other monotherapy trials. The fact many patients in the OXC treatment group (greater then 30%) exhibited their first seizure prior the expected serum MHD plateau (3 days) possibly contributed to this problem.

5.1.2.12 SPONSORS ANALYSIS:

The sponsors feel that except for the single patient, (Hasegawa 105/609) who was administered the wrong medication bottle, there were no significant protocol violations or differences in demographic variables. They conclude efficacy based upon significant findings of the primary endpoint and the secondary frequency measure.

5.1.2.13 REVIWER'S ANALYSIS:

This reviewer agrees with the comparability of demographic variables. The confusion regarding issues surrounding entry eligibility for open label study may be considered sufficiently significant. This resulted in considerably different percent of "eligible" in OXC and Placebo groups that left the double blind phase to enter the open label study. As previously discussed, this can potentially influence seizure frequency. For this reason, it is probably best to ignore this secondary endpoint. This leaves a borderline but statistically significant primary variable and one negative secondary variable. Because of the borderline value of this endpoint it is important to weigh the results of this study against other similar investigations. As will become apparent a number of other studies have demonstrate that higher doses (2400 mg/day) of OXC can be readily proven to produce a statistically significant therapeutic effect when used as monotherapy (see above and below). Moreover 1200 mg/day was shown to produce a statistically significant therapeutic effect on the same class of seizures in adjunctive studies (see trial OT/PE1). As noted above there were factors that may have contributed to a false negative conclusion of efficacy. These include relatively large number of patients in the OXC group who experienced a seizure prior to achieving serum MHD plateau and the center that appeared to deviate from the standards of Good Clinical Practice and Compliance. There however was another factor that the may have contributed to a false positive conclusion; i.e. the slightly greater placebo baseline frequency for all seizures of partial origin. The difference however proved to be statistically insignificant.

5.1.2.14 SUMMARY:

Evidence of therapeutic efficacy in the present study is principally based upon the analysis of the primary endpoint values. Although the p value in the ITT analysis is not robust it is significant. Because of this borderline value comparisons with other monotherapy trials are necessary to draw final conclusion regarding the proposed monotherapeutic use in epilepsy of partial

origin. It is important to keep in mind, vis-a-vis labeling, that this dose is the lowest examined amongst all pivotal monotherapy trials (1200 mg/day).

5.1.3 STUDY 026

5.1.3.1 TITLE

Safety and efficacy of high versus low dose oxcarbazepine monotherapy in patients with uncontrolled partial-onset seizure.

5.1.3.2 OBJECTIVE

The primary objective was to evaluate the safety and efficacy of high dose OXC (2400 mg/day) as compared to low dose OXC (300 mg/day) in-patients with uncontrolled seizures of partial origin. The secondary objective was to examine PK characteristics of this drug when used in monotherapy.

5.1.3.3 DESIGN

This was a multicenter, randomized, double-blind, parallel-group trial that compared high and low dose OXC monotherapy in patients who were considered refractory on carbamazepine (CBZ) treatment. The study was divided into 5 separate phases: screening, open-label conversion, open-label baseline, double-blind treatment and open label long-term extension.

Patients were removed from the trial if: 1) a pregnancy was detected; 2) if the patient requested to be discontinued; 3) whenever the investigator decided it was in the patients best interest; 4) major violation; 5) intolerable adverse effects; 6) development of an exclusion criteria. There was no plan to remove patients from analysis once they completed the trial.

5.1.3.4 SCHEDULE

The schedule for the present study design is presented in the Figure 6 (from the sponsor's exhibit 3.1.-1).

Figure 6 Experimental Schedule for Trial 026

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							

5.1.3.4.1 SCREENING PHASE (DAYS –56 - 0)

Patients who were on 800-1600 mg/day of CBZ who maintained a seizure frequency of 2 to 40 seizures/month (documented by a diary or other "equivalent source") were entered into this phase. Informed consent was obtained and laboratory testing (pregnancy test, blood chemistry, drug screen, CBC, and urinalysis) were performed during this phase.

5.1.3.4.2 OPEN-LABEL CONVERSION PHASE (DAYS 1 - 28)

Patients were evaluated during this phase for trial eligibility and anticonvulsant medication (CBZ) was carefully replaced with OXC. On day 1 tests obtained during screening were reviewed with patient eligibility in mind. A complete physical and neurologic exam as well as EKG was performed and medical and seizure history was reviewed. Patients were started on an upward titration of OXC and downward taper of CBZ so that on day 21 CBZ was discontinued and patients received their final targeted dose of OXC of 1200 mg BID. Patients who could not tolerate the targeted OXC dose were allowed to discontinue treatment or enter an open-label extension trial.

5.1.3.4.3 OPEN-LABEL BASELINE PHASE (DAYS 28-84):

Patients who successfully tolerated OXC at the dose 1200 mg BID on day 28 were entered into the open-label baseline phase. Patients were maintained on this dose of OXC; no other anticonvulsants were permitted. If the patients exhibit poor seizure control or tolerability they were allowed to exit the study or enter the open-label extension phase. Like other phase's seizures were recorded in diaries during this phase.

This study used an enriched design in that only those patients who could tolerate the medication and experienced an acceptable seizure control at the present dosage were randomized. This is not different from the way this class of medication is used clinically. Thus, neurologists will try a variety of anticonvulsants until an agent is identified that will control seizures with minimal toxicity. With such a design care must be taken in the interpretation of incidences of toxicity and efficacy of seizure control in the general population. This design does not allow any conclusions, or comparison with other drugs, to be drawn on this agent's therapeutic index[10].

5.1.3.4.4 DOUBLE-BLIND TREATMENT PHASE (DAYS 84-210)

[10] The U.S. veterans cooperative study (Epilepsia 1987;28 Suppl 3:S50-8) demonstrating that although anticonvulsants exhibit equivalent efficacy they produce different incidences of toxicity. Since this study the community of treating neurologist has placed emphasis, for evaluation of anticonvulsants, on therapeutic index.

Patients that meet one of the following exit criteria during any part of this phase were considered to have completed the study and were permitted to enter the open-label extension:

Exit Criteria

1. A two-fold increase in the number seizures, as compared to the frequency during the open label baseline phase, during any 28-day period. Patients with zero or one seizure during the baseline were required to have a 28 day frequency of at least 3 to meet this exit criteria.
2. A two fold increase in the highest consecutive 2-day seizure frequency that occurred during baseline. These criteria will only be applied to patients with a two-day seizure frequency of 2 or more during the baseline period.
3. Occurrence of a single generalized seizure if none occurred during baseline.
4. A prolonged generalized seizure (of any seizure subtype) determined by the investigator to require intervention.

This phase is divided into two periods:

Down-titration period: Eligible patients were randomized on the first day of this phase (day 84 of the study) to either high or low dose treatment groups (2400 mg/day or 300 mg/day, respectively). Patients randomized to the high dose group simply continued their present medication regimen. Those randomized to the lower dose were tapered at biweekly intervals over a 6-week period by substituting active drug with placebo. This type of design may lead to a false conclusion if this drug exhibited a withdrawal syndrome that included seizures. Thus, if this drug were without anticonvulsant activity but with a distinctive seizure withdrawal syndrome a greater incidence of seizures might be expected in patients who were randomized to the placebo. Although the sponsors do not refer to any carefully controlled prospective study, they do note in the ISS that there "were no reports of withdrawal syndrome in subjects discontinuing oxcarbazepine after a duration of therapy of up to 4 years." The sponsors were requested to supply more information on this issue in a letter on June 16, 1999. They responded by: 1) arguing through analogy with phenytoin that the rate of withdrawal was to slow to produce seizures, 2) arguing by analogy to "some drug categories" that the 84 day time period before withdrawal is initiated is not sufficient to result in withdrawal seizures, 3) perhaps most importantly they point out that there has been no reports of withdrawal seizures after the post-marketing exposure of approximately 156,500 patient-years nor within any of the clinical trials.

Maintenance Period: Patients who have not meet exit criteria during the previous period will enter this period on day 140. These patients will remain on their OXC dosage till they meet exit criteria or complete this phase.

5.1.3.4.5 OPEN-LABEL EXTENSION PHASE (DAY 210-)

Anyone who completed all visits of the latter phases or meet one of the above exit criteria were permitted to enter this open-label phase. The dose was titrated to tolerability in this phase of the study.

5.1.3.5 AMENDMENTS

There were no amendments.

