CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-014

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

AUG 31 1999

NDA#: 21014

DRUG COMPANY: NOVARTIS

NAME OF DRUG: Trileptal (Oxcarbazepine)

INDICATION: Mono-therapy or adjunctive therapy in the treatment of partial seizures in adults and children with epilepsy

DOCUMENTS REVIEWED: Original NDA

I. Introduction

Trileptal has been studied in the United States under IND [redacted] in 6 controlled studies (2 in pediatric population). A total of 2,327 patients were treated, among them 2,191 with epilepsy, 1,574 were adults, 565 were children, and 52 were elderly. Trileptal is now registered in over 50 countries.

Dose Selection

Minimum 600 mg/day
Mean 1200 mg/day
Maximum 2400 mg/day

Objective: to demonstrate the efficacy and safety of oxcarbazepine in the treatment of partial seizures

Clinical Trials (6 key trials)

2 in adjunctive therapy (Protocols OT/PE1 and 011);
4 in monotherapy (Protocols 004 and 025: placebo control;
026 and 028: dose control).

All key trials were double-blind, controlled, and parallel design in epilepsy patients with partial seizures.

Trileptal Mono-therapy Trials

A total of four multi-center trials were conducted to demonstrate the efficacy of Trileptal as mono-therapy. Two trials (Study 04 and Study 025) were double-blind, placebo controlled, and two trials (Study 026 and Study 028) were double-blind, dose-controlled mono-therapy substitution trials using a high dose (2400 mg) versus a low dose (300 mg) of Trileptal as a substitute for one or more antiepileptic drugs (AEDs). Patients' age in

these 4 trials ranges from 8 to 69 years old. Table 1 summarizes the four mono-therapy trials. P-values in Table 1 are from sponsor's analyses.

Table 1. Summary of primary efficacy analyses for mono-therapy trials (ITT patients)

Trial	Primary Variable	Treatment Group	N	Statistics	P-value
004	Median time to exit criterion (days)	Trileptal 2400 mg/day Placebo	102	NA[1] 1.3 days	0.0001[2]
025	Median time to first partial seizure (days)	Trileptal 1200 mg/day Placebo	67	11.7 days 3.2 days	0.0457[2]
026	Median time to exit criterion (days)	Trileptal 2400 mg/day Trileptal 300 mg/day	94	68.0 days 28.0 days	0.0001[2]
028	Percentage of patients meeting one of the exit critertion	Trileptal 2400 mg/day Trileptal 300 mg/day	79	41.2% 93.3%	<0.0001[3]

1. NA: Statistics could not be computed because fewer patients than defined percentile met one of the exit criteria.
2. P-value based on log-rank statistic
3. P-value based on Cochran-Mantel-Haenszel statistic

Trileptal Adjunctive Therapy Trials

The effectiveness of Trileptal as an adjunctive therapy for partial seizures was evaluated in two (Study OT/PE1 and Study 011) multi-center, randomized, double-blind, placebo controlled trials, one in 692 patients (15-66 years of age) and one in 264 patients (3-17 years of age). Patients in these trials were permitted up to 2 or 3 AEDs in addition to Trileptal or placebo. Table 2 is a summary of the two adjunctive therapy trials provided by the sponsor.

Table 2. Summary of percentage change in partial seizure frequency from baseline for placebo controlled adjunctive therapy trials (ITT patients)

Trial	Treatment Group	N	% reduction	% Responders[1]
011 Pediatrics	Trileptal Placebo	138 128	34.8[2] 9.4[2]	40.7[3] 21.9
OT/PE1 Adults	Trileptal 2400 mg/day[3] Trileptal 1200 mg/dat Trileptal 800 mg/day Placebo	174 177 188 173	49.9[2] 40.2[2] 26.4[2] 7.6[2]	50.0[2] 41.2[2] 26.8[4] 12.7

1. >=50% decrease in seizure frequency relative to baseline
2. p=0.0001; 3. p=0.0005; 4. p=0.0008

In the following sections tables and figures that are copied from sponsor's report use Exhibit number (e.g., Exhibit 7.1.-1).

II. Clinical Trials

1. Study 004 (Mono-therapy)

1.1 Trial Objectives

The primary objective of this trial was to evaluate the efficacy and safety of mono-therapy Oxcarbazepine (OXC) versus placebo in patients with refractory partial-onset seizures, with or without secondarily generalized seizures, who had completed an inpatient presurgical diagnostic evaluation.

The secondary objective was to determine the trough plasma levels of MHD and DHD and to explore their relationship to efficacy.

1.2 Trial Design

This was a multi-center, double-blind, randomized, placebo-controlled, 2-arm parallel trial of mono-therapy OXC 1200 mg b.i.d., in patients with partial seizures who had undergone a presurgical evaluation for epilepsy surgery.

There were three phases in this trial: a screening phase, a double-blind phase and a long-term extension phase.

Double-Blind Phase

After the screening, eligible patients were randomized to oxcarbazepine or matching placebo in a 1:1 ratio. There was a one-day titration period. A total daily dose of 1500 mg was administered b.i.d. on Day 1 (600 mg a.m. dose and 900 mg p.m. dose).

Seizures were documented with regard to type and time. Day 1 partial seizures were recorded, but not counted toward the study endpoint. Serial seizures/status epilepticus, or emergence of new-onset secondarily generalized seizures, if secondarily generalized seizures were not present during the one-year period prior to randomization, were counted toward the study endpoint.

The 1-day titration period was followed by a 9-day maintenance period. On day 2, dosage was increased to 1200 mg every 12 hours. If the patient experienced intolerable adverse events, the dosage was reduced during the trial by one tablet (600 mg) at either dosing period (or at both, if necessary), thereby reducing the dose to either 1800 or 1200 mg OXC per day. Any seizures occurring after the administration of the first dose on Day 2 were recorded and analyzed toward the study endpoint.

For "completed patient status", treatment (including titration and maintenance) continue until:

1. Completion of 10 days, or

2. Experience of 1 fourth partial seizure, with or without secondarily generalized seizures (exclusive of seizures occurring on Day 1), or
3. Experience of two new-onset secondarily generalized seizures, if secondarily generalized seizures were not present during the one-year period prior to randomization (inclusive of secondarily generalized seizures occurring on Day 1), or
4. Experience of several seizures or status epilepticus deemed by the investigator to require intervention.

The above four criteria are also referred as exit criteria for patients to complete the trial. All termination procedures were conducted either at Day 10 or at day of exit/termination from the trial.

Trial start date: August 11, 1994
Trial end date: March 12, 1996

No interim analyses were planned.

1.3 Efficacy

1.3.1 Primary Efficacy Variable and Its Statistical Analysis

The protocol specified primary efficacy variable was time to meeting one of the exit criteria (see Section 1.2).

The protocol specified primary statistical analysis for time to meeting one of the exit criteria was based on the log-rank test. Kaplan-Meier survival curves were also computed. A secondary statistical analysis was performed using Cox's proportional hazards regression model. The covariates included in this model were treatment, center, sex, age, and total partial seizure frequency during the 48 hours prior to randomization. This analysis was also specified in the study protocol.

1.3.2 Secondary Variables and Their Corresponding Statistical Analysis

Variable 1: Percentage of patients meeting one of the exit criteria

This variable was analyzed using the Cochran-Mantel-Haenszel (CMH) test controlling for center. An additional analysis was performed using a logistic regression model. This model included treatment, center, and sex as factors and age, and total partial seizure frequency during the 48 hours prior to randomization as covariates.

Four potential ways of handling premature discontinuations with respect to the ITT patient population were considered and analyses were performed accordingly: First, a "worst case" analysis was performed. In this case, placebo patients who discontinued were classified as having completed the 10-day trial, whereas oxcarbazepine patients who discontinued were classified as met one of the exit criteria. The remaining three cases were not considered for further analysis if the CMH test controlling for center showed

statistical significance in favor of OXC. If there had been no significant treatment difference favoring OXC in the "worst case" analysis, additional analyses treating dropouts as completers, exits and missing would have been performed.

Variable 2: Total partial seizure frequency per nine days

The total partial seizure frequency per nine days was comprised of partial seizures with or without secondarily generalized seizures that occurred during the double-blind treatment period after Day 1.

The total partial seizure frequency per nine days was analyzed based on the ranks of the 9-days seizure frequencies, using the Wilcoxon Rank Sum test. This was equivalent to basing the analysis on the ranks of the time to fourth seizure except that censored outcomes (i.e., patients discontinuing from the trial or completing 10-day trial) with zero seizures were assigned the best possible rank, next best for only one seizure, etc.

The above Variable 1 and Variable 2 and their corresponding analyses were specified in the study protocol.

Variable 3: Total secondarily generalized seizure frequency per nine days

The sponsor stated that this efficacy variable was added at the request of the clinical specialist to examine the subset of Variable 2, which consisted of secondarily generalized seizures that occurred during the double-blind treatment phase after Day 1.

The total secondary generalized seizure frequency per 9-days was also analyzed based on the ranks of the 9-day seizure frequency, using the Wilcoxon Rank Sum test.

1.3.3 Criteria for efficacy

OXC was considered effective if there was a statistically significant ($p<0.05$, two-sided) difference in favor of OXC over placebo for the time to meeting one of the exit criteria.

Two data sets were used in the efficacy analyses:
1. All randomized patients who received trial medication (i.e., ITT patients), and
2. All completed patients, defined as the data set consisting of all patients who met the admission criteria, and either completed 10-day double-blind treatment phase or met one of the exit criteria.

All randomized patients were used in the analysis of the primary efficacy variable.

1.4 Results (Sponsor's Findings)

1.4.1 Demographic and Baseline Data

There were 102 patients randomized at 10 centers. A summary of demographic and baseline characteristics is presented in Table 3.

Table 3. Demographic and baseline characteristics by treatment group (All treated patients: Study 04)

Characteristic	Oxcarbazepine N=51	Placebo N=51	Total N=102
Age (year)			
Mean (Range)	33.1 (11 – 51)	33.7 (14 – 62)	33.4 (11 – 62)
Weight (kg)			
Mean (Range)	78.7 (35.0 – 110.9)	77.7 (47.5 – 144.5)	78.2 (35.0 – 144.5)
Sex			
Male (%)	31 (60.8%)	25 (49.0%)	56 (54.9%)
Female (%)	20 (39.2%)	26 (51.0%)	46 (45.1%)
Race			
White (%)	41 (80.4%)	40 (78.4%)	81 (79.4%)
Other (%)	10 (19.6%)	11 (21.6%)	21 (20.6%)
Total partial seizure frequency			
Mean (Range)	4.9	4.4	4.6
Initial use of Lorazepam			
No (%)	6 (11.7%)	4 (7.8%)	10 (9.8%)
Yes (%)	45 (88.3%)	47 (92.2%)	92 (90.2%)

1.4.2 Completion/Withdrawal Information

One hundred and two patients were randomized into the study. Of these patients, 51 received OXC and 51 received placebo. A brief summary of the distribution of patient outcomes by treatment group is in the following Table 4.

Ninety-seven (95%) of the patients completed trial by reaching a trial endpoint. Five (5%) patients (3 OXC, 2 placebo) discontinued from the trial prematurely; two (both in OXC) discontinued due to adverse experiences, and three discontinued due to administrative problems.

For the two OXC-treated patients who were discontinued from the trial due to adverse experiences, one patient developed a rash and another experienced a post-ictal psychotic episode. The latter episode was reported as a serious adverse experience.

Table 4. Distribution of patients by treatment group (All treated patients: Study 04)

	Oxcarbazepine	Placebo	Total
Randomized	51	51	102
Completed	48 (94.1%)	49 (96.1%)	97 (95.1%)
By completing 10 days	27	6	33
By meeting exit criteria			
Criterion (1)	21	39	60
Criterion (2)	0	1	1
Criterion (3)	0	3	3
Discontinued Prematurely			
Adverse experience	2 (3.9%)	0	2 (2.0%)
Other	1 (2.0%)	2 (3.9%)	3 (2.9%)
Total	3 (5.9%)	2 (3.9%)	5 (4.9%)
Intent-To-Treat Analysis	51	51	102

Reviewer's note: Criterion (1), (2) and (3) in the above table should be Criterion (2), (3) and (4), respectively.

