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2. INTRODUCTION

Trileptal film-coated tablets (dose up to 600 mg) and oral suspension (300 mg/ 5 ml) were approved for marketing in the United States for use as adjunctive therapy and monotherapy for the treatment of partial seizures (b) (4) in adults and in children 4 to < 17 years of age. The monotherapy indication for children 4 to < 17 years of age was obtained after the initial marketing authorization in the US through a pharmacokinetic pharmacodynamic bridging approach on 07-Aug-2003.

With this supplement submission, Novartis seeks to expand the currently approved indications of Trileptal for use as adjunctive therapy or monotherapy in the treatment of partial seizures in children with epilepsy (b) (4) and to qualify Trileptal for an additional 6-month exclusivity.

2.1 Overview

Two protocols, studies 2339 and 2340, were designed to be efficacy trials to establish the basis for any potential efficacy claims in pediatric patients. The efficacy data presented in this review are based on those studies.

Table 3 Summary of Controlled Efficacy Studies in Pediatric Patients (Source: Sponsor's Table 1-1 from SCE)

Study no.	Study design	Number of OXC-treated patients /ages	Treatment duration (days)	Oxcarbazepine (mg/kg/day)
2339	Randomized, multicenter, rater-blind, age-stratified, parallel-group, two doses of OXC monotherapy	92 1 month to <17 yrs	5	Low-dose = 10; High-dose = 40 to 60
2340	Randomized, multicenter, rater-blind, age-stratified, parallel-group, two doses of OXC adjunctive therapy	128 1 month to <4 yrs	9 (Low-dose) or 35 (High-dose)	Low-dose = 10; High-dose = 60

The two studies were conducted globally with 42 sites for Study 2339 in 5 countries (Brazil, Germany, Lithuania, Mexico. and United States) and 56 sites for Study 2340 in 7 countries (Argentina, Brazil, France, Germany, Mexico, Lithuania and United States). Both studies were randomized, rater-blind, parallel-group, dose-controlled and were stratified with respect to age.

Study 2339 was conducted to assess the efficacy of Oxcarbazepine as monotherapy for children 1 month to < 17 years of age. A total of 92 patients were randomized equally to high-dose group (40-60 mg/kg/day) and low-dose group (10 mg/kg/day). The primary efficacy variable was the time to meeting exit criteria based upon video-EEG confirmed seizures as determined by the Central Reader. Continuous video-EEG monitoring began with the first dose of Oxcarbazepine on Day 3 until the patient met the exit criteria or the end of 72 hours, whichever occurred first. The treatment duration was 3 to 5 days.

The efficacy for Oxcarbazepine as adjunctive therapy for children 1 month to < 4 years of age was evaluated in Study 2340. A total of 128 subjects were randomized to a high dose group (60 mg/kg/day) and a low dose group (10 mg/kg/day) in equal numbers. The treatment duration was 9 days (maintenance only) for Low-dose group and 35 days (26 days of titration and 9 days of maintenance) for High-dose group. Seizures were recorded by continuous video-EEG for 24-72 hours at baseline and during the last 3 days of the 9-day maintenance period. Patients in this study were taking up to 2 concomitant anti-epileptic drugs (AEDs) at stable doses. The primary efficacy variable for this study was the absolute change from baseline in Type 1 seizure (SST1) frequency per 24 hours.

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form. The path to CDER Electronic Document Room for the submission is listed below:

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

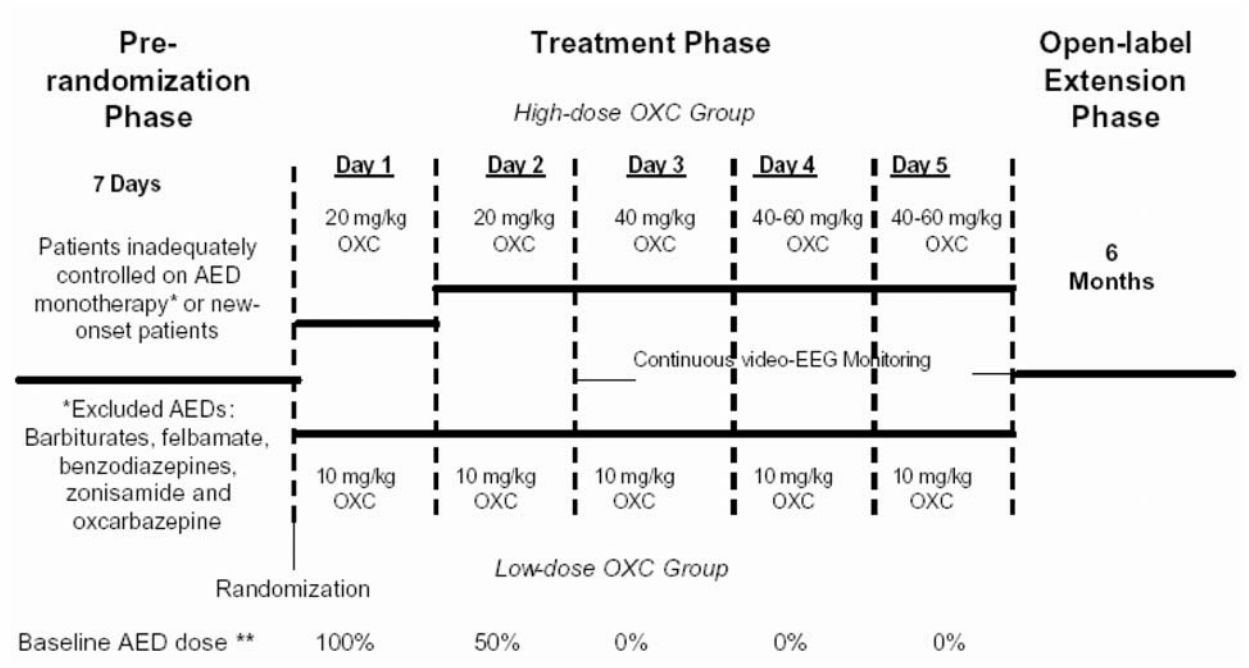
3.1.1 Evaluation of Efficacy for Protocol 2339

3.1.1.1 Study Objectives

The primary objective of this study was to evaluate the efficacy and safety of high-versus low-dose Oxcarbazepine as monotherapy in pediatric patients 1 month to < 17 years of age with inadequately controlled partial seizures or new-onset partial seizures.