5.1.3.6 ENROLMENT

APPEARS THIS WAY
ON ORIGINAL

5.1.3.6.1 INCLUSION CRITERIA

1. Male and female outpatients, aged 12 years or older.
2. Female patients who were unlikely to conceive based upon status of menarchy or form of birth control. Those biologically able to conceive had to have a negative serum β-HCG just prior to trial entry.
3. Patients with a diagnosis of partial seizures, which include the seizure subtypes of simple, complex, and partial seizures evolving to secondarily generalized seizures (based on ILAE Classification, as modified in 1981).
4. Patients with 2-40 partial seizures per 28-day period during the 56-day Screening Phase.
5. Patients treated with CBZ monotherapy at a dose of 800 to 1600 mg/day for at least 56 days prior to the Open-label Conversion Phase.
6. Patients with an EEG or CCTV/EEG prior to trial entry and who's abnormalities were consistent epilepsy of partial origin.
7. Patients with a previous CAT Scan or MRI that confirmed the absence of space occupying lesions or progressive neurological diseases. No physical examination changes suggestive of such lesions or diseases could have occurred since that imaging procedure.
8. Patients weighing at least 41 kg (90 lbs.) at Visit 1.
9. Patients with a serum sodium level of 130 m Eq/L or greater at Visit 1.

5.1.3.6.2 EXCLUSION CRITERIA

1. Patients with a treatable cause of seizures (e.g.,metabolic disturbance, toxic exposure, active infection pseudoseizures.).
2. Patients with a documented history of generalized status epilepticus in the past 3 months while complying with appropriate anticonvulsant therapy.
3. Patients with cluster seizures. A cluster was defined as numerous seizures occurring over a short period of time (i.e., <30 min.).
4. Patients with progressive disorders.
5. Patients with a history of poor compliance with past antiepileptic drug therapy, as judged by the principal investigator.

6. Patients with a significant history of medical disease within the previous 2 years (i.e., cardiovascular, hepatic, renal, gynecological, musculoskeletal, gastrointestinal, metabolic or endocrine) which could impair reliable participation in the trial or necessitate the use of medication not allowed by this protocol.
7. Patients with a malignancy or history of malignancy within 5 years of trial entry.
8. Patients with clinically significant electrocardiograph abnormalities.
11. Patients with a history of clinically relevant psychiatric or mood disorders (DSM-IV) requiring electroconvulsive therapy or chronic medication within the past six months.
9. Patients with a history of suicide attempt.
10. Patients with a history of alcohol or drug abuse during the 1-year period prior to trial participation.
11.Patients taking benzodiazepines on more than an occasional basis.
12. Patients who received an experimental drug or used an experimental device within 60 days prior to trial entry.
13. Patients who used dihydropyridine calcium channel.
14. Patients who donated blood within 30 days of trial entry.
9. Patients who, with or without assistance, are unable to comply with the protocol.

5.1.3.7 EFFICACY VARIABLES

5.1.3.7.1 PRIMARY ENDPOINT

The single primary endpoint to be examined was the time to meet the exit criteria.

5.1.3.7.2 SECONDARY ENDPOINT

The single secondary endpoint was the percent of patients meeting one of the exit criteria.

5.1.3.8 CONCOMITANT TREATMENTS

With two exceptions the use of concomitant anticonvulsant treatment was prohibited in the present study. These include: 1) The use of CBZ during open label conversion; 2) "limited administration" (not defined) of short acting bezodiazepines were allowed during open label conversion and baseline but were prohibited (except in the case of a medical emergency) during the double-blind phase. Information about other medications was solicited and recorded at each visit. See exclusion criteria for other restricted medications.

5.1.3.9 ANALYSIS METHOD

A sample size of 94 (47 per group) was determined to be required to detect a 35% difference between the two groups at a p value of 0.05 and a statistical power of 90%. This was calculated on the basis of percent of patients who would meet one of the exit criteria during the double-blind phase. A p value < 0.05 was required for statistical significance. All tests were 2 tailed.

All randomized patients who entered the double-blind phase and returned seizure diary were analyzed- this was considered as the intent-to-treat dataset.

Statistical analysis was outlined in the original protocol and the means of handling discontinuations was decided prior to unblinding.

Primary endpoint: The log–rank test (with Kaplan-Meier survival curve) analysis was used to evaluate the primary endpoint. Patients who prematurely withdrew were censored.

Secondary endpoint: The secondary endpoint of percentage of patients meeting exit criteria were analyzed using the Cochran-Mantel-Haenszel (CRH) test. Premature discontinuations were dealt with in four fashions arranged in a hierarchical fashion. According to protocol the first evaluation was a worst case scenario that would consider high and low dose patients whom prematurely discontinued medication as having exited and completed, respectively. Three other evaluations were to be carried out if this first method did not reveal a therapeutic effect. In such a case patients who dropped out of both groups would be considered as either completers, exiters or missing.

5.1.3.10 STUDY CONDUCT

5.1.3.10.1 ENROLLMENT

One hundred and forty-three patients were enrolled and received open-label OXC. Of these 96 patients were randomized in to the double-blind phase of this study (51 and 45 in the high and low dose groups, respectively). A summary of the patient accounting is presented Table 10 (from Sponsor's exhibit 6.1. -1).

Table 10 Patient Accounting for Trial 026

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	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

The majority of patients who were not randomized were not for reasons of adverse events. The remainder of patients were not randomized because of "other" reasons included 15 patients whom did not achieve a satisfactory therapeutic effect, 4 patients who withdraw consent, 1 due to laboratory abnormality, 2 from non compliance and 1 for administrative reasons. These numbers underscore the fact that this study was enriched with patients whom appeared to have an acceptable number of seizures and minimal toxicity while on high dose Trileptal.

A very small percent of randomized patients were withdrawn from the study early (10%) and none of these were withdrawn for reasons of adverse events. This belies the enriched trial design. Reasons for withdrawal are given in Table 10. The withdrawal for "other" included patients who were withdrawn for administrative reasons and 2 patients in the high dose group who are not included in the ITT analysis because withdrawal occurred prior to first double blind dose. The reasons for withdrawal in these 2 cases were death from heart failure and withdrawal of consent.

5.1.3.10.2 DEMOGRAPHICS

The mean values of the routine demographic variables measured during the open label baseline phase of sex, race, age and weight were nearly identical in both high and low OXC dosage groups. No statistical test of the significance of the minor differences between demographic variables was carried out.

5.1.3.10.3 BASELINE PHASE COMPARABILITY

Both OXC dose groups received similar mean doses of CBZ during the Baseline Phase. These values (Mean ± SD) were 1388±332 and 1275±316 per day, for high and low dose respectively.

Comparisons of baseline seizure frequencies were made between both experimental groups during the open-label OXC treatment Phase. Measures of central tendency (mean and median) as well as standard deviation were presented for the frequency of different seizure types in both groups. These include 28-day seizure frequency for simple partial, complex partial, partial seizure with secondary generalization and all seizures of partial origin (see Table 11 derived from Sponsors Table71.-3). Values for the highest 2-day seizure frequency is also calculated (see Table 11). Some minor differences can be noted in the values between the high and low dose groups. However in every case where differences between groups were greater then 10% the higher values were observed in the high dose OXC group. While this may result in some degree of bias, this bias would favor the conclusion of no therapeutic efficacy.

Table 11 Baseline Seizure Frequency for Trial 026

	OXC 2400 mg/day	OXC 300 mg/day
Simple Partial/28 days	2.6 ± 6.8	2.8 ± 9.6
Complex partial/28 days	6.9 ± 10.3	5.5 ± 10.8
Partial 2°generalized/28 days	1.3 ± 3.5	0.8 ± 1.7
All seizures/28 days	10.9 ± 12.8	9.1 ± 13.3
Highest 2 day seizure frequency for all seizures	4.4 ± 3.4	4.0 ± 3.8

N.B. Values are in terms of mean ± standard deviation

No statistical evaluation was performed by the sponsors to measure the significance of any of these differences.

