CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-014

MEDICAL REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL EFFICACY REVIEW OF NDA

Brand Name:	**Trileptal**
Generic Name:	**Oxcarbazepine (Trileptal ™)**
Sponsor:	**Novartis**
Indication:	**Partial Seizures**
NDA Number:	**21-014**
Original Receipt Date:	**September 28, 1998**
Review Author:	**N, Hershkowitz, MD,PhD**
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1. Review Sources

1.1 Materials from NDA

Table 1: Review Sources

The following includes source documentation for the present efficacy review.

Source	Submission Date	Material
NDA Volume 146	9/25/98	Protocol 004 (monotherapy placebo control trials)
NDA Volume 152	9/25/98	Protocol 025 (monotherapy placebo control trials)
NDA Volume 167	9/25/98	Protocol 026 (monotherapy low dose control trials)
NDA Volume 169	9/25/98	Protocol 028 (monotherapy low dose control trials)
NDA Volume 250	9/25/98	Protocol 011 (adjunctive pediatric control trials)
NDA volume 260	9/25/98	Protocol OT/PE1 (adjunctive control trials)
NDA volumes 182, 201,220, 235 and 246	9/25/98	Active Control Protocols-as these are not considered as definitive a more cursory review was made.
Phone inquiry	8/31/99	Sponsor's faxed response.
Response to reviewers faxed communications	7/2/99,7/7/99, 7/16/99, 7/22/99, 7/23/99, 8/5/99, 8/9/99, 8/13/99	Sponsor's response to reviewer's post NDA submission inquires.
SAS transport Files	9/25/98	Files were contained within the CDER systems under the subdirectory directory N20399
IND Division Files	2/10/92-3/9/95	IND

2. Background

2.1 Indication

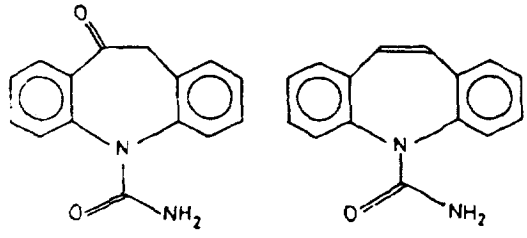
According to the labeling, Trileptal is "indicated for use

2.2 Important information from pharmacologically related agents

OXC shows a remarkable degree of structural homology to carbamazepine (see figure 1), a drug that was approved decades ago and has been found to be useful in the treatment of all varieties of partial onset seizures. This homology also extends to MHD, the principal active metabolite of OXC. MHD is a simple 10 monohydroxy derivative. Although not completely identical

the mechanistic profile of OXC and MHD appear to be rather similar to carbamazepine (Dr. Fisher's preclinical review).

Figure 1 Comparison of the structures of oxcarbazepine and carbamazepine



OXCARBAZEPINE CARBAMAZEPINE

These similarities were kept in mind throughout the review of the present application. Most interestingly, this agent appears similar, if not more potent, in producing a reversible SIADH like syndrome. This syndrome has been observed in patients on carbamazepine (see Dr. Boehm's safety review).

2.3 Administrative History

2/10/92	Submission of Trileptal IND [redacted]
3/3/92	Placed on hold because information requested regarding synthesis, stability and "color change was not provided.
2/18/93	Taken off hold because data submitted on 100 European patients attested to the relative safety of this product.
7/30/93	Request for an end of phase 2 meeting. Clinical reviewer recommended some changes in the proposed monotherapy phase 2 trials and suggested additional adjunctive studies.
11/2/94	Additional pharm/tox studies requested because of changes in the method of synthesis.
9/25/98	NDA submission.

2.4 Proposed Labeling

The sponsors make the following dosing recommendations for OXC's mono- and adjunctive therapeutic use in adults: OXC should be started at 600 mg/day (in two divided doses). The dose can be increased by 600 mg/day at weekly intervals until a desired response is achieved. The sponsors note that, while a good therapeutic response is generally seen at 600 to 2400 mg/day, a limited number of patients required up to 4200 mg/day to achieve a "maximum therapeutic effect." In cases of adjunctive therapy, concomitant anticonvulsant doses may need to be decreased or the rate of OXC increments slowed as titration progresses.

Recommendations are made for the pediatric population equal to or older then 2 years of age (sufficient data is noted to be lacking at younger ages). The recommended starting dosage in this population is 30 mg/kg/day in two divided doses with weekly increments of 10 mg/kg/day to a maximum of 42 mg/kg/day.

The only contraindication for use noted by the sponsor is known hypersensitivity to OXC or any of "its components."

Food has no effect on the absorption of OXC and therefore OXC can be taken in its presence or absence. A warning on slow withdrawal, for the prevention of "increased seizure frequency" is noted. Precautions are made for the following conditions: 1) patients who have demonstrated allergic responses to carbamazepine because of potential cross reactivity with oxcarbazepine; 2) patients on birth control pills because of potential reduction of their efficacy; 3) ingestion of alcohol because of the potential additive sedating effects. A number of "minor" drug interactions are noted in the labeling. Only a few are thought to be clinically relevant. Thus phenytoin and phenobarbital, which are strong inducers of CP450, can reduce MHD concentrations by [redacted] High doses of OXC (>1200 mg/day) may suppress phenytoin metabolism significantly so dose alteration may be required[1]. Smaller interactions with phenobarbital and carbamazepine are presented in a table.

Patients with creatanine clearance of <30 should be initiated on half the dose; patients with mild to moderate hepatic impairment generally do not need any dosage alteration.

The sponsors indicate that it is not necessary to monitor blood levels of the agent or its metabolites. Except for general recommendations to perform adjustments based on creatinine clearance, no specific recommendations are given for dosing in the elderly.

The sponsors note that generally laboratory test monitoring is not required. However, as this agent can cause some degree of hyponatremia, the sponsor believes that sodium monitoring should be considered in patients with preexisting renal conditions requiring high fluid intake, with preexisting low sodium levels (no specific value is presented), and on diuretics. The sponsors note that "sodium levels below 125mmol/L, usually asymptomatic and not requiring adjustments of therapy, have been observed in up to 2.7% of Trileptal treated patients". They suggest that aggressive treatment of hyponatremia is

[1] This is also true for other agents metabolized by the P450 isoenzyme CYP2C19. No other P450 isoenzymes exhibit any significant interactions.

generally not required and acceptable results are achieved by reduction of OXC dosage, OXC discontinuation or fluid restriction.

2.5 Foreign Marketing

Following is a list of countries that have approved the use of trileptal tablets based upon the original 1988 registration dossier and /or its 1993 update (approval date noted parenthetically): Argentina (1990, Dec 26), Austria (1992, Dec 22), Bahrain (1996, Feb 17), Belgium (1991, Oct 21), Brazil (1994, Aug 24), Bulgaria (1994, Oct 25) Chile (1996, Nov 21), China (1997, Dec. 4), Colombia (1994, Mar 14), Costa Rica (1994, Jul 4), Cyprus (1997, Jan 1), Denmark (1990, Jun 8), Dominican Republic (1995, Aug 4), Ecuador (1993, Mar 12), Egypt (1994, Sep 20), El Salvador (1994, Jun 7), Finland (1991, Apr 17), Greece (1992, Oct 27), Guatemala (1994, Apr 180, Netherlands (1991, Mar 14), Honduras (1994, Feb 25), Hong Kong (1996, Jul 10), Hungary (1998, May, 26), Iceland (1995, Jul 1), Indonesia (1996, Mar 11), Iraq (1997, Mar 20), Israel (1996, Dec 5), Italy (1994, Oct 31), Jordan (1997, Feb 12), Kuwait (1995, Oct 15), Latvia (1997), Lithuania (1994, Jun 2), Luxembourg (1992, Mar 27), Malaysia (1996, May 7), Mexico (1990, Sep 19), Nicaragua (1994, Jan 17), Panama (1994, Apr 7), Peru (1994, Nov 2), Philippines (1996, Oct 29), Poland (1997, Dec 18), Portugal (1995, Feb 21), Singapore (1995, Jun 23), Slovakia (1995, Apr 28), South Africa (1994, Mar 9), South Korea (1996, May 30), Switzerland (1994, Dec 23), Syria (1996, Aug 28), Thailand (1997, Nov 11), Turkey (1996, Jan 29), Uganda (1997, Jan 23), United Arab Emirates (1998, Feb 12), Uruguay (1992, Sep 2), Venezuela (1994, May 30), and Vietnam (1995, Jun 7).