3.1.1.2 Study Design

This was a multicenter, rater-blind, randomized, age-stratified, parallel-group monotherapy study comparing two doses of Oxcarbazepine in pediatric patients with inadequately-controlled partial seizures or new-onset seizures who were hospitalized either for conversion to alternative Oxcarbazepine monotherapy or for initiation of treatment (new-onset seizure patients). The study consisted of three phases: Pre-randomization, Treatment and Open-label Extension. The design of the study is described in Figure 1.



** Not applicable to new-onset seizure patients

Figure 1 Study Design (Source: Figure 3-1 of Study Report for Protocol 2339)

Approximately 80 patients 1 month to < 4 years of age were planned to be randomized in a 1:1 ratio to high-dose (40-60 mg/ kg/day or 2400 mg/day, whichever less) or low-dose (10 mg/kg/ day) Oxcarbazepine. The stratified age groups included in this study were: 1 to < 6 months, 6 to < 12 months, 12 to < 24 months, 24 to < 48 months, and 4 to < 8 years and 8 to < 17 years. Within each age group, patients were equally randomized to the High-dose OXC and Low-dose OXC group. Patients randomized to high-dose treatment received 20 mg/kg/day of Oxcarbazepine on Day 1 and Day 2. The dose was increased to 40 mg/kg/day on Day 3 and to 40-60 mg/kg/day on Days 4-5. Patients completed the study by either completing the 5-day Treatment Phase or by meeting one of the two allowed exit criteria.

The primary efficacy variable was the time to meeting exit criteria based upon video-EEG confirmed seizures as determined by the Central Reader. Continuous video-EEG monitoring began with the first dose of Oxcarbazepine on Day 3. No concomitant use of AED(s) was allowed during the Treatment Phase (with the exception of 100% of pre-randomization monotherapy AED on Day 1 and 50% of pre-randomization monotherapy AED on Day 2 only).

3.1.1.3 Patient Population

To be enrolled in the study patients must be

- 1 month to < 17 years of age with inadequately-controlled partial seizures;
- have a diagnosis of partial seizures, which may include seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures;
- have an EEG prior to baseline showing focal epileptiform discharges and/or a focal abnormality;
- have experienced 2-30 partial seizures during the 7-day Pre-randomization Phase, with no more than six seizures on any one day.

3.1.1.4 Efficacy Evaluation

Primary Efficacy Variable

The primary efficacy variable was the time to meeting exit criteria based upon video-EEG confirmed seizures as determined by the Central Reader. The exit criteria were defined as: 1) three SST1 seizures with or without secondarily generalized seizures or 2) a prolonged SST1 seizure. Definition of SST1 seizure and other study seizures are provided in Appendix 1. The exit criteria became effective following the first dose of Oxcarbazepine on Day 3. Any other seizure types did not count toward the exit criteria. Seizures occurring on Days 1 or 2 did not count toward the exit criteria.

Secondary Efficacy Variables

Secondary efficacy variables included:
1. The percentage of patients meeting exit criteria based on SST1 seizures.

2. Electrographic partial seizure frequency (i.e., SST1+ SST2) per 24 hours during the Treatment Phase.

Video-EEG Interpretation

It was necessary for the site primary investigator/epileptologist to initially review the seizure recordings on a daily basis during the Treatment Phase and make a judgment on exit. If it was determined that a patient had met exit criteria, the patient was exited from the study.

Once the patient completed the study (i.e., met exit criteria or completed the 5 days of the Treatment Phase) or prematurely discontinued from the study, the video-EEG recordings from the Treatment Phase were sent to a blinded Central Reader for interpretation, recording of seizure frequency/type, and meeting of the exit criteria. The Central Reader determined if exit criteria were actually met (if the patient was exited from the study) and/or how many seizures the patient actually experienced during the Treatment Phase. Video-EEG confirmed seizures were identified as SST1 or SST2. The data provided by the Central Reader was recorded and used in the efficacy analysis.

3.1.1.5 Statistical Analysis Methods

The starting time for the analysis was the same as the starting time for EEG monitoring on Day 3. The time to meeting exit criteria was tested for equality between the two dose groups using a log-rank test with evaluable video-EEG data. If a patient did not meet the exit criteria, the censoring time was the end of EEG.

The percentage of patients meeting exit criteria based on SST1 seizure data was compared between the two dose groups using Cochran-Mantel-Haenszel (CMH) test blocking on age groups. Electrographic partial seizure frequency was computed as the number of SST1+ SST2 seizures experienced during the continuous video-EEG monitoring in the Treatment Phase, divided by the length of the period in hours and multiplied by 24. Uninterpretable EEG minutes were subtracted from the total period. SST1+ SST2 seizure frequencies per 24-hours were compared between treatment groups using the Rank Analysis of Covariance

3.1.1.6 Protocol Amendments

The original protocol was amended 4 times. Protocol Amendment 1 increased pediatric age range from "1 month to < 4 years of age" to "1 month to < 17 years of age". This allowed evaluation of monotherapy efficacy in all age groups in which Trileptal was not labeled. The protocol also increased sample size from 88 to 100 patients to accommodate the expansion of the age range.

Protocol Amendment 2 changed exit criterion #2 from "partial-onset status epilepticus" to "prolonged SST1 seizures" to best reflect the definition for exit criteria #2.

Protocol Amendment 3 was to allow the inclusion of new-onset seizure patients (i.e., patients recently diagnosed with partial seizures for which they were not currently receiving drug treatment) and patients who had previously been exposed to low-dose, short-term treatment with Oxcarbazepine.

Protocol Amendment 4 changed sample size from 100 patients to 80 patients based upon a statistical power reduction from 90% to 80%, which was accepted by FDA. The amendment also removed wording from the original protocol which referenced the use of baseline seizure counts to be used as an explanatory variable in the efficacy analyses, as these seizure counts were not collected for the study database.

3.1.1.7 Patient disposition

Patient disposition by treatment is presented in Table 4. A total of 110 patients were screened; 92 patients met the entry criteria and were randomized. Of the 92 patients who were randomized, 86 (93.5%) completed the study and six (2 in the High-dose OXC and 4 in the Low-dose OXC) discontinued prematurely.