1.4.3 Analysis of Efficacy

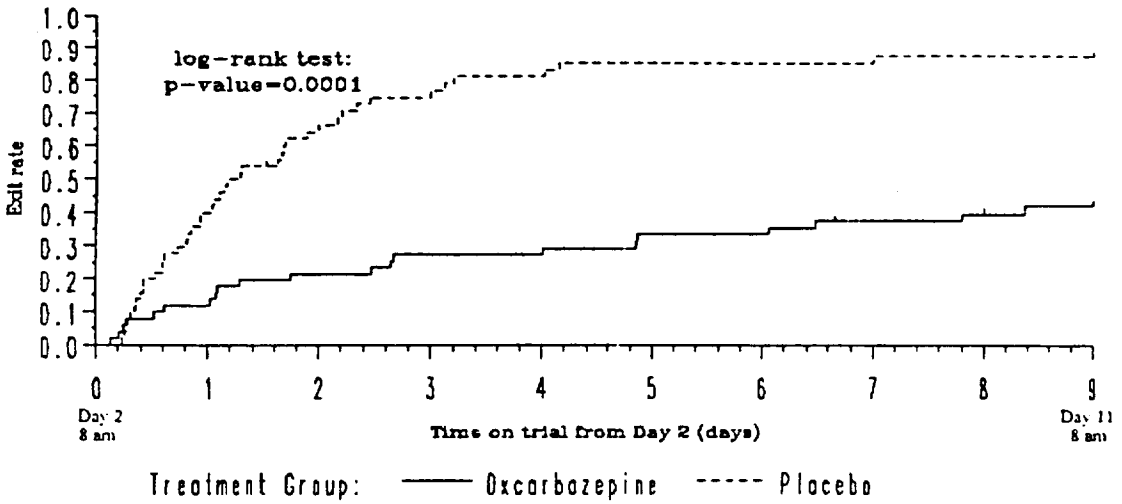
The sponsor stated that all statistical analyses for the efficacy variables were planned and specified in the protocol with the exception of the subgroup analysis of total secondarily generalized seizure frequency per nine days. Details with respect to potential ways of handling dropouts were documented in the statistical analysis plan prior to the unblinding of the drug code.

Primary efficacy analysis

For the primary efficacy variable, time to meeting one of the exit criteria, the log-rank test performed on the ITT patient population was reported statistically significant in favor of OXC (p=0.0001). The Kaplan-Meier event-rate curves is presented in the sponsor's Exhibit 8.1.-1 below. The sponsor reported that approximately 75% of the placebo-treated patients versus 25% of the OXC-treated patients exited the trial within 2.5 days of Day 2.

An additional analysis using Cox's proportional hazard model that adjusts for effect of the explanatory variables including center, age, sex, and partial seizure frequency during the 48 hours prior to randomization is performed. The sponsor reported that the results also showed statistical significance in favor of OXC (p=0.0001).

Exhibit 8.1.-1. Kaplan-Meier estimates of exit rate by treatment group (intent-to-treat patients)



Secondary efficacy variable

Variable 1: Percentage of patients meeting one of the exit criteria

Cochran-Mantel-Haenszel (CMH) test controlling for center effects was performed on the percentage of patients meeting one of the exit criteria under the "worst-case" scenario (i.e., OXC patients who dropped out were classified as having exited the trial and placebo-treated patients who dropped out were classified as having completed the 10-day trial). The sponsor reported that the CMH test showed that the percentage of patients meeting one of the exit criteria was statistically significantly lower ($p < 0.0001$) for the OXC-treated group (24/51; 47.1%) than in the placebo-treated group (43/51; 84.3%). All of the OXC-treated patients who met one of the exit criteria, exited due to experiencing their fourth partial seizure. Of the placebo-treated patients, 39/51 (76.5%) exited due to experiencing their fourth partial seizure, 1/51 (2.0%) exited due to experiencing two new-onset secondarily generalized seizures, and 3/51 (5.9%) were exited due to experiencing serial seizures or status epilepticus.

Variable 2: Total partial seizure frequency per nine-days

Only partial seizures with or without secondary generalization were used in computing the total partial seizure frequency per nine-days. The sponsor reported that strong statistically significant evidence favoring OXC over placebo was found. The OXC-treated patients had a median total partial seizure frequency of 2.0 seizures (ranged 0 – 296.23) compared with a median of 30.8 seizures (ranged 0 – 150.3) for the placebo-treated patients (p=0.0001, Wilcoxon rank sum test).

Variable 3: Total secondary generalized seizure frequency per nine days

The sponsor reported that the analysis of total secondarily generalized seizure frequency per nine days was statistically significant in favor of OXC over placebo for all patients population and sub-populations (all p <=0.0006, Wilcoxon rank sum test). In the ITT patient population, only 4/51 (7.9%) of the OXC-treated patients experienced secondarily generalized seizures, while 24/51 (47.1%) of the placebo-treated patients experienced secondary generalized seizures.

For the patients who experienced secondarily generalized seizure during the 48-hour baseline period, 3/22 (13.7%) of the OXC-treated patients experienced secondary generalized seizures during the 9-day maintenance period compared to 12/19 (63.2%) placebo treated patients. For patients who did not experience secondarily generalized seizures during the 48-hour baseline period, 1/29 (3.5%) of the OXC-treated patients experienced secondarily generalized seizures during the 9-day maintenance period compared to 12/32 (37.5%) of the placebo-treated patients.

1.5 Reviewer's Findings/Comments

Primary efficacy variable

The analysis of the log-rank test for time to meeting one of the exit criteria was the protocol specified primary analysis. This analysis was replicated and the result from the sponsor's analysis was verified. A significant difference in favor of OXC group in time to meeting one of the exit criteria was found with a p-value of 0.0001. Such difference was also found to be statistically significant in both male subjects as well as female subjects, and in younger subjects (<=35 years) as well as in older subjects (> 35 years).

The curves of log (-log survival) for the two treatment group were clearly not parallel, indicating that the assumption of proportional hazards was not satisfied and the Cox model was not appropriate.

Secondary Efficacy Variables

In the sponsor's analysis of secondary efficacy variables, 10 centers were pooled into 5 larger center groups based on the order of the center number. The pooling of centers was not specified in the protocol or statistical plan.

This reviewer reanalyzed percentage of patients meeting one of the exit criteria using CMH test with or without controlling the effect of center difference. It was found that the percentage of patients meeting one of the exit criteria was significantly lower for the OXC group compared to the placebo group with p-values of 0.001 (not 0.0001, as reported by the sponsor), with or without controlling the effect of center difference.

The analysis of the total partial seizure frequency per nine days was replicated and the result from the sponsor's analysis was confirmed (see Sponsor's Findings).

There is an error in the data set. One patient in the placebo group was characterized both as exited by criteria 3 and as prematurely discontinued. The frequency reported by the sponsor does not agree with the data due to this error.

Comments/ Conclusions

Based on the results of the protocol specified primary and secondary analysis, it can be concluded that the OXC 2400 mg/day is effective in reducing partial seizure frequency in epilepsy patients with similar disease condition such as the patients enrolled in Study 004.

2 Study 025 (Mono Therapy)

2.1 Trial Objectives

The primary objective of this trial was to evaluate the safety and efficacy of OXC mono-therapy relative to placebo in untreated patients with recent-onset partial seizures that include the subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures.

2.2 Trial Design

This was a multi-center, randomized, double-blind, placebo-controlled, parallel-group trial of OXC mono-therapy (1200 mg/day) in patients who were not currently receiving AED therapy for their partial seizures. This mono-therapy design was chosen to demonstrate unequivocal efficacy in an untreated epilepsy patient population with recent-onset partial seizures.

The trial consisted of 3 phases: Baseline, Double-blind Treatment, and Open-label Extension. The design of this trial up to and including the Double-blind Treatment Phase is presented in Exhibit 3.1.-1.

Exhibit 3.1.-1. Trial design

Phase	Baseline		Double-blind Treatment				
Period			Titration	Maintenance			
Visit		1	2	3	4	5	6
Day	-56	-7 to -1	0	7	35	63	91
Treatment	No AED(s) 90 days		Placebo or gradual titration to OXC 1200 mg/day.				
	⇑ randomization						

Double-blind Phase (Visits 2-6, Days 0-91)

At Day 0 (Visit 2), patients meeting the eligibility criteria entered the 90-day Double-blind Treatment Phase and were randomized to treatment with OXC 1200 mg/day or placebo. The Double-blind Treatment Phase had 2 periods: a 6-day Titration period and a 84-day Maintenance period. Patients completed the trial by completing all visits of the Double-blind Treatment Phase.

Trial start date: March 21, 1995
Trial end date: September 6, 1997

No interim analyses were planned.

2.3 Efficacy

2.3.1 Primary Efficacy Variable and its Statistical Analysis

The protocol specified primary efficacy variable was the time to first seizure (from first dose of medication).

The protocol specified primary analysis for time to the first seizure was to be based on the log-rank test. A secondary statistical analysis was to be performed using Cox's proportional hazards regression model, with treatment, center, and baseline seizure frequency per 28 days as explanatory variables, with or without treatment-by-baseline seizure interaction. This analysis was also specified in the protocol.

2.3.2 Secondary Efficacy Variables and Their Corresponding Statistical Analysis

Variable 1: Number of seizures per 28 days

The number of seizures per 28 days was defined as the product of 28 and (the number of seizures divided by the number of days with seizure diary data during the double-blind treatment phase). This variable was specified as secondary efficacy variable in the protocol.

The number of seizures per 28 days was to be analyzed using an ANOVA model. Treatment, center, and baseline seizure frequency per 28 days were to be used as explanatory variables. In the case that the residuals from the model do not approximate a normal distribution, a non-parametric procedure (the Wilcoxon rank-sum test) was to be used to test the treatment effect.

Variable 2: Percentage of seizure-free patients during the double-blind treatment phase

The percentage of seizure-free patients during the double-blind phase was to be analyzed using the Cochran-Mantel-Haenszel test controlling for center. Two analyses varying in

the way of handling patients who drop out without having a seizure were to be performed: 1) considered seizure-free; and 2) considered as having had seizures.

The above Variable 1 and Variable 2 and their corresponding analyses were specified in the protocol.

2.3.2 Criteria for efficacy

OXC was considered effective if there was a statistically significant difference ($p<0.05$) in the time to first seizure between the OXC and placebo groups.

2.4 Results (Sponsor's Findings)

2.4.1 Demographic and baseline data

Sixty-seven patients were randomized from 10 centers, all of them were included in the ITT patient population. A summary of demographic and baseline variables is presented in Table 5. The sponsor stated that the types and frequencies of seizures experienced by patients in the OXC and placebo groups were comparable during the baseline phase. No patient had primary generalized seizures during the baseline phase. One patient had exceptionally high number of baseline seizures (220.6 per 28 days).

Table 5. Demographic and baseline characteristics by treatment group (all treated patients: Study 025)

Characteristic	Oxcarbazepine N=32	Placebo N=35	Total N=67
Age (year)			
Mean (Range)	32.7 (8 – 63)	36.5 (10 – 69)	34.7 (8 – 69)
Weight (kg)			
Mean (Range)	69.4 (26.3 – 103.0)	76.1 (42.2 – 119.0)	72.9 (26.3 – 119.0)
Sex			
Male (%)	16 (50%)	17 (48.6%)	33 (49.3%)
Female (%)	16 (50%)	18 (51.4%)	34 (50.7%)
Race			
White (%)	31 (96.9%)	30 (85.7%)	61 (91.0%)
Other (%)	1 (3.1%)	5 (14.3%)	6 (9.0%)
Median (range) of total seizure frequency per 28 days	5.0	5.5	5.0
Median (range) of simple partial seizure frequency per 28 days	0.0	1.0	0.0
Median (range) of complex partial seizure frequency per 28 days	3.2	2.5	2.9
Median (range) of secondary generalized partial seizure frequency per 28 days	0.0	0.0	5.3)

2.4.2 Completion/Withdrawal Information

Of the 67 randomized patients, 14 (21%) (10 in OXC group, 4 in placebo group) were prematurely discontinued and 18 (27%) (5 in OXC group, 13 in placebo group) entered extension before completing Visit 6 and were not considered prematurely discontinued.

Approximately 52% (35 of 67) of the patients included in the intent-to-treat data set completed the trial by completing Visit 6 (17 in OXC group, 18 in placebo group). A brief summary of the disposition of patients is displayed in Table 6.

Table 6. Distribution of patients by treatment group (All treated patients: Study 025)

	Oxcarbazepine	Placebo	Total
Randomized	32	35	67
Completed double-blind treatment phase (Visit 6)	17 (53%)	18 (51%)	35 (52%)
Entered open-label extension before completing Visit 6	5 (15.6%)	13 (37.1%)	18 (26.9%)
Discontinued Prematurely			
Adverse experience	3 (9.4%)	2 (5.7%)	5 (7.5%)
Other[1]	7 (21.9%)	2 (5.7%)	9 (13.4%)
Total	10 (31.3%)	4 (11.4%)	14 (20.9%)
Intent-To-Treat Analysis	32	35	67
Had their first seizure	21	30	51
Completed without a seizure	7	4	11

1. Includes 1 protocol violation (pregnancy; OXC), 1 patient who was lost to follow-up (OXC), 2 withdrawn for administrative reasons (OXC), 3 who withdrew consent (2 OXC; 1 placebo), and 2 withdrawn for noncompliance (1 OXC; 1 placebo).

There was one patient in the OXC group reported adverse experience (severe personality disorder) that was judged by the investigator as severe. The sponsor reported that no serious experience occurred during the double-blind treatment phase of the trial.