The sponsor noted that "based on the limited data submitted in the original 1988 registration dossier, Australia (AUS), France (F), Germany (D), and Sweden (S) raised questions relating to the safety of Trileptal, which resulted in the application being withdrawn from review in these countries." The sponsor summarizes the issues as follows:

- Insufficient safety data (F, D, S)
- Hyponatremia not assessed adequately (AUS, D, S)
- Limited data on patients intolerant of carbamazepine re. allergic skin reactions (AUS, D,S)
- No information on the toxicological activity of the separate enantiomers of the 10-monohydroxy metabolite of oxcarbazepine (AUS, S)
- Insufficient toxicity data on the 10-monohydroxy metabolite of oxcarbazepine (AUS, F, D,S)
- Minimal data on the issue of tolerance development (AUS)
- Inadequate investigation of genotoxic potential (AUS, F, D, S)
- No fertility or peri/post-natal studies with the 10-monohydroxy metabolite of oxcarbazepine (AUS, S)

The sponsor notes that no reports of safety issues have been raised by health authorities and no warning letters to physicians, or major changes in marketing status have occurred since Trileptal's release into the markets of the

aforementioned countries. The only safety related change to the labeling that has occurred is a company-initiated update to include the results of carcinogenicity studies that were not available at the time of the earlier foreign approvals.

3. Chemistry, Manufacturing and Controls

See the pharmacology section and chemistries review.

4. Animal Pharmacology and Toxicology

This review briefly discusses animal data. For a more in-depth discussion please see Dr. Fisher's review. Before a discussion of the animal pharmacology and toxicology proceeds, a discussion of the differences in metabolism of oxcarbazepine (OXC) in animal and humans as well as a discussion of activity of metabolic products is warranted. The principal route of metabolism of oxcarbazepine in humans is through the reduction of the keto to a hydroxy group, forming the new compound MHD. This reduction creates a new center of chirality; the metabolism proceeds such that the S(+)/R(-) ratio of enantiomers is 4:1. OXC nearly completed metabolized to MHD in humans. In experimental animals, however, there is little reduction of OXC to MHD and MHD will rapidly be oxidized to OXC. This has required the sponsor to examine the pharmacology of both compounds. It may be argued that the sponsor should have simply switched to the development of MHD. The sponsor notes "Since the administration of OXC or MHD produced virtually identical pharmacokinetic profiles in humans, the decision was taken to continue with the development of OXC". To complicate the pharmacologic/toxicological investigation of OXC, when MHD is administered directly to a number of species of experimental animals, much of it will be rapidly converted to OXC (for specifics see Dr. Fisher's review).

4.1 Pharmacology

Basic Mechanisms: Both OXC and MHD inhibit repetitive, sodium dependent, action potential activity in isolated neuronal preparations. This property is thought to be mechanistically linked to the anticonvulsant activity of the structurally related compound carbamazepine (see Figure 1 presented earlier) as well as dilantin and lamotrogene. MHD also appears to inhibit T type calcium currents, a property that is purported to have some mechanistic relevance to anticonvulsant activity. With the exception of adenosine, OXC and MHD do not bind to common neurotransmitters NH: receptors? and neuromodulators. The actions on the adenosine site are interpreted by the sponsor as unrelated to the anticonvulsant activity but perhaps related to their psychotropic properties. The evidence for this conclusion seems insufficient, but is not pertinent to the application. Perhaps related to this, MHD has been shown

to decrease field potentials in neurons in neocortical slices. Both enantiomers of MHD reduce epileptiform activity in *in vitro* hippocampal slices exposed to penicillin. The sponsor suggests that this indicates that MHD does not need to be converted to oxcarbazepine through liver metabolism to express its anticonvulsant activity.

Animal models of epilepsy: Both OXC and MHD showed significant anticonvulsant activity in maximal electroshock rodent models (ED_{50} = 13-20 mg/kg po). Such activity correlates with partial and tonic/clonic anticonvulsant activity and is believed to indicate inhibition of seizure spread. The therapeutic index for OXC and MHD (8-16) was equivalent to and better then that observed for carbamazepine. Both OXC and MHD exhibited some activity against clonic seizures in a Metrazol model (a screening model for anti-absence activity) in mice but this activity required higher doses then that for MES and exhibited a complex U shaped dose/response curve. No activity was observed against clonic seizures in rats.

OXC and MHD were also found to exhibit some activity in less classical seizure models. Thus, OXC and MHD suppressed seizures produced by parenteral administration of picrotoxin and strychnine in mice with an ED_{50} (110-300 mg/kg po) that was approximately 10-fold greater than observed for its activity in tonic hindlimb extension in MES.

Studies have indicated little or no significant difference in the ED_{50} in anticonvulsant activity between the R(-) and S(+) enatiomers of MHD in a variety of rodent models, including MES-, PTZ-, strychnine- and picrotoxin-induced seizures.

Non-rodent animal models of epilepsy with partial seizures have also demonstrated some efficacy of OXC and MHD. Thus single-dose studies showed that OXC and MHD (50 and 100 mg/kg po, respectively) abolish the occurrence or reduce the duration and severity of induced chronic seizures in Rhesus monkeys. Studies in cats have also demonstrated some degree of activity of these agents.

4.2 Toxicology

The protocol for the synthesis of OXC and MHD was altered during the development of this product for ecological and economic reasons. The impurity profile did differ between the different processes. For this reason the sponsors report the results with the old and new syntheses (Synthesis 1 and 2, respectively) separately. All studies examining acute exposure used material derived from type 1 synthesis whereas chronic exposures used material derived from both methods.

Acute exposures with synthesis 1: The principal toxicity observed during acute exposures were referable to the CNS. The effects of po administration of OXC and MHD on general behavior, locomotor activity and coordination were examined in a variety of rodent species. Only mild effects on muscle tone were

apparent in mice administered 10mg/kg of either compound. Ataxia and increasing sedation occurred at doses of 100 mg/kg and greater with both compounds. MHD, however, appeared somewhat more potent, and also produced "rotatory convulsions" at this dose. Severe sedation, ophistonis and tonic clonic type convulsions could be observed with both compounds at dosages of 1000 mg/kg with both compounds. Mortality was apparent with MHD at 1000 mg/kg (LD_{50} = 5000) but not till 3,000 mg/kg with OXC (LD_{50}=5,000). Qualitatively similar findings were observed when OXC and MHD were examined in rats and hamsters except that these animals appeared slightly more resistant, on a mg/kg basis, to these toxicities. Similar toxicities were also observed in dogs, except vomiting, salivation and tachycardia were also noted at higher doses (1,000 mg/kg). Parenteral (iv and ip) administration resulted in similar tonicities as did oral administration except toxic potency, in mg/kg, was increased by a factor of ten and cardiac arrhythmias were now noted in dog studies with MHD. No significant gross necroscopy changes were apparent in any of these studies.