Table 4 Patient Disposition for Each Treatment Group (Source: Table 7-1 of sponsor's Study Report for Protocol 2339)

Patient disposition	OXC Low n (%)	OXC High n (%)	Total n (%)
Screened			110
Randomized	46 (100)	46 (100)	92 (100)
Completed	42 (91.3)	44 (95.7)	86 (93.5)
Met exit criteria	10 (21.7)	9 (19.6)	19 (20.7)
Completed 5 days without meeting exit criteria	32 (69.6)	35 (76.1)	67 (72.8)
Prematurely discontinued	4 (8.7)	2 (4.3)	6 (6.5)
Administrative problems	3 (6.5)	0 (0.0)	3 (3.3)
Adverse event(s)	1 (2.2)	2 (4.3)	3 (3.3)

The ITT patient population included 42 subjects in the High-dose OXC group and 45 subjects in the Low-dose OXC group. Inclusion of patients in the efficacy analyses was based on the Central Reader data. Due to unreadable or corrupt EEG data, three patients (two in the High-dose OXC group, one in the Low-dose OXC-dose group) who completed 5 days without meeting exit criteria were excluded from the efficacy analyses. Two of the six prematurely discontinued patients (both in the High-dose OXC group) discontinued on or before Day 3 without the video-EEG data and were also excluded from the efficacy analyses. The other four prematurely

discontinued patients provided incomplete video-EEG data; they are included in the efficacy analyses.

3.1.1.8 Baseline demographic and background characteristics

Table 5 summarizes the demographic characteristics of patients in the safety population by treatment. The groups were well balanced for age and seizure classification. More than half the patients in this study were less than 4 years of age. The majority of patients in both groups were Caucasian. There were twice as many new-onset patients in the High- dose OXC group (n= 10) as in the Low-dose OXC group (n= 5). There also appears to be an imbalance in the gender distribution, with more male patients in Low-dose OXC group (28 vs. 21, or 60.9% vs. 45.7%).

Table 5 Baseline Demographics and Disease Characteristics by Treatment Group - Safety Population (Source: Table 7-3 of Sponsor's Study Report for Protocol 2339)

	OXC Low N = 46 n (%)	OXC High N = 46 n (%)	Total N = 92 n (%)
Baseline Age			
1 - <6 months	4 (8.7)	4 (8.7)	8 (8.7)
6 - <12 months	7 (15.2)	6 (13.0)	13 (14.1)
12 - <24 months	6 (13.0)	6 (13.0)	12 (13.0)
24 - <48 months	9 (19.6)	9 (19.6)	18 (19.6)
4 - <8 years	10 (21.7)	11 (23.9)	21 (22.8)
8 - <17 years	10 (21.7)	10 (21.7)	20 (21.7)
Sex			
Male	28 (60.9)	21 (45.7)	49 (53.3)
Female	18 (39.1)	25 (54.3)	43 (46.7)
Race			
Black	8 (17.4)	4 (8.7)	12 (13.0)
Caucasian	30 (65.2)	26 (56.5)	56 (60.9)
Other	8 (17.4)	16 (34.8)	24 (26.1)
Initiation of monotherapy			
Yes	5 (10.9)	10 (21.7)	15 (16.3)
No	41 (89.1)	36 (78.3)	77 (83.7)
ILAE Classification			
Simple partial seizures	13 (28.3)	13 (28.3)	26 (28.3)
Complex partial seizures	35 (76.1)	35 (76.1)	70 (76.1)
Partial seizures with secondary GTC	22 (47.8)	23 (50.0)	45 (48.9)
Other seizures	13 (28.3)	12 (26.1)	25 (27.2)

3.1.1.9 Efficacy results Reported by Sponsor

The primary efficacy variable is the time to meeting exit criteria based upon video-EEG confirmed SST1 seizures as determined by the Central Reader. As shown in Figure 9-1 there was no significant difference between the High-dose OXC and Low-dose OXC groups for this variable (p= 0.904, log- rank test). This p-value is similar to other p-values obtained from Cox regression model where the effects of age, gender and initiation of monotherapy (yes or no) were further investigated. None of these factors significantly affected the time to meeting exit criteria.