2.4.3 Analysis of Efficacy

The sponsor stated that all statistical analyses for the efficacy variables were planned and specified in the protocol, unless otherwise mentioned. All statistical analyses for the efficacy variables were performed on the intent-to-treat population.

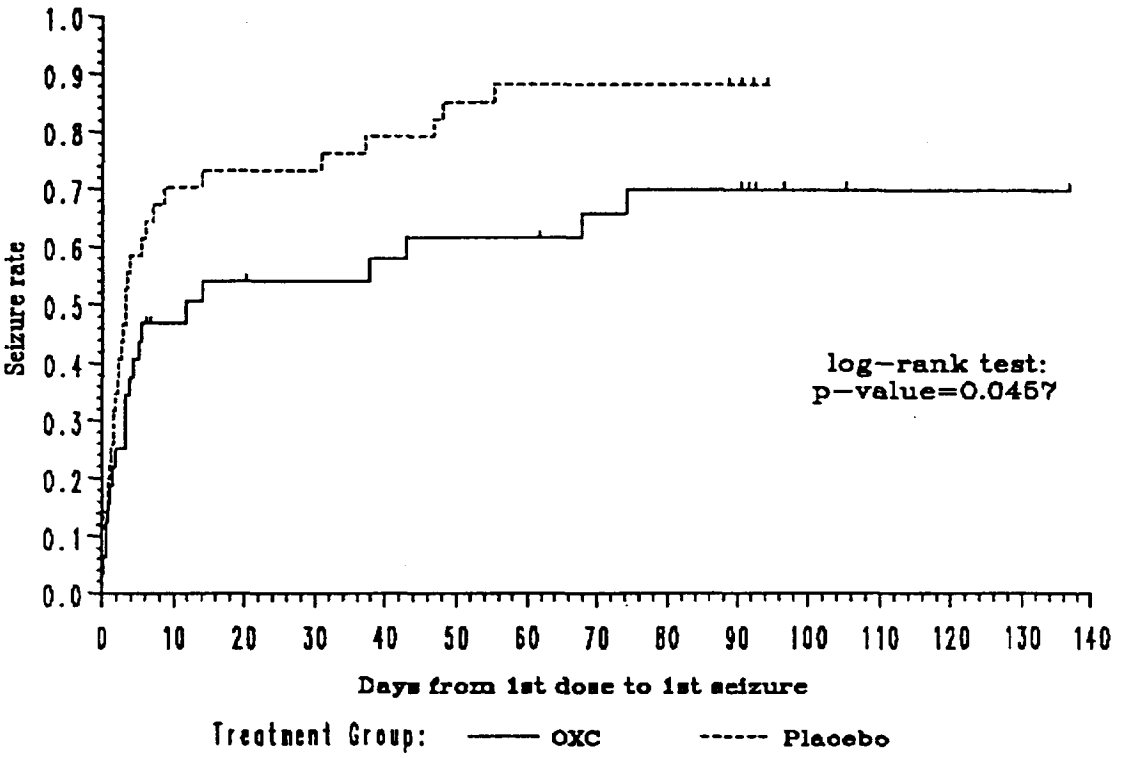
Primary efficacy analysis

The primary efficacy analysis for the time to first seizure is the log-rank test performed on the ITT patient population. The sponsor reported that the difference in the time to first seizure between the OXC group and placebo group was statistically significant in favor of OXC (p=0.0457) based on the log-rank test. The median time to first seizure was 11.67 days for the OXC group compared to 3.23 days for the placebo group. The Kaplan-Meier event-rate curves is presented in the sponsor's Exhibit 8.1.-1.

The sponsor reported that during the conduct of the trial, the Novartis Research Quality Assurance team identified one center with repeated deviations from Good Clinical Practice and compliance with the protocol, and the analysis was replicated without data from this center (Hasegawa/M0274P). The result of the log-rank test excluding the data from this center remained statistically significant in favor of OXC group (p=0.0295). The sponsor did not report the details of deviations from the protocol in this center.

Cox's proportional hazard regression analyses were also performed for time to first seizure. The model with and without treatment-by-baseline interaction result p values of 0.043 and 0.134, respectively. The proportional hazard regression model fitted by excluding one patient with an extremely large baseline seizure frequency showed results similar to those obtained from the entire ITT data set. The sponsor did not report whether the treatment-by-baseline interaction was significant at 0.10 level or not.

Exhibit 8.1.-1. Kaplan-Meier estimates of time to first seizure (intent-to-treat patients)



Seizure rate: The cumulative proportion of patients who had their first seizure
OXC: Total patients=32 (# had seizures=21, # censored=11), median days=11.67
Placebo: Total patients=36 (# had seizures=30, # censored=6), median days= 3.229

Analysis of secondary efficacy variables

The sponsor reported that during the course of the trial, it was decided that patients who could not remain in the core trial after meeting the primary endpoint (time to first seizure) would be allowed to enter the long-term extension phase deemed appropriate by the investigator and trial monitor. It turned out that more placebo-treated patients (13 out of 35) entered the extension than OXC-treated patients (5 out of 32). The sponsor stated that this decision might have some impact on the secondary efficacy variables.

Reviewer's comment: It was stated in the protocol that patients entering the open label extension by completing the 90-day double-blind phase and a 6-day blinded-conversion period.

Variable 1: Number of seizures per 28 days

It was found that the ANOVA model was not appropriate in analyzing seizure frequency per 28 days as the normal assumption of the residual did not hold by Shapiro-Wilk test ($p<0.001$) and normal probability plot. Wilcoxon rank-sum test was used to analyze Variable 1.

The sponsor reported that the rate of seizure occurrence for OXC-treated patients was significantly smaller in comparison of the placebo-treated patients ($p=0.033$, Wilcoxon rank-sum test). The results is displayed in the sponsor's Exhibit 8.1.-2. The same test performed on all patients completed Visit 6 and patients with at least 28 days of seizure diary data resulted p-values of 0.036 and 0.065, respectively.

The sponsor stated the plot of residuals from the Poisson regression model showed that the model did not provide a satisfactory fit to the seizure data.

Exhibit 8.1.-2. Percentage change from baseline in number of seizures per 28 days (intent-to-treat patients)

Seizure frequency per 28 days	OXC (N=32)		Placebo (N=35)		Mean Difference[1]	p-Value[2]
	Mean (SD)	Median	Mean (SD)	Median		
Baseline	7.4 (8.3)	5.0	14.8 (36.8)	5.5	-7.5	--
Post-randomization	4.8 (9.0)	0.7	13.6 (28.6)	3.5	-8.9	--
Percent change from baseline	-28.3 (108.8)	-89.1	11.4 (127.1)	-37.4	-39.7	0.033*

[1] Mean for OXC group minus mean for placebo group.

[2] Based on Wilcoxon rank-sum test.

* Indicates statistical significance at the 0.05 level.

Cross-reference: Table 8.1.-2A; Module III, Table 5A.

Variable 2: Percentage of seizure-free patients during the double-blind treatment phase

Exhibit 8.1.-3 displays the number of patients in each treatment group who were seizure free following randomization. Three different CMH tests, controlling for centers, were performed, each of which differed in the manner by which patients who discontinued the trial prematurely before having first seizure were handled. The results showed p-values of 0.073, 0.255 and 0.177 from the three tests.

Exhibit 8.1.-3. Proportion of patients who were seizure-free (intent-to-treat patients)

Method for handling seizure-free dropouts[1]	Number (%) of seizure-free patients				p-value[3]
	OXC		Placebo		
considered as seizure-free	11/32	34.4%	5/35	14.3%	0.073
considered as having had a seizure	7/32	21.9%	4/35	11.4%	0.255
considered as missing[3]	7/28	25.0%	4/34	11.8%	0.177

[1] Patients who discontinued double-blind treatment phase prematurely without having had a seizure.

[2] Based on Mantel-Haenszel test.

[3] Excluding seizure-free dropouts.

Cross-reference: Table 8.1.-3; Module III, Table 7.

2.5 Reviewer's Findings/ Comments

Primary Analysis

The protocol specified primary analysis for the time to first seizure was performed and the same result as from the sponsor's was obtained, i.e., the difference in the time to first seizure was found significantly different in favor of OXC group based on the log-rank test with a p-value of 0.0454.

For the secondary analysis of the time to first seizure, it was found that the treatment effect was significant with a p-value of 0.0455 from a Cox regression model that included covariates of treatment, center, baseline seizure frequency per 28 days, and the interaction of treatment-by-baseline seizure frequency. However, the interaction of treatment-by-baseline seizure frequency was not statistically significant at .10 level (p=.1216). Therefore, the interaction was removed from the model. The treatment effect was found not significant from the model without treatment-by-baseline seizure frequency per 28 days (p=0.1387). In addition, a t-test and a non-parametric Wilcoxon rank sum test were used in examining the baseline seizure frequency difference by treatment groups. No significant difference was found (t test: p=0.2500; Wilcoxon: p=0.3305). Therefore, no treatment-by-baseline seizure frequency needs to be adjusted, and treatment effect in this secondary analysis should be viewed as non-significant.

Analysis of Secondary Efficacy Variables

It was found that the effect of baseline seizure frequency on the number of seizure per 28 days was highly significant from the ANCOVA with p=0.0003 and the treatment was not significant with p=0.1965. However, the residual test showed that the normal assumption was not satisfied. By using the Wilcoxon test, the seizure frequency per 28 days was significantly different in favor of the OXC treatment group (p=0.0307). Note that 5

subjects (one in placebo group and 4 in OXC group) dropped out before having their first seizure, and their seizure frequency was recorded as zero. The same analysis was replicated after deleting those 5 subjects, and the p-value was increased from 0.0307 to 0.0848.

For the percentage of seizure free patients during the double-blind treatment phase, CMH tests controlling for center were performed. Patients who prematurely discontinued before having seizures were treated as seizure free, as having seizures, and as missing. The resulted p-values are 0.073, 0.255 and 0.177, respectively. The p-values obtained are the same as obtained by the sponsor.

Comments/ Conclusions

In this study the effectiveness of 1200 mg/day is marginally significant based on the primary analysis, and is not significant based on secondary efficacy variables. Since this is a small study with only 67 subjects in total, results from other studies need to be used to support the efficacy claim of OXC 1200 mg/day.

The effect of the large dropout rate on the primary analysis has been examined. Only those subject who drop out of the study before having their first seizure will have impact on the primary analysis. Among the 14 prematurely discontinued patients, 5 of them discontinued before having their first seizure, one in the placebo group and 4 in the OXC group. The median time to first seizure for the 4 subjects in the OXC group is 13 days, which is larger than the median survival time of 11.67 days for the whole OXC group. This finding indicates that the result of the primary analysis is at least not substantially biased toward favor of the OXC group.

3. Study 026 (Mono Therapy)

3.1 Trial Objectives

The primary objective of this trial was to evaluate the safety and efficacy of high dose (2400 mg/day) and low dose (300 mg/day) OXC mono-therapy in patients with uncontrolled partial seizures which include the subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures. The second objective was to explore any dose-and plasma-concentration relationship during OXC mono-therapy.

3.2 Trial Design

This was a multi-center, randomized, double-blind, parallel-group trial designed to investigate the safety and efficacy of high dose (2400 mg/day) and low dose (300 mg/day) OXC mono-therapy in patients with uncontrolled partial seizures which include the subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures. This mono-therapy design was chosen to demonstrate unequivocal efficacy in a refractory patient population.

The trial consisted of 5 phases: Screening, Open-label Conversion, Open-label Baseline, Double-blind Treatment, and an Open-label Long-term Extension. The design of this trial up to and including the Double-blind Treatment Phase is presented in Exhibit 3.1.-1.

Exhibit 3.1.-1. Trial design

Phase	Screen-ing	Open-label conversion				Open-label baseline		Double-blind Treatment							
Period								Down-titration				Maintenance			
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14T
Day	-56	1	7	14	21	28	56	84	98	112	126	140	154	182	210
Tx	CBZ	Conversion from CBZ to OXC monotherapy				OXC 2400 mg/day		OXC 2400 mg/day or gradual down-titration to OXC 300 mg/day							
↑Randomization															

Open-label Conversion Phase (Visits 1-5, Days 1-28) and Baseline Phase (Visits 6 – 7, Days 28 – 84)

Patients began with a weekly, fixed-dose titration schedule of OXC as follows: 300 mg b.i.d. on Day 1 (Visit 1), 600 mg b.i.d. on Day 7 (Visit 2), 900 mg b.i.d. on Day 14 (Visit 3) and 1200 mg b.i.d. on Day 21 (Visit 4). At the same time, the dose of CBZ was tapered downward in decrements of approximately 25% per week on Day 1, Day 7, and Day 14. CBZ was discontinued on Day 21.