Except for the disproportionate use of benzodiazepines between the low dose OXC group during the double blind phase, there appeared no clinically significant difference between the use of other medications between groups during any treatment phase. The benzodiazepines were administered in 11 patients in the low dose group and 6 in the high dose group. The use of benzodiazepines may have resulted in added therapeutic action that could potentially obscure the results of the present study. A fax was sent to the sponsors on the date of July 16, 1999 requesting clarification of some of this and related issues. The following are the more salient points contained in the sponsor's response. Off those patients noted to receive benzodiazepines only 3 patients in the high dose and 4 in the low dose received this medication prior to the day of exit. Three of these patients received this class of agent for conditions

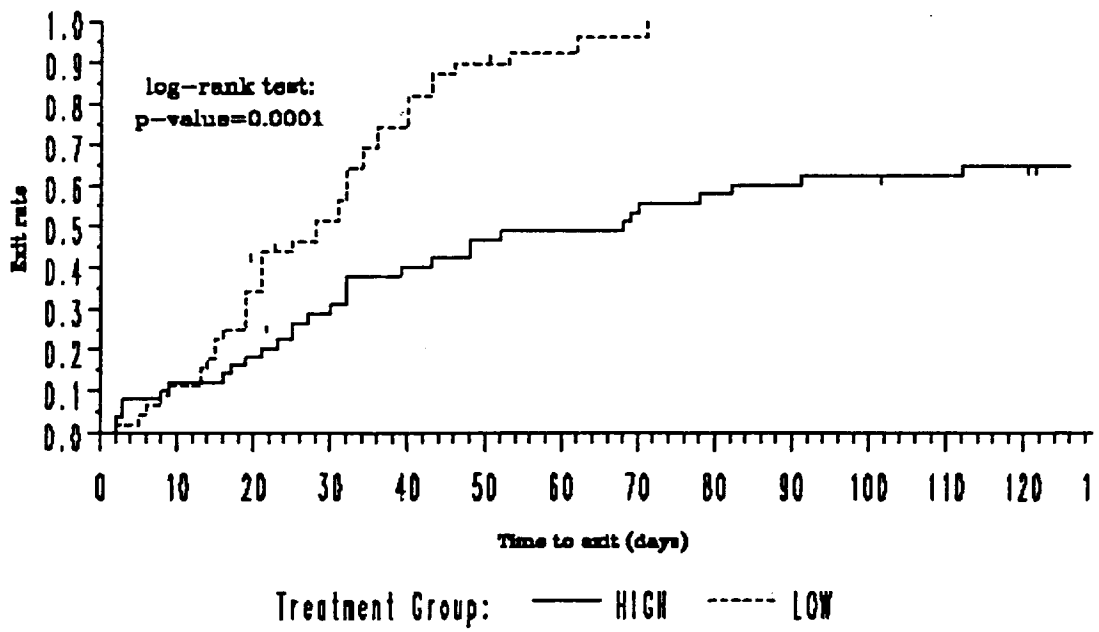
described as "nervousness" or "anxiety"[11] with the remainder receiving treatment emergently for the control of seizures. As it is difficult to definitively predict how this might effect the final result the sponsors added an additional analysis that excluded those patients who received benzodiazepines prior to the date of exit (see sponsors efficacy results)

5.1.3.11 SPONSORS EFFICACY RESULTS

5.1.3.11.1 PRIMARY ENDPOINT:

Log-rank analysis of the ITT data set revealed that the time to meeting one of the exit criteria were very much in favor of high dose treatment (p=0.0001). This can be appreciated in the Kaplan-Meier survival curves presented below (form Sponsors Exhibit 8.1.-1).[12] One center (Hasegawa/M0313V) was thought to significantly deviate from standards of Good Clinical Practice. Analysis excluding patients from this center did not effect the conclusion or the degree of significance. Evaluation excluding those patients who received benzodiazepines prior to the exit date still revealed a statistically significant (p=0.0001) therapeutic effect.

Figure 7 Kaplan-Meirer Survival Curves for Trial 026



5.1.3.11.2 SECONDARY ENDPOINTS

[11] This could be considered as a violation of the protocol (see concomitant medications).
[12] It is noteworthy that survival analysis was performed using the Cox's proportional hazards regression model comparing potential baseline features (center, age, sex, CBZ dose and baseline seizure/28days) that may influence outcome with OXC treatment. A statistically significant correlation was observed only OXC treatment.

CMH analysis of the number of patents meeting the exit criteria during the double blind phase in a worst case scenario was consistent with a greater therapeutic benefit of high dose OXC. Thus, compare 67.3% of patients in the 2400 mg/day group with 88.9% of patients in 300 mg/day group who meet exit criteria. The p values were significant to the level of 0.010. An analysis where drop outs were not included in calculations revealed that 65.2 % versus 100% of patients meet exit criteria in the high and low OXC dose groups, respectively.

A factor in favor to the sponsor's conclusion that was not discussed in the submission should be noted. Although the different exit criteria are treated as numerically equivalent entities there is no reason to believe that meeting one criterion represents a similar degree of therapeutic failure as meeting another criteria. Nonetheless a greater number of patients exited the study in the low dose then the high dose group for every one of the four exit criteria.

5.1.3.12 ADVERSE EEFFECTS AND MEASURE EFFICSY

Because of the enriched study design no patients were discontinued from the double blind phase because of serious adverse events. While adverse events may not directly influence the outcome of this study the enriched design characteristic of this trial needs to be kept in mind for reasons described above.

5.1.3.13 PK AND MEAUSURED EFFICSY

No pertinent issues are raised in regard to this issue. Seizure tendency appears to be correlated with dose and C_{min} serum values.

5.1.3.14 PROTOCOL VIOLATIONS

No patients were discontinued from trial as a result of protocol violations. Forty-nine patients, however, were allowed to enter with monitor-approved protocol deviations. These included cases where total number of seizures were somewhat greater then cut off, the length of the screening period deviated from protocol criteria and dose of CBZ were not within protocol range. According to the Sponsor's, and this reviewer concurs, these deviations should not effect conclusions on efficacy. Thirteen patients (10 in high and 3 in low dose group) who should have exited the double blind phase remained in it because of an error in calculations. These errors were discovered latter through a computer program written to monitor quality control and final data is calculated based upon the corrected day of exit. When an inquiry was made through fax the sponsors noted that all data was checked and corrected for this error.

This reviewer noted that one patient in the high OXC dose group was on acetazolamide. This agent is a known diuretic and is also thought to function as an anticonvulsant. This would appear to be a violation of protocol. A request for an explanation was sent to the sponsors on 6/22/99. In response the sponsors

justified the use of this agent by noting it was prescribed for "water retention" and that "acetazolamide is not widely considered as an antiepileptic drug nor has (it) been approved for this use." This reviewer would contest this justification. Although studies are not extensive there is a sufficient degree of data to suggest that this agent possess anticonvulsant activity that should preclude its use during the double-blind phase.[13] The use of this agent in the high dose group may minimally contribute to the measured efficacy (it appears to have been initiated during the double-blind phase). In view of the robust therapeutic signal it is doubtful that removal of this single violation would significantly influence the conclusions of this report.

5.1.3.15 SPONSOR'S ANALYSIS

The sponsor points out that there was no significant deviation to the protocol, and that the final number of patients evaluated was sufficiently close to the targeted size. They also point out that the demographic variables are well matched and that there were no significant deviations from the protocol.

An important limitation of the present study that is recognized by the sponsors is the issue of a potential withdrawal syndrome. Thus the observed differences in seizure frequency may be simply explained by earlier CBZ or later OXC withdrawal induced seizures. Seizures resulting from barbiturates and benzodiazepines are well documented phenomena. A seizure withdrawal syndrome resulting from other classes of anticonvulsants are not as well documented. Some reports suggest the absence of any such syndrome with CBZ[14]. The sponsors took effort to avoid potential seizures resulting from OXC withdrawal. To this end they used a rather slow OXC taper (over 42-days) prior to entry into the double blind phase. They argued, by analogy, that similar tapers with phenytoin have not been shown to result in withdrawal seizures[15].

Both primary and secondary endpoint (under a worse case scenario) demonstrated efficacy with very favorable p values. The sponsors believe this clearly demonstrates the efficacy of the present agent

5.1.3.16 REVIEWER'S ANALYSIS

The present study presents strong evidence that favors monotherapeutic use of OXC in the treatment of seizures of partial origin. As noted above there are some caveats in the interpretation of the data. Foremost is the concern that seizures elicited by the withdrawal of OXC or CBZ may complicate data analysis.

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[13] See Acetazolamide. In "The Medical Treatment of Epilepsy," pp409-418, Eds. Resor, SR and Kutt, H., Marcel Dekker, Inc., 1992.

[14] The Sponsors reference: Rouan MC, Decherf M, LeClanche V, Lecaillon JB, Godbillon J.. J Chromatogr 1994; 167-172. A more appropriate reference might be: Duncan JS, Shorvon SD and Trimble, MR, Epilpesia 31:324-333, 1990 , J Neurol Neursurg Psychiatry 51: 924-928, 1988.

[15] Bromfield et. al., Neurology 39: 905909, 1989.

Two factors make it unlikely that CBZ withdrawal will interfere with the present study. First, CBZ withdrawal occurred 28 days prior to the time that patients entered the double blind phase. Second, there is some reason to conclude from published reports (see above) that seizures resulting from CBZ withdrawal are unlikely occurrences. Perhaps theoretically more problematic is the issue of a potential OXC withdrawal syndrome. As described above this can lead to a false conclusion of therapeutic efficacy. The sponsors argue, by comparison with phenytoin data, that such a possibility is mitigated by the very slow rate of OXC withdrawal (42 days). This argument is based upon an assumption that both drugs exhibit identical clinical behavior. No direct information is provided in the study report that deals with the issue of OXC withdrawal seizures. Perhaps the best argument against a seizure withdrawal syndrome is the information that was provided by the sponsor that no such syndrome has been reported in any of the clinical trials and following 156,500 patient-years of non-US post-marketing exposures. Because postmarking observations cannot replace carefully performed scientific investigations final conclusions regarding the mono-therapeutic activity should include confirmation in other types of monotherapy trials that are not contaminated by this potential flaw.