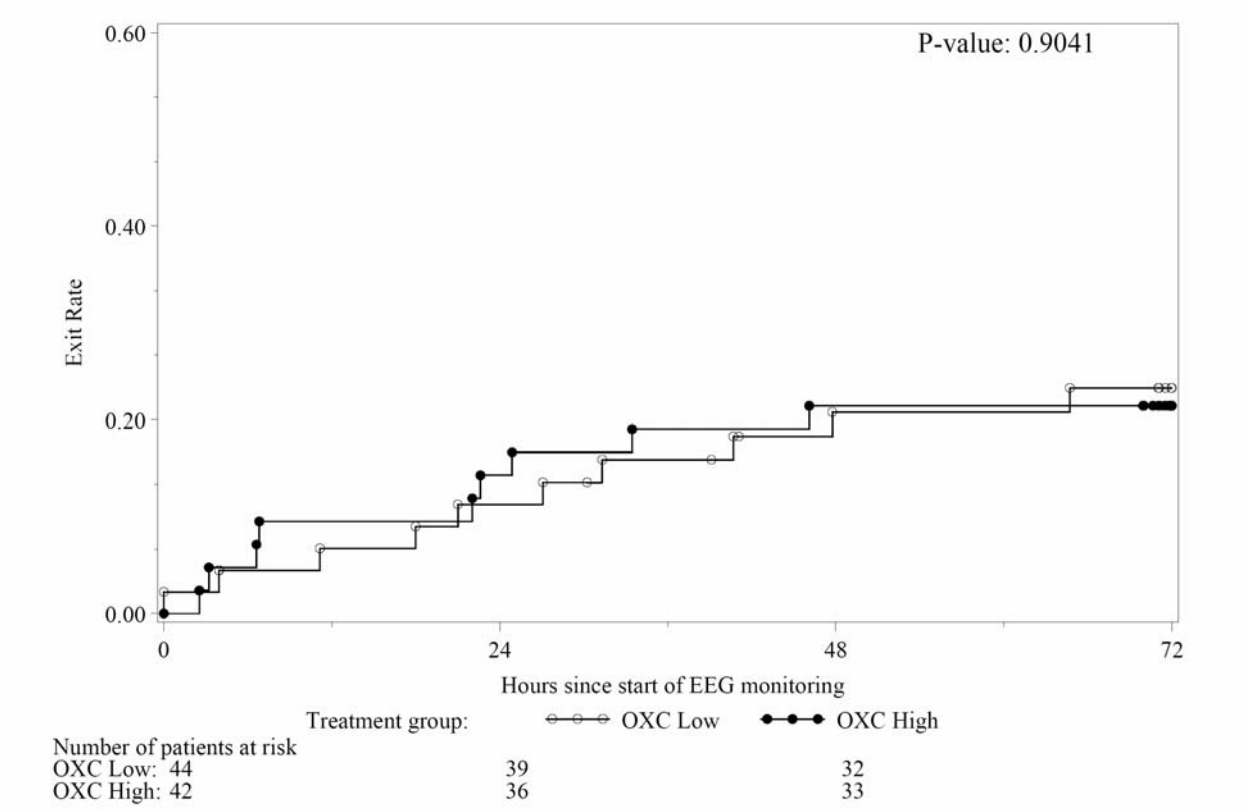


Figure 2 Time to Meeting Exit Criteria Based on SST1 Seizure Data (Source: Figure 9-1 of Sponsor's Study Report for Protocol 2339)

3.1.1.10 Reviewer's analysis

The reviewer applied protocol specified log-rank test to the primary efficacy variable of time to meeting the exit criteria. The results presented by the sponsor were verified to be correct. There were few events for either of the treatment group (10 events for the Low-dose group and 9 events in the High-dose group) and most subjects did not meet the exit criteria by the end of the 72-hour EEG monitoring time. Therefore, the median time to exit was censored for both treatment groups. More than half of the patients in each treatment group had 0 seizure during the treatment period (69% in low dose and 64% in the high dose). Secondary efficacy data are not presented due to the nature of the data.

3.1.2 Evaluation of Efficacy of Protocol 2340

3.1.2.1 Study Objective

The primary objective of this study was to evaluate the efficacy and safety of high-versus low-dose Oxcarbazepine as adjunctive therapy in pediatric patients 1 month to < 4 years of age with inadequately controlled partial seizures.

3.1.2.2 Study Design

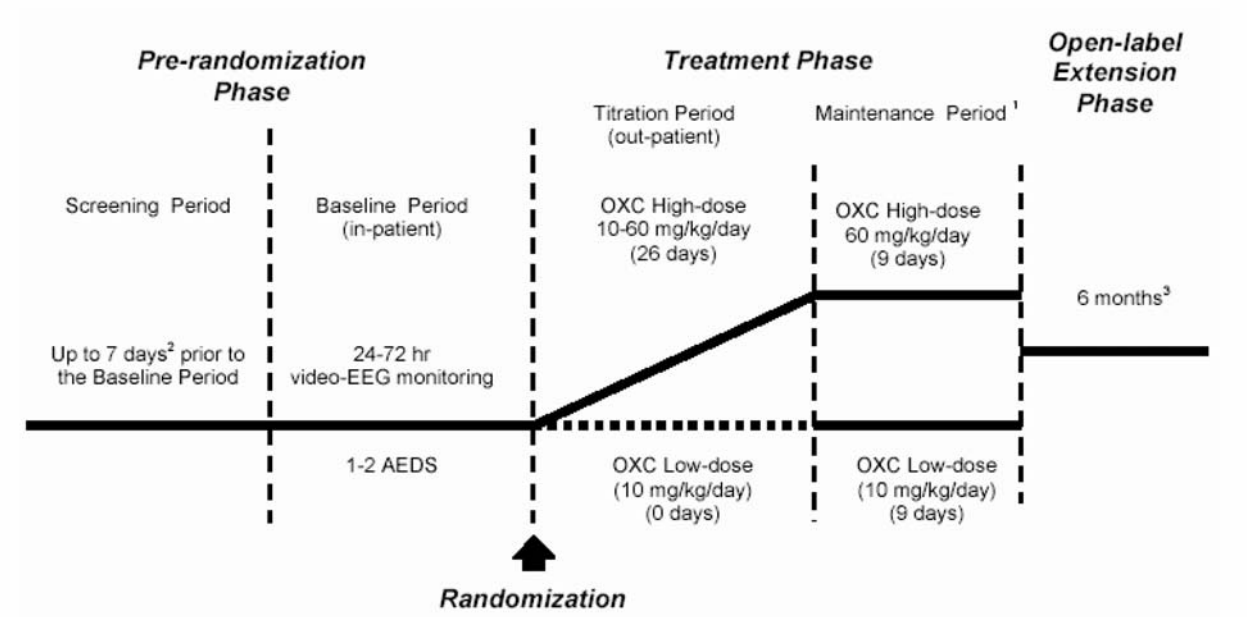
This was a multicenter, rater-blind, randomized, age-stratified, parallel-group, adjunctive therapy study comparing two doses of Oxcarbazepine in pediatric patients with inadequately-controlled partial seizures who were taking up to two concomitant AEDs. No changes in concomitantly used AEDs were allowed during the treatment phase.

Approximately 128 patients, 1 month to < 4 years of age, were planned to be randomized in a 1:1 ratio to High-dose (60 mg/kg/day) or Low-dose (10 mg/kg/day) Oxcarbazepine. The stratified age groups included in this study were: 1 to < 6 months, 6 to < 12 months, 12 to < 24 months, and 24 to < 48 months. Within each age group, patients were equally randomized to High-and Low-dose Oxcarbazepine.

The study consisted of three phases: Pre-Randomization Baseline, Treatment and Open-label Extension. The Baseline Period was 24-72 hours in duration and was conducted on an in-patient basis during which time the patient was continuously monitored by video-EEG. Patients were maintained on stable doses of their concomitant AEDs during the baseline period. Patients could have been randomized any time after the first 24 hours of monitoring provided they had experienced at least two SST1 seizures. Patients who did not experience at least two SST1 seizures in 72 hours of continuous monitoring were not eligible to be randomized into the Treatment Phase.

