with a baseline SBP, the mean increase when compared to maximum value documented was 23.3.

Diastolic Blood Pressure (DBP)

Twenty one patients had a documented DBP at baseline and then again at 12 months. The mean DBP at baseline was 70.1 (SD = 8.8) with a median of 69 (range: 55, 86). At 12 months the mean DBP was 73.4 (SD = 9.7) with a median of 70 (range: 63, 99). This suggests an ~3 point increase in DBP from baseline to 12 months. When baseline DBP is compared to highest documented the mean increase in DBP was 13.1 mmHg.

Reviewer's note: The findings in the SBP and DBP suggest an increase in BP associated with everolimus therapy. This however appears to be clinically mild in most patients as only one patient had the need for treatment of elevated BP.

Height

In this study 23 patients were 18 years of age or younger. Twenty one of these patients had a documented height at baseline and then again at last visit. All but one of these patients had a documented height increase. Mean height increase was 8.1 cm (SD = 6.2) with a median of 6.1 cm (range: 0, 20.6). This pattern seems to be consistent with pediatric patients who are growing.
Reviewer's note: The other 2 pediatric age patients, # 3 and 19, also demonstrated evidence of continued growth. The heights of the 5 adult age patients remained stable (within measurement error) as expected.

Weight

The first and last documented weights for all patients enrolled on C2485 were compared. Eight patients had a negative weight change while 20 patients appeared to have an increase in their weight. Mean weight change for patients was 3.12 kg (SD = 7.3) with a median of 2.55 kg (range: -13.6, 22.1). The mean age of patients experiencing weight loss was 18.9 (SD = 8.2) and for patients gaining weight it was 9.9 (SD = 5.6). Although this seems to suggest a pattern of growth in the younger age patients there are several patients whose weight change may be concerning. Specifically, patient #7 had a 13.6 kg weight loss while patient #11 had a 9.6 kg weight loss. Both patients appear to have been obese for age at baseline. Patient # 7 was 14 years old and weighed 84.7 kg at baseline and patient # 11 was 12 years old and weighed 76.3 kg at baseline. Both patients also appear to be in the highest quartile in terms of # of AEs with 37 and 25 AEs during the course of therapy respectively. Additionally 4 patients (patients #6, 10, 12 and 16) had weight gain of > 10 kgs. These patients however appear to have been having simultaneous height gain which may suggest normal growth.

Reviewer's note: The small size of the study and the baseline characteristics of the patients involved including the presence of TS and secondary mental retardation make any kind of firm conclusions regarding effects on weight changes difficult.

7.4.4 Electrocardiograms (ECGs)

No EKGs were performed as part of study C2485.

The everolimus labeling however indicates that in a randomized, placebo-controlled, crossover study, 59 healthy subjects were administered a single oral dose of everolimus (20 mg and 50 mg) and placebo. There was no indication of a QT/QTc prolonging effect of everolimus in single doses up to 50 mg.

7.4.5 Special Safety Studies/Clinical Trials

The safety of everolimus has previously been evaluated in patients with moderate hepatic impairment (Child Pugh class B). A dose reduction is generally recommended in patients with Renal Cell Carcinoma receiving everolimus who have moderate impairment. Everolimus however has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population.

No clinical studies were conducted with everolimus in patients with decreased renal function. Renal impairment is not expected to influence drug exposure and no dosage adjustment of everolimus is recommended in patients with renal impairment.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency of adverse events was difficult to determine in this study as patients were dosed based upon therapeutic drug levels and the target therapeutic drug range and the drug levels achieved were both very wide. Additionally, the study was small, number of grade ≥ 3 AEs relatively low and low grade AEs common. Based on the clinical pharmacology teams review of the data even though there may be a trend towards increased stomatitis and infections with higher drug levels, the numbers are too small to make a definitive assessment.

Reviewer's note: Please see clinical pharmacology review for further details.

7.5.2 Time Dependency for Adverse Events

The number of AEs experienced by each patient enrolled on C2485 were assessed to see if there was a direct correlation to length of therapeutic exposure. The number of AEs did not appear to be closely related to length of time on therapy. Ten patients experienced ≤ 15 AEs on C2485. The mean # of months on study for these patients was 19.8 months (SD = 8.2) with a median of 18.5 months (range: 5.1, 36.2). Thirteen patients had between > 15 to ≤ 30 AEs. Mean number of months on study for these patients was 25.9 months (SD = 7.4) with a median of 24.1 (range: 14.5, 37.0). Five patients had > 30 AE. The mean time on study for these patients was 23.7 months (SD = 3.3) with a median of 24.1 (range: 18.3, 27.4). This seemed to suggest that although prolonged time on study increases the risk of having an AE there does not appear to be cumulative toxicities that arise with increased dose exposure.

