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Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA Serial Number: 203985 / 00

Drug Name: Afinitor® / Everolimus

Indication(s): Subependymal Giant Cell Astrocytoma (SEGA) Associated with
Tuberous Sclerosis Complex (TSC)

Applicant: Novartis

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Table of Contents

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES	1
FOOD AND DRUG ADMINISTRATION	1
STATISTICAL REVIEW AND EVALUATION	1
1. EXECUTIVE SUMMARY	3
2. INTRODUCTION	4
2.1 OVERVIEW.....	4
2.1.1. <i>Class and Indication</i>	4
2.1.2. <i>Regulatory History</i>	4
2.1.3. <i>Study Reviewed</i>	5
2.2 DATA SOURCES	5
3. STATISTICAL EVALUATION	5
3.1 DATA AND ANALYSIS QUALITY	5
3.2 EVALUATION OF EFFICACY	5
3.2.1. <i>Study Design and Endpoints</i>	5
3.2.2. <i>Sample Size Consideration</i>	6
3.2.3. <i>Statistical Methodologies</i>	6
3.2.4. <i>Patient Disposition, Demographic and Baseline Characteristics</i>	7
3.2.5. <i>Results and Conclusions</i>	8
3.3 EVALUATION OF SAFETY	11
3.4 BENEFIT-RISK ASSESSMENT	11
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	12
4.1 GENDER, RACE, AGE, AND GEOGRAPHIC REGION	12
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS	12
5. SUMMARY AND CONCLUSIONS	13
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE	13
5.2 CONCLUSIONS AND RECOMMENDATIONS	14

1. EXECUTIVE SUMMARY

Novartis submitted data and final study reports of a pivotal study to support approval for everolimus and a new pediatric-appropriate formulation of dispersible tablets indicated for the treatment of pediatric and adult patients with subependymal giant cell astrocytoma (SEGA) and tuberous sclerosis complex (TSC) who require therapeutic intervention but are not likely to be cured by surgery. Novartis is also requesting a pediatric exclusivity determination. Everolimus tablet was previously approved for the treatment of adults and children ≥ 3 years of age with SEGA associated with TSC who require therapeutic intervention but are not candidates for curative surgical resection under the accelerated approval program in 2010 based on a single arm study C2485CRAD001C2485 under NDA 22334/06.

This application was based on a randomized trial, Study CRAD001M2301 (Study M2301), titled “A randomized, double-blind, placebo-controlled study of RAD001 in the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC)”, and the updated results from the single arm study C2485. In this review, Study M2301 will be discussed. Please refer to Dr. Martha Donoghue’s clinical review for more details of Study CRAD001C2485.

In Study M2301, the primary endpoint was SEGA response rate. Secondary endpoints included change from baseline to week 24 in frequency of epileptiform events (seizures); time to SEGA progression (TTSP); and skin lesion response rate.

The data and analyses from current submission showed that there is a statistically significant difference in the overall SEGA response rate as per central radiology review. There are 34.6% of the patients in the everolimus arm responded to the treatment with 95% CI (24.25, 46.2%), and 0 patient in the placebo arm responded. The p-value from the one-sided exact Cochran-Mantel-Haenszel (CMH) test was <0.0001 .

The three key secondary endpoints were tested according to the pre-defined fixed-sequence testing procedure used to control for multiplicity. Seizure frequency from baseline to week 24 was the first being tested, and no significant difference was found between the two treatment arms (one-sided rank ANCOVA, $p=0.20$). Therefore the two other secondary points cannot be formally tested. For time to SEGA progression (TTSP), no patient in the everolimus arm progressed while 6 patients (15.4%) in the placebo arm progressed. For best overall skin lesion response, 30 of 72 patients (41.7%) in the everolimus responded while 4 of 38 patients (10.5%) in the placebo arm responded.

Although the data and analyses from current submission showed that there is a statistically significant difference in the overall SEGA response rate, whether the results provide an overall risk-benefit assessment will be determined by the clinical reviewing team.

2. INTRODUCTION

The applicant submitted data and final study reports of a pivotal study to seek a new indication for everolimus. This application was based on Study CRAD001M2301 (Study M2301), a Phase III randomized, double-blind, placebo-controlled, multicenter study comparing the efficacy of everolimus with placebo.