During the Treatment Phase, patients randomized to the High-dose OXC treatment group entered a 26-day Titration Period followed by a 9-day Maintenance Period. Patients randomized to the low-dose treatment group immediately entered a 9-day Maintenance Period. The Treatment Phase was conducted on an out-patient basis except for the last 3 days of the maintenance period, during which time the patient stayed in the study site for a 72-hour continuous video-EEG monitoring. To allow flexibility for scheduling the second in-patient video-EEG monitoring, the maintenance period could have been extended up to an additional 5 days.

The central reader, who read and interpreted the video-EEG data was blinded to the treatment assignment, while the investigators and patients were not blinded in this trial. Whether or not the unblinding of the investigator and patients would affect the interpretability of the study results needs to be assessed by the medical reviewer.



[1] All patients were hospitalized and continuously monitored by video-EEG during the last 72 hours of the Maintenance Period

[2] Up to 30 days and at least 1 day prior to the Baseline Period for sites in France (French National Amendment 1)

[3] At sites in France, the Open-label Extension Phase could be extended beyond 6 months, until the commercial availability of Trileptal® oral suspension 60mg/ml (French National Amendment 2). During this Post-Extension Period, safety data were collected.

Figure 3 Study Design (Source: Figure 3-1 of Sponsor's Study Report for Protocol 2440)

3.1.2.3 Efficacy Assessment

Primary Efficacy Variable

The primary efficacy variable was the absolute change in SST1 seizure frequency per 24 hours during the last 72 hours of continuous video-EEG monitoring in the Treatment Phase compared to the seizure frequency at Baseline. Definition of SST1 seizure and other study seizures are provided in Appendix 1.

Secondary efficacy variables

1. The percentage change in SST1 seizure frequency per 24 hours
2. The absolute change in SST1 + SST2 seizure frequency per 24 hours
3. Response to treatment was characterized by at least a 50%, 75%, and 100% reduction in SST1 seizure frequency per 24 hours.

EEG Interpretation

The video- EEG recordings from both the Baseline and Maintenance Periods were sent to a Central Reader for interpretation and recording of seizure frequency and type. The Central Reader, who was an independent pediatric neurologist not involved with the conduct of the study, was blinded. Video-EEG confirmed seizures were identified and recorded as SST1 or SST2. Seizures occurring during the Baseline Period were initially evaluated by the on-site epileptologist in order to determine patient eligibility for randomization.

3.1.2.4 Statistical Analysis Methods

Analysis of Primary Efficacy Variable

The primary variable of absolute change in SST1 seizure frequency per 24 hours was compared between the treatment groups using the Rank Analysis of Covariance stratifying by age groups with the SST1 seizure frequency per 24 hours at baseline as covariate.

Analyses of Secondary Variables

1. The percentage change in SST1 seizure frequency per 24 hours was compared between the treatment groups using the Rank Analysis of Covariance stratified by age groups with the SST1 seizure frequency per 24 hours at baseline as covariate. For patients with zero SST1 seizures during the Treatment Phase, the percent change in SST1 seizure frequency per 24 hours was defined as 0 %. For patients with non-zero SST1 seizures during the Treatment Phase, the highest observed percent change among the patients with non-zero SST1 seizures at baseline was assigned.

2. The absolute change in SST1 + SST2 seizure frequency per 24 hours was compared between treatment groups using the Rank Analysis of Covariance stratifying by age groups with the SST1 + SST2 seizure frequency per 24 hours at baseline as covariate.

3. A patient was categorized as responding to treatment if he/she experienced at least a 50% reduction in SST1 seizure frequency per 24 hours. A patient with zero seizures at baseline was categorized as a non-responder to treatment regardless of the seizure counts during the Treatment Phase. The proportion of having a response to treatment was compared between the two dose groups using Cochran-Mantel-Haenszel (CMH) test blocking on age groups.

3.1.2.5 Protocol Amendments

Three international amendments were made to the original protocol. Amendment 1 allowed the inclusion of patients who had previously been exposed to low-dose, short-term treatment with Oxcarbazepine. Amendment 2 allowed patients who failed screening to enter the Open-label Extension Phase of the Study. Amendment 3 changed the primary efficacy variable from “percent change in SST1 seizure frequency” to “absolute change in SST1 seizure frequency”

based on an agreement reached with the FDA during the pre-sNDA meeting on March 24, 2004. Absolute change was chosen as the primary variable in order to avoid the use of imputation for data with zero baseline seizure count.

3.1.2.6 Patient Disposition

Patient disposition by treatment is presented in Table 6. A total of 191 patients were screened and 128 patients were randomized. Of the 128 patients who were randomized, 115 (89.8%) completed the study and 13 (8 in high-dose OXC and 5 in low-dose OXC) discontinued prematurely.

Table 6 Patient Disposition by Treatment Group (Source: Table 7-1 of Sponsor's Study Report for Protocol 2440)

Patient disposition	OXC Low n (%)	OXC High n (%)	Total n (%)
Screened*			191
Randomized	64 (100)	64 (100)	128 (100)
Completed	59 (92.2)	56 (87.5)	115 (89.8)
Prematurely Discontinued	5 (7.8)	8 (12.5)	13 (10.2)
Adverse Event(s)	2 (3.1)	3 (4.7)	5 (3.9)
Subject withdrew consent	2 (3.1)	2 (3.1)	4 (3.1)
Unsatisfactory therapeutic effect	1 (1.6)	3 (4.7)	4 (3.1)

Source: Post-text tables 7.1-1, 7.3-1, and 7.3-2.

*Note: 54 of the 63 patients who were not randomized did not meet the SST1 seizure requirement during baseline monitoring. Patients not meeting the SST1 seizure requirement after Protocol Amendment 2 was approved were eligible to enter the Open-label Extension Phase.

3.1.2.7 Baseline demographic and background characteristics

The demographic and background characteristics of patients in the safety population are summarized in Table 7. The groups were adequately balanced for age, sex, race and seizure classification with the exception of an increased percentage of patients in the High-dose OXC group having secondarily generalized partial seizures. The majority of patients in both groups were Caucasian. There were slightly more male patients than female patients.

