Table 24 Median Baseline Seizure Frequencies not included in the Original Application

	Placebo	600 mg/day	1200 mg/day	2400 mg/day
Simple Partial frequency	11.2	7.3	8.3	6.6
Complex Partial frequency	6.4	6.9	7.0	7.0
All Partial seizure frequency	8.6	9.6	9.8	10.0

The differences between placebo and OXC groups are probably not significant.

Although there were some minor differences in the number of subjects who were randomized and taking a given number of concomitant anticonvulsant medications, the differences between placebo and treatment groups were only a few percentile points and likely did not reflect any major differences among the different data sets. A similar frequency of use of particular concomitant anticonvulsants was reported in all groups.

5.2.1.11.3 PROTOCOL VIOLATIONS

Nineteen patients were withdrawn from the study during the double blind phase because of protocol violations and 10 because of non-compliance. The numbers are relatively small in comparison to the number of randomized patients. They would therefore not likely undermine the study.

5.2.1.12 SPONSORS EFFICACY RESULTS

5.2.1.12.1 PRIMARY ENDPOINTS

Data describing the primary endpoint for the ITT data set is presented in Table 25 (derived from Sponsors table 8.1.-1). Individual analysis of each dose group with the placebo revealed a p value of 0.0001(Wilcoxon rank-sum). Bonferroni-Holm analysis of the 1200 and 2400 mg/day groups meet the criteria previously noted, for statistical significance ($p<0.05$).

Table 25 Analysis of the Percent Change from Baseline in Experimental Groups from Trial OT/PE1

	Placebo	OXC 600 mg/day	OXC 1200 mg/day	OXC 2400 mg/day
Number of Patients	173	168	177	174
Median Baseline 28-day Frequency	8.58	9.59	9.78	9.96
Median double-blind 28-day Frequency	9.33	8.15	6.93	4.67
Median Percent change	-7.59	-26.45	-40.22	-49.95
Mean Percent Change ± SD	6.5 ± 73.0	-13.4 ± 70.2	-20.9 ± 92.1	-34.2 ± 73.0
Uncorrected p value Wilcoxin rank sum		0.0001	0.0001	0.0001

An analysis of the interaction of demographic variables revealed a greater reduction in partial seizure frequency in females then males (no statistics noted). Age could not be evaluated because of the low number of patients younger then age 18.

Analysis of the "steady state population" reveals statistical significance (Wilcoxon rank-sum) for all three OXC groups compared to placebo. A Bonferroni-Holm analysis was not performed on this data.

It is noteworthy that the sponsors carried out a Poisson regression analysis of seizure counts. This was to be the original primary endpoint but was subsequently changed by amendment 5 (see above) because of questions as to its statistical sensitivity. Only the 600 and 1200 mg groups exhibited statistically significant therapeutic benefit in this analysis. The sponsors point that the lack statistical significance in the high dose range may have resulted from the large early number of dropouts in the high dose range as well as the large dispersion "high over-dispersion."

5.2.1.12.2 SECONDARY ENDPOINTS

Seizure frequency: The ITT and steady state analysis of seizure frequency indicated a significant difference of all OXC dose groups with placebo (p for ITT population was 0.0001 to 0.0055- without corrections for multiple comparisons). This analysis revealed no significant effect of explanatory variables of country, sex, or age group.

Response to treatment: Analysis of both ITT and steady state populations indicated a statistically significant therapeutic benefit of OXC in all dose groups ($p<0.0001$, without corrections for multiple comparisons). Examination of country, sex and age covarients revealed similar results to primary endpoint evaluation. No relationship was observed except women appeared to exhibit a greater response to treatment.

GATE: A greater percent of patients achieved the highest score of "very good" on the GATE scale in all drug treatment groups when compared to placebo (see Table 26, derived from sponsors table 8.1.4-1). Comparing the 4 levels of responses by Wilcoxon rank sum the 1200 and 2400 mg/day OXC groups were statistically significantly different from the placebo group. No corrections were made for multiple comparisons. The 600 mg/day group failed to achieve statistical significance. A response was elicited for only 637 out of the 692 patients in the ITT data set. The reasons for "not stated" was not noted but was likely a result of early discontinuations because of adverse effects. This conclusion is consistent with the apparent dose response relationship for the percent of none-responders (see "not stated" in Table 26). Indeed there were a rather large number of non-responders, as compared to control, in the high OXC dose group (more then 4 times placebo). These problems make this analysis rather difficult to interpret.

Table 26 GATE Score Breakdown for Trial OT/PE1

	Placebo	600 mg/day	1200 mg/day	2400 mg/day
Very Good	6.9%	10.1%	17.0%	23.6%
Good	34.1%	38.7%	32.2%	32.2%
Poor	22.5%	19.1%	18.1%	13.8%
None	33.5%	25.7%	24.3%	16.1%
Not stated	2.9%	6.6%	8.5%	14.4%

LSSS: This evaluation was unable to demonstrate an effect of any dose of OXC or overall treatment effect when compared to placebo. The sponsors feel that because this sharply contrasted with the primary outcome it simply indicates the insensitivity of this measure. It is noteworthy that there has been some issues regarding the sensitivity of the older LSS scale and the new scale, used here, has not been completely validated. [24]

5.2.1.13 ADVERSE EEFFECTS AND MEASURE EFFICACY

As previously noted the high dose group exhibited a greater number of early discontinuations then found in any other pivotal study provided by the sponsor in this application. This can be gleaned from the Table 28 (from sponsors exhibit 9.1.-1) that lists the adverse events that resulted in early discontinuations in ≥5% of patients in a particular group. These events are similar to those expected for this class of agent and should not interfere with analysis. Perusal of all early discontinuations revealed that 2 patients in the 600 mg/day and 1 in the placebo group exited because of grand mal convulsions. One patient in the 2400 mg/day group discontinued early because of an "abnormal EEG." This abnormality appears to constitute increased slowing in the area of the cortex around the focus. The cause of this slowing cannot be determined but one potential reason may be post-ictal slowing due to increase seizure activity.

[24] See Cramer, JA, J. Epilepsy, 11: 256-260, 1998.

Table 27 Summary of Adverse Experiences Causing Premature Discontinuation in 5 % or more patients in any Treatment Group during Titartion and Maintenace Period

Treatment group	OXC 600 mg/day	OXC 1200 mg/day	OXC 2400 mg/day	Placebo
Adverse experience	n (%)	n (%)	n (%)	n (%)
Number of patients	168	177	174	173
Number (%) of patients with AEs causing premature discontinuation	20 (11.9)	64 (36.2)	116 (66.7)	16 (9.2)*
Nervous system	19 (11.3)	51 (28.8)	96 (55.2)	12 (6.9)
Dizziness	9 (5.4)	24 (13.6)	41 (23.6)	5 (2.9)
Ataxia	6 (3.6)	20 (11.3)	47 (27.0)	4 (2.3)
Somnolence	3 (1.8)	12 (6.8)	30 (17.2)	2 (1.2)
Nystagmus	4 (2.4	15 (8.5)	21 (12.1)	2 (1.2)
Headache	5 (3.0)	12 (6.8)	12 (6.9)	1 (0.6)
Abnormal gait	1 (0.6)	7 (4.0)	15 (8.6)	0 (0)
Tremor	0 (0)	5 (2.8)	16 (9.2)	1 (0.6)
Special senses	6 (3.6)	40 (22.6)	66 (37.9)	3 (1.7)
Diplopia	5 (3.0)	25 (14.1)	43 (24.7)	2 (1.2)
Vertigo	1 (0.6)	13 (7.3)	19 (10.9)	0 (0)
Abnormal Vision	1 (0.6)	9 (5.1)	17 (9.8)	1 (0.6)
Digestive system	11 (6.5)	31 (17.5)	60 (34.5)	3 (1.7)
Vomiting	7 (4.2)	21 (11.9)	41 (23.6)	1 (0.6)
Nausea	8 (4.8)	16 (9.0)	33 (19.0)	2 (1.2)
Body as a whole	4 (2.4)	6 (3.4)	22 (12.6)	2 (1.2)
Fatigue	2 (1.2)	4 (2.3)	15 (8.6)	1 (0.6)

*Includes one patient who discontinued due to abnormal laboratory values but had hyponatremia recorded as AE causing premature discontinuation

5.2.1.14 PK AND MEAUSURED EFFICACY

Dose response analysis of data revealed a statistically significant dose response analysis for all experimental doses. Seizure control was also found to be statistically proportionally related to serum MHD concentration (Kendall's τ Statistic).