2.1 Overview

2.1.1. Class and Indication

Everolimus is a rapamycin derivative that inhibits the mammalian target of rapamycin (mTOR) pathway by acting on the mammalian target of rapamycin complex-1 (mTORC1). The mechanism of action by which everolimus exerts its anti-tumorigenic activity is of relevance in SEGA growth. The indication sought was the treatment of children and adults with SEGA and TSC who require therapeutic intervention but are not likely to be cured by surgery.

2.1.2. Regulatory History

In April 2010 FDA issued a written request for studies in patients with SEGA and TSC which included Studies C2485 and M2301, and age appropriate formulation.

Everolimus was granted accelerated approval under NDA 22334/06 in October 2010 for the treatment of patients with SEGA who require therapeutic intervention but are not candidates for curative surgical resection based on a single arm study CRAD001C2485 (C2485), and in March 2012 for the treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex (TSC) not requiring immediate surgery.

The post-marketing requirements for the 2010 accelerated approval included:

- Submit long term (minimum 5 years) follow-up data from Study C2485, including analyses evaluating risk of adverse long-term effects of everolimus on growth and development of pediatric patients. This is due November 2014.
- Submit final study report and datasets with at least 4 years of follow-up for Study M2301, including analysis of growth and development milestones. This is due March 2015.

The goal of this NDA submission is to fulfill the components of the written request, updating results from Study C2485 used to gain accelerated approval and including data from primary analysis of randomized study M2301. The applicant also requests a pediatric exclusivity determination.

2.1.3. Study Reviewed

Study M2301 is an on-going, Phase III, placebo-controlled, randomized, double-blind, multicenter trial of everolimus versus placebo in 117 patients with TSC who have SEGA irrespective of age. The cut-off date for this submission was March 02, 2011.

Subjects were randomized in a 2:1 ratio to receive everolimus or placebo at a starting dose of 4.5 mg/m² daily, which was subsequently titrated to attain trough concentrations of 5 to 15 ng/mL. Dose adjustments were permitted based on safety and whole blood trough concentrations. Patients could continue treatment until SEGA progression or unacceptable toxicity occurred.

The primary objective of this study was to compare SEGA response rate on everolimus versus placebo in patients with TSC associated SEGA. The secondary objectives were to compare everolimus versus placebo with respect to change from baseline in frequency of epileptiform events, time to SEGA progression (TTSP), and skin lesion response rate.

2.2 Data Sources

Data used for review is from the electronic submission received on February 29, 2012. The network path is <\\CDSESUB1\EVSPROD\NDA203985\0000>.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. The applicant submitted data for both studies as well as the related SAS programs for analysis.

The reviewer was able to perform most of the analyses using the submitted data. .

3.2 Evaluation of Efficacy

3.2.1. Study Design and Endpoints

Study M2301 is an ongoing, prospective, double-blind, randomized, parallel-group, placebo-controlled, multicenter Phase-III study evaluating treatment with everolimus versus placebo in patients with TSC-associated SEGA.

Subjects were randomized in a 2:1 ratio to receive everolimus or placebo at a starting dose of 4.5 mg/m² daily, which was subsequently titrated to attain trough concentrations of 5 to 15 ng/mL. The randomization was stratified by use of enzyme-inducing anti-epileptic drugs (EIAEDs).

Patients could continue treatment until SEGA progression or unacceptable toxicity occurred. The core treatment phase lasted from randomization of the first patient until the last randomized patient was treated with everolimus or placebo for 6 months. The core treatment phase was divided into two periods: the double-blind treatment period in which all patients were randomized to everolimus or placebo, and the open-label period in which patients who had been receiving placebo and experienced a SEGA progression during the blinded treatment phase were offered open-label everolimus.

The primary efficacy endpoint was SEGA response rate as determined by independent central radiology review. SEGA response was defined as: (1) a $\geq 50\%$ reduction in SEGA volume relative to baseline (where SEGA volume was the sum of all target SEGA lesion volumes identified at baseline); and (2) no unequivocal worsening of non-target SEGA lesions, no new SEGA lesions (≥ 1 cm in longest diameter), and no new or worsening hydrocephalus. Key secondary efficacy endpoints included: absolute change in total seizure frequency per 24 hours from baseline to Week 24, time to SEGA progression (TTSP), and skin lesion response rate.

3.2.2. Sample Size Consideration

A total of 99 patients were planned for this study. Assuming the response rates are 0% in the placebo arm and $\geq 20\%$ in everolimus arm, a total of 99 patients would provide 93% power for a 2:1 randomization at a significance level of 0.025 using a 1-sided exact Cochran-Mantel-Haenszel (CMH) test.