Table 7 Baseline Demographic and Disease Characteristics by Treatment Group (Source: Table 7-3 of Sponsor's Study Report for Protocol 2440)

	OXC Low N=64 n (%)	OXC High N=64 n (%)	Total N=128 n (%)
Baseline Age			
1 - <6 months	10 (15.6)	11 (17.2)	21 (16.4)
6 - <12 months	12 (18.8)	12 (18.8)	24 (18.8)
12 - <24 months	19 (29.7)	19 (29.7)	38 (29.7)
24 - <48 months	23 (35.9)	22 (34.4)	45 (35.2)
Sex			
Male	35 (54.7)	38 (59.4)	73 (57.0)
Female	29 (45.3)	26 (40.6)	55 (43.0)
Race			
Black	3 (4.7)	5 (7.8)	8 (6.3)
Caucasian	42 (65.6)	47 (73.4)	89 (69.5)
Other	19 (29.7)	12 (18.8)	31 (24.2)
ILAE Classification			
Simple partial seizures	20 (31.3)	23 (35.9)	43 (33.6)
Complex partial seizures	46 (71.9)	50 (78.1)	96 (75.0)
Partial seizures, secondarily generalized	24 (37.5)	35 (54.7)	59 (46.1)
Other seizures	18 (28.1)	22 (34.4)	40 (31.3)

3.1.2.8 Efficacy results Reported by Sponsor

3.1.2.8.1 Primary efficacy results

The primary variable was the absolute change in SST1 seizure frequency per 24 hours. As shown in Table 8, the reduction in SST1 seizure frequency per 24 hours was statistically significantly greater in the High-dose OXC group than in the Low-dose OXC group (p= 0.043). Results for the per-protocol population were similar (p= 0.044).

Table 8 Absolute Change in Partial Seizure Frequency (SST1) per 24 Hours - ITT Population (Source: Table 9-1 of Sponsor's Study Report for Protocol 2440)

	OXC Low N=57	OXC High N=59	P-value*
Baseline Mean (SD)	13.29 (22.34)	10.27 (17.82)	
Treatment Mean (SD)	10.50 (24.08)	2.67 (4.40)	
Absolute Change Mean (SD)	-2.79 (16.02)	-7.60 (17.38)	
Median Absolute Change	-1.37	-2.00	0.043

3.1.8.2.2 Secondary efficacy results

As seen in Table 9, the percentage reduction in SST1 seizure frequency per 24 hours was statistically significantly greater in the High-dose OXC group than in the Low-dose OXC group (p= 0.047). Results for the per-protocol population were similar (p= 0.030).

Table 9 Percent Change in Partial Seizure Frequency (SST1) per 24 Hours - ITT Population (Source: Table 9-2 of Sponsor's Study Report for Protocol 2440)

	OXC Low N=57	OXC High N=59	P-value*
Baseline Mean (SD)	13.29 (22.34)	10.27 (17.82)	
Treatment Mean (SD)	10.50 (24.08)	2.67 (4.40)	
Percent Change Mean (SD)	-12.80 (114.66)	-45.73 (90.36)	
Median Percent Change	-46.18	-83.33	0.047

As shown in Table 10, the absolute reduction in electrographic partial seizure frequency (SST1 + SST2) per 24 hours was statistically significantly greater in the High- dose OXC group than in the Low- dose OXC group (p= 0.020).

Table 10 Absolute Change in Electrographic Partial Seizure Frequency (SST1+SST2) per 24 Hours - ITT Population (Source: Table 9-3 of Sponsor's Study Report for Protocol 2440)

	OXC Low N=57	OXC High N=59	P-value*
Baseline Mean (SD)	14.03 (23.23)	10.82 (18.06)	
Treatment Mean (SD)	10.77 (24.11)	3.07 (5.11)	
Absolute Change Mean (SD)	-3.26 (16.78)	-7.76 (17.13)	
Median Absolute Change	-1.64	-2.32	0.020

As shown in Table 11, the percentage of patients who were categorized as responding to treatment (i.e., experienced at least a 50% reduction in SST1 seizure frequency per 24 hours) was greater in the High-dose OXC group compared with the Low-dose OXC group, although the difference did not reach statistical significance (p= 0.088).

Table 11 Response to Treatment - ITT Population (Source: Table 9-4 of Sponsor's Study Report for Protocol 2440)

	OXC Low N=57 n (%)	OXC High N=59 n (%)	P-value*
≥ 50% Reduction	27 (47.37)	38 (64.41)	0.088
≥ 75% Reduction	19 (33.33)	32 (54.24)	--
100% Reduction	10 (17.54)	19 (32.20)	--

3.1.2.9 Reviewer's Analysis

The protocol specified analysis methods were applied to primary and secondary efficacy variables correspondingly. All results reported by the sponsor and presented in Section 3.1.8.2 were confirmed to be correct.

The primary efficacy variable (absolute change from baseline in SST1 seizure frequency) and two secondary efficacy variables (percent change in SST1 seizure frequency and absolute change in SST1+SST2 seizure frequency) were analyzed by Rank Analysis of Covariance. The analysis consisted of 3 steps. First, the change from baseline in SST1 seizure frequency and baseline SST1 seizure frequency were ranked separately within each of the age groups. The rank scores for the change were then regressed against rank scores of baseline for each of the age groups. Finally, residuals from each of the regression models (one for each age group) were combined and analyzed by CMH test for treatment effect, controlling for age group.

In this primary analysis the variation of the primary endpoint was first explained by baseline effect, assuming that baseline effect could be different for each age group. After the baseline effect has been accounted for, the remaining differences were attributed to treatment effect and random error.

Baseline effect was significant in all age groups in the analyses of absolute change in seizure frequency; SST1 seizures for the primary endpoint and SST1+SST2 for secondary endpoint. The results showed that the larger the baseline, the larger the seizure reduction across all age groups. Though the treatment effect was statistically significant after accounted for baseline effect, the magnitude of the treatment effect varies among age groups. Specifically, most treatment effect came from the oldest age group of 24 months to 48 months, while very little effect was seen in the other 3 age groups. The age difference in treatment effect is discussed in more detail in Section 4.

3.2 Evaluation of Safety

Please refer to Clinical Review by Dr. Norman Hershkowitz for Evaluation of Safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Comparisons of treatment groups for seizure frequencies by demographic characteristics were carried out by this reviewer. The results of the comparisons are discussed in the following sub-section.