In addition, all AEs were grouped by MedDRA SOC and then by MedDRA PT by the applicant. The days of onset of adverse events were grouped by year of onset (< 1 yr, 1 to < 2 yrs, ≥ 2 yrs). No significant trends were detected to suggest that there was an association with prolonged administration of everolimus. Furthermore a similar analysis was performed based on CTCAE grade of the toxicity and revealed no specific associations.

Reviewer's note: These calculations were repeated and conclusions were confirmed.

7.5.3 Drug-Demographic Interactions

The distribution of adverse events was evaluated based upon gender, age and race. These are discussed in more detail under each category below.

Gender

All patients enrolled on study C2485 experienced an AE. The number of AEs per patient were similar however the number of SAEs and grade ≥ 3 AEs were higher in male patients. Additionally, the number of each individual AE categorized by MedDRA PT was compared between the sexes and the number of AEs appeared to be evenly split. All of these numbers were confirmed. The small size of this study and the rarity of high grade or serious AEs however precludes any definitive conclusions. Table 47 summarizes the general breakdown of AEs by gender.

Table 47 AEs by Gender

Sex			**Male (n=17)**	**Female (n=11)**
AE	# of patients		17 (100%)	11 (100%)
	# of events	Mean	20.5 (12.4)	19.6 (7.3)
		Median	19 (2, 45)	19 (11, 32)
Grade ≥3 AE	# of patients		7 (41%)	4 (36%)
	# of events	Mean	2 (2.2)	1 (0)
		Median	1 (1, 7)	1
SAE	# of patients		3 (18%)	1 (9%)
	# of events	Mean	1.3 (0.6)	1 (0)
		Median	1 (1, 2)	1

Age

The AEs, grade ≥ 3 AEs and SAEs were for the most part distributed equally between the three age groups listed in Table 48. Additionally the more common adverse events of upper respiratory tract infections and stomatitis had similar distributions between the age groups although otitis media and sinusitis appeared to be slightly less common in the oldest age group. The AEs of rash, gastric infection, excoriation, injection site hematoma, irritability, neutrophil decrease, rhinorrhea, and hematuria were exclusively reported in the youngest age group while urinary tract infection was only seen in those ≥ 18 years.

Reviewer's note: The small number of patients enrolled on this study makes any kind of definitive assessment of differential rates of AEs in the different age groups difficult. For the most part the data suggest equal distribution of the different AEs between different patient populations.

Race

The majority of patients enrolled on study C2485 were Caucasian with 2 patients of labeled as "Black" and 2 as "other" race.
The 2 patients who were labeled as "Black" had a very low number of adverse events. Patient # 24 had 2 AEs and patient # 20 had 8 AEs. None of these AEs were SAEs and only patients 20 had 2 grade 2 AEs with the rest being grade 1.

The 2 patients who were labeled as "other" race were patients # 2 and #19. Patient #2 was the only withdrawn from study prior to finishing the core 6 month period of therapy and had 13 AEs reported. Patient #19 had 16 AEs reported. Neither patient had a grade 3 AE although patient 2 did have an SAE of convulsion.

Reviewer's note: The number of non-Caucasian patients on this study is too small to reach any definitive conclusions. It however does appear that this group of patients may have had a smaller number of reported AEs.

Table 48 Adverse Events by Age

Age			3 to < 12 years (n = 16)	12 to < 18 years (n = 6)	≥ 18 years (n = 6)
AE	# of patients		16 (100%)	6 (100%)	6 (100%)
	# of events	Mean	19.1 (11.2)	23 (10.5)	20.3 (10.0)
		Median	16 (6, 45)	23 (11, 37)	22 (2, 30)
Grade ≥3 AE	# of patients		5 (31%)	3 (50%)	3 (50%)
	# of events	Mean	2.2 (2.7)	1 (0)	1.3 (0.6)
		Median	1 (1, 7)	1	1 (1, 2)
SAE	# of patients		3 (19%)	0	1 (17%)
	# of events	Mean	1.3 (0.6)	0	1 (0)
		Median	1 (1, 2)	0	1

7.5.4 Drug-Disease Interactions

There is no evidence suggesting an everolimus effect on increasing prolonged QTc. For more details please see 7.4.4 Electrocardiograms (ECGs).