From August 2009 to August 2010, the study enrolled 117 patients from 24 centers in 10 countries, among which 78 were randomized to the everolimus arm and 39 to the placebo arm. Sixty seven patients were in the USA.

3.2.3. Statistical Methodologies

An exact CMH test at the one-sided 2.5% level stratified by EIAED use was used to analyze the primary endpoints SEGA response rate.

A last observation carried forward (LOCF) approach was applied to secondary endpoint seizure frequency, which was tested at the one-sided 2.5% level using the rank ANCOVA model stratified by EIAED use. TTSP was tested using a one-sided log-rank test at the 2.5% significance level, stratified by EIAED use, and the HR was estimated using a Cox model. Skin lesion response rate was tested using a one-sided exact CMH test at 2.5% level.

The primary and secondary null hypotheses were tested using a hierarchical analysis strategy. The order of the test procedure for the secondary endpoints is:

1. seizure frequency from baseline to Week 24;
2. TTSP;
3. skin lesion response rate.

3.2.4. Patient Disposition, Demographic and Baseline Characteristics

Study M2301 is still on-going and the data cut-off date for this submission was March 2, 2012. Of the 117 patients randomized into the ITT population, 78 were in the everolimus arm and 39 were in the placebo arm. As of the cut-off date, 2 patients in the everolimus arm and 8 patients in the placebo arm discontinued treatment. The patient disposition is summarized in Table 3.2.3.1 (adapted from applicant's CSR).

Table 3.2.3.1 Patient Disposition

	Everolimus	Placebo
	N (%)	N (%)
Total	78 (100)	39 (100)
Ongoing in Double-Blind Period	76 (97.4)	31 (79.5)
Discont. From Double-Blind Period	2 (2.6)	8 (20.5)
Reason for Discontinuation		
patient withdrew consent	1 (1.3)	1 (2.6)
lost to follow-up	1 (1.3)	0
disease progression	0	6 (15.4)
administrative problems	0	1 (2.6) *

* This patient was not compliant with study visits.

Demographic characteristics at baseline for the ITT population are summarized in Table 3.2.3.2.

Table 3.2.3.2 Demographics at Baseline

	Everolimus	Placebo
	N (%)	N (%)
Randomized	78 (100)	39 (100)
Gender		
Male	49 (62.8)	18 (46.2)
Female	29 (37.2)	21 (53.8)
Race		
Caucasian	73 (93.6)	36 (92.3)
Non-Caucasian	5 (6.4)	3 (7.7)
Age		
< 3	13 (16.7)	7 (17.9)
3 - <18	55 (70.5)	26 (66.7)
≥ 18	10 (12.8)	6 (15.4)
Region		
U. S.	49 (62.8)	18 (46.2)
Others	29 (37.2)	21 (53.8)

Characteristics at baseline for the ITT population are summarized in Table 3.2.3.3.

Table 3.2.3.3 Characteristic at Baseline

	Everolimus	Placebo
	N (%)	N (%)
Randomized	78 (100)	39 (100)
Stratum: EIAED		
with	15 (19.2)	7 (17.9)
without	63 (80.8)	32 (82.1)

Reviewer's comments:

The patient disposition, demographic and baseline characteristics of the ITT population are generally balanced over the two arms for race, age and the stratification factor. There were more male patients and more patients from the U.S. in the everolimus arm. However the study size was relatively small.

3.2.5. Results and Conclusions

Primary Endpoint Analysis: SEGA Response Rate

There were a total of 27 responders (34.6%) in the everolimus arm and 0 (0%) in the placebo arm, as per central radiology review.

Table 3.2.5.1 summarizes the main efficacy analysis results for SEGA response rate.

Table 3.2.5.1 Results of SEGA Response Rate Analysis

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

Reviewer's comments:

The reviewer conducted other analyses, including subgroups analysis (see Section 4), using a logistic regression, analyzing change from baseline in the volumes of target SEGA lesions, to check the robustness of the primary analysis results. The results are consistent with the primary analysis results. These supportive/sensitivity analyses were also reported by the applicant.

In this submission the median follow-up was reported as 9.7 months, which was calculated as the median of the duration from the randomization date to the data cut-off date. FDA disagrees with this definition because it does not reflect the actual follow-up time. Novartis modified the definition to be the median of the duration between the randomization date and the patient's last contact date, which was 8.4 months.