4.1 Gender, Race and Age

4.1.1 Analysis for Protocol 2339

The following table presents the results from subgroup analyses by gender, race and age. Age was broken by younger than 4 years old and 4 years and older due to the reason of few events. No discrepancies were found among subgroups with regard to number of subjects meeting the exit criteria. Estimate of time to exit could not be obtained because the median times were all censored.

Table 12 Time to Meeting Exit Criteria (Source: Reviewer's Analysis)

Characteristic	Low Dose (Number (%))		High Dose (Number (%))	
	Exit	Censor	Exit	Censor
Gender				
Male	7 (26%)	20 (74%)	4 (22%)	14 (78%)
Female	3 (17%)	15 (83%)	5 (21%)	19 (79%)
Race				
Caucasian	5 (17%)	24 (83%)	5 (20%)	25 (80%)
Black	3 (37%)	5 (63%)	0 (0%)	3 (100%)
Other	2 (25%)	6 (75%)	4 (29%)	10 (71%)
Age				
< 4 years	5 (19%)	22 (81%)	6 (27%)	16 (73%)
>= 4 years	5 (25%)	15 (75%)	3 (15%)	17 (85%)

4.1.2 Analysis for Protocol 2340

In the section of Reviewer's Analysis we have discussed that the change in seizure frequency was dependent on the baseline. That is, the larger the baseline seizure frequency, the larger the reduction. This dependency is true in all age groups. There was a large variation in baseline seizure frequency, especially in the two younger age groups, and the distributions for both baseline and the change in seizure frequency were skewed. For example, the mean SST1 seizure frequency in the youngest age group of < 6 months was much larger in the low dose group than in the high dose group (21.32 vs. 13.56), while the medians of the SST1 seizure frequency was just in opposite direction (6.70 vs. 11.04) (Table 13). It is therefore difficult to see the difference in treatment effect across the age groups by looking at the baseline or the change in seizure frequencies.

Table 13 SST1 Seizure Frequency by Age Group (Source: Reviewer's Analysis)

Age Group	Low Dose		High Dose		Nominal p-value
	Mean (SD)	Median	Mean (SD)	Median	
< 6 months					
n	7		10		
Baseline	21.32 (38.06)	6.70	13.56 (12.93)	11.04	
Final	9.57 (18.51)	1.06	4.94 (6.34)	2.68	
Change	-11.75 (20.18)	-3.50	-8.62 (8.61)	-6.78	
Residual	0.02 (3.64)	-1.37	-0.02 (2.32)	-0.60	.9762
6 months to < 12 months					
n	12		12		
Baseline	24.49 (33.51)	10.14	8.83 (8.78)	7.98	
Final	18.65 (33.60)	5.32	4.14 (5.28)	2.00	
Change	-5.84 (13.01)	-3.65	-4.69 (10.06)	-0.98	
Residual	0.26 (6.49)	-2.16	-0.26 (5.15)	-2.93	.8218
12 months to < 24 months					
n	16		18		
Baseline	9.34 (12.73)	3.03	11.25 (22.65)	4.50	
Final	9.42 (31.50)	0.40	1.32 (2.06)	0.62	
Change	0.08 (24.16)	-0.92	-9.93 (22.92)	-2.28	
Residual	0.17 (8.23)	-2.78	-0.15 (6.65)	-2.98	.8962
24 months to < 48 months					
n	22		19		
Baseline	7.51 (8.51)	6.19	8.50 (19.90)	2.99	
Final	7.13 (9.87)	3.83	1.82 (3.80)	0.00	
Change	-0.37 (4.22)	-0.57	-6.68 (19.13)	-1.97	
Residual	3.88 (11.83)	1.39	-4.49 (9.59)	-4.43	.0204

As it has been pointed out in the previous section in the Reviewer's Analysis, difference in the seizure frequency change was first explained by baseline seizure frequency by the analysis model. After the baseline effect has been taken into account, the remaining difference was attributed to treatment effect and random error. The remaining difference is shown as residuals from the regression model.

From the residuals presented in Table 13, there was little difference between the treatment groups in all age groups except the oldest one. The treatment difference in the oldest age group carried a nominal p-value of 0.0204 with less than half of the size of all patients.

Analyses of secondary efficacy variables by age groups showed the similar results (see Appendix 2), that the treatment difference was mainly contributed by the oldest age group.

Results from efficacy analyses by subgroup of gender and race are presented in the following table. There was no discrepancy between the two gender groups. Of the 116 patients in the ITT patient population, 36 (63%) of the low dose group and 44 (75%) of the high dose group were Caucasians, 3 in the low dose group and 5 in the high dose group were Black, and the rest of the patients were categorized as "Other". The treatment difference in Caucasians was in line with the

whole patient population (nominal p=.0305). The other two race groups were too small to have any reliable conclusion to be drawn.

Table 14 SST1 Seizure Frequency by Gender (Source: Reviewer's Analysis)

Gender	Low Dose		High Dose		Nominal p-value
	Mean (SD)	Median	Mean (SD)	Median	
Gender					
Male					
n	31		33		
Baseline	10.22 (20.30)	5.43	8.95 (8.67)	6.81	
Final	6.22 (16.15)	1.06	3.04 (4.52)	0.58	
Change	-4.00 (8.38)	-1.98	-5.91 (8.20)	-2.99	
Residual	0.81 (8.54)	-1.74	-2.05 (8.20)	-2.96	.1915
Female					
n	26		26		
Baseline	16.96 (24.44)	10.20	11.94 (25.20)	2.88	
Final	15.60 (30.60)	3.76	2.20 (4.29)	0.50	
Change	-1.35 (22.06)	-0.98	-9.74 (24.62)	-1.25	
Residual	2.55 (9.90)	-1.05	-0.91 (5.73)	-1.82	.1517
Race					
Caucasian					
n	36		44		
Baseline	12.66 (21.41)	6.50	9.46 (15.85)	4.18	
Final	9.90 (21.34)	2.24	2.19 (4.02)	0.34	
Change	-2.76 (7.86)	-0.91	-7.28 (15.54)	-2.61	
Residual	1.74 (9.46)	-0.81	-2.42 (6.67)	-2.93	.0305
Black					
n	3		5		
Baseline	1.88 (2.01)	1.65	4.49 (6.09)	2.21	
Final	2.23 (1.50)	2.36	3.91 (3.95)	2.67	
Change	0.35 (1.85)	0.67	-1.03 (3.41)	0.00	
Residual	4.20 (7.03)	1.06	5.04 (7.26)	2.06	.7690
Other					
n	18		10		
Baseline	16.46 (25.78)	8.54	16.46 (27.70)	3.33	
Final	13.07 (30.86)	3.17	4.18 (6.01)	2.02	
Change	-3.38 (26.75)	-1.99	-12.28 (27.18)	-2.02	
Residual	0.89 (9.14)	-2.40	-1.03 (8.26)	-1.16	.6701

4.2 Other Special/Subgroup Populations

No other special/subgroup analyses were performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The submission of this supplement NDA by Novartis contains documents of two clinical studies, one as monotherapy and one as adjunctive therapy, of Oxcarbazepine for treatment of partial seizures in pediatric patients with epilepsy.