The relationship of MHD concentrations and alterations in serum concentrations of concomitant anticonvulsants were performed. Significant effects were observed for phenytoin, Phenobarbital and carbamazepine. Carbamazepine levels were decreased whereas Phenobarbital and phenytoin levels were increased. These effects appeared to be dependent on MHD concentration and were minimal at low (0-20 uM/L) to medium MHD (20-43 uM/L) concentrations in the case of carbamazepine and phenobarbital. These changes reached their maximum at high MHD concentrations (>43 um/L)[25] with a mean increase in Phenobarbital (17 patients) and mean decrease in carbamazepine (73 patients) of 15 and 13 percent, respectively. The effect on phenytoin was

[25] Generally 43 % of patients in the medium OXC dose group and 85% in the high dose group exhibited serum OXC concentrations in the high range.

more pronounced with the high MHD concentration range associated with a 40 % mean increase in the phenytoin serum concentrations (n=18). The increase in Phenytoin levels could potentially lead to an increase in seizure control and result in a false conclusion of efficacy. This may be ameliorated by the fact that this constituted only 18 (out of 352) patients from both the medium and high OXC dose groups. The sponsor was requested to perform an analysis of the primary endpoint that excludes patients on phenytoin (8/9/99). This analysis demonstrated a statistical significant effect (not corrected for multiple comparison) for all groups. The p value for the 1200 and 2400 was less then 0.0001 and for the 600 mg group was less then 0.0038. All groups were significant when a post-hoc Bonferroni correction was performed.

5.2.1.15 SPONSORS CONCLUSION

The Sponsors conclude that this study demonstrated efficacy of OXC in the treatment of epilepsies of partial etiology. They support this contention by pointing out the lower seizure frequencies that were demonstrated in measurement of the primary endpoint and support this claim by the positive results in some of the other secondary endpoint. They feel the study demonstrates that all doses produce some therapeutic benefit and state " this trial indicate that the minimum effective dose of OXC in this patient population was 600 mg/day." The sponsors recommend a 600 mg/day starting dose based upon this information. The Sponsors also point out the large number of patients who discontinued medication because of adverse effects in the 2400 mg/day group. They argue that indeed this dose may have been tolerated had the titration been slower. Another confounding factor contributing to the incidence of withdrawal was potential phamacodynamic interactions resulting from multiple AED use. The Sponsors therefore feel that the 2400 mg/day dose may have been better tolerated in the appropriate clinical situation.

5.2.1.16 REVIEWER'S ANALYSIS

This is the only pivotal adjunctive trial in adults. The study includes a large number of patients. From a purely statistical perspective the study has only demonstrated significant effect of the OXC on the primary endpoint for the intermediate and high OXC dosages. Other primary endpoint analysis did demonstrate efficacy in the low OXC groups. These analysis, however, either did not correct for multiple comparisons (steady state data set) or can be considered post hoc (Poisson). It is also incorrect to use the secondary endpoints as a guide since those analyses demonstrating a statistically significant effect in the low OXC dose group was not corrected for multiple comparison. Analysis using the more subjective GATE and LSSS testing was unable to demonstrate significant efficacy in certain dose groups. This more likely reflects the

insensitivity of these tests then a real lack of efficacy. Nonetheless, although rigorous statistical evidence is lacking, examination of results would suggest a seizure reduction at the lowest dose. This effect was robust. Had the sponsor chosen, in advance, to perform a Bonferroni correction on the primary endpoint a statistically significant therapeutic effect would have been concluded. It is this reviewers opinion that the 600 mg/day probably exerts a therapeutic effect, although the only doses that have been proven to be efficacious from a purely statistical basis are 1200 and 2400 mg/day.

A number of problems that predominately effect the high dose group may have complicated analysis in the present study. Perhaps the most problematic of these is the high rate of adverse events. This likely compromised the blind. Additionally, the adverse events also caused a rather large number of early discontinuations with resulting short term drug exposures. In addition to indicating problems of tolerability of this dose these short exposures complicates generalization of results to long term anticonvulsant use. Thus, the anticonvulsant activity of some drugs will habituate following a brief exposure[26]. Long term adjunctive therapeutic benefit of high doses of this agent would therefore be a matter of conjecture. The fact that the effect for the high dose group was so robust, that a substantial effect was still observed for the intermediate dose group, and that this dosage was observed to be therapeutic in monotherapy trials indicates that the sponsor's conclusion regarding the high dose is probably justified. The potential reduction in phenytoin metabolism could conceivably cause an overestimation of OXC's therapeutic effect. The requested additional analysis excluding patients on phenytoin made this an unlikely contributing factor.

5.2.1.17 SUMMARY

The present study has provided sufficient evidence to support the sponsor's claim for the efficacy of OXC in seizures of partial origin when used as adjunctive treatment in the doses of 1200. Although the highest dose (2400 mg/day) was found statistically effective, analysis of this group was complicated by the high level of adverse events and early dropouts. Lastly, while the lower dose (600 mg/day) was likely effective, the study design hampered definitive statistical conclusions regarding it's efficacy.

5.2.2 PROTOCOL 011

5.2.2.1 *OBJECTIVES:*

[26] See discussion of protocol 04.

The primary objective of this study was to evaluate the safety and efficacy of OXC, as adjunctive therapy, relative to placebo in children with inadequately controlled partial seizures. Secondary objectives included the examination of the relationship of safety and efficacy with pharmacokinetic/pharmacodynamic parameters as well as the examination of potential drug interactions with other anticonvulsants.

5.2.2.2 DESIGN:

This was a multinational, multicenter, double-blind, randomized, placebo-control, parallel-group 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 (including the seizure subtypes of simple, complex, and partial seizures evolving to secondarily generalized seizures). The study was divided into three principal phases; baseline, double blind and open label extension (see Table 28, derived from sponsors Exhibit 3.1. -.1).

Table 28 Experimental Schedule for Trial 011

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.

5.2.2.3 SCHEDULE:

5.2.2.3.1 BASELINE PHASE

Patients were evaluated for trial eligibility on visit 1. This included an interview, examination and laboratory evaluations (see eligibility). Briefer exams and interviews with routine laboratory examinations (and drug and metabolite levels) were performed at subsequent visits throughout the study. Patients were maintained on their stable AED drug and dose during the 56-day baseline period. Additional AEDs and disallowed medications were not permitted 28 days prior to the baseline period. Seizure counts during this and subsequent phases were

evalusted through diaries maintained by patients and/or their parent or guardians. Up to 28 days of the 56 days in the baseline phase could be obtained retrospectively from patient diaries if deemed accurate by the investigator[27]; this would shorten the requirement of a 56 day baseline. Final eligibility determination and randomization was made at the end of the baseline period on visit 2 when all data was examined.

5.2.2.3.2 DOUBLE BLIND PHASE

The double-blind phase was divided into two periods as shown in Table 28. The target dose was 30 to 46 mg/kgs. The 14-day titration period was divided into four stages with a scheduled dosage increment occurring every 1 to three days. Titration intervals and dosages could be adjusted provided the target dose was not exceeded. Those who completed the titration period entered the 98-day maintenance period.

Dosing:

According to the sponsors, at the time that the protocol was written, the available data (positive control double blind studies) was insufficient to determine a minimum effective dose. The final dose was determined by a number of factors including information on pharmacokinetics and dosages used in adult studies. All dosing was on a Q 12 hour schedule (with food; not necessarily equally divided). During the 14-day titration period, patients were titrated to an optimum daily dose (defined as the lowest dose that provided seizure control with acceptable tolerability). Three target doses, based on absolute weight (in kgs dosing), were established and are as follows:

- 20.0 to 29.0 kg → 900 mg/day
- 29.1 to 39.0 kg → 1200 mg/day
- 39.1 kg and greater → 1800 mg/day

As the final dose was based upon the investigators perceived optimal therapeutic benefit it tended to be less then targeted dose (see below).

Generally dosing was not altered during the Maintenance Phase but exceptions were permitted, with approval by the sponsor's monitor, if problems with tolerability or seizure control were observed.

5.2.2.3.3 OPEN LABEL EXTENSION

Open label extension trial was open to all subjects completing the treatment phase if they elected to do so.