Another issue that should be noted is the fact that this study used an enriched sample selection. This does not allow for any generalizations to be made regarding this agent's therapeutic index in the general population or comparisons with other anticonvulsant with regard to efficacy or adverse events.

5.1.3.17 SUMMARY

This study has provided relatively strong evidence that OXC is effective in monotherapy at a dose of 2400 mg/day. Because of the trial design this conclusion is based upon the reasonable assumption that there is no OXC epileptic withdrawal syndrome. The study utilized an enriched design such that comparisons of therapeutic index with other anticonvulsant agents may be difficult.

5.1.4 STUDY 028

5.1.4.1 TITLE

Safety and efficacy of high- versus-low dose oxcarbazepine monotherapy in patients with inadequately controlled partial-onset seizures.

5.1.4.2 OBJECTIVE

The primary objective was to examine safety and efficacy of OXC monotherapy in treatment in patients with inadequately controlled seizures of partial origin. PK parameters were also examined in this study.

5.1.4.3 DESIGN

This is a multicenter, randomized, double-blind, parallel-group trial that compared safety and efficacy of a high (2400mg/day) and low dose of OXC (300mg/day).

5.1.4.4 SCHEDULE

This study was divided into 3 phases: baseline, double-blind and open-label extension. The schedule of these phases is outline in Table 8 (from Sponsor's Exhibit 3.1.-1)

Figure 8 Experimental Schedule for Trial 028

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								

5.1.4.4.1 BASELINE PHASE (DAYS –56 TO 0)

Screening evaluation performed during this phase included a general medical and epilepsy history as well as a physical and neurologic examination. Screening laboratory testing was also performed during this phase. Patients were maintained on the "stable dose" of their AEDs. A minimum AED dose and as a specified documented seizure frequency range was required in order to enroll in this phase (see inclusion criteria). Patients were randomized during this phase on visit 1. This visit occurred within 7 days of the initiation of the double-blind treatment phase. A seizure diary or an "equivalent source document" was used to evaluate the preceding remainder of the time spent in this phase, retrospectively. Sufficient precautions were made throughout the study to monitor patients for compliance.

5.1.4.4.2 DOUBLE-BLIND TREATMENT PHASE (DAYS 1-126)

Patients who meet eligibility requirements began this phase on day 1. Adverse events were monitored by interviews, physical exams and laboratories throughout the study. Seizure diaries were also examined. Patients were followed on a weekly basis either through a clinical visit or phone call. The scheduled clinic visits are presented in Figure 8. All OXC doses were administered on an equally divided BID regimen.

Patients were considered completors if they finished this phase or meet one of the following exit criteria:

1. A twofold increase from baseline in partial onset seizure frequency during any 28-day interval.
2. A twofold increase in frequency of seizures from the highest 2-day baseline frequency except were the highest 2-day seizure court was 1. In the latter case the patient had to have a 2-day seizure count of 3.
3. Occurrence of a single generalized seizure if none occurred 6 months prior to randomization.
4. A prolongation or worsening of generalized seizure that is deemed by the investigator to require intervention.

This phase is divided into two periods, the titration and maintenance period.

Titration period (day 7-27): The first period was the 3 week long titration period so named for the upward titration of OXC that is completed during this phase. Patients randomized to the 2,400-mg/day dose were initially started on 1200 mg/day. This dose was maintained for the next 7 days but was then subsequently increased to 1,800 mg/day on day 8 and finally to 2,400 mg/day on day 15. This final dose was maintained for the remainder of the phase (both periods). Patients who were randomized to 300 mg/day were started on that dose on day 1. This dose was maintained for the remainder of the complete phase. Simultaneously to the addition of OXC patients were weaned off of their baseline AEDs. The primary AED[16] was decreased by 25% of the original dose on days 1,8 and 15 and then completely discontinued on day 42 (this extended weaning into the next period). The secondary AED was completely discontinued on Day 1. The fact that baseline AEDs were withdrawn during the period of time that patients were eligible for meeting exit criteria raises the issue as to wither this can be truly considered a monotherapy trial. This issue will be expanded upon in the sections on Results and Reviewer's Analysis.

Maintenance Period (day 28-126): The maintenance period started on day 28 and ended on day 126. Patients who could not tolerate high dosages had their dosage decreased to 2100 or 1800 mg/day. The adjustment was performed in a blinded fashion, allowing for placebo reductions in the low OXC dose groups. As

[16] Primary and secondary AEDs appeared to be defined by the dose of that AEDs. The drug whose dose (or serum concentration) was higher according to standard of treatment was considered as the primary AED. See inclusion/exclusion criteria for the definition of primary and secondary AEDs.

noted above, weaning of the primary AED extended into this period with complete discontinuation of this medication on day 42.

5.1.4.4.3 OPEN LABEL EXTENSION PHASE (DAY126-):

This phase was available to any patients whom completed the latter phase. Patients first enter an 8-day blinded-conversion period. During this period, those patients randomized to the 300-mg/day group were converted to a dose of 2,400 mg/day. Those patients in the high dose group simply had their dosage maintained.

5.1.4.5 AMENDMENTS

One amendment was added to the protocol. The amendment was implemented prior to any patient entry into the study. This amendment:

- Clarified measurement of simple partial seizures (included non-motor simple seizures: i.e. auras).
- Excluded patients with *only* simple partial onset seizures presumably to increase sensitivity.
- Changed minimum effective doses and therapeutic levels of other AEDs.
- Modified exit criteria to protect patients and increase sensitivity of the study. The final criteria are presented above.

5.1.4.6 ENROLMENT

5.1.4.6.1 INCLUSION CRITERIA:

1. Male and female outpatients, aged 12 years or older, with a minimum body weight of 41 kg.
2. Female patients who were not at risk of pregnancy based on status of menarche or through the use of effective birth control (not including birth control pills). Female capable of bearing children required a negative β HCG at onset of the study.
3. Patients with a diagnosis of partial onset seizures, which include the subtypes of simple, complex and partial onset, seizures evolving to secondarily, generalized seizures (based on the ILAE classification, 1981).
4. Patients with 2-40 partial onset seizures per 28-day period during the 56-day Baseline Phase.
5. Patients treated with a standard AED at a therapeutic level (upper 50% of the therapeutic blood level range) for at least 56 days prior to the Double-blind Treatment Phase. For AEDs for which no therapeutic serum concentration range has been established the AED dose was to be higher than the minimally effective

dose. Patients who were receiving carbamazepine as the primary AED were to be receiving a dose of 1000 to 1800 mg/day, inclusive.
6. Patients receiving two AEDs with the second AED at less than 50% of its accepted therapeutic trough range or minimum effective dose if an effective plasma concentration was not available. [17]
7. Patients with an EEG or CCTV/EEG prior to trial entry. Any abnormalities noted should be consistent with localization-related epilepsy.
8. Patients with a previous CAT Scan or MRI that confirmed the absence of space occupying lesions or progressive neurological diseases and with no evidence from the physical exam that indicate that such processes have occurred since that imaging procedure.
9. Patients with a serum sodium level of 130 mEq/L or greater at Visit 1.
10. Patients with an ECG without significant findings during screening.

5.1.4.6.2 EXCLUSION CRITERIA

1. Nursing females.
2. Patients who did not have epilepsy, such as patients with a treatable cause of seizures (e.g., metabolic disturbance, toxic exposure, active infection, or pseudosiezures).
3. Patients with only simple partial onset seizures.
4. Patients with a documented history of generalized status epilepticus in the past three months while complying with appropriate anticonvulsant therapy.
5. Patients with seizures occurring only in clustered patterns. A cluster was defined as numerous seizures occurring over a short period of time (i.e., <30 min.). Or patients with a progressive seizure condition.
6. Patients with a history of poor AED compliance.
7. Patients who failed more than one AED that were taken at a clinically toxic dose.[18]
8. Patients currently on or with exposure to Felbatol within one month of the beginning of the 56-day Baseline Phase.
9. Patients with a significant history of medical disease within the previous two years which could impair participation in the trial or with a malignancy or history of malignancy within five years of trial entry.
10. Patients with clinically significant electrocardiographic (ECG) abnormalities.
11. Patients with a history of clinically relevant psychiatric disorder requiring electroconvulsive therapy, major tranquilizers or monoamine oxidase (MAO) inhibitors within the past six months and patients who are schizophrenic or exhibited any psychotic symptomatology (unless symptoms were isolated as post-ictal occurrences) or a history of attempted suicide.