Study 2339 was conducted to assess the efficacy of Oxcarbazepine as monotherapy for children 1 month to < 17 years of age. The primary efficacy evaluation in time to meeting exit criteria (based upon video-EEG confirmed seizures as determined by a Central Reader) showed no significant difference between the two dose groups (p= 0.904). More than half of the patients (69% in the low dose group and 64% in the high dose group) did not have any seizures during the 72-hour EEG monitoring. The majority of patients from both dose groups completed the 5-day study without exiting. The rates of meeting exit criteria were 21% and 22% for the High-and Low-dose OXC groups, respectively.

The expected exit rates of 35% and 70% for the High-and Low-dose OXC groups, respectively, were assumed in the protocol based on the exit rates observed in a previous pre-surgical monotherapy study with duration of 10 days. The treatment duration of 5 days for this study might be too short to capture the treatment difference, if any, especially when patients were on monotherapy AED on Day 1 and Day 2. The effect of monotherapy AED might have been carried over to the next 3 days and contributed to the results of the study.

The efficacy for Oxcarbazepine as adjunctive therapy for children 1 month to < 4 years of age was evaluated in Study 2340. In this study, High-dose Oxcarbazepine treatment (target dose 60 mg/kg/day) was statistically significantly more effective in controlling partial seizures than treatment with Low-dose Oxcarbazepine (10 mg/kg/day) in the analysis of all subjects.

Although the treatment difference in Study 2340 reached statistical significance with a p-value of 0.043, the evidence of the effectiveness of Oxcarbazepine was weak as the treatment effect was not shown consistently across age groups. The effect of Oxcabazepine was mostly seen in the oldest age group of 24 months to 48 months, with little effect seen in the 3 younger age groups of patients aged 1 month to < 24 months. Analyses of secondary efficacy variables showed the same age discrepancy.

5.2 Conclusions and Recommendations

Study 2339 failed to establish the efficacy of Oxcabazepine as monotherapy in pediatric patients aged 1 month to < 17 years. The study compared high dose (40-60 mg/kg/day) to low dose (10 mg/kg/day) of Oxcabazepine. No treatment difference was observed in time to meeting the exit criteria based on seizure frequency/severity recorded by continuous video-EEG during the last 3 days of the 5-day treatment period.

The effectiveness of Oxcarbazepine as adjunctive therapy in pediatric patients 1 month to < 4 years old was difficult to interpret, as Study 2340 showed large discrepancy in the treatment difference among the four age groups. The study compared Oxcarbazepine at dose 60 mg/kg/day to a low dose of 10 mg/kg/day. The treatment difference has reached statistical significance in the overall patient population. However, the effect of Oxcabazepine was mostly seen in the oldest age group of 24 months to 48 months, with little effect seen in the 3 younger age groups of patients aged 1 month to < 24 months.

APPENDICES

Appendix 1 Study Seizures

Study Seizure Type 1 (SST1), characterized by all of the following:

- a recognizable focal ictal pattern on EEG involving at least two contiguous electrodes, which must demonstrate a spatial and temporal evolution consistent with an ictal discharge and be distinct from the patient's background cerebral electrical activity, and
- an electrographic duration of at least 20 seconds, and
- a behavioral correlate as observed on video or by a parent/trained site personnel.

Study Seizure Type 2 (SST2), characterized by all of the following:

- a recognizable focal ictal patterns on EEG involving at least two contiguous electrodes, which must demonstrate a spatial and temporal evolution consistent with an ictal discharge and be distinct from the patient's background cerebral electrical activity, and
- an electrographic duration of at least 20 seconds.

Appendix 2 Secondary Efficacy Results by Age Group

Efficacy results are presented as residuals only, since that is the measure relevant.

Table 15 Residuals from the Analysis of Percent Change from Baseline in SST1 Seizure Frequency per 24 Hours (Source: Reviewer's Analysis)

	Low Dose		High Dose		Nominal
Age Group	Mean (SD)	Median	Mean (SD)	Median	p-value
< 6 months					
n	7		10		
Residual	-0.63 (5.42)	1.15	0.44 (4.94)	-1.09	.6653
6 months to < 12 months					
n	12		12		
Residual	1.13 (6.54)	1.82	-1.13 (6.93)	-1.71	.4070
12 months to < 24 months					
n	16		18		
Residual	0.10 (10.25)	1.02	-0.09 (9.74)	-1.77	.9570
24 months to < 48 months					
n	22		19		
Residual	4.12 (10.56)	3.47	-4.77 (11.50)	-13.01	.0158

Table 16 Residuals from the Analysis of Absolute Change from Baseline in SST1+SST2 Seizure Frequency per 24 Hours (Source: Reviewer's Analysis)

	Low Dose		High Dose		Nominal
Age Group	Mean (SD)	Median	Mean (SD)	Median	p-value
< 6 months					
n	7		10		
Residual	-0.14 (3.85)	-1.38	0.10 (2.62)	-1.22	.8724
6 months to < 12 months					
n	12		12		
Residual	0.33 (6.44)	-2.16	-0.33 (5.21)	-2.93	.7762
12 months to < 24 months					
n	16		18		
Residual	0.18 (8.20)	-2.70	-0.16 (6.84)	-3.00	.8914
24 months to < 48 months					
n	22		19		
Residual	4.34 (11.85)	1.18	-5.02 (6.80)	-4.31	.0057

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