Chronic exposures with synthesis 1: Sub-chronic studies (12-13 weeks) of oral OXC (10 to 3000 mg/kg) and of MHD (200 to 2,000 mg/kg) were performed in rats. Sedation was noted in doses of 600 mg and higher for both compounds. Ataxia, increased salivation and severe sedation were noted to occur at doses ≥ 1000 mg/kg in studies with OXC. Elevations of BUN and reductions in body weight were also noted at doses of OXC greater then 600 mg/kg, whereas elevations in ALT and a mild thrombocytopenia were seen with MHD doses of 3,000 mg/kg. No treatment-related deaths occurred with either treatment. Necroscopy identified increase in the size of several organs (liver, kidneys, adrenals and thyroid), but histological examination did not reveal pathologic changes in the OXC and low dose (600 mg) MHD studies. Centrolobular hepatocellular hypertrophy occurred at all doses of MHD and scattered necrotic hepatocytes were apparent at doses of ≥600 mg/kg. Investigators attributed these changes to enzyme induction. Changes with MHD were studied following a month recovery period and all above-noted effects were partially reversible. Longer (6 month studies) were carried out that examined toxicity OXC (100 to 1,000 mg/kg) in rats. These studies demonstrated increases in alanine aminotransferase, alkaline phosphotases and BUN at all doses. Microscopic examination of kidneys revealed vacuolar epithelial degeneration in cortical tubules, hyaline droplet and cast formation among other changes at doses of ≥ 300 mg/kg. Increases in BUN, hyaline droplets were not reversible during a 4-week recovery period. A 6 month study of MHD (doses of approximately 50 to 600 mg/kg) in rats failed to demonstrate alterations in renal functions although elevations in alaninine aminotrasferase and alkaline phosphatase were noted in females at doses of ≥ 187 mg/kg. There were no drug related microscopic organ/tissue changes. There was a prolongation of thrombin time in these studies.

Three month studies examining the effects of OXC and MHD (doses of 60 to approximately 600mg/kg) were carried out on dogs. Emesis and elevation of

liver function tests were noted with MHD at doses of 600 mg/kg. Microscopic examination in MHD studies revealed reversible increase in hemosiderin laden Kupffer cells in the liver and kidneys at doses ≥200 mg/kg. MHD produced these effects as well as ataxia, salivation; reduction of food intake, emesis at doses ≥200 mg/kg. Higher doses of MHD resulted in an increase in serum NA and decrease in K and albumin. Microscopic findings at these higher doses include centolobular hepatocellualr changes, atrophic and hemorrhagic thymus. 60 mg/kg of OXC and MHD tended to be well tolerated in these studies. All changes were reversible upon recovery. Similar findings were obtained in 12-month studies examining OXC and MHD in dogs. The maximal dose studied was reduced because of the problem of maintaining chronically toxic animals for extended periods of time; i.e. 400 mg for OXC and 200 mg/kg for MHD.

Sub-chronic exposure with synthesis 2: Subchronic exposures to OXC and MHD derived through synthesis 2 had a somewhat similar spectrum of toxicities except for an apparent greater degree of toxicity observed for synthesis 2-derived compounds. Thus a significant number of rats exposed to 3,000 mg/kg OXC died during the study (1/15 males and 14/15 females). The male to female differences appeared to be a result of pharmacokinetic differences. Similar exposures to synthesis 1-derived products produced no deaths at a similar dosage; the studies appeared to differ principally in that animals studied with synthesis 2 were older (8 weeks as opposed to about 4 weeks). Similar studies examining synthesis 2 of MHD likely revealed a higher rate of deaths in rats of similar age at the highest dosage examined (2,000 mg/kg; 2/10 male and 1/10 female). Moreover, synthesis 2-derived OXC tended to have a greater degree of renal toxicity in rats with significant polydipsia, polyurea, proteinurea and microscopic nephropathy. Similar findings were not observed in studies of similar length, although more prolonged synthesis 1 studies did demonstrate evidence of nephropathy. For a more depth review of this information please refer to Dr. Fisher's review.

5. Pivotal Efficacy Trials

APPEARS THIS WAY
ON ORIGINAL

5.1 Monotherapy Trials

5.1.1 PROTOTOCOL 04

5.1.1.1 *TITLE*

Multicenter, Double-Blind, Randomized Placebo-Controlled, 2-Arm Parallel Trial of Oxcarbazepine in In-patients with Epilepsy Undergoing Evaluation for Epilepsy Surgery.

5.1.1.2 OBJECTIVES

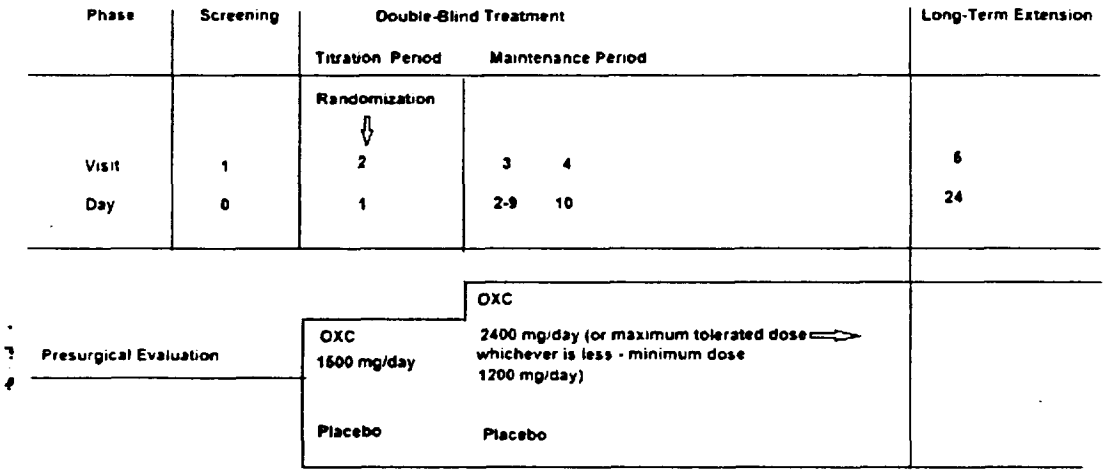
The primary objective of this trial was to evaluate the efficacy and safety of monotherapy OXC versus placebo in patients with refractory partial-onset

seizures, with or without secondarily generalized seizures, who had completed an inpatient pre-surgical diagnostic evaluation. The secondary objective was to determine the trough plasma levels of MHD and DHD and to explore their relationship to efficacy.

5.1.1.3 DESIGN and SCHEDULE

This was a multicenter, double-blind, randomized, placebo-controlled, 2-arm parallel trial of monotherapy OXC. The study was performed in a hospital setting in in-patients with partial seizures who had undergone a presurgical evaluation for epilepsy surgery. There were 3 phases in this trial: a screening phase, a double-blind treatment phase and a long-term extension phase. The study design is diagrammatically represented in figure 2 (sponsor's exhibit 3.1.-1).

Figure 2 Experimental Schedule for Trial 04



Visit 1 was for the purpose of screening and occurred 24 hours prior to randomization. Patients were randomized on visit 2 (at the start of the single day titration period). Visit 3 occurred on Days 2-10; the actual date depended upon when and whether the patient met one of the exit criteria. Visit 4 occurred the day following (or the day of) trial completion or premature discontinuation.

Hospitalized patients were eligible for randomization into the study on the single titration day (day 1) if they were off anticonvulsants, and had greater then 2 but fewer then 11 seizures during the prior 48 hours. Patients also had to fulfil all inclusion and exclusion criteria (see below). An equal number of patients were to receive placebo and OXC. Lorezapam was administered on a prn basis (1-4 mg dose up to 8 mg qD) 48 hours prior to and 18 hours after randomization. All OXC doses were administered in a BID divided regimen. A single day titration period was followed by a 9-day maintenance phase. The 1500-mg daily dosage given during titration was increased to 2400 mg/day on the first day of the maintenance period. If the patient was unable to tolerate this higher dosage, medication was reduced to 1800 or 1200 mg daily doses. Seizure count was

initiated on the day of titration (day 2) and proceeded to completion that is defined as:

1. Completion of 10 days, or
2. Experience of a fourth partial seizure, with or without secondarily generalized seizures (exclusive of seizures occurring on Day 1), or
3. Experience of two new-onset secondarily generalized seizures, if secondarily generalized seizures were not present during the one-year period prior to randomization (inclusive of secondarily generalized seizures occurring on Day 1), or
4. Experience of serial seizures or status epilepticus deemed by the investigator to require intervention

The criteria for early completion (criteria 2, 3 and 4) are somewhat arbitrary and were based upon perceived equivalencies of the seizure events and issues of patient safety. This may be problematic if the distribution of reasons for early completion is not similar between both experimental groups (see below).