[27] This was included as one of the points in amendment 1 that was implemented prior to the first patient visit.

5.2.2.4 Concomitant AEDs:

The "rare" use of short acting benzodiazepines were permitted in instances of multiple seizures within 24-hour period

5.2.2.5 Removal of Patients from Trial:

Criteria were as follows:

- Pregnancy
- Parent/guardian decision
- Investigators decision that is in the best interest of the patient (investigators were asked, when possible, to confer with the sponsors monitor)
- Intolerable adverse experience
- Major protocol violation

5.2.2.6 ENROLLMENT:

Deviations from the following criteria were allowed if pre-approved by the sponsors medical monitor.

5.2.2.6.1 KEY INCLUSION CRITERIA:

1. Male and female outpatients aged 4 to 17 years.[28]
2. A diagnosis of partial seizures (including subtypes of simple, complex, and partial secondarily generalized).
3. Patients with poorly controlled seizures despite treatment with a stable dose 1 to 2 AEDs (defined as 8 partial seizures during the 56-day Baseline Phase, with at least 1 occurring during each 28-day period of the 56-day Baseline Phase).
4. Confirmatory EEG evidence of the diagnosis of focal epilepsy.
5. Neuroimaging (CAT or MRI) demonstrating the absence of a progressive lesion.

5.2.2.6.2 KEY EXCLUSION CRITERIA:

1. Female patients of childbearing potential.
2. A documented history of generalized status epilepticus in the past 6 months.
3. Seizures having a metabolic, neoplastic or active infectious origin.
4. A history of noncompliance with medical regimens or who were potentially unreliable as judged by the principal investigator.

[28] Except in Canada where law requires age 6 and above (this constituted amendment 2).

5. Evidence for or a history of a systemic, a neurologic or a psychiatric disorder requiring current medical intervention or likely to have a significant impact on the outcome of the trial.
11. History of known or suspected substance abuse (including alcohol) or a positive drug screen.
12. Patients who participated in another investigational drug trial within 60 days of the screening visit, or who had previously received OXC therapy.
13. A known hypersensitivity to carbamazepine.
14. Current use of Felbatol or receiving it within 90 days of beginning the Baseline Phase b. The use of Felodipine, verapamil or monoamine oxidase inhibitors within 30 days of beginning the Baseline Phase.
15. A clinically significant laboratory abnormality.

5.2.2.7 CONCOMITANT MEDICATIONS:

Patients were required to maintain stable anticonvulsant doses during baseline and the experimental phase. The use of benzodiazepines as concomitant anticonvulsant treatment was permitted. The "rare use" of short-term benzodiazepines was permitted in cases where patients experience "multiple seizures within a 24-hour period."

5.2.2.8 EFFICACY VARIABLES:

5.2.2.8.1 PRIMARY OUTCOME MEASURES:

Percentage of change in partial seizure frequency per 28 days (PCH) of the treatment phase from baseline phase was the primary measure of efficacy and was calculated from the intent to treat population as follows[29]:

$$PCH=(PST_{28}-PSB_{28})/PSB_{28} \times 100$$

where:

PST_{28}= partial seizures per 28 days during treatment phase of treatment
= (# of partial seizure during treatment phase / # of days of this phase) X 28,

and

PSB_{28}=partial seizures per 28 days during baseline phase

[29] Variable abbreviations in formula are reviewers and not sponsors.

= (# of partial seizure during baseline phase / # of days of this phase) X 28.

Partial seizure are counted as all partial seizures; i.e. = simple partial + complex partial + partial secondarily generalized.

5.2.2.8.2 SECONDARY OUTCOME MEASURES:

Numerous secondary outcome measures were calculated. Unless otherwise noted all analysis was performed on intent to treat populations. Half of these outcomes endpoints included measures of secondarily generalized seizures. A list of these outcomes measures follows:

- The Comparison of the frequency of double-blind phase seizure frequency; i.e. PST_{28} versus PSB_{28} (as calculated above).
- Responder rates; i.e. number of patients with ≥50% reduction in seizures per 28 days (baseline compared to treatment). This endpoint was added, according to sponsor, to allow comparisons with other studies where this was the primary measure of efficacy (it was not included in the original protocol nor is a part of any amendment).
- Time to tenth partial seizure during treatment. Patients who prematurely discontinued were classified as a censured observation.
- Percentage change in secondarily generalized seizure frequency of treatment phase (PCHSG). Calculated in an identical fashion as the primary endpoint, PCH (see above), except only secondary generalized seizures are counted. This analysis was only performed on subjects experiencing secondary generalized seizures during baseline. Change (not in terms of percent) in generalized seizures where also calculated for those who did not have seizures during baseline and for intent to treat populations (this appears to have been added post-hoc).
- At the FDA's request the sponsor obtained a measure of reduction of the percent partial seizures that would go onto secondary generalization. This analysis was performed after removal the data base lock. The analysis was performed by calculating the ratio of secondarily generalized seizure per 28 days / all partial seizures per 28 days. Comparison of this ratio was made between Baseline and Treatment Phases. A patient was considered a "winner" if the ratio during treatment was less then baseline; presumably indicating fewer partial seizures going onto generalization. Data sets that were examined included both intent to treat and patients experiencing generalized seizures during the baseline phase.
- Secondary generalized seizure frequency for the entire intent-to-treat population.

5.2.2.9 ANALYSIS METHOD:

Calculations approximated that 274 patients (137 per treatment arm) were required to observe a 20% difference, at an $\alpha<0.05$, between groups with a statistical power of 0.85.

5.2.2.10 STUDY CONDUCT:

5.2.2.10.1 ENROLLMENT:

A total of 267 patients were randomized into this study. The breakdown and fate of these patients are presented in Table 29 (from sponsor's Exhibit 6.1.-.1).

Table 29 Patient Accounting for Trial 011

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 Avendac 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.

A breakdown for patients who discontinued for "other" as noted in the above table are presented in Table 30 (derived from sponsors Table 6.1.- 3).

Table 30 Breakdown for Reasons of Patient Discontinuations in Trial 011

PATIENT NON-COMPLIANCE	4 (2.9%)	0 (0.0%)
PATIENT WITHDREW CONSENT	2 (1.4%)	1 (0.8%)
PATIENT LOST TO FOLLOW-UP	0 (0.0%)	1 (0.8%)
DEATH	1 (0.7%)	0 (0.0%)

There were not an inordinate number of dropouts. A greater number of dropouts occurred in the OXC group for adverse events as might be expected. The majority of these adverse events are those that would be anticipated for this class of agent: i.e. nausea, vomiting, ataxia, and rash. It is not anticipated that these dropouts would effect the final efficacy analysis. Two of the 4 dropouts that occurred in the placebo group did so because of seizures; if anything such dropouts may lead to an underestimation of the efficacy of OXC. Any concern that may be raised by dropouts is obviated by the ITT analysis.

No patients were withdrawn because of protocol violations. Three patients (2 OXC and 1 Placebo) were not included in the intent to treat analysis because they did not provide seizure information during treatment phase. One patient (Leonor Avendao Kunstmann/1088) was noted not to keep an accurate diary for the first six visits of the double-blind Treatment Phase." The patient remained in the intent to treat evaluation of the primary efficacy value only.

Table 31 Demographics for Trial 011

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%)

5.2.2.10.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS:

Demographic differences between OXC and Placebo are presented in Table 31 (from sponsor's exhibit 5.1.-1). There were little or no apparent differences between placebo or drug groups with regard to sex or race. Statistical differences between experimental group with regard to sex, race, age and weight were examined and found not to be significant.

Age distribution is presented in the Table 32 (from sponsors Table7.1-1). While there did not appear to be substantial difference in the age distributions between drug and placebo groups there were a rather small number of patients enrolled in the study who were less then 6 years old.

Table 32 Age Distribution for Trial 011

	TREATMENT GROUP		
	OXCARBAZEPINE	PLACEBO	ALL TREATMENTS
AGE (YEARS)			
< 6	14 (10.1%)	16 (12.4%)	30 (11.2%)
6 - 12	56 (40.6%)	51 (39.5%)	107 (40.1%)
13 - 16	68 (49.3%)	62 (48.1%)	130 (48.7%)

Statistical analysis (see Table 33; from sponsor's Table 7.1.-2), by the sponsor, revealed no significant difference of baseline partial seizure frequency between the OXC and placebo groups (Wilcoxon-rank sum). The low median value of generalized seizure frequency results from the large number of patients who did not experience this form of seizure during the baseline phase. Statistical analyses of the difference between groups were not performed. Of note is the fact that means of the baseline frequency between groups did not numerically differ (5.8 and 5.5 in the OCX and placebo groups, respectively.