The dose of OXC was to remain unchanged during the Open-label Baseline Phase, and concomitant antiepileptic drugs (AEDs) were not permitted. Patients unable to maintain OXC mono-therapy at a dose of 2400 mg/day due to poor seizure control or tolerability were allowed to prematurely discontinue from the core trial and continue OXC treatment in the Open-label Extension Phase.

Double-blind Phase (Visits 8 - 10, Days 84 - 210)

At day 84 (Visit 7), patients completing the Open-label Baseline Phase entered 126-day (18-week) Double-blind Treatment Phase and were randomized to treatment with OXC 2400 mg/day or OXC 300 mg/day. The double-blind treatment phase had 2 periods: down-tatration and maintenance. Patients could complete the double-blind treatment phase and enter the open-label extension phase by meeting one of the exit criteria (see Exit Criteria) or by completing all visits during the double-blind treatment phase.

Down-titration period: During the down-titration period, patients who were randomized to high dose (2400 mg/day) group continued taking 2400 mg/day of OXC. Patients who were randomized to the OXC 300 mg/day group were taped at biweekly intervals over a 6-week period (Days 84 – 126) to OXC 300 mg/day by substituting matching placebo tablets.

Maintenance period: On Day 140 (Visit 11), patients who completed the down-titration period entered the 70-day maintenance period, and remained on the dose of OXC they received on Day 126 (Visit 10).

Exit Criteria

Patients were considered to have completed the trial if they completed all visits of the core trial or met one of the four predefined exit criteria during the double-blind treatment phase. Discontinuation for any other reason, such as adverse experience, were considered premature discontinuations and are not "exits".

The guidelines for exiting the trial required one of the following criteria to be met.

1. A twofold increase in partial seizure frequency in any 28-day period during the double-blind phase (not necessarily at visits). Patients can meet the criteria between visits. If zero or one seizure occurred per 28 days during the baseline phase, three or more seizures in a 28-day period of the treatment phase were needed to satisfy the criteria.
2. A twofold increase in the highest consecutive 2-day seizure frequency that occurred during the baseline phase. The criteria was applicable only to patients who experienced two or more seizures in a two-day period during the baseline phase.
3. Occurrence of a single generalized seizure if none occurred during the baseline phase.
4. Prolongation of generalized seizure duration (serial seizures or status epilepticus of any seizure subtype) deemed by the investigator to require intervention.

Trial start date: April 15, 1995
Trial end date: July 14, 1997

No interim analyses were planned.

3.3 Efficacy

3.3.1 Primary Efficacy Variable and its Statistical Analysis

The protocol specified primary efficacy variable was the time to meet one of the exit criteria.

The protocol specified primary statistical analysis for the time to meet one of the exit criteria was a log-rank test. A secondary statistical analysis, also specified in the protocol, was a Cox's proportional hazard regression model. Explanatory variables included in the Cox's model were: treatment, center, carbamazepine dose (mg/day) during the screening phase, and partial seizure frequency per 28 days during baseline phase. Both statistical analyses were performed on the ITT patient population, where patients who prematurely discontinued from the trial were classified as censored observations.

Reviewer's comment: sex and age were not included in the Cox's model in the original study protocol.

3.3.2 Secondary Efficacy Variable and its Statistical Analysis

The secondary efficacy variable is the percentage of patients meeting one of the exit criteria.

The percentage of patients meeting one of the exit criteria was to be analyzed using the Cochran-Mantel-Haenszel (CMH) test controlling for center. This secondary efficacy variable and the CMH test was specified in the protocol. An additional analysis was to be performed using a logistic regression model. The explanatory variables included in the regression model were: treatment, center, CBZ dose (mg/day) during the screening phase and partial seizure frequency per 28 days during the baseline phase.

Reviewer's comment: sex and age were not included in the logistic regression model in the original study protocol.

Four potential ways of handling premature discontinuations with respect to ITT patient population were considered and analyses were to be performed accordingly. First, a "worst case" analysis was to be performed that the patients in the OXC 2400 mg/day group who prematurely discontinued were classified as exited, and patients in the OXC 300 mg/day group who prematurely discontinued were classified as completed the double-blind treatment phase.

If the statistically significant treatment difference favoring OXC 2400 mg/day treatment group was not found with the "worst case" analysis, additional statistical analyses that classify prematurely discontinuations as "completers", "exits" and "missing" were to be performed accordingly.

3.3.3 Criteria for efficacy

OXC was considered efficacious if the time to meeting one of the exit criteria for the OXC 2400 mg/day group was a statistically significantly lower ($p<0.05$;two-sided) than the OXC 300 mg/day groups.

3.4 Results (Sponsor's Findings)

3.4.1 Completion/Withdrawal Information

One hundred and forty-three patients were enrolled into the trial, receiving open-label OXC, and were included in the safety analysis. Of these patients, 96 (67.1%) were randomized into the double-blind treatment phase (51 to the OXC 2400 mg/day group and 45 to the OXC 300 mg/day group). Of the randomized patients, 94 were included in the ITT data set for efficacy analyses. Two patients randomized to the OXC 2400 mg/day

group were excluded from the ITT data set because they prematurely discontinued prior to receiving their first dose of double-blind trial drug.

A brief summary of the distribution of patients outcomes by treatment group is displayed in Exhibit 6.1.-1.

Exhibit 6.1.-1. Distribution of patients by treatment group (all treated patients

Number of patients	Non-randomized	OXC 2400 mg/day	OXC 300 mg/day	Total
Enrolled	47	51	45	143
Randomized	0	51	45	96
Completed Double-blind Treatment Phase (intent-to-treat)	0	46	40	86
Met predefined exit criteria[1]	0	30	40	70
Completed double-blind treatment	0	16	0	16
Discontinued prematurely (all treated)				
Total	47	5	5	57
For adverse experience	24	0	0	24
Death	0	1	0	1
Other	23	4	5	32
Included in efficacy analyses[2] (intent-to-treat)	0	49	45	94
Included in safety analyses (all treated)				
Laboratory Tests	47	51	45	143
Adverse experiences	47	51	45	143
Included in pharmacokinetics analyses				
Population-pharmacokinetic analysis	15	46	43	104
Pharmacokinetic-efficacy relationship	0	46	43	89
Pharmacokinetic-safety relationship	0	46	43	89

[1] Exit criteria (see protocol for details).

[2] Two patients prematurely discontinued prior to receiving double-blind treatment.

Cross-references: Tables 6.1.-1 and 6.1.-2; Table IV-6.1.-1; Module II, Data Listing 1; Module VI, Data listing 1.

Of the randomized patients, 86 (89.6%) completed trial by completing the double-blind treatment phase (16 in the OXC 2400 mg/day group, 0 in the OXC 300 mg/day group) or by meeting one of the four exit criteria (30 in the OXC 2400 mg/day group, 40 in the

OXC 300 mg/day group). Ten (10.4%) randomized patients (5 in the OXC 2400 mg/day group, 5 in the OXC 300 mg/day group) prematurely discontinued for administrative reasons. Two patients randomized to the OXC 2400 mg/day group prematurely discontinued prior to receiving the double-blind trial medication. One withdrew consent and the other died as a result of ischemic heart failure.

Of the 47 non-randomized patients, 21 (44.7%) prematurely discontinued during the open-label conversion phase, and 26 (55.3%) prematurely discontinued prematurely discontinued during the open-label baseline phase. Twenty-four (51.1%) patients were prematurely discontinued due to adverse experiences, 8 of which occurred during the open-label conversion phase and 16 during the open-label baseline phase. Twenty-three (48.9%) patients prematurely discontinued due to other reasons: 15 (31.9%) patients due to unsatisfactory therapeutic effect, 4 (8.5%) patients due to non-compliance and 1 due to administrative reasons. All 15 prematurely discontinued due to unsatisfactory therapeutic effect occurred during the baseline phase.

3.4.2 Demographic and baseline data

A brief summary of demographic and baseline characteristics for the ITT patient population is presented in Exhibit 7.1.-1, and a brief summary of seizure frequency during the baseline for the ITT patients is presented in Exhibit 7.1.-2.

Exhibit 7.1.-1. Demographics and baseline characteristics by treatment group (intent-to-treat patients)

Characteristic	OXC 2400 mg/day (N=49)	OXC 300 mg/day (N=45)	Total (N = 94)
Sex			
Male (%)	22 (44.9%)	24 (53.3%)	46 (48.9%)
Female (%)	27 (55.1%)	21 (46.7%)	48 (51.1%)
Race			
White (%)	42 (86.1%)	39 (86.7%)	81 (86.2%)
Other (%)	7 (13.9%)	6 (13.3%)	13 (13.8%)
Age (yr)			
Mean (Range)	35.6 (12.0-65.0)	34.6 (18.0-53.0)	35.1 (12.0-65.0)
Weight (kg) at Visit 1			
Mean (Range)	76.5 (46.4-152.4)	75.2 (41.0-113.6)	75.9 (41.0-152.4)
Carbamazepine dose (mg/day) at screening			
Mean (Range)	1308.2 [redacted]	1275.6 [redacted]	1292.6 [redacted]
Cross-references: Table 7.1.-1; Module III Table 1; Table IV-7.1.-1; Module VI, Data listing 2.			

Exhibit 7.1.-2 Summary statistics of seizures in Open-label Baseline Phase (intent-to-treat patients)

Treatment	OXC 2400 mg/day (N=49)	OXC 300 mg/day (N=45)	Total (N=94)
Median (range) partial seizure frequency per 28 days	6.5	5.5	6.0
Median (range) secondarily generalized seizure frequency per 28 days	0.0	0.0	0.0
Median (range) highest consecutive 2-day seizure frequency	4.0	3.0	3.0
Cross-reference: Table 7.1.-3; Module VI, Data listing 7A.			

The sponsor stated that the type and frequency of seizures experienced by patients in the OXC 2400 mg/day and 300 mg/day treatment groups were similar during the baseline phase. The median baseline seizure frequency per 28-day period was 6.5 in the OXC 2400 mg/day group and 5.5 in the OXC 300 mg/day group. The highest consecutive two-day seizure frequency during the baseline phase was also similar.

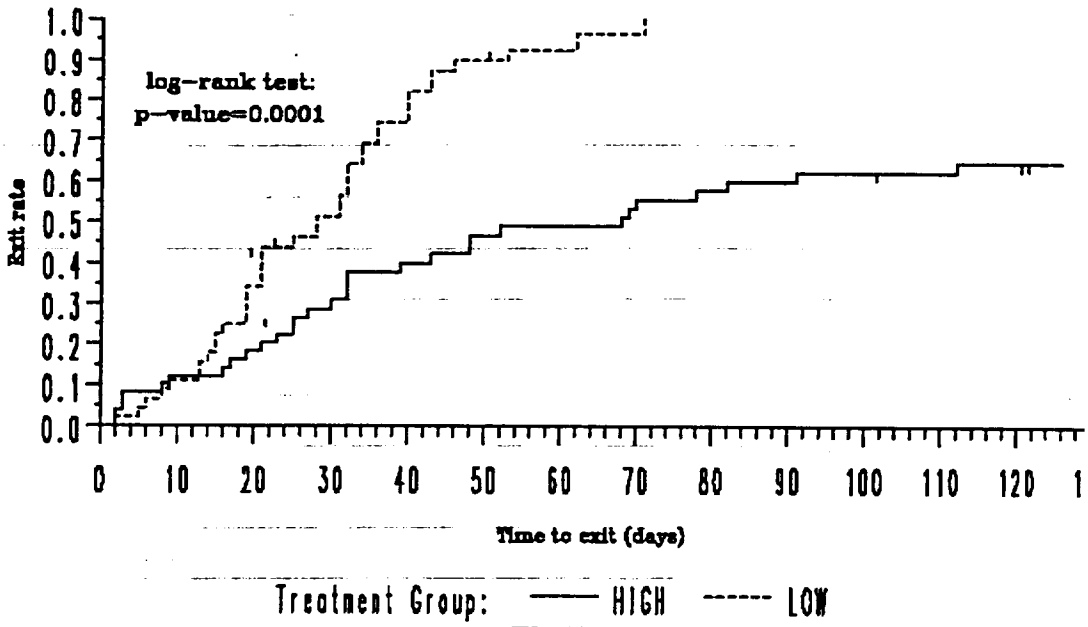
3.4.3 Analysis of Efficacy

The sponsor stated that all statistical analyses for the efficacy variables were planned and specified in the protocol or planned prior to the unblinding of the trial.

Primary efficacy analysis

The sponsor reported that time to meeting one of the exit criteria was statistically significant in favor of OXC 2400 mg/day group (p=0.0001) based on the log-rank test. The magnitude of the difference in exit rates is presented in Exhibit 8.1.-1. The median time to meeting one of the exit criteria was 68 days for the OXC 2400 mg/day group compared to 28 days for the OXC 300 mg/day group. An additional analysis using Cox's proportional hazard regression model with treatment, center, sex, age, CBZ dose during the screening phase and partial seizure frequency per 28 day during baseline as explanatory variables confirmed the results shown by the log-rank test (p=0.0001).