Termination procedures were conducted upon completion or exit from the trial. If they desired, patients who completed the study were given an option to enter an open label long-term extension trial.

5.1.1.4 AMENDMENTS

The following amendments were added to the protocol:

1. This amendment was instituted prior to patient enrollment. It allowed participation in the trial when patients were admitted for a second presurgical evaluation if judged "medically appropriate by the physician." Other salient points of this amendment included: a) Removal of the requirement that all seizures be manifested on EEG, b) reduced the stringency of exclusionary criteria for identifying clusters, c) excluded patients who experienced only simple partial seizure.
2. This amendment was initiated prior to patient enrolment and added felbatol as an exclusionary medication. This was because of the newly described apalastic anemia seen with this agent.
3. This amendment allowed patients who had received an experimental Tc based agent (Ceretec) used in imaging of seizure foci to participate in the study.

5.1.1.5 ENROLLMENT

The trial included male and female hospitalized patients aged 12-65 with partial seizures, with or without secondarily generalized seizures.

5.1.1.5.1 KEY INCLUSION CRITERIA

1. Either sex between 12 and 65 years old.
2. Two to 10 partial seizures with or without secondary generalization during the 48 hours prior to randomization. No more than two seizures could be accompanied by secondary generalization. To exclude patients with clustering of seizures, the shortest permissible period between two consecutive seizures was 30 minutes.[2]
3. Patients, who had their AEDs withdrawn as part of their routine surgical evaluation or patients who had previously had an in-patient presurgical evaluation but required another evaluation for diagnostic or therapeutic reasons[3].
4. Adequate birth control in women of childbearing capacity (excluding birth control pills).
5. Except for clinically insignificant deviations patients must have normal chest x-ray, EKGs, and routine clinical labs.
6. No AEDs (with the exception of lorazepam) 48 hours prior to randomization.
7. Non-AED drug use needed to have prior Novartis approval and its use needed to be stable prior to randomization and during trial.[4]
8. The weaning from chronic use of barbiturates or benzodiazepines had to be completed at least 15 days prior to admission.

5.1.1.5.2 KEY EXCLUSION CRITERIA

1. History of oncological or major organ system disease.
2. Seizures due to active metabolic or neoplastic disorders, disorders of an infectious origin or other disorders that will lead to a progressive seizure disorder.
3. History of major psychiatric disease that may affect results and/or taking psychoactive medications.
4. Patients with >10 partial seizures or > 2 generalized seizures 48 hours prior to randomization.
5. Substance or ETOH abuse within the past 6 months or positive tox-screen.
6. Previous use of OXC, present use of calcium channel blockers or MAO inhibitors or use of investigational drugs within 30 days of study[3].
7. History of status epilepticus within 3 months of study.
8. Patients who, in the opinion of the investigators, were likely to have poor tolerance to oxcarbazepine or who had life-threatening experiences from previous AEDs.
9. History of noncompliance or observed inability to report seizures

[2] Amendment 1 decreased the time between two consecutive seizures (60 to 30 minutes).
[3] Added as part of amendment 1.
[4] Except Ceretec. See Amendment 3.

5.1.1.6 EFFICACY VARIABLES

5.1.1.6.1 PRIMARY ENDPOINT MEASURES:

- Time to meeting one of the exit criteria.

5.1.1.6.2 SECONDARY ENDPOINT MEASURES:

- Percentage of patients meeting exit criteria. Four methods were used to evaluate patients who prematurely left study. The most stringent was the "worst case scenario" that categorized patients who prematurely left the study in the placebo group as completors and in the OXC group as having exited.
- Total partial seizure frequency during the 9-day maintenance phase.
- Total generalized seizures during the maintenance phase. This endpoint was not included in the original protocol nor was it part of any amendment. It may therefore be considered post hoc.

5.1.1.7 ANALYSIS METHOD

The sample size of each treatment group, 47, was calculated based on the requirement of the detection of a 30 % difference between treatment for the secondary objective of percentage of patients meeting exit criteria. The predetermined p value of <0.05 (two tailed) was established as the criteria for efficacy. Two separate analyses were carried out 1) Intent to treat (ITT); 2) Only patients who completed the study.

All analysis were planned and specified in the protocol with the exception of the secondary outcome measure of total generalized seizures.

5.1.1.7.1 PRIMARY ENDPOINT

The primary efficacy variable, time to exit, was analyzed using the log-rank test. Kaplan-Meier survival curves were also computed. A secondary statistical analysis was performed with Cox's proportional hazards regression model: covariants in this model included treatment, center, sex, age and total partial frequency during 48 hours prior to randomization. These analyses were based on intent to treat with dropouts treated as censored observation.

5.1.1.7.2 SECONDARY ENDPOINT

- Percentage of patients meeting exit criteria was analyzed by the Cochran-Mantel-Haenszel (CMH) test for center. As noted above, four separate

analyses for different ways of handling premature discontinuations in the intent to treat analysis were considered and performed. However as the "worst case" scenario analysis (see below) was the most conservative the other analysis were not considered if this showed significance in favor of OXC.

- The total partial seizure frequency per nine days was analyzed with the Wilcoxon rank sum test. This was calculated as:
  =(total seizures during maintenance)/days in maintenance X 9
  This analysis was performed on both an intent-to-treat basis and with dropouts excluded.
- Total secondary generalized seizures frequency was analyzed according to the methods used in the analysis of partial seizures. This post hoc analysis was performed on intent-to-treat patients who suffered secondary generalized seizures during the 48-hour baseline as well as those who did not experience such seizures.

5.1.1.8 STUDY CONDUCT:

5.1.1.8.1 ENROLLMENT

A total of 102 patients were randomized in 10 centers. Table 2 (derived from sponsors Exhibit 6.1.-1)summarizes the fate of the patients randomized for efficacy evaluation.

Table 2 Patients accounting for Trial 04

Number of patients	OXC	Placebo	Total
Randomized	51	51	102
Completed	46	49	97
Met predefined exit criteria*	21	43	64
Completed 10-day period	27	6	33
Discontinued prematurely			
Total	3	2	5
For Adverse experience	2	0	2
For Administrative Reasons	1	2	3
Efficacy Analysis			
Intent-To-Treat Analysis	51	51	102

Few subjects were discontinued for administrative reasons or adverse experience. These few discontinuations were included in a worst case scenario

analysis, as previously noted, allowing intent to treat analysis on all patients entered into the study.

5.1.1.8.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The general demographic profile characteristics of the drug and placebo group is presented in Table 3 (derived from Exhibit 7.1.-1 of sponsor).

Table 3 Patient demographics for Trial 04

Characteristic	Oxcarbazepine (N = 51)	Placebo (N = 51)	Total (N = 102)
Age (yr)			
Mean (Range)	33.1 (11.0-61.0)	33.7 (14.0-62.0)	33.4 (11.0-62.0)
Weight (kg)			
Mean (Range)	78.7 (35.0-110.9)	77.7 (47.5-144.5)	78.2 (35.0-144.5)
Sex			
Male (%)	31 (60.8%)	25 (49.0%)	56 (54.9%)
Female (%)	20 (39.2%)	26 (51.0%)	46 (45.1%)
Race			
White (%)	41 (80.4%)	40 (78.4%)	81 (79.4%)
Other (%)	10 (19.6%)	11 (21.6%)	21 (20.6%)
Total partial seizure frequency*			
Mean (Range)	4.9 (2.0-19.0)	4.4 (2.0-11.0)	4.6 (2.0-19.0)
Initial use of lorazepam**			
No (%)	6 (11.7%)	4 (7.8%)	10 (9.8%)
Yes (%)	45 (88.3%)	47 (92.2%)	92 (90.2%)

* During the 48 hours prior to randomization
** During the 48 hours before and the 18 hours after randomization

Except for the over representation of males in the drug group, there appeared to be no ostensible differences between demographics of both groups. A statistical comparison, however, was not performed.