[17] In the case where patients were receiving two anticonvulsants, the one administered at a higher relative dose was considered primary and that administered at a lower relative dose was considered secondary AED,
[18] The study objective was to examine OXC in patients with inadequately controlled seizure. It must be kept in mind that this population of seizure patients is not equivalent with a population with truly intractable seizures.

12. Patients with a history of alcohol or drug abuse during the one-year period prior to trial participation.
13. Patients taking benzodiazepines on more than an occasional basis or barbiturates at a dose of 15 mg/day or greater.
14. Patients who received an experimental drug or used an experimental device within 60 days prior to trial entry. Patients who had previously received OXC therapy.
15. Patients using dihydropyridine calcium channel blockers.
10. Patients unable to take their medication and/or unable to maintain a seizure calendar either independently or with assistance.

5.1.4.7 EFFICACY VARIABLES

5.1.4.7.1 PRIMARY ENDPOINT

The primary efficacy endpoint was the number of patients who meet exit criteria.

5.1.4.7.2 SECONDARY ENDPOINT

Time to meeting one of the exit criteria.

5.1.4.8 CONCOMITANT MEDICATIONS

Concomitant AED use was prohibited during the double-blind phase. Low dose tricyclics and SSRIs were permitted with Sponsors approval. Information about other concomitant medications or therapies were solicited and recorded at each follow up. Other excluded drugs are listed in exclusionary criteria.

5.1.4.9 REMOVAL OF PATIENT FROM STUDY

Routine criteria already noted for other studies were used.

5.1.4.10 ANALYSIS METHOD

The sample size (based on a 15% drop out rate) was selected so as to permit the analysis a 40% difference of the primary efficacy endpoint between both experimental groups with a power of 90% with a $p<0.05$ (two tailed). All analysis performed were those indicated in the original protocol. Statistical analyses were all two tailed and had to meet a p value of 0.05 to prove significance.

5.1.4.10.1 PRIMARY ENDPOINT

The primary endpoint of percent of patients meeting the exit criteria was evaluated using the Cochran-Mantel-Haenszel (CMH) test controlling for center if deemed appropriate. An additional analysis using a logistic regression model was to be performed. The model was to include treatment as a factor and center and baseline partial seizure frequency as covariates. The protocol directed principal format of this analysis was to treat dropouts as "missing." A secondary protocol driven analysis was performed that treated dropouts as either having meet exit or not meet exit criteria.

A worst case scenario analysis was added following database lock. This was performed by classifying patients who discontinued in high and low dose groups as having exited and completed, respectively. This is the most rigid type analysis of this data.

A CMH analysis was performed on groups subdivided as to whither they had a generalized seizure during a 6-month period prior to randomization. This analysis appears to be post hoc and was presumably performed to show the robust nature of the results.

5.1.4.10.2 SECONDARY ENDPOINT

The secondary efficacy endpoint, time to exit, was analyzed using the log-rank test. Kaplan-Meir survival curves were also constructed. This endpoint was additionally evaluated by Cox's Proportional Hazard regression model that examined potential factors that may contribute to outcome. All secondary analysis was on the intention-to-treat population where patents that prematurely discontinued were classified as censored observation.

5.1.4.11 STUDY CONDUCT

5.1.4.11.1 ENROLMENT

Eighty-seven patients were enrolled and randomized (41 high and 46 low dose). Of the 87 patients, 79 completed the double blind phase by meeting one of the exit criteria or receiving treatment for the duration of this phase. Six patients from the high dose group and one from the low dose group were discontinued for adverse experiences and one patient in the high dose group was removed for an abnormal lab value ($\bar{N}a^{+}$ of 121 mEq/L).

A summary of the disposition of patients is presented in Table 12 (from sponsors Exhibit 6.1.-1). All patients who prematurely left the study did so because of an adverse experience or abnormal laboratory. As might be expected, the majorities of patients who drop out were in the high dose group.

Table 12 Patiemts Accounting for Trial 028

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	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)

5.1.4.11.2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographic characteristics of the treatment groups are presented in Table 13 (from Sponsors Exhibit 7.1.-1).

Table 13 Demographics for Trial 028

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%)

Except for specific anticonvulsant use demographics were comparable between groups. Examination of the number of anticonvulsant used from the above table suggests that more patients in the low dose group were on two anticonvulsants. The number of patients on one versus two anticonvulasants can be calculated from this table and are presented below.

Table 14 Number of Baseline Anticonvulsants Used in Trial 028

	# Patients on 1 AED	# Patients on 2 AEDs	Total # Patients
2400 mg/day	37 (90 %)	4 (10%)	41 (100%)
300 mg/day	38 (83%)	8 (17%)	46 (100%)

N.B. Number in parenthesis represents the percent of patients whom were included in the particular group.

As is apparent from this table a slightly greater number of patients in the low dose group entered the study on two anticonvulsants (4 more). This may indicate a somewhat higher propensity toward seizures in the low dose group. Thus, the use of multiple, as opposed to a single, anticonvulsant may potentially be a result of an historically more intractable form of epilepsy. Moreover, although a seizure withdrawal syndrome is less likely in non-GABAergic anticonvulsants, withdrawal from two anticonvulsant would be expected to be more epileptogenic then withdrawal from one. This is particularly important in the present study considering that no attempt was made to wean patients off of the secondary AED[19], it was simply discontinued. Both these factors may bias the results in favor of a false positive conclusion. As this only involved 4 patients it likely did not have a significant effect on the interpretation of the study.

The baseline seizure frequencies are presented in Table 15 (derived from Sponsors table 7.1.-4).

Table 15 Baseline Seizure Frequency in Trial 028

	OXC 2400 mg/day	OXC 300 mg/day
Simple Partial/28 days	4.5 ± 11.6 (0.0)	1.7 ± 3.7 (0.0)
Complex partial/28 days	8.4 ± 8.7 (5.5)	8.2 ± 9.2 (5.0)
Partial 2°generalized/28 days	0.6 ± 1.8 (0.0)	0.5 ± 1.1 (0.0)
All partial seizures /28 days	13.5 ± 13.1 (10.5)	10.5 ± 9.3 (6.5)
Highest 2 day seizure frequency	4.6 ± 5.2 (3.0)	4.2 ± 3.4 (3.0)

N.B. Values are in the form of Mean ± standard deviation. Median values are noted in parenthesis.

[19] By amended protocol criteria the exposures to the secondary AEDs, however, was rather low and no secondary AED were GABAergic..

Although the Sponsor's conclude that that "frequencies experienced by patients in both OXC treatment groups were comparable during baseline phase" examination of the data suggests some degree of disparity. Median and mean seizure frequency tended to be slightly greater in the high dose group. This is most marked in "all partial" seizure frequency. This baseline disparity would have the effect of biasing against the demonstration of therapeutic effect.

A number of patients received concomitant medication during the baseline and experimental phase of the study. Excluding the aforementioned baseline anticonvulsants the vast majority of these medications were NSAIDs. There were however a variety of other medications. Among these were those that can be classified as antihistamines, antibiotics, laxatives, antihypertensives and dietary supplements. They were generally evenly divided between groups and should not influence the outcome of the present study. Two patients in each group did receive lorazepam during the double-blind phase. One of these patients, in the low dose group, received it after he had exited from the study. The remainder (2 in the high dose and 1 in the low dose group) received it on sporadic occasions during the double blind phase. This imbalance could potentially contribute seizure control in patients in the high dose group that will in turn leads to a false conclusion of efficacy. This error is mitigated by the fact that lorazepam's use was limited to a very small number of patients.

5.1.4.12 SPONSORS EFFICACY RESULTS

5.1.4.12.1 PRIMARY EFFICACY ENDPOINT:

Analysis of the primary endpoint of percent of patients meeting exit criteria, with the exclusion of patients who prematurely discontinued, revealed a significant therapeutic effect. This effect was robust and statistically significant. These conclusions were the same regardless of the method of handling the early discontinuations, including the most rigorous (i.e. "worst case scenario")." See Table 16 (derived from exhibit 8.1.-1).

Table 16 Analysis of Percent Patients Meeting Exit Criteria in Trial 028

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.

When broken down by exit criteria a substantially greater percentage patients in the 300 mg/day group meet all exit criteria except "new onset generalized seizures." In the later case only a slightly slightly greater percent of patients on high dose meet criteria as compared to low dose patients. See Table 17 (from sponsor's exhibit 8.1-2). This should allay concerns raised in other protocols of non-equivalence between exit criteria.