Table 33 Baseline Seizure Frequency for Trial 011

Treatment	OXC		Placebo	
Number of patients	138		129	
	Median	Range	Median	Range
Secondarily generalized seizure frequency per 28 days	0.0	[redacted]	0.0	[redacted]
Partial seizure frequency per 28 days	12.3	[redacted]	13.0	[redacted]

The difference between the placebo and OXC groups in the number AEDs that patients are on when they enter the baseline phase of the study is not presented[30]. Important information regarding the number of placebo and OXC patients entering the study on one or two AEDs are not presented in the body of the text. Examination of the SAS transport files reveals no statistical difference between groups

Although the use of benzodiazepines anticonvulsants are documented on a patient per experimental group basis (see Sponsors Table 7.2-3 or Table in PK section), the "rare" use of anticonvulsants is not documented. This information is relevant as it can effect final seizure counts and was provided later in communications with the sponsor during the review process (see below).

[30] Such Information may be useful in establishing an historical clinical measure of the degree seizure intractability between groups with the presumption that patients on greater number of medications may have a greater degree of intractability.

5.2.2.11 *SPONSORS EFFICACY RESULTS:*

5.2.2.11.1 PRIMARY EFFICACY VARIABLE:

An ITT analysis of the primary efficacy variable revealed that OXC was significantly superior to Placebo. A summary of this data can be found in Table 34 (from Sponsor' Exhibit 8.1.-1). There was a significant difference between

Table 34 Change in 28-day Seizure Frequency for Trial 011

	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

percentage change of seizures from baseline between placebo and the OXC groups (Wilcoxin rank-sum).

With one exception ("black"[31] race), the superiority of OXC over placebo was numerically maintained when data were broken down by the demographic variables (sex, race, age group and country), was examined. No statistical evaluation was performed on this data. Note, no other pivotal trial identified race as a factor in efficacy.

The protocol allowed for the "rare" intermittent use of short acting benzodiazepines in the treatment of recurrent seizures when it was deemed medically necessary by the investigator. This has the potential of effecting actual endpoint measures. The observation that a similar percent of patients required benzodiazepines in the OXC (15.6%) and placebo (15.4%) may mitigate concern over this issue. Moreover, upon inquiry regarding this (6/7/98) the sponsors calculated median seizure reduction in groups with and without this "rare" intermittent use of benzodiazepines. These data are presented in Table 35. Apparent from this table is the observation that a therapeutic effect is evident in both data sets (with and without rare use). This supports the absence of effect exerted by this element of the design.

[31] Only 16 "black" patients were examined (8 OXC and 8 placebo).

Table 35 Median Percent Change in Seizure Frequency in Patients Divided by Use of Benzodiazepines

	Placebo		OXC	
	Rare Use	No Rare Use	Rare Use	No rare Use
Median	8.4	-10.6	-7.5	-39.8
n	20	108	21	115

N.B. A negative value indicates a drop in seizure frequency during the expeimental phase.

5.2.2.11.2 SECONDARY ENDPOINTS

These can be divided into two general categories: those that examined all seizures of partial origin and those that examined only partial secondary generalized seizures.

All seizures of partial origin: Identical conclusions to those above were obtained when an ITT analysis was performed on the secondary endpoints of mean double blind phase partial seizure frequency (PST_{28} Vs PSB_{28}), responder rates and time to tenth partial seizure with p values of 0.0108, 0.0005, and 0.0001, respectively. It should be remembered that responder rates were a post hoc variable.

The mean seizure frequency computation was performed using an analysis of covariance model with repeated measures model that included treatment, and adjusted for the effects of the explanatory variables: baseline partial seizure. Center, sex, age and weight were found not to be pertinent factors effecting this secondary endpoint.

Secondarily generalized seizures: Examination of the drug effect on "secondary generalized" seizures was not as clear and is presented below according to specific evaluations:

Percent reduction in generalized seizure frequency (protocol driven): A statistically significant greater percent reduction was observed in the OXC group when comparison was limited to those patients whom experienced generalized seizures during baseline (Wilcoxin rank-sum). These data are presented in Table 36 (from sponsors Exhibit 8.1.-4).

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 021014

Trade Name: TRILEPTAL TABLETS

Generic Name: OXCARBAZEPINE

Sponsor: NOVARTIS PHARMACEUTICALS CORPORATION

Approval Date: 01/10/1999

INDICATION(s): MONTHERAPY OR ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL SEIZURES IN ADULTS WITH EPILEPSY AND AS ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL SEIZURES IN CHILDREN AGES 4-16 WITH EPILEPSY.

Table 36 Percent Reduction in Generalized Seizure Frequency for Patients with Generalized Seizures during the Baseline Phase

	OXC (N=48)		Placebo (N=57)	
	Median	Range	Median	Range
Baseline secondarily generalized seizure frequency per 28 days	5 0	[redacted]	6 0	[redacted]
Double-blind treatment secondarily generalized seizure frequency per 28 days	0 9	[redacted]	4 8	[redacted]
Percentage change in secondarily generalized seizure frequency per 28 days from baseline	-78.2	[redacted]	-33.3	[redacted]

[1] Includes patients who experienced this seizure type during the Baseline Phase only

Wilcoxon rank-sum test P-value = 0.0012

Change in seizure frequency (ad hoc): A Wilcoxin rank-sum analysis was perform on the absolute change in the seizures occurring during double blind phase for patients who did not have seizures during baseline and for the intent to treat population. This analysis demonstrated statistically significant difference for patients without seizures during baseline (p=0.0098) but not for the ITT population (p=0.1092). This analysis was based upon the absolute seizure frequency change whereas the analysis performed in patients with seizures during the baseline phase was based upon percent change in frequency. This may contribute to the unexpected absence of statistical significance in the ITT population.

Change in the percent of seizures that go onto generalization: This recommended FDA analysis demonstrated that while there appeared to be a trend towards a reduction by OXC the reduction was only found to be statistically significant in the group that did not experience secondary generalized seizures during the baseline phase (see Table 37, from sponsor's exhibit 6.1.-5). This effect was quite marginal and ststitically insignificant when the intent to treat data set was evaluated (Table 37). Although the sponsors present many permutations the

only appropriate one appears to be the ITT analysis. In this case we can assume that the drug did not produce any statistically significant alteration in this value.

Table 37 Percent of Patients Fulfilling Criteria based Change in Secondarily Generalized Seizures when Double Blind was Compaired to Baseline Phase

Patient Population	Criteria	OXC		Placebo		P-value[2]
		#	(%)	#	(%)	
Experienced sec. gen. seizures. during the Baseline Phase	Decrease in Ratio	34/48	(70.8%)	31/57	(54.4%)	0.085
Did not experience sec. gen. seizures. during the Baseline Phase[1]	Increase in Ratio	5/87	(5.8%)	13/71	(18.3%)	0.014[3]
Intent-to-treat[1]	Decrease in Ratio	34/135	(25.2%)	31/128	(24.2%)	0.856

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

[2] P-value based on Cochran-Mantel-Haenszel test

[3] Indicates statistical significance at the 0.05 level

5.2.2.12 *ADVERSE EFFECTS AND MEASURED EFFICACY:*

Fourteen patients in the OXC and 4 in the Placebo group had to be discontinued from the study because of adverse events. In no cases in the OXC were these events associated with an increase in seizure frequency, as was the case for 2 patients in the Placebo group. Because of the size of the study, the removal of the latter two patients in the placebo group probably only causes a minor underestimation of the efficacy of OXC. One death was noted in the study; this occurred following a fall subsequent to a seizure in a patient in the OXC group who already exhibited a mild degree of seizure reduction while in the treatment phase (SUDEP is the presumptive cause). It is unlikely that this event would effect the conclusions of outcome in this study.