5.1.1.8.3 SEIZURE HISTORY

As noted above (see table 3), the total number of partial seizures was quite similar between groups when measured during the 48 hours prior to randomization. A greater percent of patients experienced secondarily generalized seizures in the OXC group (43%) than the placebo group (37 %). No statistical comparisons were carried out on these values.

5.1.1.8.4 CONCOMITANT MEDICATIONS

Although this study is ostensibly designed to evaluate monotherapy, a number of issues should be raised regarding potential design flaws that may complicate data interpretation. Examination of the study reveals that greater than 95% of patients were on anticonvulsant medications at the time of visit 1 (48 hours prior to randomization). See Table 4 (derived from sponsor's Table 7.2.-2).This raises the issue as to whether this is truly a monotherapeutic challenge: some degree of medication will still be present in the serum during the experimental phase of the study.

Table 4 Anticonvulsants Received 48 Hours Prior to Trial 04 Randomization

	OXC	Placebo
Carbamazepine	30 (58%)	30 (58%)
Gabapentine	23 (45 %)	15 (29%)
Phenytoin	15 (29%)	20 (39%)
Lamotrigine	9 (18%)	13 (26%)
Felbatol	1 (2%)	0 (0%)
Valproic Acid	16 (32%)	11 (22%)

Note: Values presented as number of patients with percent of total experimental group presented parenthetically.

This is particularly troublesome in those patients who were discontinued from drugs that exhibited a relatively long $T_{1/2}$ such as phenytoin and lamotrigine (see Table 4). Furthermore, a greater number of placebo patients received these long lasting anticonvulsants; this might have the effect of biasing the results away from the demonstration of therapeutic efficacy. Of minor concern, examination of concomitant medications used following randomization (after visit 2) revealed one patient was on carbamazepine. This would appear to be a violation in the protocol, although none were noted. Although these issues are notable they do not fatally flaw the study.

5.1.1.8.5 PROTOCOL VIOLATIONS

The sponsor notes that no patients were discontinued due to protocol violations.

5.1.1.8.6 PROTOCOL IRREGULARITIES

There were some deviations in the protocol that the sponsor did not describe as violations. No deviation was considered by the sponsor to significantly affect the study outcome. The deviations are as follows:

- Some patients were allowed to enter with monitor-approved deviations including co-medications for stable conditions, epilepsy associated with a

non-progressive cerebral "situation" (e.g. cyst, "lesion"), no recent CAT scan if disease was stable, minor seizure clustering and primary generalized seizures (interpreted as complex partial with rapid generalization).

- A small number of deviations occurred without monitor approval including 48-hour seizure counts >10, one patient with chronic lorezepam use, one patient with only simple partial seizures, some patients having been given greater than 8 mg/24 hour of lorezepam.

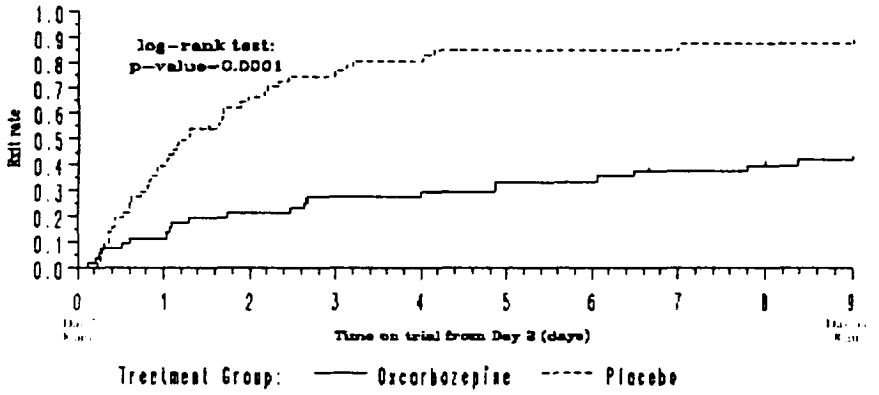
5.1.1.9 SPONSORS EFFICACY RESULTS:

The study was designed so as to allow patients to be weaned down to lower doses if they so required. Of the 51 patients in the OXC group, 5 required a wean to 1800 mg/day and 2 required a wean to 1200 mg/day.

5.1.1.9.1 PRIMARY EFFICACY MEASURES

Survival analysis of data, as described in the primary objective, using Kaplan-Meier event-rates, with dropouts treated as censored observations, is presented in fig 3 (sponsors exhibit 8.1.-1). Log-rank test revealed statistical significance between the two groups (p=0.0001).

Figure 3 Kaplan-Meier Survival Curves for Trial 04



An additional analysis using Cox's proportional hazards (PH) regression model that adjusts for the effect of the explanatory variables including: center, age, sex, and partial seizure frequency during the 48 hours prior to randomization for the intent-to-treat patients still revealed significance between treatment and placebo groups. Few patients were discontinued because of adverse events or administrative reasons (see table 2). Because of this and the fact that they were

well distributed across control and placebo groups these discontinuations likely did not complicate therapeutic measures. Secondary analysis, using a worst case scenario, confirmed conclusions from this analysis (see below).

5.1.1.9.2 SECONDARY EFFICACY MEASURES

Percent of patients meeting exit criteria: The Cochran-Mantel-Haenszel was performed on the percentage of patients meeting one of the exit criteria under the "worst-case" scenario. This analysis revealed that the percentage of patients meeting one of the exit criteria was statistically significantly lower ($p < 0.0001$) for the OXC-treated group (24/51; 47.1%) than for the placebo-treated group (43/51; 84.3%). All of the OXC-treated patients, who met one of the exit criteria, exited due to experiencing their fourth partial seizure. Of the placebo-treated patients, 39/51 (76.5%) exited due to experiencing their fourth partial seizure, 1/51 (2.0%) exited due to experiencing two new-onset secondarily generalized seizures, and 3/51 (5.9%) exited due to experiencing serial seizures or status epilepticus. As exit criteria are somewhat arbitrary it would give us comfort if the distributions of reasons for early completion are similar between both experimental groups. Although not identical these values were close. Thus all patients in the OXC group who meet the criteria for early completion did so because of a fourth seizure (21 of 21 patients) while 39 of 43 patients in the placebo group completed for this same reason.

Analysis revealed that on Day 2, first day of titration, only 6/48 (12.5%) of the OXC-treated patients had exited the trial while 20/49 (40.8%) of the placebo-treated patients had exited the trial. This indicates somewhat surprising rapid effect. Pharmacokinetic studies however support this data by demonstrating that plateau serum MHD concentrations are achieved after only 2-3 days following the initiation of dosage.

Total partial seizure frequency per nine-days: An ITT evaluation of the differences in total partial seizure frequency demonstrated a statistically significance therapeutic benefit in the OXC group as measured by Wilcox Rank-Sum test.

Total secondary generalized seizure frequency per nine day: Analysis of generalized seizures was not a part of the original protocol and appears to have been added post hoc. Because of this, such an analysis must be viewed with caution. Analysis of all intent to treat patients revealed that during treatment phase a greater fraction of patients receiving placebo experienced secondarily generalized seizures (24/51) as compared to the OXC treatment group (4/51). Statistical analysis of the total frequency per nine days in the ITT population revealed the placebo group (1.10) to be significantly greater then drug treatment group (0.48).