Table 17 Patient Exiting Broken Down by Specific Exit Criteria in Trial 028

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.

The percentage of patients exiting was always greater in the low dose group when sex, age or race broke down patients.

Perhaps because there was an equivocal effect on the exit criteria for new onset generalized seizures, the sponsors performed a subgroup analysis of number of patients meeting exit criteria in two separate groups: 1) those who experienced a generalized seizure within the last 6 months a (same time period used in the exit criteria) and those who did not. Regardless of whether patients experienced a generalized seizure in the last 6 months there was always a statistically significant greater number of patients who meet the exit criteria in the lower OXC group.[20]

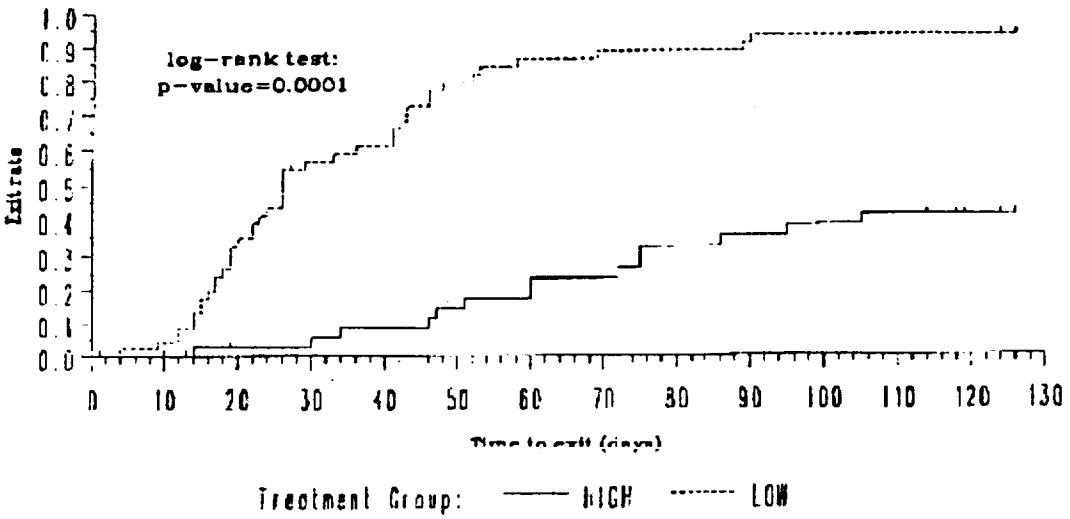
Logistic regression model analysis that examined the treatment effect, adjusting for center, age, and baseline seizure frequency still revealed therapeutic superiority of the 2,400 mg/day dose over the 300 mg/day dose ($p<0.0001$).

5.1.4.12.2 SECONDARY ENDPOINT

[20] This was true no matter what fashion premature discontinuations were handled.

Log-rank analysis on the intent to treat population revealed a statistically significant therapeutic effect in favor of the 2400 mg/day dose ($p<0.0001$). These differences between groups can be appreciated in the Kaplan-Meier survival curves that are presented in the Figure 9 (from Sponsors Figure 8.1-2).

Figure 9 Kaplan-Meier Survival Curve for Trial 028



The survival curves speaks to another issue raised by this reviewer earlier. As noted, because the period of time that qualifies patients in fulfilling exit criteria overlaps with baseline medication titration (first 42 days of the double-blind phase) it may be argued that this design does not allow a true test of monotherapeutic efficacy. The majority of patients who exited in the low dose group did so during the first 28 days. Few patients in the high dose group exited during the first 30 days period. However, following this time those who exited in the high dose group did so at a rather steady rate till the completion of the study. As can be appreciated from the slope of the survival curves, this rate was substantially less then that observed during the initial period for the low dose group. This would seem to indicate that even during the period when little or no concomitant anticonvulsant would be expected to be present that the high dose of OXC was exerting a therapeutic effect.

An additional analysis using Cox's proportional hazards confirmed the therapeutic effect ($p<0.0001$). It also revealed no effect of the explanatory variables of age, and baseline seizure frequency. This mollifies any concern there may have been regarding slight differences in baseline seizure frequencies. Sex appeared to be a factor with male patients having a 1.9 times greater chance of meeting one of the exit criteria.

5.1.4.13 ADVERSE EEFFECTS AND MEASURE EFFICACY

Of the patients who withdrew early from the study because of adverse events 6 were from the high dose and 1 was from the low dose group. The common reasons for these discontinuations were attributable to the CNS (e.g. dizziness, somnolence, headache and nausea). One patient in the high dose group withdrew because of laboratory abnormalities (low sodium). These early withdrawals should not adversely influence the study.

5.1.4.14 PK AND MEAUSURED EFFICACY

MHD concentrations were measured at various times following drug administration at various visits. As would be excepted MHD concentrations in the high dose group were approximately 6 to 11 times greater then the concentrations in the lower dose group.

5.1.4.15 PROTOCOL VIOLATIONS

There were no violations in protocol. Four patients, however, were allowed to enter the trial with monitor–approved protocol deviations. Two patients were one year younger then the lower age limit. Two were allowed in the trial even though there 28 seizure rate were greater then the upper limit; they were both randomized to the lower dose. One of these, randomized to the lower dose group, had a seizure rate 131% of upper limit and the other, randomized to the high dose group, had a seizure rate 184% of the upper limit. These factors probably did not adversely effect the study.

5.1.4.16 SPONSORS CONCLUSION

The Sponsors argue that the present study successfully demonstrated the efficacy of OXC. This was demonstrated by practically all permutations of analysis performed that examined both the primary and secondary endpoints. Differences between high and low dose groups were statistically significant and numerically robust.

The sponsors note there were no systematic extensive violation of the protocol and that baseline demographic features were comparable.

The Sponsors feel that the present study design (similar to that of 026) has many benefits that are not present in adjunctive studies including the absence of complex anticonvulsant drug interactions and the use of patient populations that are not as refractory to anticonvulsants as is frequently used in adjunctive therapy trials. The one complication in efficacy interpretation of the study design noted by the sponsors is the induction of withdrawal seizures. Thus, these studies may simply study the efficacy of the studied agent in preventing anticonvulsant withdrawal seizures and not seizures resulting from the preexisting epilepsy. Because of the relatively slow taper the sponsors do not

believe this to be a problem. There were no major or systematic deviations from the protocol.

The Sponsors concludes that this drug presents an acceptable risk/benefit profile. They conclude, "epilepsy patients previously inadequately treated on standard AED therapy can be successfully converted to OXC monotherapy."

5.1.4.17 REVIEWER'S ANALYSIS

This reviewer concurs that the present study demonstrates strong evidence for the efficacy of OXC in the treatment of seizures of partial origin. There are some factors in this study that complicate interpretation. Among these is the issue of withdrawal seizures resulting from the discontinuation of baseline AEDs. The sponsor's argument against this is cogent. Moreover, as noted elsewhere in this document, there is no definitive evidence that non-GABAergic anticonvulsants produce a withdrawal syndrome associated with seizures.

There is some reason to believe that this design is not completely optimal for concluding monotherapeutic efficacy. Thus medication was not completely discontinued till 42 days into the double blind phase. Examination of the survival curves would, however, suggest that the drug is effective following concomitant anticonvulsant washout. This issue is not as problematic as it was in study 04 where the double blind phase was of such short duration. It does however complicate interpretation..

Two factors have the potential to contribute to a false conclusion of efficacy. Thus, as described above, a greater number of patients appeared to be on multiple baseline AEDs medication in the low (n=8) as compared to the high dose group OXC (n=4). There was also a greater number of patients using intermittent benzodiazepines during the study in the high OXC (n=2) then the low OXC (n=1) dose group. Considering the robust nature of the observed effect (i.e. the degree of statistical significance) these factors become less worrisome.

5.1.4.18 SUMMARY

This sponsors presents compelling evidence in this protocol that OXC at the dose of 2400 mg/day have a beneficial therapeutic effect in the control of seizures of partial origin. While the sponsors wish to draw a conclusion as to OXC monotherapeutic effect from this protocol there were some designs flaws that complicate such an interpretation.

5.2 Adjunctive Therapy Trials

5.2.1 OT/PE1

5.2.1.1 TITLE

Multicenter, double-blind, randomized, placebo-controlled, 4-arm, parallel group trial in patients with partial seizures with and without secondary generalization on 1 to 3 concomitant antiepileptic drugs to investigate efficacy and tolerability of Trileptal (dosages 600 / 1200 / 2400 mg/day and placebo) in patients between the ages of 15 and 65.