Exhibit 8.1.-1. Kaplan-Meier estimates of exit rate by treatment group (intent-to-treat patients)



Analysis of secondary efficacy variable

The sponsor reported that the percentage of patients meeting one of the exit criteria was statistically significant in favor of OXC 2400 mg/day group (p=0.010) based on CMH test controlling for center with prematurely discontinuations classified using a "worst case" scenario. The percentage of patients meeting one of the exit criteria was 67.3% (33/49) for the OXC 2400 mg/day group compared to 88.9% (40/45) for the OXC 300 mg/day group. The sponsor also reported that a Breslow-Day test for treatment-by-center interaction was not statistically significant (p=.662). All pooled centers used in the test for treatment-by-center interaction had a lower percentage of patients meeting one of the exit criteria in the OXC 2400 mg/day group relative to the OXC 300 mg/day group.

The percentage of patients meeting one of the exit criteria was also analyzed using a logistic regression model with treatment, center, sex, age, CBZ dose during the screening phase and partial seizure frequency per 28 days during the baseline phase as explanatory variables. The treatment difference from the results of the logistic regression was statistically significant in favor of OXC 2400 mg/day group (p=.0035).

The distribution of patients in each treatment group who met the 4 exit criteria is summarized in Exhibit 8.1.-3. In both treatment groups, the most common reason for exiting the trial was a twofold increase in monthly partial seizure frequency in any 28-day period relative to the baseline phase.

Exhibit 8.1.-3. Frequency distribution of exit criteria met by treatment group (intent-to-treat patients)[1]

Exit criteria	OXC 2400 mg/day (N=46)		OXC 300 mg/day (N=40)	
Twofold increase in monthly partial seizure frequency in any 28-day period relative to the Baseline Phase[1]	15	(32.6%)	17	(42.5%)
Twofold increase in the highest consecutive two-day seizure frequency relative to the Baseline Phase[2]	7	(15.2%)	8	(45.0%)
New onset generalized seizure if none occurred during the Baseline Phase	5	(10.9%)	10	(25.0%)
Experienced a seizure event that required investigator intervention	3	(6.5%)	5	(12.5%)

[1] Excludes patients who prematurely discontinued during the Double-blind Treatment Phase.

[2] If less than 2 seizures occurred per 28 days during the Open-label Baseline Phase, three or more seizures were required during any 28-day period to exit due this criterion.

[3] This criterion applied only if two or more seizures occurred during any 2-day period during the Baseline Phase.

Cross-reference: Table 6.1.-1; Module VI Data Listings 12B, 13.

3.5 Reviewer's Findings/ Comments

Primary Analysis

The primary analysis, the log-rank test, was performed on the time to exit. A p-value of 0.0001 was obtained from the log-rank test representing the significance of difference in the time to exit in favor of the OXC 2400 mg/day group. Such difference was also found to be statistically significant ($p<.05$) in male subjects as well as in female subjects. The log (-log) survival curves for the treatment groups showed that the assumption of proportional hazard for the Cox model was not satisfied. Therefore, the Cox's regression model is not appropriate.

Analysis of secondary efficacy variable

The CMH test was performed on the percentage of patients meeting one of the exit criteria. The analysis showed a p-value of 0.017 without controlling for center and a p-value of 0.011 with controlling for center using the worst case scenario for prematurely discontinued patients. Center pooling was not specified in the protocol, but the method used in pooling the centers is considered reasonable and consistent with other studies.

Comments/ Conclusions

The effectiveness of OXC 2400 mg/day is established in this study based on the primary analysis and the analysis of the secondary efficacy variable. However, it needs to be noted that due to the study design, a large number of subjects were dropped out before double-blind treatment started. This causes that the subjects entered the double-blind treatment phase are selective, and may not represent the target patient population at large. Therefore, the effectiveness of OXC 2400 mg/day is established only for those patients who have adequately seizure control and who can tolerate the dose of 2400 mg/day.

4 Study 028 (Mono-therapy, Dose control)

4.1 Trial Objectives

The primary objective of this trial was to evaluate the safety and efficacy of high dose (2400 mg/day) and low dose (300 mg/day) OXC mono-therapy in patients with inadequately controlled partial seizures which include subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures. The secondary objective of this trial was to explore the dose-and plasma-concentration relationship of OXC.

4.2 Trial Design

This was a multi-center, double-blind, randomized, parallel-group trial designed to investigate the safety and efficacy of high dose (2400 mg/day) and low dose (300 mg/day) OXC mono-therapy in patients with adequately controlled partial seizures which include seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures, despite treatment with one or two AEDs. This mono-therapy design was chosen to demonstrate unequivocal efficacy in a refractory patient population.

The trial consisted of three phases: baseline phase, double-blind treatment phase and an open-label extension phase. The design of the trial up to and including the double-blind treatment phase is presented in Exhibit 3.1.-1.

Exhibit 3.1.-1. Trial design

Phase	Baseline		Double-blind Treatment						
Period			Titration		Maintenance				
Visit	1		2	3	4	5	6	7	8
Day	-56	0	7	14	28	42	70	98	126
Treatment	One or two AEDs		OXC 300 mg/day or gradual titration to OXC 2400 mg/day. Gradual withdrawal of standard AEDs over the first 42 days.						
	⇑ randomization								

Double-Blind Phase

At Day 0, patients meeting the eligibility criteria entered the 126-day (18-week) double-blind treatment phase and were randomized to treatment with OXC 2400 mg/day or OXC 300 mg/day. The double-blind phase had two periods: titration and maintenance.

Titration period

Patients were randomized on Day 0 to either the 2400 mg/day or 300 mg/day OXC group. Patients randomized to the OXC 300 mg/day group received a dose of 300 mg/day throughout the double-blind treatment phase, beginning at Day 1. Patients randomized to the 2400 mg/day group received 1200 mg/day on Days 1 – 7, 1800 mg/day on Days 8 – 14 and 2400 mg/day on Days 15 – 126.

Patients were taped and discontinued from their AED regiments over a 6-week period, beginning on Day 1. On Days 1, 8 and 15 the primary AED was reduced by 25%; the primary AED does was maintained at 25% of the initial does between Day 15 and 42 and then discontinued on Day 43. The secondary AED was discontinued on Day 1.

Maintenance period

Patients completed the titration period entered the 112-day maintenance period and remained on the dose of OXC they received on Day 15. Patients unable to tolerate the 2400 mg/day dose were able to have their dosage adjusted by a decrease of one tablet at each dose to either 2100 mg/day or 1800 mg/day. This dosage adjustment was done in a blinded fashion so that patients receiving OXC 300 mg/day had their dosage adjusted by one or two placebo tablets.

Reviewer's comment: It is not clear why patients receiving OXC 300 mg/day needed to have their dose adjusted by one or two placebo tablets, since not all patients receiving 2400 mg/day had their dose adjusted.

Exit Criteria

Patients were considered to have completed the trial if they completed all visits of the core trial or met one of the four pre-defined exit criteria during the double-blind treatment phase. Discontinuations for any other reason, such as adverse experience, were considered premature discontinuations and not "exits".

The guidelines for exiting the trial required one of the following:

1. A twofold increase in partial onset seizure frequency in any 28-day period during the double-blind treatment phase (not necessarily at visits). Patients could meet the criteria between visits.
2. A twofold increase in the highest consecutive 2-day seizure frequency that occurred during the baseline phase (only if two or more seizures occurred in a 2-day period during the baseline phase). If the highest consecutive 2-day seizure frequency was 1

during the baseline phase, the patient must have exited the trial if three or more seizures occurred in the highest 2-day consecutive period during the double-blind treatment phase.

3. Occurrence of a single generalized seizure if none occurred during the 6 months prior to randomization.
4. A prolonged or worsening of generalized seizure duration (serial seizures or status epilepticus of any seizure subtype) or frequency deemed by the investigator to require intervention.

Trial start date: September 11, 1996
Trial end date: October 1, 1997

No interim analyses were planned.

4.3 Efficacy

4.3.1 Primary Efficacy Variable and its Statistical Analysis

The protocol specified primary efficacy variable is the percentage of patients meeting one of the exit criteria (see Section 3.1).

The protocol specified primary statistical analysis for the percentage of patients meeting one of the exit criteria was based on a Cochran-Mantel-Haenszel (CMH) test controlling for center. An additional analysis was performed using logistic regression model. This model included treatment, center, sex, age, and baseline total partial seizure frequency per 28 days as explanatory variables. Both statistical analyses were performed by excluding patients who prematurely discontinued from the double-blind treatment phase. Supplementary analyses that classified patients as 1) having met one of the exit criteria, 2) not having met one of the exit criteria were also performed.

The sponsor stated that in addition, after database lock, "worst case" analyses were performed for the CMH test and logistic regression model. These analyses classified patients in the OXC 2400 mg/day group who prematurely discontinued as exited patients, and patients in the 300 mg/day group who prematurely discontinued as completed double-blind treatment phase.

The CMH test controlling for center performed for the primary efficacy variable were repeated for the subgroups of patients based on whether or not they experienced secondarily generalized seizures during the six months prior to randomization. The sponsor stated that these analyses were performed as specified in the statistical analysis plan.

4.3.2 Secondary Efficacy Variable and its Statistical Analysis

The secondary efficacy variable is the time to meeting one of the exit criteria.

The statistical analysis for the time to meeting one of the exit criteria was based on the log-rank test. A secondary analysis was performed using Cox's proportional hazard (PH) regression model. This model included treatment, center, sex, age, and baseline partial seizure frequency per 28 days as explanatory variables. Both statistical analyses were performed on the intent-to-treat patient population, where patients who prematurely discontinued from the trial were classified as censored observations. The above secondary efficacy variable and its statistical analysis was specified in the protocol.

4.3.3 Criteria for efficacy

OXC was considered efficacious if the percentage of patients in the OXC 2400 mg/day group meeting one of the exit criteria was a statistically significantly lower ($p<0.05$, two-sided) than the percentage in the OXC 300 mg/day group.

4.4 Results (Sponsor's Findings)

4.4.1 Completion/Withdrawal Information

Eighty-seven patients were enrolled into the trial and randomized to double-blind treatment (41 in OXC 2400 mg/day, 46 in OXC 300 mg/day). All 87 randomized patients were included in the ITT data set for efficacy analyses. A brief summary of the distribution of patient outcomes by treatment group is displayed in Exhibit 6.1.-1.

Exhibit 6.1.-1. Distribution of patients by treatment group (all treated patients)

Number of patients	OXC 2400 mg/day	OXC 300 mg/day	Total
Randomized	41	46	87
Completed Double-blind Treatment Phase (intent-to-treat)	34	45	79
Met predefined exit criteria[1]	14	42	56
Completed double-blind treatment	20	3	23
Discontinued prematurely (all treated)			
Total	7	1	8
For adverse experience	6	1	7
Other (Abnormal laboratory value)	1	0	1
Included in efficacy analyses (intent-to-treat)	41	46	87
Included in safety analyses (all treated)			
Laboratory tests	41	46	87
Adverse experiences	41	46	87
Included in pharmacokinetics analyses	30	15	45

[1] Exit criteria (see Section 3.1 for details).

Cross-references: Tables 6.1.-1, 6.1.-2, 6.1.-3, 6.1.-4; Table IV-6.1.-1; Module II, Data listing II.1; Module VI, Data listing 1.

Of the randomized patients, 91% (79/87) completed trial either by completing the double-blind treatment phase (20 in OXC 2400 mg/day; 3 in OXC 300 mg/day) or by meeting one of the four exit criteria (14 in OXC 2400 mg/day; 42 in OXC 300 mg/day).

Eight patients (9%) (7 in OXC 2400 mg/day, 1 in OXC 300 mg/day) discontinued the trial prematurely. Six patients in the OXC 2400 mg/day and one in OXC 300 mg/day group were discontinued for adverse experience. The remaining patient in the OXC 2400 mg/day group was discontinued due to an abnormal laboratory value. There were no deaths reported during the baseline and double-blind treatment phase of this trial.

4.4.2 Demographic and Baseline Data

Eighty-seven patients were randomized at 9 centers and are included in the all treated patient population. The all treated population was 39.1% (N=34) male and 92.0% (N=80) white. The mean patient age was 35.7 years. During the 6 months prior to randomization, 32.2% (N=28) of the patients experienced secondarily generalized seizures. During the baseline phase, 49.4% (N=43) were receiving carbamazepine as a concomitant AED.

A brief summary of demographic an baseline characteristics for all treated patients is presented in Exhibit 7.1.-1. A brief summary of seizure frequency during the baseline phase for the ITT patient population is presented in Exhibit 7.1.-2.