5.2.2.13 *PHARMACOKINETICS FACTORS AND MEAURED EFFICACY:*

Treatment with OXC resulted in alterations of serum levels of only two non-benzodiazepine anticonvulsants. Thus there was a median decrease in carbamazepine level of 15% and increase in Phenobarbital level of 14%. Other anticonvulsants were not significantly effected. The resulting alterations in baseline AED levels may complicate data interpretation. The effect in the present study on average, however, would cause an underestimation of OXC's therapeutic effect as less then 10 patient in the OXC received Phenobarbital whereas 77 patients in the same group received carbamazepine. It is noteworthy that the lack of effect that OXC (or its metabolite MHD) has on phenytoin levels contrasts with findings in study OT/PE1 that examined efficacy in a predominately adult population. The latter study demonstrated that patients with high MHD serum concentrations appeared to exhibit an average increase in phenytoin concentrations of 40%; this differed with changes in phenobarbital and carbamazepine serum concentrations that were similar to the present study.

The use of benzodiazepines anticonvulsants were also permitted in the present protocol. This class of agents was allowed as a baseline anticonvulsant and for use for acute management of seizures. A similar argument to that above can be made regarding the benzodiazepines if a drug/drug interaction existed. No information was supplied in the application regarding an OXC-MHD/ benzodiazepines interaction. In response to an inquiry (6/7/98) the sponsors note that although no patient data exists in vitro human microsomal data indicates no significant interaction. Furthermore, information supplied in response to this reviewer's enquiry demonstrated that efficacy was still evident when data sets were broken down by whether patients received treatment with benzodiazepines or not.

Analysis of the primary efficacy variable using Kendall's tau statistic revealed a statistically significant concentration/response relationship when all groups (OXC and Placebo) were compared. Although there was no significant difference when only the OXC was included in the analysis there was a "trend" toward a concentration efficacy relationship.

5.2.2.14 PROTOCOL VIOLATIONS AND OTHER ADMINISTRTIVE ISSUES:

As noted above three patients were not included in the ITT analysis because they failed to provide seizure diaries. The final sample size was 4% less then target size.

According to the Sponsors although protocol irregularities occurred none where sufficient to be considered in violation. One patient as noted above, who's diary proved to be inaccurate (in OXC group) was included in the ITT evaluation but not other evaluations. Although data from this patient is suspect, ITT analysis would require inclusion under the assumption that such irregularities would be evenly represented in both experimental groups. Other minor

irregularities occurred. This include 4 patients who did not exhibit a sufficient number of seizures during the baseline period, 2 patients who were below the protocol age cut off, and 10 patients who did not meet the minimum weight requirements. Except for those who did not meet weight requirements, these patients were equally distributed in both experimental groups. In the case of the weight requirement, 7 patients were from OXC group and 3 were from the placebo group. It is doubtful this disparity would effect the final outcome of the protocol as it is rather small, the significance of absolute weight in a study like this is not as pertinent, and the final means weights were not significantly different between groups (see demographics).

5.2.2.15 FINAL DOSAGE ACHIEVED IN STUDY

Because the study design allowed for the dosage titration to one that was perceived to produce optimal seizure control, the final dosage tested varied. Forty-four percent of patients (62 of 138) received a dose lower then the targeted dose $\leq$ 30 mg/kg/day. The median dose received by all OXC patients was 31.4 and ranged from [redacted]

5.2.2.16 SPONSORS CONCLUSIONS:

The sponsors conclude, "the outcome of this trial supports the safety and efficacy of OXC, given as adjunctive treatment, in pediatric patients with inadequately controlled partial seizures, which include the seizure subtypes of simple, complex, and partial seizures evolving to secondarily generalized seizures." The key primary and secondary measures of seizures of partial origin support this the claim of OXC's efficacy.

While the sponsors point out the that a number of outcome measures demonstrated that the OXC treated group exhibited a statistically significant lower frequency of generalized seizures they do not claim that the study demonstrates efficacy in this subgroup of generalized seizures.

The sponsors also note that, "pharmacokinetics variability of patients on oxcarbazepine had no impact on safety, and thus there is no need for therapeutic drug monitoring."

5.2.2.17 *REVIEWER'S ANALYSIS:*

The sponsors rightfully conclude that OXC produces a statistically significant therapeutic benefit in controlling partial seizures when all seizures of presumed partial origin are included. Thus statistical analysis of the ITT population for the primary and all secondary endpoints demonstrated a reduction in seizure occurrence in the OXC group. There are no obvious factors that may lead to a false positive conclusion in this adjunctive study. There were an average number of drop outs for a study like this (15% in the drug treated group),

As discussed previously pharmacokinetic interactions with non-benzodiazepine anticonvulsants were studied and should not complicate data the interpretation. The use of benzodiazepines was rather similar between the experimental groups and pharamcokinetic interaction with these should theoretically not influence the final results. The sponsors supplied more convincing evidence on this lack of influence. These were discussed above and are in response to the inquiry made on 6/7/99. Protocol irregularities and violations were not of a sufficient magnitude or bias to have significantly altered the results. Baseline and demographic variables appeared to be evenly distributed across both the OXC and placebo groups.

As noted above the issue of secondary generalized seizures is more complex. Using the protocol driven analysis the sponsors demonstrated a statistically significant reduction in generalized seizures in the OXC as compared to placebo group. Two principal arguments mitigate the value of this data. First, this was not an ITT analysis. The group selected for analysis consisted of those patients whom exhibited secondarily generalized seizures during the baseline phase presumably to simplify mathematical analysis seizures (seizures can be measured as a percent change from baseline). As seizures frequency tend to be cyclical[32] and baseline sampling period short (56 days), the selection of only patients who are experiencing seizures results in a biased sample population. There would be a tendency of selecting a population of patients for whom there would be a greater natural tendency for a reduction then an increase in mean seizure frequency. Although both OXC and Placebo group would be expected to be similarly effected,[33] a bias could be introduced. When post hoc ITT analysis was performed on the change in the absolute seizure frequency no statistical significance was observed. The second, and perhaps more important, criticism of this data is that the FDA requested analysis, an ITT evaluation of the percent of seizures that go on to become secondarily generalized, failed to demonstrate the desired effect. It must be kept in mind that the present study was designed to examine the endpoint of the frequency of *all seizures of focal origin*. In summary, no conclusions could be drawn on this agent's effect on secondarily generalized seizures nor does it appear the sponsors are doing so.

The present protocol was designed to examine OXC's efficacy as adjunctive therapy in a "pediatric population that was defined by the inclusion criteria of 4 to 17 years of age. Examination of the age distributions (see Table 32) revealed a very small number (n=14) of the 138 subjects who received OXC were under the age of 6 years. For this reason it is hard to make any definitive conclusions regarding the efficacy of OXC in this substrata of the pediatric population.

The amount of medication required to produce this effect was well tolerated as measured by the relatively small number and reversibility[34] of

[32] See Rescor, S.R., Assessing the effectiveness of treatment, in The medical Treatment of epilepsy. Ed. Rescor, S.R. and Kutt, H.,Marcel Dekker, Inc.,1992.
[33] This is born out by the observation that both the placebo and OXC groups exhibited a reduction in seizure frequency during the double-blind phase.
[34] Except for one seizure related death that does not appear to be drug related.

serious adverse side effect that lead to patient withdrawal in the OXC group. This low rate of adverse events is likely contributed by the flexible design for dosage adjustment.

Except for an apparent lack of efficacy in "black" individuals OXC produced a similar effect in all demographic variables examined. As the protocol was not designed to study demographic differences any conclusions and definitive statements drawn from these data are at best tentative. Furthermore, no other studies in this application confirmed this racial trend.

5.2.2.18 SUMMARY:

The present study has provided strong evidence for the adjunctive use of OXC in the treatment of seizures of partial origin in a pediatric population. The flexible design of the study does not allow for a definitive statement regarding dosage but I believe it is fair to say that dosages around the median of 31 mg/kg/day may be considered effective. Because the data included so few young patients the pediatric population for which this study is applicable must be considered inclusive of only patients 6 years or older.

6. Other Control Trials

The sponsors present 2 double-blind active control trials for that compared OXC to phenytoin. OT/F02 examined 287 randomized adults with newly diagnosed epilepsy. OT/F04 examined 193 pediatric patients (age 5 to 18) with newly diagnosed epilepsy. Both studies used a 14 day screening phase, and a 56-week double blind phase. Phenytoin and OXC were administered on a TID schedule and titrated to the optimal dose for seizure control. The highest daily phenytoin and OXC dose permitted in both studies were 800mg and 2400 mg, respectively. Both studies demonstrated no statistically significance between phenytoin and OXC groups with regard to seizure frequency or percent of patients who remained seizure free. Similar, but not identical trials were carried out in protocols OT/FO1 and OT/E25 that used valproate and carbamazepine as the active control, respectively. The statistical evaluation tended to be less rigid and more descriptive. The conclusions from these trials were of no significant difference between OXC and active control.