Based upon the everolimus labeling, the safety of everolimus has previously been evaluated in patients with moderate hepatic impairment (Child Pugh class B). A dose reduction is generally recommended in patients with Renal Cell Carcinoma receiving everolimus who have moderate impairment. Everolimus however has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population.

No clinical studies were conducted with everolimus in patients with decreased renal function. Renal impairment is not expected to influence drug exposure and no dosage adjustment of everolimus is recommended in patients with renal impairment.

Reviewer's note: For further detail please see clinical pharmacology review.

7.5.5 Drug-Drug Interactions

The current Afinitor label recommends that strong inhibitors of CYP3A4 or PgP not be co-administered with everolimus while 2.5 mg everolimus dose should be administered to patients taking moderate CYP3A4 or PgP inhibitors. According to the current

approved Afinitor label, in healthy subjects, co-administration of everolimus with a strong inducer of CYP3A4, decreased everolimus AUC and C_{max} compared to everolimus treatment alone. Thus, strong CYP3A4 inducers should be avoided, but if needed a dose increase may be considered.
This poses a potential problem as many patients with SEGA have chronic seizures or other disorders that require treatment with medications that may be strong CYP3A4 inducers or inhibitors. As discussed earlier, 14 (50%) of patients on study did receive medications that were CYP3A4 inducers/inhibitors. These patients did have response equivalent to the rest of the cohort with 13 (93%) having a best overall volumetric response of >30% and 10 (71%) response of > 50%. These patients also had responses equivalent to the rest of the cohort at 6 months (86% of patients with > 30% response) and at censoring (79% of patients with > 30% response).

Reviewer's note: Similar analysis showing no change in efficacy for patients only receiving inducers was performed by the clinical pharmacology team. Please see clinical pharmacology report for details.

In addition, the patients who were on CYP3A inducers/inhibitors did not as a cohort show an increase in number of AEs. These patients had a mean of 20.8 (SD = 10.2) AEs with a median of 19 (range: 8, 45). The rest of the patients had a mean of 19.6 (SD = 11.2) with a median of 18 (range: 2, 41). The number of patients with ≥ grade 3 AE was also evenly divided between the two cohorts. It however has to be noted that the only patients who were on a possible CYP3A4 inhibitor were patients #3, 11 and 14. Patients 2 and 14 both experienced SAEs and while patient #14 had the most number of overall AEs (45), grade ≥ 3 AEs (7) and SAEs (2) than any patient on study. Patient #14 also had the highest total number of days of drug interruptions receiving < 50% of his therapy from the first 12 weeks on study. This patient's drug exposure was considered inadequate for him to be considered part of the "Per-protocol Population."

Reviewer's note: The small number of patients on study precludes any definitive conclusions regarding increased toxicity or decreased efficacy in patients receiving CYP3A4 inhibitors or inducers respectively. For further details please see clinical pharmacology review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Based upon the current AFINITOR labeling ,administration of everolimus for up to 2 years did not indicate oncogenic potential in mice and rats up to the highest doses tested (0.9 mg/kg) corresponding respectively to 4.3 and 0.2 times the estimated clinical exposure ($AUC_{0\text{-}24h}$) at the recommended human dose for patients with advanced RCC. Additionally, everolimus was not genotoxic in a battery of *in vitro* assays (Ames mutation test in *Salmonella,* mutation test in L5178Y mouse lymphoma cells, and chromosome aberration assay in V79 Chinese hamster cells). Everolimus was not

genotoxic in an *in vivo* mouse bone marrow micronucleus test at doses up to 500 mg/kg/day (1500 mg/m^2/day, approximately 255-fold the recommended human dose for patients with advanced RCC, and 103-fold the maximum dose administered to patients with SEGA, based on the body surface area), administered as two doses, 24 hours apart.

Based on the applicant's current proposal, patients with SEGA are to remain on therapy for a prolonged period of time. Secondary to concerns regarding the risks of secondary malignancy associated with prolonged treatment with an immunosuppressive agent, an inquiry was sent to the sponsor on 6/30/2010 requesting an assessment of this risk.