Exhibit 7.1.-1. Demographics and baseline characteristics by treatment group (all treated patients)

Characteristic	OXC 2400 mg/day (N=41)	OXC 300 mg/day (N=46)	Total (N = 87)
Sex			
Male (%)	15 (36.6%)	19 (41.3%)	34 (39.1%)
Female (%)	26 (63.4%)	27 (58.7%)	53 (60.9%)
Race			
White (%)	38 (92.7%)	42 (91.3%)	80 (92.0%)
Other (%)	3 (7.3%)	4 (8.7%)	7 (8.0%)
Age (yr)			
Mean (Range)	35.1 (13.0-59.0)	36.3 (11.0-66.0)	35.7 (11.0-66.0)
Weight (kg) at Visit 1			
Mean (Range)	75.8 (44.5-124.8)	81.8 (48.2-130.9)	79.0 (44.5-130.9)
Secondarily generalized seizures in 6 months prior to randomization			
Yes	14 (34.1%)	14 (30.4%)	28 (32.2%)
Concomitant AED at Baseline			
Carbamazepine	22 (53.7%)	21 (45.7%)	43 (49.4%)
Phenytoin	8 (19.5%)	13 (28.3%)	21 (24.1%)
Valproate	6 (14.6%)	6 (13.0%)	12 (13.8%)
Lamotrigine	5 (12.2%)	7 (15.2%)	12 (13.8%)
Gabapentin	4 (9.8%)	7 (15.2%)	11 (12.6%)
Cross-references: Table 7.1.-1; Module III Tables 1 and 2; Table IV-7.1.-1; Module VI, Data listing 8.			

Exhibit 7.1.-2 Summary statistics of seizures in Baseline Phase (all treated patients)

Treatment	OXC 2400 mg/day	OXC 300 mg/day	Total
Number of patients	41	46	87
Median (range) partial-onset seizure frequency per 28 days	10.5	6.5	8.0
Median (range) secondarily generalized seizure frequency per 28 days	0.0	0.0	0.0
Median (range) highest consecutive 2-day seizure frequency	3.0	3.0	3.0
Cross-reference: Table 7.1.-3; Module VI, Data listing 8.			

4.4.3 Analysis of Efficacy

The sponsor stated that all statistical analyses for the efficacy variables were planned and specified in the protocol. Details with respect to the subgroup analysis of the percentage of patients meeting one of the exit criteria by whether or not a patient experienced secondarily generalized seizures during the six months prior to randomization, were documented in the statistical analysis plan prior to the unblinding of the drug code.

Primary efficacy analysis

The sponsor reported that the primary efficacy variable, percentage of patients meeting one of the exit criteria, was statistically significantly lower (CMH test controlling for center, $p<0.0001$) for the OXC 2400 mg/day group (14/34; 41%) relative to the OXC 300 mg/day group (42/45; 93.3%), excluding patients who prematurely discontinued. An additional analysis that classified patients who prematurely discontinued using a "worst case" scenario also provided statistical significant results in favor of the OXC 2400 mg/day group ($p<0.0001$). No significant treatment-by-center interaction was found for the above CMH analyses ($p>0.80$). A summary of these results is presented in Exhibit 8.1.-1.

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Exhibit 8.1.-1. Between-treatment comparisons for the percentage of patients meeting one of the exit criteria (intent-to-treat patients)

Premature discontinuations classified as	No. (%) who met one of the exit criteria		
	OXC 2400 mg/day	OXC 300 mg/day	P-value[1]
Excluding patients who prematurely discontinued	14/34 (41.2%)	42/45 (93.4%)	<0.0001
"Worst-case scenario"	21/41 (51.2%)	42/46 (91.3%)	<0.0001

[1] P-value based on Cochran-Mantel-Haenszel test.

Cross-references: Tables 8.1.-1 and 8.1.-2; Module III, Tables 3 and 4; Figure 8.1.-1; Module VI, Data listing 11B, 12.

The percentage of patients who met the exit criteria was also analyzed using a logistic regression model that adjusting for center, sex, age, and baseline partial seizure frequency per 28 days. It was found that OXC 2400 mg/day treatment was statistically significantly superior to the OXC 300 mg/day treatment regardless of how premature discontinuations were handled ($p<0.0001$).

Reviewer's comment: The covariates sex and age were NOT specified in the protocol.

The sponsor found that patients in the OXC 2400 mg/day group were most likely to exit from the trial due to a twofold increase in partial seizure frequency in any 28-day period relative to the baseline phase (17.6%), while patients in the OXC 300 mg/day group were most likely to exit due to a twofold increase in the highest consecutive two-day seizure frequency (40.0%). A summary of the distribution of the exit criteria met by each treatment group is presented in Exhibit 8.1.-2.

Exhibit 8.1.-2. Frequency distribution of exit criteria met by treatment group (intent-to-treat patients)[1]

Exit criteria	OXC 2400 mg/day (N=34)	OXC 300 mg/day (N=45)
Twofold increase in partial seizure frequency in any 28-day period relative to Baseline Phase	6 (17.6%)	16 (35.6%)
Twofold increase in the highest consecutive two-day seizure frequency relative to Baseline Phase[2]	3 (8.8%)	18 (40.0%)
New onset generalized seizure	5 (14.7%)	5 (11.1%)
Prolongation or worsening of generalized seizure duration or frequency requiring investigator intervention	0 (0.0%)	3 (6.7%)

[1] Patients who prematurely discontinued were excluded from the frequency distributions.

[2] If the highest consecutive two-day frequency was one during the Baseline Phase, three or more seizures were required to occur in the highest two-day consecutive period during the double-blind phase.

Cross-reference: Table 6.1.-1, Module VI, Data Listings 11B, 12.

Secondary efficacy variable

The sponsor reported that for the secondary efficacy variable, time to meeting one of the exit criteria, the log-rank test performed on the ITT patient population was statistically significant in favor of the OXC 2400 mg/day group (p=0.0001). The magnitude of the difference in exit rates during the double-blind phase is presented in Exhibit 8.1.-5. The median time to meeting one of the exit criteria could not be computed for the OXC 2400 mg/day group since fewer than 50% of the patients in this treatment group met one of the exit criteria. In comparison, the median time to meeting one of the exit criteria was 26 days for the OXC 300 mg/day group.

An additional analysis using Cox's proportional hazard regression model that adjust for the effects of the explanatory variables of treatment, center, sex, age, and baseline partial seizure frequency per 28 days also found statistically significant in favor of OXC 2400 mg/day group (p<0.0001).

Reviewer's comment: Variables sex and age were not included in the Cox's model in the protocol.

Exhibit 8.1.-5. Between-treatment comparison for time to meeting one of the exit criteria (intent-to-treat patients)

OXC 2400 mg/day (N = 41)			OXC 300 mg/day (N = 46)			
Quantiles (days)			Quantiles (days)			
25th	Median[1]	75th	25th	Median[1]	75th	P-value[2]
72	—[3]	—[3]	18	26	46	<0.0001

[1] Time when 50% of patients met one of the exit criteria

[2] P-value based on the log-rank test, p<0.05.

[3] Could not be computed because fewer than 50% of patients in this treatment group met one of the exit criteria

Cross-references: Table 8.1.-5; Module III, Tables 7 and 8; Figure 8.1.-2; Module VI, Data Listings 11B and 12.

4.5 Reviewer's Findings/ Comments

Primary efficacy analysis

The protocol specified primary analysis, CMH test, was performed to the percentage of patients meeting one of the exit criteria, and the results obtained by the sponsor was verified. It was found that the percentage of patients meeting one of the exit criteria was significantly lower for the OXC 2400 mg/day group than the OXC 300 mg/day group with a p-value of 0.0001 based on a CMH test with controlling for center as well as without controlling for center. Such difference in favor of OXC 2400 mg/day group was also found to be statistically significant (p<.05) in both gender groups as well as both age groups of <=35 years old and > 35 years old. The premature discontinuation was treated using worst case scenario in the analysis.

Secondary efficacy variable

Log-rank test was performed to the time to meeting one of the exit criteria. It was found that the time to meeting one of the exit criteria for the two groups was significantly different in favor of OXC 2400 mg/day group with a p-value of 0.0001.

A Cox regression model was also used in analyzing the time to meeting one of the exit criteria. The covariates included in the Cox's model were treatment, center, baseline seizure frequency per 28 days. The treatment effect was found significant in favor of OXC 2400 mg/day group with a p-value of 0.0001. In another Cox's model, age and sex were added to the above model. It was found that sex effect was significant (p=0.0337). Male patients have higher risk to meet one of the exit criteria compared to female patients. The risk ratio of meeting one of the exit criteria for a male patient compared to a female patient is 1.938.

Comments/ Conclusions

Both Study 026 and Study 028 compare high dose of 2400 mg/day and low dose of 300 mg/day, but with different design. In Study 026, all subjects started with dose 2400 mg/day, and then the dose for subjects who randomized to 300 mg/day group were tapered down. In Study 028, dose was titrated up. The primary and secondary efficacy variables were switched around in the two studies. The results from these two studies supported and confirmed each other. It can be concluded that OXC 2400 mg/day is efficacious for the patient population similar to the ones in Studies 026 and 028.

5 Study 011 (Adjunctive therapy)

5.1 Trial Objectives

The primary objective of this trial was to evaluate the efficacy and safety of OXC, as adjunctive therapy, relative to placebo in children with inadequately controlled partial seizures. The secondary objective of this trial was to explore the pharmacokinetic-pharmacodynamic (efficacy and safety) relationships of OXC in the pediatric population, as well as explore the drug-drug interaction potential of OXC when given with other AEDs.

5.2 Trial Design

This was a multinational, multi-center, double-blind, randomized, placebo-controlled, 2-arm parallel trial designed to investigate the efficacy and safety of OXC compared to placebo as adjunctive therapy in children aged 4 to 17 years with inadequately controlled partial seizures, which include seizure types of simple, complex, and partial seizures evolving to secondarily generalized seizures. This design allowed patients with inadequate seizure control to continue on a stable regimen of one or two AEDs, in addition to receiving the investigational drug or placebo.

There were three phases in this trial: Baseline, Double-blind Treatment, and Open-label Extension. The design of the trial including the double-blind treatment phase is presented in Exhibit 3.1.-1.

Exhibit 3.1.-1. Trial design

Phase	Baseline[1]		Double-blind					
Period			Titration	Maintenance				
Visit	1	2	3	4	5	6	7	8
Day	-56 to -1	0[2]	14	28	42	56	84	112
Treatment	1 to 2 AEDs		OXC or placebo plus 1 to 2 AEDs					
	⇑ randomization							

[1] Up to 28 days of Baseline Period seizure counts were allowed to be obtained from patient seizure diaries, provided those diaries were complete, accurate, and well-documented.
[2] Randomization occurred at Visit 2, however the actual Titration Period began between Visit 2 and Visit 3.

Baseline Phase

During the 56-day baseline phase, patients were maintained on their stable dose of 1 or 2 AEDs. Additional AEDs and non-allowed concomitant medications were required to be discontinued 30 days prior to the start of the baseline phase.

Documentation confirming trial eligibility was collected on the last day of the baseline phase, i.e., at Visit 2. Patients meeting the eligibility criteria were then randomized to treatment with OXC or placebo and entered the 112-day (16-week) double-blind treatment phase.

Double-Blind Phase

The double-blind treatment phase consisted 2 periods: a 14-day titration period and a 98-day (14-week) maintenance period. Concomitant AED dosages were required to remain constant during both periods of the double-blind treatment phase.

Titration period:

Based on the body weights recorded at Visit 2, patients' target randomized trial drug doses were determined on a mg/kg basis, based on the following weight categories as shown in Exhibit 3.1.-2. A 14-day titration schedule was employed to achieve the target randomized daily dose. Titration intervals and dosages could be adjusted to allow for tolerability, provided the target randomized dose for the appropriate weight category was not exceeded.

Exhibit 3.1.-2. Target randomized daily dose by body weight

Body Weight on Visit 2	Target Randomized Daily Dose
20.0 to 29.0 kg	900 mg (31 mg/kg to 45 mg/kg)
29.1 to 39.0 kg	1200 mg (31 mg/kg to 41 mg/kg)
39.1 to 60.0[1] kg	1800 mg (30 mg/kg to 46 mg/kg)
[1] Protocol displayed the above table showing an upper weight limit of 60.0 kg, but after the trial began, body weights greater than 60.0 kg were allowed, with a target randomized daily dose of 1800 mg.	

Maintenance period:

Patients who completed the titration period entered the 98-day maintenance period and remained on the total daily dose of the trial drug achieved at the end of the titration period.

Before any patient entered the trial, an amendment permitted dosage adjustments to trial drug during the maintenance period in the event of inadequate seizure control or poor tolerability with the prior approval of the trial monitor.

Trial start date: May 3, 1995
Trial end date: September 18, 1997

No interim analyses were planned.

5.3 Efficacy

5.3.1 Primary Variable and its statistical analysis

The protocol specified primary efficacy variable is the percentage change in partial seizure frequency per 28 days of double-blind treatment phase from baseline phase (PCH).