7. Safety Review

Please see Dr Boehm's review.

8. Integrated Summary And Conclusions

8.1 Data Quality and Completeness

The data in these clinical trials were of good quality and complete with the exception of two issues, seizure clustering and status epilepticus. Problems that surround this issue are discussed in the following sections

8.1.1 Measurement of seizures in clusters

Seizure clustering can sometimes lead to difficulty in the actual quantification of therapeutic effects. The degree to which this can influence data in clinical studies is unknown. Although there does not appear to be a simple solution in dealing with this phenomena it is probably best to follow a consistent rules in handling such events and to quantify their occurrence. Little or no information was included in the application on this phenomenon except for the mention that a history of seizure clustering was one of the exclusionary criteria in the monotherapy trials. Because of the dearth of information an inquiry was faxed to the sponsors on 7/2/99 with additional questions submitted on 7/21/99. What follows is a discussion of the salient points that arouse from the sponsor's response.

The sponsors note that an attempt was made to limit problems that may result from seizure clustering by excluding patients with a history of such events in the monotherapy trials. Although probably helpful the lack of a history of seizure clustering does not guarantee that clusters will not occur. No attempt was made to do the same in adjunctive trials because as the sponsors argue such patients were assumed to exhibit a lowered propensity for such seizure behavior as these patients were on multiple medications. However a contrary argument may be made. Thus, because of differences in inclusionary/exclusionary criteria patients in the monotherapy trials tended to have a less severe seizure disorder and therefore may be expected to have a lower incidence of clustering. As little information exists on temporal pattern of seizures much of the above discussion is theoretical.

Along with excluding patients with a history of seizure clustering the best approach to this problem is to document the phenomena and to develop consistent protocol driven rules for the measurement of seizures in each cluster. The sponsors note in their response to my query that "the investigators were asked to quantify these seizures as much as possible and to be consistent in this calculation." No specific documented instructions regarding the counting of seizures in clusters were included in any protocols or amendments. Moreover, no attempt was made to tabulate or analyze seizure clusters.

8.1.2 Documentation of status epilepticus

The principal issue regards the equivalency of status and other secondarily generalized seizure events. An episode of status may not be considered equivalent to a single secondarily generalized seizure. The sponsors attempted to reduce the number of patients experiencing status by excluding patients who had suffered an episode within 3 to 24 months in different trials. It

is my opinion that, because the actual quantification of status is somewhat arbitrary, the issues surrounding the equivalencies are vague, and the occurrence of these events tends to be infrequent careful analyses of these seizures may not be necessary. It would, however, be helpful to have some information on the incidence of these seizures in placebo and drug groups during the double-blind phase of the study. This information was requested in a fax sent on July 29, 1999. The sponsors provided information on incidences of status in protocols 011, 025 and OT/PE1. Off the 337 and 691 patients in the placebo and OXC groups, respectively, 2 and 4 cases of status epilepticus was reported. This supports the contention the infrequency of this event. No reason was given as to why the sponsors failed to provide me with similar information the three remaining protocols.

8.1.3 Conclusions regarding problems in the measurement of status and clusters

The problems of measurement of seizures in clusters and episodes of status detract from the quality of data in this application. Nonetheless as all pivotal trials are blinded there is no reason to believe that miscounts of seizure or issues resulting from errors in seizure weighting should favor one group over another. Furthermore the importance of these measurement problems are mitigated by the fact that all six studies demonstrated statistical significance in the primary endpoint and, with the exception of one study, the degree of significance was robust. The clinical trials 04, 026 and 028 have some indirect evidence that support this claim. Each of these trials includes an exit criterion that included patients who required medical intervention for the treatment of their seizures. Included among these patients were those who experienced clustering and status. Examination of each study revealed a greater number of patients exiting because of the need for medical intervention in the control then the therapeutic group.

8.1.4 Measuring Generalized seizures:

In all other protocols included in this application it was assumed that all generalized tonic/clonic seizures in patients whom carried the diagnosis of partial seizures were secondarily generalized unless there was some seizure characteristic that would lead the investigator to believe otherwise. Every attempt before and during the studies was made to characterize these seizures as partial in origin through EEG and clinical features. However the final decision appears to be based upon the investigators best clinical judgement. Although this assumption may not be completely correct, knowing the limitations of such studies this reviewer feels that it was reasonable.

8.1.5 Pediatric Studies

The following tables presents pediatric sample sizes of OXC and placebo exposures in all pivotal monotherapy (Table 38) and adjunctive therapy studies (Table 39). Information from these tables was derived from sponsors demographic tables presented in the sponsor's application.

Table 38 Pediatric Age Distribution in Pivitol Monotherapy Trials

		Study 04	Study 25	Study 026*	Study 028*	Total
6 -11 years	OXC	1	2	0	0	3
	Control	0	1	0	2	3
12 - 17 years	OXC	3	6	2	4	15
	Control	4	3	0	3	10

* Control in these cases constitutes of low dose (300 mg/day) monotherpy treatment. All other cases patients in control group receives placebo.

APPEARS THIS WAY
ON ORIGINAL

Table 39 Pediatric Age Distribution in Pivotal Adjunctive Therapy Trials

		011	0T/PE1	Total
< 6 years	OXC	14	0	14
	Control	16	0	16
6-11 years	OXC	56	0	56
	Control	51	0	51
12-17 years	OXC	68	18*	86
	Control	62	7	69

* The value of the OXC experimental group is a summation of 3 separate experimental groups receiving different OXC doses. In all other cases presented in pediatric tables the OXC group data is derived from patients in a single dose group.

Most notable from Table 38 is that there was an insufficient exposure to allow for conclusions regarding the monotherapeutic efficacy of OXC. There is however a reasonable degree of exposure to OXC as adjunctive treatment in seizures of partial origin in the pediatric population in age groups of 6 and above. There is little exposure in younger age groups.

8.2 Efficacy Summary

8.2.1 Monotherapy

A summary of the pertinent design features for the pivotal monotherapy trials can be found in Table 40 (from sponsors Exhibit 1.2.-2).

Table 40 Pivotal Monotherapy Trial Summaries

Therapy	Control	Protocol	# of centers	Design	Age (years)	Randomized Treatment	Total # Randomized	Duration of Double-blind treatment
Monotherapy	Placebo	004	10	Double-blind, parallel, presurgical, inpatient	11-65	OXC 2400 mg/day Placebo	51 51	10 days
Monotherapy	Placebo	025	10	Double-blind, parallel recent-onset patients	≥ 10	OXC 1200 mg/day Placebo	32 35	90 days
Monotherapy	Low-dose	026	12	Double-blind, parallel substitution of CBZ by OXC	≥ 12	OXC 2400 mg/day OXC 300 mg/day	51 45	126 days[1]
Monotherapy	Low-dose	028	9	Double-blind, parallel substitution of 1-2 AEDs by OXC	≥ 12	OXC 2400 mg/day OXC 300 mg/day	41 46	126 days

[1] Patients in Protocol 026 also received treatment during a 28-day Open-label Conversion Phase and a 56-day Baseline Phase

A summary of outcomes in primary endpoints is presented in Table 41.

Table 41 Primary Endpoint Outcomes for Pivotal Monotherapy Trials

Protocol	Endpoint/test	Outcome**		P value
04	25th quantile Time to Exit /Log-Rank Test*	Placebo	0.6 days	0.0001
		OXC 2400 mg	2.6 days	
025	Median Time to Exit/Log-Rank Test	Placebo	3.2 days	0.0457
		OXC 1200 mg	11.7 days	
026	Median Time to Exit/Log-Rank Test	OXC 300 mg	28 days	0.0001
		OXC 2400 mg	68 days	
028	% Meeting Exit Criteria/ Cochran-Mantel-Haenszal*	OXC 300 mg	91.3%	0.0001
		OXC 2400 mg	51.2%	

* 25th quantile presented because < 50% of patients in OXC group meet exit criteria at the end of the double blind phase.
* Worst case scenario analysis is presented.
** Doses are presented in terms of dose per day.