The applicant performed a search of their oncology pre- and post-marketing safety database using the neoplasm Standardised MedDRA Query (SMQ) "benign, malignant and unspecified (including cysts and polyps)" up to a cut-off date of 6/20/2010. Eight cases of secondary malignancy were identified amongst the 8500 cancer patients treated on clinical trials with everolimus. Based on this the calculated frequency of secondary malignancies in the oncology clinical trial setting is 0.1%. There were no cases of secondary malignancy in the post-marketing setting. None of these cases were considered to be related to everolimus therapy. These cases are summarized in Table 49.

A search of the safety data base in the solid organ transplant was also performed by the applicant using the same search strategy. The analysis of this search summarized the overall experience of reported malignancies in the 12-month databases of everolimus for Study A2309 and other controlled studies in the indications of both renal and cardiac transplantation. These patients however for the most part were treated with combination regimens that included calcineurin inhibitors, corticosteroids and possibly other immunosuppressive agents. Out of 2,335 transplant patients treated with everolimus, malignancies were reported in 2.6% of patients, including 1.0% of skin cancers and 0.43% of lymphomas. An additional 4 transplant patients with secondary malignancies were identified using the FDA AERS data base. These included a case of colon cancer, a case of metastatic carcinoma of the "large intestine", a case of prostate carcinoma and a case of supratentorial primitive neuroectodermal tumor. All 4 of these patients were receiving other immunosuppressive medications also.

Table 49 Cases of Secondary Malignancy amongst Cancer Patients Treated with everolimus

Case ID	Age / gender	Primary malignancy	Secondary malignancy	TTO (days)	Causality	Other
PHHO2009 CA01563	61/M	Advanced carcinoid tumor	Glioblastoma multiforme	194	Not suspected	Co-suspect study drug: Sandostatin LAR
PHHO2009 US09735	65/F	Advanced pancreatic NET	Invasive malignant melanoma	330	Not suspected	N/A
PHHO2010 IT06585	60/F	DLBCL	Papillary carcinoma thyroid	110	Not suspected	Patient with prior history of thyroid nodule
PHHO2009I T11500	66/F	Advanced pancreatic NET	Thyroid cancer	485	Not suspected	NA
PHHO2009 DE00921	44/M	Metastatic renal carcinoma	Cancer of the salivary gland	44	Not suspected	NA
PHHO2007 US14444	74/F	Metastatic renal carcinoma	Cancer at base of tonsil and tongue	~ 90	Not suspected	N/A
PHHO2010 US05516	74/F	Advanced carcinoid tumor	Right temporal meningioma	1022	Not suspected	NA
PHHO2010 US02978	59/M	Advanced solid tumor	Basal cell carcinoma of nose	696	Not suspected	Patient received prior radiation therapy

DLBCL: Diffuse large B-Cell lymphoma; NET: Neuroendocrine tumor; TTO: Time to onset

Adapted from amendment to NDA 22334 of 7/14/10, page 4, Table 2-1.

In addition 4 patients on C2485 had an AE that coded to the Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC. This included 1 patient with a lipoma (#6), 1 patient with a skin papilloma (#9), 1 patient with an angiofibroma (#17) and 1 with an acrochordon (# 20). In addition to these cases there was a single case of post transplant lymphoproliferative disease identified in study B351.

In addition to this analysis, the applicant presented data from multiple studies in the solid organ transplant setting that suggest that as a general rule the rate of secondary malignancies are higher in the transplant setting because of prolonged immunosuppression with multiple agents and the prevalence of chronic viral infections such as EBV and CMV. The applicant also provided data demonstrating that patients who receive m-TOR inhibitors such as sirolimus as part of their immunosuppression have lower rates of secondary malignancy. This is thought to be due to antineoplastic characteristics of mTOR inhibitors. [xiii, xiv, xv, xvi]

Reviewer's note: The data provided by the applicant suggest lower rates of secondary malignancies in patients receiving monotherapy with everolimus or other m-TOR 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 m-TOR inhibitor therapy. It is however suggested that the antiproliferative characteristics of mTOR inhibitors do decrease the inherent risks associated with their immunosuppressive characteristics.

7.6.2 Human Reproduction and Pregnancy Data

Everolimus is currently considered a pregnancy category D drug. There are no adequate and well-controlled studies of everolimus in pregnant women. However, based on the mechanism of action, everolimus may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures for advanced RCC and SEGA patients. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use an effective method of contraception while receiving everolimus and for up to 8 weeks after ending treatment.