5.2.1.2 OBJECTIVE

The primary objective was to evaluate the safety and efficacy of adjunctive OXC in the treatment of seizures of partial origin in-patients with refractory epilepsy on as much as 3 other anticonvulsants. The secondary objective was to examine PK parameters of OXC that included serum trough values and it's association to efficacy, safety and the metabolism of other anticonvulsant agents.

5.2.1.3 DESIGN

This was a multicenter (non-US multinational), double-blind, randomized, placebo-control, parallel-group trial with four arms (placebo as well as 600, 1200 and 2400 mg/day).

5.2.1.4 SCHEDULE

The trial consisted of three phases: baseline, double-blind and open-label extension phases. The schedule for these phases is presented in Figure 10 (from Sponsors Exhibit 3.1.-1).

Figure 10 Experimental Schedule for TrialOT/PE1

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

5.2.1.4.1 BASELINE PHASE

Entry criteria were evaluated at visit 1. This included the eliciting of a general medical and neurologic history and performing a general physical and neurologic exam. Routine laboratory analysis, urine pregnancy tests (where appropriate), anticonvulsant drug levels, and EKG were also obtained. Patients were maintained on their stable anticonvulsant doses. The plasma concentrations of at least one anticonvulsant were required to be within the recommended serum therapeutic range or dosage range (if no serum criteria had been established for the drug). No changes in anticonvulsant drug or dosages were permitted during this phase. Patients who were found to experience an average of 4 seizures per month documented by a seizure diary or equivalent source and fulfilling appropriate eligibility criteria (see below) were randomized on visit 3 into one of four groups: placebo, 600 mg/day, 1200 mg/day and 2400 mg/day.

5.2.1.4.2 DOUBLE-BLIND TREATMENT PHASE

This phase was divided into three periods (see Figure 10); the titration, maintenance and tapering periods. Of note, all OXC doses were administered in a BID regimen with equally divided doses. Patients were required to stay on the same dose of their baseline anticonvulsants throughout this phase.

Titration period (week 1-2): Patients randomized to the OXC group initiated treatment with 300 mg/day. Patients in all OXC groups had their dosage titrated up at the same rate over the two-week titration period. Those who had a lower target dose reached their final dose at an earlier time. Patients maintained a seizure diary throughout the titration period in which they recorded all seizures by type. Patients were monitored for adverse events and compliance during the titration phase.

Maintenance period (week 3-28): Patients who completed the titration period entered the Maintenance Period. Initially, patients unable to tolerate OXC were prematurely discontinued from the study. A later amendment (see below) allowed patients experiencing problems tolerating the 2400 mg/day dose to have their medication reduced to 1800 mg/day. These reductions were blinded so that patients who had difficulty tolerating the lower OXC doses or placebo were given a placebo reduction trial that had no effect on the true OXC dose. Throughout the maintenance phase seizures were monitored by documentation in a seizure diary. Compliance and adverse events were also monitored.

Tapering period: Except for the 600 mg/day dose group whom simply had OXC discontinued, patients in the 1200 and 2400 mg/day group had there medication tapered over a 1 and 2 week period, respectively. Patients who completed the maintenance period and elected to enter the open-label-extension phase did not enter this period.

5.2.1.4.3 OPEN-LABEL EXTENSION PHASE

The recommended starting dose for this phase was 600 mg/day but the dose could be titrated at the discretion of the investigator.

5.2.1.5 AMENDMENTS

The following amendments were added to the protocol:

1. Patients taking Felbamate were excluded when the first reports of deaths from aplastic anemia were released (this amendment was requested prior to patient randomization).
2. Patients receiving 2400 mg/day were allowed to have dose reduced to 1800 mg/day when it was discovered that large percent of patients were suffering intolerable side effects. This amendment effected 25 % of patients randomized to the high dose group.
3. This amendment was to change the informed consent so as to contain an explanation of the potential for dose reduction that is outlined in amendment 2.
4. This amendment was to extend the time period of the open label extension to allow for uninterrupted medication use till OXC was approved in one particular country.
5. This amendment was a request to alter the statistical analysis of the primary endpoint from a Poissson to a Wilcoxin rank-sum to make the analysis more consistent with similar type studies. The actual primary endpoint was altered by this amendment as well. The number of seizures observed during the maintenance period was changed to the percentage change, from baseline, in a period including both the maintenance and titration period. This analysis was similar to the only other adjunctive trial in this application, 011. This was requested because of the concern of lack of monotonicity of the dose response curve and after discussion with the FDA and implemented prior to the locking of the database.

5.2.1.6 ENROLMENT

5.2.1.6.1 INCLUSION CRITERIA

1. Male or female patients of any ethnic group aged 15 to 65 years.
2. Patients with a diagnosis of simple partial seizures and complex partial seizures with or without secondarily generalized seizures.
3. Patients currently receiving treatment with 1 to 3 AEDs with at least 4 seizures per month on the average in the 8-week period prior to entry into the Baseline Phase.

4. The dosage of concomitant AED therapy was to be kept constant for a period of at least 8 weeks prior to entry into the Baseline Phase. The plasma concentration of at least one anticonvulsant was required to be in the recommended serum levels. If no serum criteria had been established the agents must be within the recommended dosage range.

5.2.1.6.2 EXCLUSION CRITERIA

1. Pregnant or lactating women or women of childbearing potential whom were not practicing a reliable form of birth control. A positive pregnancy test.
2. Patients with seizure types other than partial seizures with or without secondarily generalized seizures.
3. Patients with a history of status epilepticus within the 24-month period prior to inclusion into the trial.
4. Patients with any progressive neurological disorders.
5. Patients with a history of clinically relevant psychiatric disorders within the 24-month period prior to inclusion into the trial.
6. Patients with a history of suicidal ideation or of attempted suicide.
7. Patients with clinically relevant abnormalities on physical examination, EKG, or laboratory evaluation.
8. Patients with any concomitant clinically relevant disorders other than epilepsy.
9. Patients with a history of malignant tumors or those with AIDS or known to be HIV positive
10. Patients with a history of alcohol and/or drug abuse.
11. Patients with a history of alcohol withdrawal convulsions.
12. Patients with plasma levels of concomitant AEDs which were above the accepted therapeutic range.
13. Patients with a history of OXC treatment prior to inclusion into the trial.
14. Patients with a history of monoamine oxidase (MAO) inhibitors treatment within a 15-day period prior to inclusion into the trial.
15. Patients with concomitant treatment of ethosuximide and felbamate
16. Patients with concomitant treatment of more than three AEDs.
17. Patients with any concomitant therapy other than AEDs, that is known to interact with OXC.
18. Patients with concomitant treatment of any investigational drug.
19. Patients with a history of participation in any clinical trials within the 3-month period prior to inclusion into the trial.
20. Patients with any disorders or conditions which, in the opinion of the investigator would preclude successful compliant participation in the study.

5.2.1.7 CONCOMITANT MEDICATIONS

Any drugs that were known to interact with OXC (birth control pills included) were not permitted. See exclusionary criteria for more details on

medications that were not permitted. Information on new drug treatment and other forms of therapy were solicited at each clinical visit.

5.2.1.8 PATIENT REMOVAL FROM STUDY:

In addition to routine criteria for removal, patients were removed from the study if they needed any alteration in anticonvulsant regimen (except for the 2400 mg/day OXC down titration) and an increase in concomitant AED plasma levels to those above the therapeutic range. All patients who received medication were included data analysis.

5.2.1.9 EFFICACY VARIABLES

5.2.1.9.1 PRIMARY ENDPOINTS

The percentage change in seizure frequency per 28 days in double blind treatment phase from baseline was the revised primary endpoint (see amendment 5). The calculations were performed in a fashion that was identical to that used for the primary endpoint of the other adjunctive study in this application, 011. The twenty-eight day seizure frequency was calculated as follows:

28-day seizure frequency = (# seizures during specified time/ # days during specified time) X 28

The calculation was determined for the 8-week baseline phase and the 26-week double-blind phase (excluding the tapering period).

The final calculation of percent change was calculated as follows:

Percent change in seizure frequency = (T-B)/B X 100

Where T= 28-day treatment seizure frequency and B=28-day baseline seizure frequency.

5.2.1.9.2 SECONDARY ENDPOINTS

There were a number of irregularities noted regarding the selection of the secondary endpoints (see below). Upon an inquiry made by this reviewer (7/13/99) the sponsors justified these irregularities by alluding to a discussion with Dr. Todd Sahlroot, statistician with the FDA, where it was "confirmed" that "all secondary variables were considered exploratory variables by both parties."