All trials demonstrated a monotherapeutic efficay of OXC in the control of seizures of partial origin as indicated by a statistically significant effect on the ITT data set analysis of the primary endpoint. Except for protocol 025, that examined the lowest dose, this effect was robust with low α value. In the vast majority of cases this effect was confirmed by secondary endpoint analysis. While each study contained flaws, these tended to be mitigated by confirmatory data from other pivotal trials that did not suffer from the same design problem. Thus, there was reason to believe that protocol 04 and 028 (to a lesser degree) may not have constituted a true monotherapeutic challenge because baseline medications may have been present in the serum during part of the measurement period. This however was not a problem in protocols 025 and 026. The design of trial 026

suffered from a potential but unproven possibility that an OXC seizure withdrawal syndrome could lead to an overestimation of OXC efficacy. No other trials suffered this same potential problem.

With the above issues in mind it is reasonable to conclude that therapeutic efficacy has been proven for the monotherapeutic treatment of seizures of partial origin in adults at doses of 1200 to 2400 mg/day. Lower doses have not been demonstrated as efficacious nor has monotherapy been sufficiently explored in the pediatric population.

8.2.2 Adjunctive Therapy

A summary of the pertinent design features for the pivotal adjunctive therapy trials can be found in Table 43. Trial 011 and OT/PE1 were performed on a pediatric and adult population, respectively.

Table 42 Pivotal Adjunctive Trial Summaries

Therapy	Control	Protocol	# of centers	Design	Age (years)	Randomized Treatment	Total # Randomized	Duration of double-blind treatment[2]
Adjunctive	Placebo	011	47	Double-blind parallel patients on 1-2 AEDs	3-17	OXC (30-46 mg/kg/day) Placebo	138 129	112 days
Adjunctive	Placebo	OT/PE1	60	Double-blind, parallel patients on 1-3 AEDs	15-65	OXC 2400 mg/day OXC 1200 mg/day OXC 600 mg/day Placebo	174 177 168 173	182 days

[1] This treatment group includes 47 patients who were dosed at 1800 mg/day per protocol amendment
[2] The length of double-blind treatment excludes any tapering periods that may have occurred

A summary of outcomes in primary endpoints is presented Table 44.

Table 43 Primary Endpoint Outcomes for Pivotal Adjunctive Therapy Trials

Protocol	Endpoint/Test	Outcome*		p Value
011	Median % Change in Seizure Frequency/ Wilcoxon Rank Sum	Placebo	–9.4%	0.0001
		OXC 31* mg/kg	–34.8%	
OT/PE1	Median Percent Change in Seizure Frequency/ Wilcoxin Rank Sum Test with Bonferroni-Holm Correction (for comparison of the mid and high dose only)	Placebo	-7.59%	P<0.05
		OXC 600 mg	-26.45%	
		OXC 1200 mg	-40.22%	
		OXC 1800-2400 mg	-49.95%	

* Doses are in terms of dose per day.
* Because 011 allowed for dose adjustment the dose presented is the median of final dose achieved (range 6.4 to 51.4) .

As previously noted protocol 011 presents evidence for adjunctive therapeutic efficacy at a median dose of 31 mg/kg/day. While it is only a single

study the effect was robust and is supported from findings in the adult adjunctive trial. Conclusions of efficacy should be limited to the ages of 6 to 17 years old for reasons previously stated.

Data from Protocol OT/PE1 supports adjunctive use of OXC in adults. Although only a single adult study is presented it consisted of a large number of patients and results were supported by the single pediatric study. Strong evidence, supported by a robust p value for the primary endpoint (not corrected for multiple comparisons), are presented for OXC adjunctive use in therapy at the doses of all doses (600 1200 and 2400 mg/kg/day). Factoring in the protocol driven planned correction for multiple comparison would indicate that only the intermediate and high doses are effective. From a statistical perspective the design of this study was flawed. This is because corrections for multiple comparisons were not included in the planned analysis of the low dose primary endpoint. The sponsor states that this was done because it was not anticipated that this dose would prove effective. It would appear the they were "hedging their bets." The therapeutic effect at this dose was however robust and post hoc analysis of the primary endpoint corrected for multiple comparisons strongly suggests that this dosage to be effective. Although statistical conclusions regarding efficacy of the high dose are justified the large number of adverse events and resulting dropouts complicates this interpretation. The demonstration of efficacy at this dose in monotherapy trials does lend support for its adjunctive use. Tolerability at this dosage will likely be a problem.

9. Labeling Discussion

9.1 Edited Labeling

What follows is an edited copy of the sponsor's submitted draft labeling. This was edited using the Microsoft Word Tracking macro. Crossed out text is deleted sponsors text. Underlined text was added by this reviewer. Footnotes present the reviewers justification for text edits.

CLINICAL STUDIES

[redacted]

Trileptal Monotherapy Trials

[35] There was insufficient data on monotherapeutic use in the pediatric population.

[36] Very few children under the age 6 years were included in adjunctive therapeutic trials.

6 pages
REDACTED

DRAFT
LABELING

DRAFT

LABELING

10. Conclusions

Based upon the presented efficacy data this reviewer agrees with the appovability of this application. The labeling will need to be revised. Suggestions are provided above.

11. Recommendations

Approvable.

[56] There is a potential for increase and *decrease* in other anticonvulsant drug levels.

/S/

N Hershkowitz MD PhD
Medical Reviewer

R. Katz, M.D. _____

CC: NDA21-014/Katz/Boehm/Yan/Fisher

APPEARS THIS WAY
ON ORIGINAL

Review and Evaluation of Response to issues of Clinical Efficacy

NDA (Serial Number)	**21-014**
Sponsor:	**Novartes**
Drug:	**Trileptal**
Proposed Indication:	**Epilepsy (partial origin)**
Material Submitted:	**Response to Approvable Letter**
Correspondence Date:	**Nov. 15, 1999**
Date Received / Agency:	**Nov. 16, 1999**
Date Review Completed	**Jan. 4, 1999**
Reviewer:	**Norman Hershkowitz MD, PhD**

1. Introduction

In this division's reviews and an approvable letter we previously acknowledged that the Sponsor has successfully demonstrated efficacy of Trileptal in the treatment of epilepsy of partial origin so as to allow labeling under the following circumstances:

2. Major Labeling Issues

2.1.1 *Trend analysis of efficacy in the young pediatric population*

The Sponsor contests the exclusion of adjunctive therapy in the pediatric age group of 3-6. They first argue that when age groups are subdivided by the 1994 FDA definition of pediatric populations[1] (<12 and ≥ 12) that statistical significance is achieved in both groups (see table below). When narrower range subgroups are examined the Sponsor points out that while not achieving statistical significance there appears to be a "trend" in that direction (see table below).

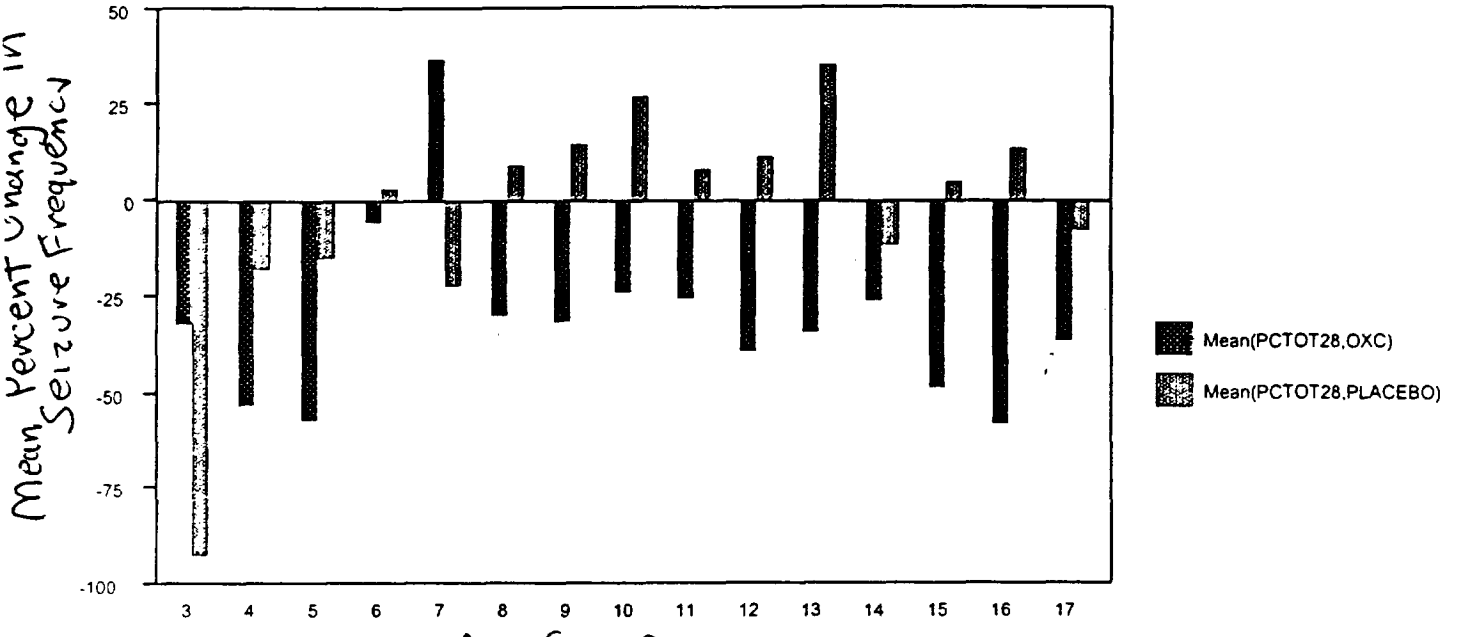
Exhibit L1-1. Summary statistics of the percentage change in partial seizure frequency from baseline by age group in adjunctive therapy, Study 011 (intent-to-treat patients)