Secondary Endpoints Analyses:

Changes in Seizure Frequency from baseline to Week 24

In this analysis a last observation carried forward (LOCF) approach was used so that all patients in the FAS are included in the analysis: if the 24 week video EEG was done before the lower bound of the 24 week time window and after the baseline time window, then the seizure frequency at this earlier EEG will be used.

No change in median seizure frequency was observed from baseline to Week 24 based on the LOCF approach for either treatment arm (0.00; 95% CI 0.00; 0.00), and therefore no statistically significant difference was observed between the two treatment arms (p=0.2004). There were 5 patients in each treatment arm that had missed data and used LOCF. Seventy three patients in the everolimus arm and 34 patients in the placebo arm had complete data.

Table 3.2.5.2 summarizes the main efficacy analysis results for seizure frequency.

Table 3.2.5.2 Results of Seizure Frequency Analysis (LOCF)

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

Reviewer's comments:

The results showed that there was also no statistically significant difference between the two arms in seizure frequency, as defined by the protocol. This reviewer conducted a

sensitivity analysis with non-LOCF approach (see Table 3.2.5.3.), which only used data from patients with complete follow-up at 24 weeks and no data imputation was applied, and the results were consistent with the LOCF approach.

Table 3.2.5.3 Results of Seizure Frequency Analysis (non-LOCF)

	Everolimus N = 73	Placebo N = 34
Baseline		
Mean (Standard Deviation)	3.51 (8.63)	6.10 (15.94)
Median	0	0
Range	(0, 42.6)	(0, 78.9)
Week 24 (non-LOCF)		
Mean (Standard Deviation)	2.18 (5.00)	5.83 (16.59)
Median	0	0
Range	(0, 31.6)	(0, 91.5)
Change from baseline to week 24 (non-LOCF)		
Mean (Standard Deviation)	-1.32 (6.32)	-0.27 (6.12)
Median	0	0
Range	(-34.0, 13.0)	(-15.9, 14.4)
p-value	0.1262	

Since this endpoint is the first to be tested in the fixed testing procedure, the next two secondary endpoints can not be formally tested.

Time to SEGA Progression (TTSP)

There were a total of 6 patients who progressed at time of the primary analysis (data cut-off date was March 2, 2011), all of which were in the placebo arm.

Table 3.2.5.4 summarizes the analysis results for TTSP. The median TTSP was not reached for either treatment arm.

Table 3.2.5.4 Results of TTSP Analysis

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

Reviewer's comments:

Since the first secondary endpoint failed the statistical testing, this endpoint cannot be formally tested. The observed p-value is nominal. In addition, the number of events is too small to generate a reliable result.

Skin Lesion Response Rate

There were no complete response observed and a total of 34 partial responses were observed, of which 30 were in the everolimus arm and 4 in the placebo arm.

Table 3.2.5.5 summarizes the analysis results for skin lesion response rate.

Table 3.2.5.5 Results of Skin Lesion Response Analysis

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

Reviewer's comments:

Since the first secondary endpoint failed the statistical testing, this endpoint cannot be formally tested. The observed p-value is nominal.

3.3 Evaluation of Safety

Please refer to the clinical review of this application for details of the safety evaluation.

3.4 Benefit-Risk Assessment

This is a supplement application and the benefit was deemed favorable by the clinical team. Please refer to the clinical review of this application for details of the benefit-risk assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 4.1.1 presents the summary statistics of SEGA response rate by different subgroups.

Table 4.1.1 Results of SEGA response analysis by subgroups

	Everolimus		Placebo		Difference (95% CI)
	n / N	ORR (95% CI)	n / N	ORR (95% CI)	
Age <3	3 / 13	23.1 (5.0, 53.8)	0 / 7	0 (0, 40.9)	23.1 (-24.1, 63.0)
Age 3 - <18	21 / 55	38.2 (25.4, 52.3)	0 / 26	0 (0, 13.2)	38.2 (15.0, 58.7)
Age ≥18	3 / 10	30 (6.7, 65.3)	0 / 6	0 (0, 45.9)	30.0 (-21.2, 72.7)
Male	12 / 49	24.5 (13.3, 38.9)	0 / 18	0 (0, 18.5)	24.5 (-2.4, 49.5)
Female	15 / 29	51.7 (32.5, 70.6)	0 / 21	0 (0, 16.1)	51.7 (24.8, 72.9)
Caucasian	27 / 73	37.0 (26.0, 49.1)	0 / 36	0 (0, 9.7)	37.0 (17.7, 54.7)
Non-Caucasian	0 / 5	0 (0, 52.2)	0 / 3	0 (0, 70.8)	NE
USA	16 / 49	32.7 (20.0, 47.5)	0 / 18	0 (0, 18.5)	32.7 (5.8, 56.9)
non-USA	11 / 29	37.9 (20.7, 57.7)	0 / 21	0 (0, 16.1)	37.9 (10.2, 61.7)