The following measurements were considered secondary endpoints in the present study:

1. 28-day seizure frequency in the Double-blind phase as defined above. This endpoint was not a part of the initial protocol nor is it mentioned in any amendment. It is an intermediate measurement that is derived in the process of the calculation of the revised primary endpoint. In response to a faxed

query (7/13/99) the sponsors note that the decision to use this was made prior to the database lock at an internal company meeting held between June and December 1996 ("Working Group Two Meeting"). Because there is no original documentation of this the endpoint it must be considered a post hoc variable.

2. Response to treatment that was defined as the number of patients whom responded with a 28-day reduction in seizure frequency (as calculated above) equal or greater then 50%. The decisions and problems regarding the choice of this endpoint are identical to the latter endpoint. Like that endpoint this endpoint should be considered to have been selected post hoc.
3. Global Assessment of Therapeutic Effect (GATE). This is a protocol driven subjective investigator assessment of drug effectiveness. It asks the investigator to quantify the response to drug on a four-point scale in terms of seizure frequency and severity from none to very good. The scale is unbalanced in that it does not allow for the contingency of an increase in seizure frequency or severity.
4. Liverpool Seizure Severity Scale (LSSS) is a protocol driven assessment which consists of a series of patient directed questions dealing with impressions of the number of major and minor seizures that he/she experienced over the last 4 weeks, associated ictal or post-ictal phenomena that may indicate "severity" (e.g. falling, incontinence etc) and his/her satisfaction with the present treatment.
5. The total number of seizures during periods used for evaluation of primary endpoints. This appeared in the original protocol as the primary endpoint.
6. Time the next epileptic event. Weighted in order of importance as follows: the 4th seizure, the first seizure, the first partial complex and first generalized. Although this appeared as a secondary endpoint in the original protocol the evaluation was never performed; no explanation is given in the original protocol. Upon inquiry (7/13/99) the sponsors note that this was dropped after discussions with Dr Sahlroot of the FDA when it was decided that this variable was neither "relevant" nor "standard" in a study like this. According to the sponsors this decision was made prior to the database lock. This reviewer agrees with this conclusion, however there is no documented explanation of this action.

5.2.1.10 ANALYSIS METHOD

The sample size was selected to detect a 25% difference between the high dose OXC group and placebo with a significance level of 0.05 at a statistical power of 0.95. This required the randomization of approximately 165 patients per group. These values were exceeded in the actual study.

5.2.1.10.1 PRIMARY ENDPOINT

The criteria for efficacy determination using the primary endpoint was based on an ITT analysis that included comparisons of high and mid dose differences with placebo through a Wilcoxon rank-sum test (two-sided). A Bonferroni test was used to correct for multiple comparisons. In this case the medication was considered effective if the mid dose and/or high dose was found effective. The sponsors note that the low dose was excluded, as there was no expectation for efficacy at this dose. The exclusion of the lower dose from analysis was described in amendment 5 (see above) that was submitted before the locking of the database but not in the original protocol. In addition to the ITT evaluation, an analysis was also performed on patients who remained in the study following visit 6 (the first day of the maintenance period)[21]. This was refereed to as a steady-state analysis. An evaluation was also performed on only those patients completing the full double-blind period.

A dose response analysis was also performed using the primary endpoint. All doses were included in this analysis. The analysis was performed without correction for multiple comparisons. This analysis was included neither in the original protocol nor in amendment 5 and can therefore be considered as post hoc.

The results were also examined with regard to demographic variables.

5.2.1.10.2 SECONDARY ENDPOINTS

1. Seizure frequency per 28 days- used multiple regression analysis and included evaluation of other potential factors that may influence seizure frequency. This analysis compares each OXC dose group to the placebo control group and does not appear to make allowances for multiple comparisons. ITT and "steady state" data sets were used in this evaluation.
2. Response to treatment (percent patients with a 50% reduction in seizures) was carried out using a logistic regression analysis and included examination of other explanatory variables. Both steady state" and ITT analysis was performed. Covariates of sex, age and country were also examined in this analysis. The analysis does not appear to make corrections for multiple comparisons.
3. The GATE scores were analyzed by comparing each dose group with the single placebo group using the Wilcoxon rank-sum test. No adjustments were made for multiple comparisons.
4. LSSS was evaluated by analysis of covariance that included analysis of not only dose and placebo but other potential factors, such as age, that may influence the results

[21] This was initially described in the experimental protocol as the principal data set for the analysis of the primary endpoint. Amendment 5 however altered this so that the ITT data set would be used for this analysis.

5.2.1.11 STUDY CONDUCT

5.2.1.11.1 ENROLMENT

Eight hundred and twenty six patients were enrolled in the baseline phase of the study. One hundred and thirty two patients did not meet criteria leaving 694 patients who were randomized.

The reasons and distributions for randomized patient withdrawal from study is presented in Table 18 (from sponsors exhibit 6.1.-1).

Table 18 Patient Accounting in Trial OT/PE1

Number of patients	OXC 600 mg/day	OXC 1200 mg/day	OXC 2400 mg/day	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[1]	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.

Noteworthy in the examination of this table is that the greatest number of dropouts occurred as a result of an adverse experience. As might be expected, this appeared dose dependent with the lowest percent in the placebo (8.7%) group and highest in the in the high dose group (66.7%). The latter rate is greater then that seen in any other pivotal study. This might not be completely unexpected. Thus, both the relatively high dose and the-add on feature of the

experimental design likely contributed to a high rate of adverse events. Although the issue of blind compromise resulting from adverse events is always present in studies like this, the rate in the high dose group of the present study is so great that it is likely to be more problematic then usual.

The second most common cause for early discontinuation was for "unsatisfactory therapeutic effect." A much smaller percent of patients dropped out for this reason (see Table 18). As may be expected for an agent with anticonvulsant activity this was greatest in the placebo and was inversely proportional to the OXC dose. Two patients who were randomized were not included in the ITT analysis because they dropped out prior to receiving a single dose of trial medication.

Premature discontinuations resulted in a substantial reduction in exposure to drug for the high dose group. The Table 19 summarizes the average exposure to OXC during the Titration and Maintenance periods (derived Sponsor's Table 6.4.-3)

Table 19 Mean OXC Exposures Times during the Titartion and Maitenetance Periods in Trial OT/PE1

	Mean (days)	Median (days)
Placebo	156	182
600 mg/day	157	182
1200 mg/day	117	181
2400 mg/day	66	18

5.2.1.11.2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Except for minor variations, age, sex and weight were evenly distributed amongst the placebo and the treatment groups. These are presented in Table 20 (from sponsor's exhibit 7.1.-1).

Table 20 Patient Demographics for Patients on Trial OT/PE1

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)

A similar percent of patients with seizure subtype diagnosis were randomized to the different experimental groups (see Table 21, derived from sponsor's table 7.1.-4).

Table 21 Seizure Diagnosis in Patients in Trial OT/PE1

	Placebo	OXC 600 mg/day	OXC 1200 mg/day	OXC 2400 mg/day
Simple partial	53.8%	52.4%	46.3%	50.6%
Complex partial	83.2%	86.9%	89.3%	84.5%
Secondary Generalized	58.4%	57.7%	63.3%	61.5%

A summary of baseline 28-day seizure frequency (inclusive of all seizures of focal origin) for the ITT data set is presented in the following table (Table 22, derived from sponsor's Table 8.1.-1). Apparent from this table is the observation that the placebo group appeared to have a somewhat lower 28-day seizure frequency. If this discrepancy would have any effect, it would be expected to cause an underestimation of the drug's therapeutic effect.

Table 22 Baseline Frequency of All Seizures of Focal Origin in Trial OT/PE1

	Mean	Median
Placebo	23.9	8.6
OXC 600 mg/day	38.5	9.6
OXC 1200 mg/day	28.2	9.8
OXC 2400 mg/day	25.0	10.0

The Sponsors point out that frequencies of seizures broken down by subtypes were also found to be "similar." Specific information on this issue, however, is only presented for secondarily generalized seizures.[22]. Thus, while a greater percent of patients on mid and high doses of OXC[23] experienced generalized seizures during the baseline phase the 28-day frequency in the placebo group tended to be higher then in the drug groups. This information is presented in Table 23. It is uncertain how this imbalance may influence the study outcome.

Table 23 Baseline Statistics on Secondarily Generalized Seizures in Trial OT/PE1

	Placebo	600 mg/day	1200 mg/day	2400 mg/day
% subjects ≥ 1 seizure (n)	29% (51)	29% (49)	38% (68)	34% (60)
Median 28-day frequency	3.5	3.5	2.0	2.4

The missing baseline information on other seizure types was supplied by the sponsors following a inquiry that was faxed on 7/13/99. The additional information is presented in Table 24 below.

[22] Breakdown intc simple partial and complex partial seizures is not presented in text, table or SAS transport files supplied by the sponsors.
[23] This statement excludes low dose OXC as this was not included the in analysis of the primary endpoint (see above).