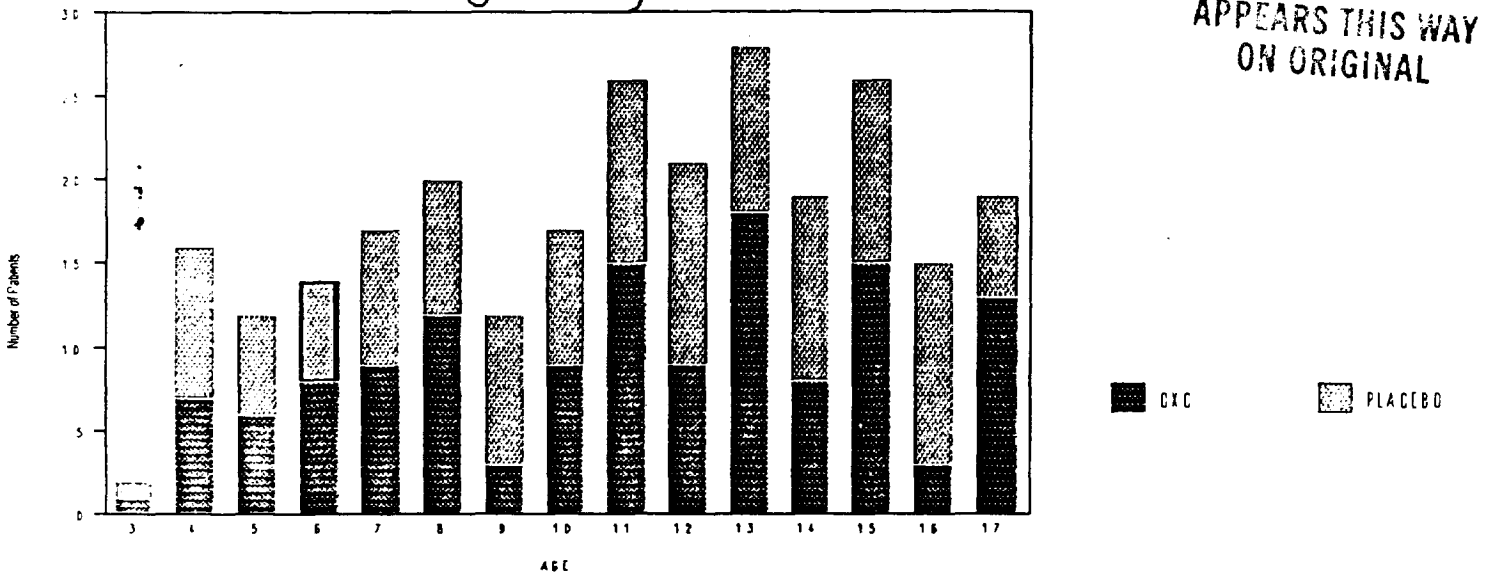
Age group	OXC			Placebo			
	N	Median	Range	N	Median	Range	P-value
FDA guidelines[2]							
< 12 yrs	70	-32.3		66	-12.7		0.0181*
12-17 yrs	66	-44.5		62	-8.0		0.0001*
ISS & ISE grouping							
3- 5 yrs	14	-53.5		16	-17.3		0.0585
6-11 yrs	56	-27.0		50	-10.0		0.0628
12-17 yrs	66	-44.5		62	-8.0		0.0001*

[1] Includes one OXC-treated patient (7 yrs old) with inaccurate seizure diary data (seizure freq. change: 301%) *Denotes statistical significance at 0.05 level.
[2] 1994 rule : 201.57(f)(9)(I))
Source: Integrated Summary of Efficacy, Section 3.1.6

To better appreciate whether there are any age dependent trends I have plotted the primary outcome (% change in seizures) by single year bins in the first figure below. The histogram immediately below this figure presents the number of patients in each group. Noteworthy from the first figure is the observation that the 7 year old age group appear to be an outlier; a factor that probably contributes to the absence of statistical significance in the sponsors grouping in age 6-11. Most important is that this figure does not reveal any obvious age dependent alteration in efficacy (i.e. no trends). There appears to be a similar therapeutic effect in ages 4 and 5 as is observed at older ages. No therapeutic effect is observed at age 3. There, however, was only a single drug and placebo patient included at this dose.

[1] Rule 201.57 (f), (9) (I).





APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

2.1.2 Pharmacokinetic similarity between the adult and pediatric population

The Sponsor notes that the equivalency in efficacy of Trileptal across age groups is supported by studies that have shown that during adjunctive use "average clearance is similar between pediatric and adult patients." The data

presented to support this included only ranges that were derived from pediatric study 011 and two other adult studies. No statistical analysis was performed. Nonetheless, in a study that the sponsors presented in the original application (reviewed by Pharmacokinetics), which was designed to study this issue, the influence of age on AUC was significant with a 30 % higher values in older children.[2] A total of 34 children with epilepsy on other adjunctive treatments were studied. This study was apparently sufficiently convincing to the Sponsor so that the submitted draft labeling included information of increased clearance younger children. Based upon this information this reviewer feels that the differences amongst age groups are sufficient to result in differences in therapeutic dosage range.

2.1.3 ILAE statement regarding the lack of need for pediatric trials

The Sponsor quotes a statement published[3] by the ILAE which states that "because the efficacy of AEDs seems to be the same in childhood...partial epilepsy...there is no obvious reason to repeat controlled efficacy studies of childhood partial epilepsy previously performed in adults." The Sponsor argues that they have gone beyond that which should be necessary; i.e. they performed not only adult studies but children studies as well. This reviewer agrees with the ILAE statement that AEDs should exhibit similar efficacy in anticonvulsant effect of agents in both pediatric and adult population. The issue is not one of efficacy it is that of potency and therapeutic index (i.e. efficacy Vs toxicity). It is well established that drugs in general may exhibit a different pharmacokinetic and pharmacodynamic profile between a pediatric and adult population. Without this information the FDA is unable to evaluate necessary labeling regarding dose and toxicity. Notwithstanding this, when the study is viewed as a whole there is sufficient information ("proof of principal") on efficacy for adjunctive labeling from study 011. The question however that remains, however, if any age dependent labeling instructions need to be added (see below).

2.1.4 Comparison with other approved drugs

The Sponsor raises the issue that other drug received inclusive pediatric labeling with a similar "overall efficacy" evaluation. Presumably they are referring to the lack of careful subset analysis. They specifically identify the example of topiramate. This reviewer agrees with the Sponsor. The topiramate study is a reasonably good example for comparison as it's design was relatively similar to that in the Trileptal study; i.e. titration to target dosage was attempted but allowance were made to reduce the dose as required by tolerance. Narrow age range subset evaluation was not performed in the approval of this agent in spite

[2] Statistical significance could however not be demonstrated when a group of ages 2-5 and 6-12 was compared.
[3] Epilepsia 35: 94-100, 1994.