Attesting to the baseline equivalence of these groups a similar percent of patients experience "secondarily generalized seizures " during a 48 hour time period prior to randomization (Placebo=67% and OXC 56%). When an identical analysis was performed on patients grouped by whether they experienced

seizures during the baseline phase a similar statistically significant difference was observed between OXC and placebo groups.

The analysis, that the FDA has requested in the past for a claim on partial secondary generalized seizures, of the difference of percent of focal seizures going on to secondary generalization was not carried out.

It is noteworthy that in a number of patients there was no record of an obvious focal seizure preceding the generalization. These were allowed into the study and counted as a secondary generalized seizure under the assumption that this event represented very rapid generalization.

5.1.1.10 *PHARMACOKINETICS*

Pharmacokinetic evaluations that were carried out by the measurement of daily trough serum MHD measures demonstrated that steady state was achieved rapidly following one day of titration and two days of maintenance dosing. OXC appears to not have been measured; the presumption being that little would be present as metabolism into MHD would be. The mean steady state MHD concentration (±SD) during the plateau was 106 (±26.2) μM/L. There was no apparent difference between the mean steady state serum level of completors and those who meet exit criteria prior to completion. Scatergram analysis (including control and placebo groups) of day 2 trough levels and time to meet exit criteria did not reveal any relationship. Similar analysis of day 4 levels did reveal some degree of correlation. The analysis appears descriptive; no r-value or other statistic is given. While an association between therapeutic level and seizure control would have been supportive of efficacy it's absence does not detract from the conclusion of efficacy.

5.1.1.11 SPONSORS CONCLUSIONS:

The sponsors believe that the present study demonstrates Trileptal efficacy as a monotherpeutic agent in the treatment of seizure of partial origin (simple partial, complex partial and secondarily generalized). They support this conclusion by the finding that all primary and secondary measures of efficacy proved to show statistical superiority of OXC over Placebo. The sponsors also point out that the data in this study appears to suggest that OXC may have some therapeutic effect on "secondarily generalized seizures." They rightfully, however, do not state that a claim for secondary generalized seizure can be made based upon this study nor is such a specific claim included in drug labeling

5.1.1.12 REVIEWERS ANALYSIS

This reviewer agrees with the sponsor that the present study supports the claim for the efficacy of OXC in the treatment of seizures of partial origin. The

principal endpoint was appropriate and there were not sufficient deviations from the original protocol to cause concern. The principal concern this reviewer has, however, is as to whether the design of this study was rigid enough to allow for the conclusion of this agent's efficacy in monotherapy. As noted above, at least a majority of patients had their anticonvulsant treatment discontinued at approximately 48 hours prior to the maintenance period and in at least 30% of patients (and maybe higher) the discontinued medications had a relatively long half life. Thus, the average half-life for phenytoin and lamotrigin are 22 and 25 hours, respectively.[5] A measurable, albeit subtherapeutic, amount of medication would be expected to be present when the study starts. This issue may have been made moot had serum levels of discontinued medications been measured during the double-blind phase. It, however, may be argued that the ability of the OXC to maintain a low rate of patents meeting exit criteria later (when serum anticonvulsant levels would be expected to be very low) in the study indicates monotherapeutic efficacy.

The present study was of a very short duration. Some agents, such as diazepam, are perceived to function as an excellent anticonvulsant on short term but not long term basis because of tachyphylaxis. Conclusions drawn from this study can therefore only be applied to short term treatment.

A general issue that should be addressed in this and other monotherapy trials is the question how seizures resulting from anticonvulsant withdrawal may complicate interpretation. There is little doubt that seizures can result, even in non-epileptic individuals, from abrupt withdrawal of GABAergic mediated agents such as barbiturates and benzodiazepines. Because of this the sponsor has required that patients must be weaned of off these agents 15 days prior to hospital admission. There is some debate as to whether withdrawal from other anticonvulsants can cause a syndrome of withdrawal associated with seizures. Thus, in a series of prospective studies, Trimble and colleagues could not find convincing evidence for withdrawal seizures when "non-GABAergic anticonvulsants" were discontinued in epilepsy patients[6]. These studies somewhat mitigates but does not remove the concern on the issue of withdrawal seizures. This is of particular concern when the rather abrupt nature of anticonvulsant withdrawal is considered. Thus, studies in the literature examine rapid wean whereas the present study is more of an abrupt withdrawal.

Although the sponsor does not argue that analysis of generalized seizures indicated definitive proof of efficacy they seem to argue this data is supportive. There are a number of issues that should raise some degree of caution in the interpretation of this data. First and foremost the analysis of generalized seizures was established post hoc. Another important issue is the fact that this division has argued that to demonstrate activity against partial secondary generalized seizures it is required to show that the percent of partial seizures that progress to generalization is reduced. Lastly, the data were analyzed under the

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[5] Physicians' Desk Reference, Published by Medical Economics Co. 1999.

[6] Duncan JS, Shorvon SD and Trimble, MR, Epilpesia 31:324-333, 1990 , J Neurol Neursurg Psychiatry 51: 924-928, 1988. Drugs examined included dilantin, carbamazepine and valproic acid.

assumption that a tonic clonic generalized seizure, whether or not it is clinically preceded by a focal seizure, in patients with focal epilepsy is assumed to be secondarily generalized. The FDA has contested this assumption in the past. At best this data can only act as supportive evidence for the claim of the efficacy of Trileptal secondarily generalized seizures.

5.1.1.13 SUMMARY:

The present study has demonstrated a statistically significant therapeutic effect of OXC at a dose of at least 2400 mg/day for seizures of partial origin. This effect is somewhat obscured by issues of drug withdrawal. There is some question as to whither the experimental design is optimal for the drawing of a conclusion regarding monotherapy. For this reason this study must be considered as supportive and not *prima facie evidence* in the demonstration of mono-therapeutic efficacy of OXC. Because of the brief duration of the present study, therapeutic conclusions can only be applied to short term anticonvulsant treatment.

5.1.2 PROTOCOL 025

5.1.2.1 *OBJECTIVES:*

According to the sponsors "the primary objective of this trial was to evaluate the safety and efficacy of OXC monotherapy relative to placebo in untreated patients with recent-onset partial seizures which include the subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures."

5.1.2.2 *DESIGN:*

This was a multicenter, randomized, double-blind, placebo-control, parallel-group trial that studied single dose OXC monotherapy (1200 mg/day) in patients who were not currently receiving AED therapy for their partial seizures (simple, complex and secondarily generalized). The trial was divided into three phases (baseline, double-blind treatment and open-label extension) with efficacy evaluation limited to data obtained from the first two phases. Figure 5 (derived from Sponsors Exhibit 3.1.-1) presents a summary of the trial design for the first two phases.

Figure 4 Experimental Schedule for Trial 025

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

5.1.2.3 SCHEDULE:

5.1.2.3.1 BASELINE PHASE (DAY –56 TO –1):

A single visit occurred during this phase (day 0, visit 1). This visit occurred within 7 days before randomization. Patients were required to have not received AED treatment for at least 90 days. These patients were also required to have experienced at least 2 seizures per month during the prior 56 day baseline period. Portions of this phase were retrospective; i.e. all that was required during this time was a documented record of seizure occurrence. This documentation was through "source records". Entry criteria were assessed (see inclusion and exclusion criteria) and screening evaluations and laboratory testing was performed on visit 1.

5.1.2.3.2 DOUBLE-BLIND TREATMENT PHASE (DAYS 0-91):

Titration period: Patients who meet eligibility criteria were randomized on visit 2 to treatment with OXC 1200 mg/day (600 mg BID) or Placebo and entered into the 7-day titration period. Seizure diaries were distributed during this visit and patients were instructed in their use. Evaluations and necessary laboratories were also obtained at this time. Patients randomized to the OXC group was started on a dose of 300 mg BID (600 mg/day) and increased by 150 BID (300 mg/day) every third day till the final dosage of 600 mg BID was achieved. The latter dosage was maintained throughout the remainder of the phase. Patients randomized to the placebo received matching inactive tablets.