7.6.3 Pediatrics and Assessment of Effects on Growth

A pediatric Written Request was issued by the FDA on 4/1/2010. This written request consists of two studies. A single arm, phase 2 study in patients with SEGA in the setting of TS (C2485) and a randomized, double blind, phase 3 study (M2301) also in the same patient population. C2485 is the core of this sNDA. Study M2301 is currently ongoing and has recently finished enrollment. Additional long-term pediatric safety data were also provided from study B351 that was performed in patients with renal transplants.

Due to the small, single-arm, open-label nature of C2485 no definitive conclusions can be reached about the effects of everolimus on growth. Additionally, considering the nature of this study, at the time of the pre-NDA meeting no requests were made regarding a formal analysis of effects on growth. It is however notable that multiple patients on C2485 exhibited evidence of appropriate growth while on therapy including increases in height and weight. This is summarized in the 7.4.3 Vital Signs section.

Reviewer's note: A formal analysis of effect on growth in patients enrolled on the randomized, placebo-controlled study, M2301 will be requested as a Post Marketing Requirement (PMR).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdosage
The AFINITOR label states that "In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity were observed in either mice or rats given single oral doses of 2000 mg/kg (limit test).
Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been administered. The acute toxicity profile observed with the 70 mg dose was consistent with that for the 10 mg dose."
General supportive measures are recommended in cases of overdose.

Drug Abuse Potential
There are no reports of everolimus being used as a drug of abuse. This agent is an immunosuppressive and antineoplastic agent with multiple side effects and no known association with drug induced euphoria. It is unlikely for this agent is intentionally misused or abused.

Withdrawal and Rebound
The applicant has not provided any data in regards to risks of withdrawal or rebound effects in association with this agent.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Everolimus is marketed in the US as Afinitor® for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. This indication was approved on 3/30/2009. Additionally, everolimus is marketed in the US as Zortress® 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. Everolimus is currently approved in 49 countries for treatment of RCC and > 65 countries for prophylaxis of renal and cardiac organ transplantation. It's estimated that 3,275 oncology patients and 4,975 transplant recipients have received treatment with everolimus in Novartis sponsored studies. Total exposure based on commercial usage only currently exceeds 537 patient-years in oncology and 51,000 patient-years in solid organ transplant.

Since the approval of everolimus for treatment of RCC, 3 periodic adverse drug experience reports have been submitted to this NDA. These are summarized in Table 50.

Table 50 Periodic Adverse Drug Experience Reports Submitted for Afinitor

Date of submission	Sequence number	Period covered	# of reports
7/28/09	0052	3/30/09 – 6/29/09	216
10/29/09	0059	6/30/09 – 9/29/09	446
1/28/10	0063	9/30/09 – 12/29/09	?
4/26/10	0066	12/30/09 – 3/29/10	486

These reports include safety reports generated under the brand name Certican® which everolimus is marketed under in several countries outside the US. Additionally, 2 Periodic Safety Update Reports, PSUR-1 covering 3/30/09 to 9/30/09 and PSUR-2 covering 10/1/09 to 3/31/10, were submitted for review. The labeling for everolimus was not altered for safety reasons during the period covered by these PSURs. The following safety concerns have been identified in the Risk Management Plan of everolimus for further monitoring:

- Non-infectious pneumonitis
- Severe infections including exacerbation of background diseases (such as HBV)
- 'exacerbation', reactivation' and 'aggravation'
- Hypersensitivity / anaphylactic reactions
- Stomatitis
- Increased creatinine / renal failure
- Hyperglycemia / new-onset diabetes mellitus
- Drug interaction with CYP3A4 and PgP inhibitors, inducers and substrates

Additionally, the following safety concerns were identified in the Risk Management Plan for close monitoring as potential or pharmacological class risks:

- Cardiac failure

- Wound healing complications
- Lymphopenia
- Hypophosphatemia
- Dyslipidemia
- Hemorrhages

Reviewer's note:

- *Based on our review we did not identify any new safety concerns from the current submission. The relevance of above reports to the SEGA patient population remains unknown.*
- *Events from these reports have been described in the current labeling.*

9 Advisory Committee Meeting

None.