The protocol specified primary efficacy variable, PCH, was to be analyzed using an analysis of covariance model. Covariates in the model were treatment, center, age, sex, and baseline partial seizure frequency per 28 days. In the case that the residuals from the model did not approximate a normal distribution, a non-parametric procedure (the Wilcoxon rank-sum test) was to be used to test for treatment effect.

5.3.2 Secondary Variables and Their Statistical Analyses

Variable 1: Total partial seizure frequency per 28 days

Partial seizure frequency per 28 days was defined as the number of partial seizures experienced over a specified period in the double-blind phase divided by the number of days in the double-blind phase multiplied by 28. This variable was specified in the protocol.

The analysis of the total partial seizure frequency per 28 days specified in the protocol was a Poisson regression model with a log-linear form for the rate function. Covariates in this model included treatment, center, sex, age, and baseline partial seizure frequency.

Variable 2: Response to treatment

A responder to treatment was defined as a patient who experienced at least a 50% reduction in partial seizure frequency per 28 days during the double-blind treatment phase from the baseline. This efficacy variable was added in the Statistically Analysis Plan.

Response to treatment was analyzed using a logistic regression model with treatment, center, sex, age, and weight as explanatory variables.

The sponsor stated that the analysis of this variable was added in the statistical analysis plan in order to achieve consistency with the efficacy variables analyzed in the other adjunctive therapy trial (Protocol OT/PE1).

Variable 3: Percentage change in the secondarily generalized seizure frequency of double-blind treatment phase from baseline phase.

This variable was specified in the protocol and was to be analyzed identically to the primary variable for the subgroup of patients who experienced this seizure type during the baseline phase.

Reviewer's Comment: The variable Response to Treatment was not specified in the protocol. Instead, Variable 2 of the secondary efficacy variables in the protocol was Time to tenth partial-onset seizure.

5.3.2 Criteria for efficacy

OXC was considered efficacious if the percentage reduction in partial seizure frequency per 28 days during the double-blind treatment phase from the baseline phase was statistically significantly greater ~~(p<0.05, two-sided)~~ than placebo.

5.4 Results (Sponsor's ~~Findings~~)

5.4.1 Completion/Withdrawal Information

Two hundred sixty-seven patients were randomized into the double-blind treatment phase (138 to OXC and 129 to placebo). Of the randomized patients, 88.4% (236/267) completed double-blind treatment phase (117 OXC, 119 placebo). Thirty-one randomized patients (11.6%) prematurely discontinued from the double blind treatment phase of which 21 were OXC-treated patients (15.2%) and 10 were placebo-treated patients (7.7%). Overall, the most common reason for premature discontinuation was due to

adverse experiences (14 (10.1%) OXC, 4 (3.1%) placebo). Three of the randomized patients (2 OXC, 1 placebo) did not provide double-blind seizure diary and were excluded from the ITT patient population for efficacy analyses. A brief summary of patient disposition by treatment group is presented in Exhibit 6.1.-1.

Exhibit 6.1.-1. Distribution of patients by treatment group

Number of patients	OXC	Placebo	Total
Randomized	138	129	267
Completed	117	119	236
Discontinued prematurely (all treated)			
Total	21	10	31
For Adverse experience	14	4	18
Other	7	6	13
Efficacy Analyses (intent-to-treat)[1]	136	128	264
Safety Analyses (all treated)			
Laboratory Tests	138	129	267
Adverse experiences	138	129	267
Pharmacokinetics Analyses	109	128[2]	237

[1] One OXC-treated patient (Leonor Avendao Kunstmann/1088) who was prematurely discontinued due to inaccurate seizure diary information was included in the efficacy analyses of the primary efficacy variable only.

[2] For concomitant AED levels.

Cross-references: Tables 6.1.-1, 6.1.-2, 6.1.-3, Table IV-6.1.-1; Module II Data Listing II.1; Module VI Data Listing 1

Thirty-two (23%) of OXC-treated patients compared to 14 (11%) of placebo-treated patients reported severe adverse experience, whether or not trial drug related. A total of 15 patients (7 OXC, 8 placebo) experienced adverse experience during the double-blind treatment phase that met the criteria for being serious, and 11 of them (5 OXC, 6 placebo) were considered not related or unlikely related to treatment.

There was one death: an OXC-treated patient died on Day 9 of the double-blind treatment phase.

5.4.2 Demographic and Baseline Data

Two hundred sixty seven patients were randomized at 47 centers in five countries, and are included in the all-treated patient population. A brief summary of demographic and baseline characteristics for all treated patients is presented in Exhibit 7.1.-1, and a brief

summary of seizure frequency during the baseline phase for all treated patients is presented in Exhibit 7.1.-2.

Exhibit 7.1.-1. Demographics and baseline characteristics by treatment grou (all treated patients)

Characteristic	OXC (N=138)		Placebo (N=129)		All treated (N=267)	
Sex						
Male (%)	70	(50.7%)	71	(55.0%)	141	(52.8%)
Female (%)	68	(49.3%)	58	(45.0%)	126	(47.2%)
Race						
white (%)	120	(87.0%)	112	(91.3%)	232	(86.9%)
Other (%)	18	(13.0%)	17	(13.2%)	35	(13.1%)
Age (yrs)						
Mean (Range)	11.1 (3-17)		10.9 (3-17)		11.0 (3-17)	
Weight at randomization (Visit 2) (kilograms)						
Mean (Range)	43.5 (15.9-130.0)		44.2 (16.1-89.0)		43.9 (15.9-130.0)	
Experienced secondarily generalized seizures during the Baseline Phase						
No (%)	88	(63.8%)	72	(55.8%)	160	(59.9%)
Yes (%)	50	(36.2%)	57	(44.2%)	107	(40.1%)
Carbamazepine administered during the Baseline Phase						
No (%)	61	(44.2%)	74	(57.4%)	135	(50.6%)
Yes (%)	77	(55.8%)	55	(42.6%)	132	(49.4%)
Cross-references: Tables 7.1.-1; Module III Table 1; Table IV-7.1.-1; Module VI Data Listing 10						

Exhibit 7.1.-2 Summary statistics of seizures in Baseline Phase (all treated patients)

Treatment	OXC		Placebo		All treated	
Number of patients	138		129		267	
	Median	Range	Median	Range	Median	Range
Secondarily generalized seizure frequency per 28 days	0.0	[redacted]	0.0	[redacted]	0.0	[redacted]
Partial seizure frequency per 28 days	12.3	[redacted]	13.0	[redacted]	13.0	[redacted]
Cross-references: Tables 7.1.-2, 8.1.-2, 8.1.-7, and IV-7.1.-2, and Module VI Data Listing 10						

5.4.3 Analysis of Efficacy

The sponsor stated that all statistical analyses for the efficacy variables were planned and specified in the protocol or planned prior to the unblinding of the trial.

Primary efficacy analysis

The statistical analysis for percentage change in partial seizure frequency per 28 days (PCH) was performed based on the ranks of PCH using the Wilcoxon rank-sum test. The sponsor stated that this analysis was performed since normality assumption required for the analysis of covariance model could not be satisfied.

The sponsor reported that the primary efficacy variable, percentage change in partial seizure frequency per 28 days from the baseline, was statistically significant in favor of the OXC treatment group over placebo (Wilcoxon rank-sum test, p=0.0001). OXC-treated patients experienced a 34.8 % median reduction in partial seizure frequency per 28 days from the baseline phase compared to a 9.4% median reduction for placebo treated patients. A brief summary of these results are presented in Exhibit 8.1.-1.

Exhibit 8.1.-1 Summary of percentage change in partial seizure frequency per 28 days from baseline (intent-to-treat patients)[1]

	OXC (N=136)		Placebo (N=128)	
	Median	Range	Median	Range
Baseline partial seizure frequency per 28 days	12.5	[redacted]	13.1	[redacted]
Double-blind treatment partial seizure frequency per 28 days	7.9	[redacted]	14.3	[redacted]
Percentage change in partial seizure frequency per 28 days from baseline	-34.8	[redacted]	-9.4	[redacted]

Wilcoxon rank-sum test P-value = 0.0001

[1] Includes OXC patient Leonor Avendao Kunstmann/1088 who was prematurely discontinued due to inaccurate seizure diary information.

Cross-references: Table 8.1.-1; Module III Table 2; Table IV-8.1.-1; Module VI Data Listing 12A

The OXC treatment group showed a greater reduction in seizure frequency per 28 days from baseline for each of the seizure types (simple, complex, and partial seizures evolving to secondarily generalized seizures).

The sponsor also reported that with respect to the demographic subgroups of sex, race, age and country, the OXC group showed a greater reduction in partial seizure frequency per 28 days from baseline for all but one category. Only the black race group (OXC n=8, placebo n=8) did OXC treated patients have a slightly smaller reduction in partial seizure frequency per 28 days (median 46.3%) relative to placebo (median 57.8%).

Secondary efficacy variable

Variable 1: Total partial seizure frequency per 28 days

The sponsor stated that due to the large variability in patient partial seizure frequency per 28 days, the assumption of equal mean and variance for the Poisson regression model could not be met. To account for the variability in partial seizure frequency per 28 day over time, total partial seizure frequency per 28 days was analyzed using an analysis of covariance model with repeated measures. This model included treatment and adjusted for the effects of the explanatory variables: baseline partial seizure frequency, time period, center, sex, age, and weight.

The sponsor reported that the total partial seizure frequency per 28 days was statistically significantly lower for OXC-treated patients relative to placebo-treated patients (p=0.0108). This significant difference was base on an analysis of covariance model with repeated measures that included treatment, and adjusted for effects of the explanatory variables: baseline partial seizure frequency time-period, center, age, and weight. The magnitude of the treatment difference was found consistent over time.

Variable 2: Response to treatment

The sponsor reported that the response to treatment was statistically significantly higher in OXC-treated patients relative to placebo-treated patients (p=0.0005). The analysis was based on a logistic regression model that included treatment, center, sex, age, and weight as explanatory variables. Of the OXC-treated patients, 40.7% experienced at least 50% reduction in partial seizure frequency per 28 days from the baseline phase compared to 21.9% of the placebo treated patients. The corresponding odds ratio was 2.675. Five OXC-treated patients were seizure free during the double-blind treatment phase (including one premature discontinuation) compared to one placebo-treated patient. A brief summary of these results is presented in Exhibit 8.1.-3.

Exhibit 8.1.-3. Summary of response to treatment (intent-to-treat patients)

OXC (N=135)[2]		Placebo (N=128)			
#	(%)	#	(%)	Odds Ratio[1]	P-value
55	(40.7%)	28	(21.9%)	2.675	0.0005[3]

[1] The odds of an OXC-treated patient experiencing at least a 50% reduction in partial seizure frequency per 28 days from baseline relative to the odds of a placebo-treated patient experiencing at least a 50% reduction in partial seizure frequency per 28 days relative to baseline.

[2] Excludes OXC patient Leonor Avendao Kunstmann/1088 who was prematurely discontinued due to inaccurate seizure diary information.

[3] Denotes statistical significance at a 0.05 level

Cross-references: Tables 8.1.-7 and 8.1.-8; Module III Tables 6 and 7; Module VI Data Listing 12a

In addition, the change between double-blind phase and baseline secondarily generalized seizure frequency per 28 days was analyzed for patients without secondarily generalized seizures during the baseline phase and for the ITT population. This variable was calculated as the number of partial seizures per 28 days in the double-blind treatment phase minus the number of partial seizures per 28 days in the baseline phase.
This variable was analyzed identically to the primary efficacy variable using a Wilcoxon rank-sum test for patients who experienced secondarily generalized seizures during the baseline phase.

5.5 Reviewer's Findings/ Comments

Primary efficacy variable

The protocol specified analysis for the percentage change in partial seizure frequency per 28 days was performed. The result showed that the percentage of partial seizure frequency per 28 days was significantly lower in the OXC group than in the placebo group based on the Wilcoxon rank-sum test ($p=0.0001$). Such difference was also found to be statistically significant ($p<.005$) in both gender groups.

Secondary efficacy variables

Variable 1: Total partial seizure frequency per 28 days

The protocol specified analysis, the Poisson model, was not performed. The sponsor stated that due to the large variability in patient partial seizure frequency per 28 days, the assumption of equal mean and variance for the Poisson regression model could not be met.

The analysis of covariance model was performed to the total partial frequency per 28 days. It was found that the residuals were not normally distributed, and therefore, the assumption for the covariance model was not satisfied. The alternative method, the Wilcoxon rank-sum test was then applied to the variable. It was found that the treatment effect was significant in favor of OXC group with a p-value of 0.0020 based on the Wilcoxon rank-sum test.

Comments/ Conclusions

This is an adjunctive therapy in pediatric patients. The dose used in this study is 30 to 45 mg/kg/day, which ranges 900 mg/day to 1800 mg/day. Based on the results of the primary analysis and the analysis of total partial seizure frequency, the study drug is effective in this pediatric population. Other secondary efficacy variables reported were changed from the ones specified in the protocol and were not analyzed.