Maintenance period: Patients who completed the 6-day titration period entered an 84-day Maintenance period. Patients unable to tolerate 1200 mg/day of OXC (or Placebo) were allowed to have their dose decreased to 900 mg/day (or equivalent placebo formulation). Seizure diaries, adverse events, laboratory, pharmacokinetic and physical evaluations were made at each subsequent visit during the Maintenance Period. No concomitant AEDs were allowed in this study.

According to the protocol, patients completing the 90-day double-blind phase may enroll in the long-term extension trial. This appeared to result in some degree of confusion and required the distribution of a letter of clarification. The sponsor states that it was their intention (as described in response to an inquiry made by me on 6/7/99) to allow certain patients to enter the extension trial at the time that they meet protocol exit criteria. According to the distributed letter while patients "who meet the primary efficacy variable ...should stay in the core trial...patients who cannot (stay in the trial) may be allowed to enter the long-term extension phase."

Patients were permitted to withdraw from the study if the patient or the investigator deemed it necessary, patient experienced an intolerable event, there was a major trial violation or the patient developed an exclusionary criterion.

5.1.2.4 AMENDMENTS:

Although there were no amendments a letter was distributed to the investigators, as described above, to clarify issues of admission into the open label extension phase.

5.1.2.5 *ENROLLMENT:*

Deviations from the following criteria were allowed if pre-approval by the sponsor's medical monitor was obtained.

5.1.2.5.1 KEY INCLUSION CRITERIA:

1. Male and female outpatients, aged 10 years or older, with a minimum body weight of 32 kg (70 lbs.) and residing in a well-controlled environment.
2. Female patients who were not at risk of pregnancy based on status of menarche or the use of effective birth control (not including birth control pills) and with a negative β HCG at onset of the study.
3. Patients with a diagnosis of partial seizures, which include the subtypes of simple, complex or partial seizures evolving to secondarily generalized seizures (based upon the 1981 ILAE classification scheme).
4. Patients with the onset of partial seizures within the previous 2 years and experiencing at least 2 partial seizures per month during the 56-day Baseline Phase. These patients also had to be seizure-free for at least 1 year without therapy prior to the current seizure "onset."
6. Any observed abnormalities observed on EEG or video/EEG during the Baseline Phase, must be consistent with focal epilepsy.
7. Previous CAT scan or MRI was required to confirm the absence of a space-occupying lesions or progressive neurological diseases. The absence of other physical stigmata that would indicate such progressive disease was also required.
8. Patients with serum sodium level ≥130 m Eq/L.

5.1.2.5.2 KEY EXCLUSION CRITERIA:

1. Patients with seizures of psychogenic origin or resulting from a treatable etiology (e.g. metabolic disturbance, toxic exposure, active infection or neoplasm).

2. Patients with generalized status epilepticus in the past 6 months while complying with appropriate anticonvulsant therapy
3. Patients experiencing seizures occurring only in clustered patterns defined as numerous seizures occurring over a short period of time (i.e., < 30 min).
4. Patients receiving standard AED(s) within 90 days prior to randomization.
5. Patients with a history of poor compliance with AED therapy.
6. Patients with a significant history of medical disease within the previous 2 years or malignancy within the past 5 years.
7. Patients with clinically significant EKG abnormalities.
8. Patients with a history of suicide attempt or history of clinically relevant psychiatric or mood disorders (DSM-IV) within the past 6 months requiring electroconvulsive therapy or chronic medication.
9. Patients with a history of alcohol or drug abuse during the 1-year period prior to trial participation.
10. Patients who received an experimental drug or used an experimental device within the 60-day period preceding the 56-day Baseline Phase.
11. Patients who used benzodiazepines on more than an occasional basis.
12. Patients (and/or patient's parents/guardians) who are unable to comply with the regimen or maintain a seizure calendar.

5.1.2.6 EFFICACY VARIABLES:

5.1.2.6.1 PRIMARY OUTCOME MEASURES:

- Time to first seizure (of partial onset) from the first dose of medication (titration period included).

5.1.2.6.2 SECONDARY OUTCOME MEASURES:

- Number of seizures per 28-days (seizure frequency).
- Percentage of seizure free patients during the double-blind treatment phase.

5.1.2.7 ANALYSIS METHOD:

A total of 64 (32 per arm) patients were required for the study; this was derived from calculations based upon a power of 0.85 and a $p \leq 0.05$. All analysis was performed on the intent-to-treat population (unless otherwise noted) All analysis was preplanned with one important exception. One patient (Green 101/509) entered the study with an exceptionally high baseline seizure frequency (220.6 / 28-days). To deal with this exceptional outlier, the sponsors also performed analysis excluding this patient. This decision was made prior to unblinding.

5.1.2.7.1 PRIMARY ENDPOINT:

The primary efficacy measure was evaluated by log-rank test with the construction of Kaplan-Meir survival curves. A secondary evaluation of this variable was performed using Cox's proportional hazard with baseline seizure frequency as an explanatory variable.

5.1.2.7.2 SECONDARY ENDPOINT:

Number of seizures per 28 days: This secondary endpoint was calculated in the following manner:

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[7]:

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

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
= (# of partial seizure during baseline phase / # of days of this phase) X 28.
N.B. Partial seizure are counted as all partial seizures; i.e. = simple partial + complex partial + partial secondarily generalized.

The protocol directed primary analysis was to be an analysis of covariance (ANCOVA). However the protocol specified the use of the Wilcoxon rank-sum based on the contingency of non-normality. As normality was not encountered in residuals from the model the Wilcoxoxin rank-sum test was used. According to protocol, this analysis was to be performed on the ITT data set. Two additional data sets were evaluated post-hoc. These included patients who completed the double blind phase and "patients who had at least a 28 days of seizure diary." The sponsors also note in the original protocol that a "secondary" evaluation of these data was to be performed using a Poisson regression model.

Percentage of seizure free patients: The secondary variable of percentage of seizure free patients was analyzed using the Cochran-Mantel-Haenszel test. As per protocol, the test was performed with two ways of handling dropouts; i.e. they will be considered seizure free or considered to have had seizures. A third method of handling dropouts was added after unblinding; i.e. they would be considered as missing.

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

5.1.2.8 STUDY CONDUCT:

5.1.2.8.1 ENROLLMENT:

Sixty-seven patients were randomized (32 OXC and 35 placebo) all of whom were included in the ITT data set.

5.1.2.8.2 DISPOSITION:

A breakdown of the patients disposition during the double-blind phase is presented in Table 5 (derived from sponsor's exhibit 6.1-.1). A greater number of patients in the OXC then placebo treatment group discontinued the study prematurely (compare 10 to 4). Patients who discontinued the study did so for a variety of reasons (see Table 6, from sponsors Table 6.1.-3). These discontinuations included patients who were discontinued either before or after their first seizure during the double-blind phase. Because of irregularities in this protocol (see below) the primary efficacy endpoint is likely the sole important measure in this protocol. The more pertinent number would then be dropouts prior to the first seizure as all primary endpoint data collection ceases following the achievement of this first endpoint. These values are not identified in the report but can be calculated form Table 5 and are 4 and 1 premature discontinuations for patients prior to their first seizure in the OXC and placebo group, respectively.