However, DDOP requested a consultation individually with each of three special government employees (SGEs) who are the field experts on the treatment of patients with SEGA associated with TS and one SGE with expertise on neurologic radiology. The consensus opinion from these consultations are summarized below:

1. SEGA diagnosis is based on the clinical and imaging criteria
2. SEGA patients should be followed closely. If they manifest symptoms for SEGA growth or their SEGAs are located in a location that is anticipated to cause clinical problem, these patients would need therapy, usually curative surgical resection.
3. Volumetric reduction of SEGAs may have clinical importance, especially for those tumors that may cause pressure effects due to their anatomic locations.
4. Long-term follow up on the pediatric growth is indicated for patients who are on prolonged therapy with everolimus.
5. Everolimus should not be recommended to all patients with SEGAs, until further data is available, due to unknown treatment duration and long-term toxicities in pediatric population.

10 Appendices

10.1 Labeling Recommendations

Please see the revised AFINITOR labeling.

10.2 Literature Review/References

We performed a literature review on the following topics:

- The Biology of TS and SEGA
- The natural history of SEGA,
- Available treatments for SEGA and indications for treatment, and
- Published studies of treatment of SEGA using sirolimus.

No additional information regarding the efficacy or safety of everolimus was obtained via literature review.

[i] Plon SE and Owens J. Tuberous sclerosis. UpToDate Online 18.1, January 13, 2010.
[ii] Curatolo P, Bombardieri R and ozwiak SJ. *Tuberous sclerosis.* The Lancet, 2008, Aug 23, Vol 372, 657-68.
[iii] Goh S; Butler W; Thiele EA. Subependymal giant cell tumors in tuberous sclerosis complex. Neurology 2004 Oct 26;63(8):1457-61.
[iv] Roach ES; Gomez MR; Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. Journal of Child Neurology 1998 Dec;13(12):624-8.
[v] Cuccia V, et al. Subependymal giant cell astrocytoma in children with tuberous sclerosis. Childrens Nervous System, 2003, 19: 232-243.
[vi] Torres OA, et al. Early Diagnosis of Subependymal Giant Cell Astrocytoma in Patients With Tuberous Sclerosis. Journal of Child Neurology; April 1998, 13, 4: 173-177.
[vii] Adriaensen MEAPM, et al. Prevalence of subependymal giant cell tumors in patients with tuberous sclerosis and a review of the literature. European Journal of Neurology 2009, 16: 691-696.
[viii] O'Callaghan FJK, et al. Subependymal nodules, giant cell astrocytomas and the tuberous sclerosis complex: a population-based study. Arch Dis Child 2008 93:751-754.
[ix] Franz DN, Leonard J, Tudor C, Chuck G, Care M, Sethuraman G, Dinopoulos A, Thomas G and Crone K. *Rapamycin Causes Regression of Astrocytomas in Tuberous Sclerosis Complex.* Annals of Neurology, 2006; 59:490-498.
[x] Lam C, Bouffet E, Tabori U, Mabbott D, Taylor M and Bartels U. Rapamycin (Sirolimus) in Tuberous Sclerosis Associated Pediatric Central Nervous System Tumors. Pediatric Blood and Cancer, 2010;54:476-479.
[xi] Mayr NA, Yuh WTC, et al. Serial Therapy-Induced Changes in Tumor Shape in Cervical Cancer and Their Impact on Assessing Tumor Volume and Treatment Response. American Journal of Radiology, July 2006; 187: 65-72.
[xii] Ehninger D, Han S, Shilyansky C, et al. Reversal of learning deficits in a Tsc2+/- mouse model of tuberous sclerosis. Nat Med 2008; 14:843–848.
[xiii] Kauffman HM, Cherikh WS, et al. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of *de novo* malignancies. Transplantation; 80: 883-9.
[xiv] Kauffman HM, Cherikh WS, et al. Post-transplant *de novo* malignancies in renal transplant recipients: The past and present. Transplant International; 19: 607-20.

[xv] Majewski M, Korecka M, et al. The immuno-suppressive macrolide RAD inhibits growth of human Epstein-Barr virus-transformed B lymphocytes *in vitro* and *in vivo*: a potential approach to prevention and treatment of posttransplant lymphoproliferative disorders. Proc Natl Acad Sci USA; 97(8): 4285-90.
[xvi] Campistol JM, Eris J, et al. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. J Am Soc Nephrol; 17: 581-9.

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

/s/

AMIR SHAHLAEE
10/26/2010

SOMESH CHATTOPADHYAY
10/26/2010

SHENGHUI TANG
10/26/2010

KE LIU
10/26/2010