The target patient population in this study was pediatric subjects aged 3 to 17 years old. The differences shown in the primary efficacy variable and in total partial seizure frequency were all came from relatively older child group aged 8 to 17, whereas no

difference between the treatment groups was found among the 61 patients aged 3 to 7 (30 on OXC group and 31 in placebo group). The mean percentage change in patients aged 3 to 7 for the two groups were –16.77 for the OXC group and –14.80 for the placebo group, where a larger number (-14.80 in this case) indicating better treatment effect. A p-value of .9213 was obtained from the Wilcoxon rank-sum test on this age group.

6 Study OT/PE1 (Adjunctive therapy)

6.1 Trial Objectives

The primary objective of this trial was to evaluate the efficacy and safety of an OXC dose range as adjunctive therapy in patients with refractory partial seizures (which include seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures), who were being treated with up to three concomitant AEDs. The secondary objectives were to determine the through plasma concentrations of MHD, and concomitant AEDs and to evaluate their relationship to efficacy and safety.

6.2 Trial Design

This was a multi-center, double-blind, randomized, placebo-controlled, parallel-group trial designed to investigate the efficacy and safety of three oral b.i.d. dosage of OXC (600 mg/day, 1200 mg/day and 2400 mg/day) and placebo as adjunctive therapy in patients with refractory partial seizures, who were being treated with one to three concomitant AEDs.

There were three phases in this trial: Baseline, Double-blind Treatment, and Open-label Extension. The design of the trial including the double-blind treatment phase is presented in Exhibit 3.1.-1.

Exhibit 3.1.-1. Trial design

Phase	Baseline	Double-blind Treatment										Open-label Extension			
Period		Titration	Maintenance								Tapering				
Visit	1 2 3	4	5	6	7	8	9	10	11	12*	13**	14	15	16	XX
Week	0 4 8	1	2	3	6	10	14	18	22	26	28	2	4	every 3 months	
⇑ randomization															
OXC (mg/day) / placebo		600/1200/1800-2400 mg/day or placebo										600 mg***			

** Post-tapering visit of the Double-blind Treatment Phase after 28-weeks (only recommended for those patients who did not continue in the Open-label Extension Phase).
*** Recommended starting dose in the Open-label Extension Phase

Baseline Phase

During the 8-week baseline phase, patients were maintained on their stable dose of up to three concomitant AEDs. No changes in concomitant AEDs or changes in their total daily dose regimen or route of administration were permitted during the baseline phase. Patients who experienced an average of at least 4 seizure per month were eligible for randomization into the double-blind treatment phase.

Double-blind Phase

Patients meeting the eligibility criteria were randomized to treatment with OXC 600 mg/day, 1200 mg/day, 2400 mg/day (reduced to 1800 mg/day by Amendment 2 dated 18-Sep-95) or placebo. Trial drug was administered in a b.i.d. regimen. The double-blind treatment phase had 3 periods: a two-week titration period, a six-month maintenance period and an optional two-week tapering period.

Patients had to remain on the same dose of trial medication during the maintenance period. Patients unable to tolerate trial treatment were prematurely discontinued from the trial.

Trial start date: June 4, 1994
Trial end date: April 10, 1997

No interim analyses were planned.

6.3 Efficacy

6.3.1 Primary Efficacy Variable and its Statistical Analysis

The protocol specified primary efficacy was the number of seizures, and this variable was to be analyzed by Poisson regression method. However, in the final report, the sponsor stated that the primary efficacy variable was the percentage change (PCH) in seizure frequency per 28 days in the double-blind treatment phase from baseline phase. The analysis for PCH was performed based on the ranks of PCH using the Wilcoxon rank-sum test as specified in the protocol. This analysis was performed since normality assumption required to fit an analysis of covariance model could not be satisfied.

The dose-response relationship was examined based on the complete set of dose-to-placebo comparisons from the primary analysis without adjustment for multiple testing and by examination of the summaries of percentage reduction.

6.3.2 Secondary Variables and Their Statistical Analyses

The secondary efficacy specified in the protocol was the time interval between seizures, which can be estimated by the time to first or nth event. The other secondary efficacy variables specified in the protocol were:

1. intent-to-treat analysis of seizure count;
2. exploratory analyses of seizure count;
3. time to the next epilepsy event;
4. liverpool seizures severity scale.

The following variables were specified by the sponsor in the final report.

Variable 1: Seizure frequency per 28 days in the double-blind treatment phase

A multiple regression model was fitted to the data to confirm the lack of influence of covariates other than baseline seizure frequency on the seizure frequency in the double-blind treatment phase, to permit a test of treatment-by-country interaction, and to explore the differences between the doses in terms of seizure frequency. This analysis was not specified in the protocol. The ITT data set was used.

Because a small number of zero seizure counts was expected, 1/6 was added to all seizure frequencies before taking logarithms. Explanatory variables in the analyses were considered fixed and included ln(baseline seizure frequency + 1/6), dose, country, sex, body-weight, age group (< 18 years, >=18 years), and the number of concomitant AEDs taken by the patient.

Variable 2: Response to treatment

Responder to treatment was defined as a reduction in seizure frequency of 50% or more in the double-blind treatment phase (excluding data from tapering period) from the baseline.

This variable was analyzed using a logistic regression model. Explanatory variables in the analysis (considered fixed) were ordinal dose, country, baseline seizure frequency (increased by 1/6 and log-transformed), sex, and age group. The ITT data set and Steady-state data set were used.

Variable 3: Global assessment of therapeutic effect (GATE)

The GATE was an assessment of the perceived effect of the trial treatment made by the investigator for the patient on a four-point scale. The responses range from very good to none.

Values of GATE were analyzed using pairwise Wilcoxon rank-sum tests in which each dose was compared separately with placebo.

6.3.3 Criteria for efficacy

To determine the efficacy of OXC, two pairwise comparisons were performed: OXC 2400 mg/day (including the 1800 mg/day dose implementation by Amendment 2) vs. placebo and OXC 1200 mg/day vs. placebo.

The sponsor stated that 2400 mg/day and 1200 mg/day doses were chosen for the determination of efficacy because these doses were expected to be more effective than the 600 mg/day dose. To adjust for multiple testing in the primary analysis, a sequentially rejective Bonferroni test was used as specified in protocol Amendment 5; the smaller and the larger of the p values obtained from the two pairwise Wilcoxon rank-sum tests of treatment defference in the percentage change in seizure frequency were to be declared significant at the 0.025 and 0.05 (two-sided) level, respectively.

Trileptal was to be considered effective if OXC 1200 mg/day and/or OXC 2400 mg/day was found to be associated with a significantly greater percentage reduction in seizure frequency from baseline compared to placebo.

The ITT data set was used in the primary analysis.

6.4 Results (Sponsor's Findings)

6.4.1 Completion/Withdrawal Information

A total of 826 patients from 73 centers in 11 countries were enrolled in the baseline phase. Of these patients, 132 did not meet randomization criteria and 694 were randomized to double-blind treatment (169 to OXC 600 mg/day, 178 to OXC 1200 mg/day, 174 to OXC 2400 mg/day, and 173 to placebo). Following Amendment 2 to the study protocol, 43 (25%) of the 174 patients randomized to the high-dose group were titrated to 1800 mg/day instead of 2400 mg/day. Additionally, 4 patients who were titrated to 2400 mg/day had a subsequent dose reduction to 1800 mg/day during double-blind treatment phase.

Of the 694 patients who were randomized, one in the OXC 600 mg/day group and one in the OXC 1200 mg/day group were excluded from the ITT data set because they prematurely discontinued before taking any trial medication. Thus, 692 (99.7%) of the randomized patients were included in the ITT data set.

Approximately 57% (397/692) of the patients included in the ITT data set completed the 26-week titration and maintenance periods of the double-blind treatment phase (77.4% in the OXC 600 mg/day group, 54.8% in the 1200 mg/day group, 26.4% in the OXC 2400 mg/day group, and 71.7% in the placebo group). The most frequent reason for premature discontinuation was occurrence of adverse experience which accounted for 215 withdrawals: 20 (11.9%) of the patients in the OXC 600 mg/day group, 64 (36.2%) of the patients in the OXC 1200 mg/day group, 116 (66.7%) of the patients in the 2400 mg/day group, and 15 (8.7%) of the patients in the placebo group. A total of six patients died (three in OXC 600 mg/day group, one in OXC 2400 mg/day group, and one in placebo group). The distribution of patients outcomes and of all reasons for premature discontinuation by treatment group is presented in Exhibit 6.1.-1. Withdrawals from the tapering period are not included.

Exhibit 6.1.-1 Distribution of patients by treatment group

Number of patients	OXC 600 mg/day	OXC 1200 mg/day	OXC 2400 mg/day[1]	Total OXC	Placebo
Randomised	169	178	174	521	173
Randomised and treated (ITT)	168	177	174	519	173
Completed Double-blind Treatment Phase (Titration and Maintenance Periods)	130	97	46[2]	273	124
Discontinued prematurely					
Total	38	80	128	246	49
Adverse experience	20	64	116	200	15
Abnormal lab value	1	1	1	3	2
Abnormal test procedure result	0	0	0	0	1
Unsatisfactory therapeutic effect	6	5	1	12	15
Violation of protocol criteria	2	6	6	14	5
Non-compliance	2	3	1	6	4
Withdrawal of consent	3	0	2	5	4
Lost to follow-up	1	0	0	1	1
Administrative problems	0	1	0	1	0
Death	3	0	1	4	2
Included in efficacy analyses (ITT)	168	177	174	519	173
Included in safety analyses					
Laboratory tests	168	177	174	519	173
Adverse experiences	168	177	174	519	173
Included in pharmacokinetics analyses	127	107	66	300	0

[1] Includes 47 patients treated with 1800 mg/day during the Double-blind Maintenance Phase.
[2] 12 of 46 patients in the 2400 mg/day group, who completed the trial, were treated with 1800 mg/day.

The proportion of patients who experienced severe adverse experiences during the double-blind treatment phase increased with OXC dose (600 mg/day: 16.7%, 1200 mg/day: 23.2%, 2400 mg/day: 44.3%, placebo: 6.4%).

Eighteen OXC-treated patients had serious adverse experiences that were considered by the investigator to be at least possibly related to trial treatment. Four OXC-treated patients (0.8%) and two placebo-treated patients (1.2%) died during the double-blind treatment phase of this trial. The sponsor stated that none of these deaths was considered to be related to trial treatment.

6.4.2 Demographic and Baseline Data

Six hundred ninety-four patients were randomized at 73 centers in 11 countries and 692 patients were included in the ITT patient population. A brief summary of demographic and baseline characteristics for the ITT population is presented in Exhibit 7.1.-1, and a brief summary of seizure frequency during the baseline phase for the ITT population is presented in Exhibit 7.1.-2. The sponsor stated that the types and frequencies of seizures

experienced by patients in all OXC treatment groups were similar during the baseline phase.

Exhibit 7.1.-1 Demographic and baseline characteristics by treatment group (intent-to-treat patients)

Characteristic	OXC 600 mg/day (n=168)	OXC 1200 mg/day (n=177)	OXC 2400 mg/day (n=174)	Placebo (n=173)
Sex				
male	86 (51.2%)	80 (45.2%)	98 (56.3%)	77 (44.5%)
female	82 (48.8%)	97 (54.8%)	76 (43.7%)	96 (55.5%)
Age (years) mean (range)	34.6 (15-65)	33.8 (16-64)	35.2 (15-66)	34.3 (15-65)
Weight (kg) mean (range)	73.1 (44-139)	70.5 (45-135)	70.9 (44-131)	70.2 (35-120)

Exhibit 7.1.-2 Summary statistics of seizures in Baseline Phase (intent-to-treat patients)

Characteristic	OXC 600 mg/day (n=168)	OXC 1200 mg/day (n=177)	OXC 2400 mg/day (n=174)	Placebo (n=173)
Median 28-day baseline seizure frequency (total number of seizures)	9.6	9.8	10.0	8.6

6.4.3 Analysis of Efficacy

The sponsor stated that all statistical analyses for the efficacy variables were planned and specified in the protocol or planned prior to unblinding of the trial.

The sponsor stated that two important amendments to the protocol were implemented by Protocol Amendment 5 (dated 7-Mar-97). The primary analysis was revised prior to locking and unblinding the database and after informal discussions with the FDA, and in order to be consistent with the statistical methodology used in other similarly designed adjunctive therapy trials. The poisson regression analysis of seizure counts from the Steady-state Period was replaced by a Wilcoxon rank-sum test using the ranks of percentage change in seizure frequency per 28 days in the double-blind treatment phase from the baseline phase.

An ITT data set including all data obtained during the double-blind treatment phase, excluding data from tapering period, was chosen for the new primary analysis. This replaced the data set obtained in the Steady-state Period, which excluded data collected during the three weeks after randomization and from the tapering period.