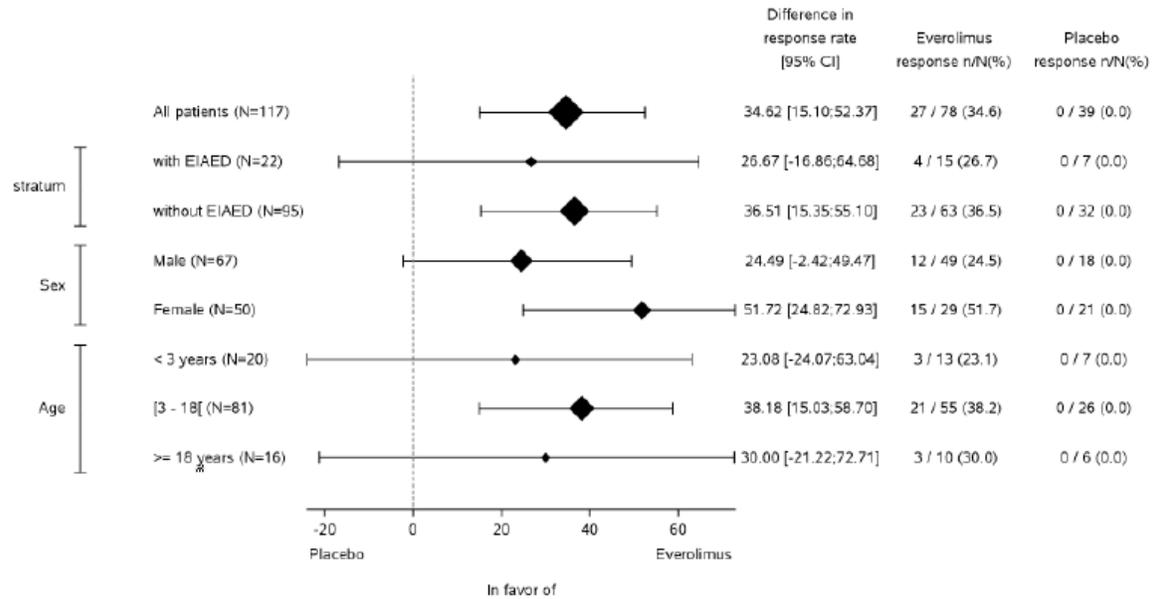
Reviewer's comments:

The analyses showed that the analysis results for subgroups of SEGA response rate were consistent with the primary analysis. .

4.2 Other Special/Subgroup Populations

The applicant also reported analysis for certain subgroups. The following figures summarize the subgroup analysis of SEGA response rate. (The graphics in this section are adapted from the applicant CSR.)

Figure 4.2.1 Subgroup Analysis of SEGA Response Rate



Reviewer's comments:

The analyses showed that the analysis results for subgroups of SEGA response rate were consistent with the primary analysis. .

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The data and analyses from current submission showed that there is a statistically significant difference in the overall SEGA response rate as per central radiology review. There are 34.6% of the patients in the everolimus arm responded to the treatment with 95% CI (24.25, 46.2%), and 0 patient in the placebo arm responded. The p-value from the one-sided exact Cochran-Mantel-Haenszel (CMH) test was <0.0001.

The three key secondary endpoints were tested according to the pre-defined fixed-sequence testing procedure used to control for multiplicity. Seizure frequency from baseline to week 24 was the first being tested, and no significant difference was found between the two treatment arms (one-sided rank ANCOVA, p=0.20). Therefore the two other secondary points cannot be formally tested. For time to SEGA progression (TTSP), no patient in the everolimus arm progressed while 6 patients (15.4%) in the placebo arm progressed. For best overall skin lesion response, 30 of 72 patients (41.7%) in the everolimus responded while 4 of 38 patients (10.5%) in the placebo arm responded.

5.2 Conclusions and Recommendations

Although the data and analyses from current submission showed that there is a statistically significant difference in the overall SEGA response rate, whether the results provide an overall risk-benefit assessment will be determined by the clinical reviewing team.

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/s/

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