Table 5 Patient Accounting for Trial 025

Number of patients	OXC	Placebo	Total
Randomized	32	35	67
Completed Double-blind Treatment Phase (Visit 6)	17	18	35
Entered Open-label Extension Phase before completing Visit 6	5	13	18
Discontinued prematurely post randomization			
Total	10	4	14
For adverse experience	3	2	5
Other	7	2	9
Efficacy analyses (intent-to-treat)	32	35	67
Had their first seizure	21	30	51
Completed Visit 6 without a seizure	7	4	11
Safety analyses			
Laboratory tests	32	35	67
Adverse experiences	32	35	67
Pharmacokinetics	24	34	58

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

Table 6 Reasons for Post-randomization Discontinuation in Trial 025

	OXC(N=32)	Placebo(N=35)
Reasons		
Adverse experience	3 (9.4%)	2 (5.7%)
Does not meet protocol criteria	1 (3.1%)	0 (0.0%)
Patient non-compliance	1 (3.1%)	1 (2.9%)
Patient withdrew consent	2 (6.3%)	1 (2.9%)
Lost to follow-up	1 (3.1%)	0 (0.0%)
Administrative problems	2 (6.3%)	0 (0.0%)
Total discontinued	10 (31.3%)	4 (11.4%)

A number of patients left the study to enter the open-label extension study following their first seizure and before completing the full 91 day phase. Evaluation of the data revealed that higher percents of eligible patients[8] in the placebo group were allowed to exit the double-blind phase to be entered in the open label phase. Thus, 43 % of eligible placebo (30 patients) and 24 % of eligible OXC patients (21 patients) entered the open-label following their first seizure. This may influence the outcome the secondary endpoint frequency because of the large numbers of patients who left early and the disparity between groups. Although it is difficult to definitively predict what sign this effect will take this reviewer believes it may potentially lead to an overestimation of the double blind placebo frequency with a resulting overestimation of drug efficacy. If one assumes that seizures are of constant frequency[9] removal of patients from evaluation following their first seizure may result in an overestimation of that patients actual seizure frequency. As a greater percent of eligible patients in the

[8] This was calculated from the data in sponsors Table 6.1.-3 as follows:

= exited/total X 100

Where:
Exited = number of patients in a particular group with a single seizure who "prematurely" entered the open label phase.
Total = total number of patients in that particular group who had at least one seizure.

[9] This is not a completely justifiable assumption as seizures can be cyclical. Depending upon the period of such cyclical behavior the opposite conclusions might be drawn.

placebo group were routed for early discontinuation the seizure frequency of this whole group may have been overestimated. Because of this frequency should not be included as part of the evaluation of this drugs therapeutic effect.

5.1.2.8.3 DEMOGRAPHIC AND BASELINE CHARACTERISTICS:

The demographic profile of the study population is presented in Table 7 (from Sponsors 7.1-.1). Analysis by the sponsor revealed no significant difference ($p < 0.05$) between placebo and OXC with regard to sex, age and race. Evaluation of weight differences was not performed but it is doubtful that any differences in the samples would effect conclusions.

Table 7 Patient Demographics for Trial 025

Characteristic	OXC (N=32)	Placebo (N=35)	Total (N=67)
Sex			
Male	16 (50.0%)	17 (48.6%)	33 (49.3%)
Female	16 (50.0%)	18 (51.4%)	34 (50.7%)
Race			
White	31 (96.9%)	30 (85.7%)	61 (91.0%)
Other	1 (3.1%)	5 (14.3%)	6 (9.0%)
years)			
Mean ± SD (Range)	32.7 ± 15.6 (8.0-63.0)	36.5 ± 14.7 (10.0-69.0)	34.7 ± 15.2 (8.0-69.0)
Weight (kg) at Visit 1			
Mean ± SD (Range)	69.4 ± 16.9 (26.3-103.0)	76.1 ± 22.6 (42.2-119.0)	72.9 ± 20.2 (26.3-119.0)

5.1.2.8.4 BASELINE PHASE COMPARABILITY:

Table 8 presents median baseline seizure frequency for the OXC and placebo groups. These values are broken down in a number of fashions (see Table).

Table 8 Median Seizure Frequency during Baseline Phase for Trial 025

Treatment	OXC (N=32)	Placebo (N=35)
Median (range) of total seizure frequency per 28 days	5.0	5.5
Median (range) of simple partial seizure frequency per 28 days	0.0	1.0
Median (range) of complex partial seizure frequency per 28 days	3.2	2.5
Median (range) of secondary generalized partial seizure frequency per 28 days	0.0	0.0

Examination of the breakdown of seizures of partial origin reveals that there is a small discrepancy in the frequencies of simple partial and complex partial seizures. There appears to be a substantially greater frequency of simple partial and somewhat lower frequency of complex partial seizures in the Placebo group. This problem of the frequencies of one subtype of seizure being somewhat different between two groups would indicate non-comparability between both groups but will it effect results of the study? Certainly if the study design was comparing active controls this would be a factor; i.e. simple partial tend to be more easily controlled then partial complex. This study is a placebo control comparison and this question would have to remain open.

5.1.2.8.5 CONCOMITANT MEDICATIONS:

As noted above concomitant AEDs are not permitted in this study. Seventy six percent of patients were on other medications. These included a variety of antihypertensives, NISAIDs, antidepressants and multivitamins. There are isolated cases of the use of medications that could potentially act as anticonvulants. These cases included the following cases: 2 patients receiving lorazepam, 1 patient receiving clonezapam, 2 patients receiving chloral hydrate. Most patents receiving such medication were in the placebo group and therefore any effect these small deviations may have had should result in an underestimation of OXC's anticonvulsant activity.

5.1.2.8.6 PROTOCOL VIOLATIONS AND OTHER ADMINISTRATIVE ISSUES:

One patient was withdrawn as result of a discovered pregnancy (Hasegawa 105/609). Although the initial β HCG was negative this patient was noted to have missed her next menstrual period and subsequent analysis was positive. One patient (also in the Hasegawa center) received medication on third visit meant for another patient and was subsequently withdrawn from the

experimental stage. As noted above Novartes quality assurance team identified that the study center Hasegawa/M0274P deviated from the standard for good clinical practice criteria; efficacy data was reanalyzed (see below) without its inclusion. Two patients, age 8 and 9, were allowed to enter the study even though they were younger then the protocol the age criteria.

5.1.2.8.7 PATIENT WHO HAD BLIND BROKEN:

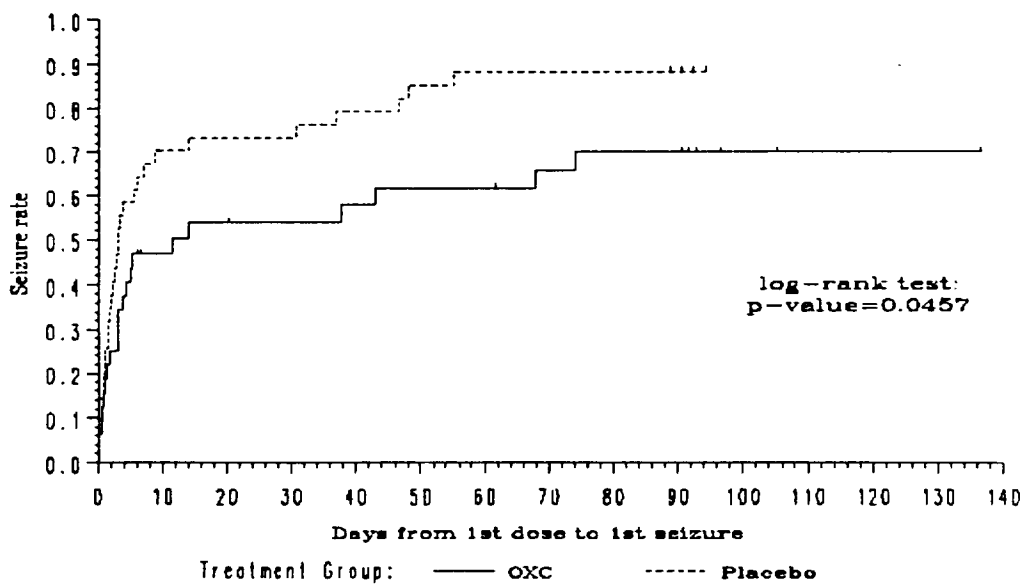
No patient blinds were broken during this study.

5.1.2.9 SPONSORS EFFICACY RESULTS:

5.1.2.9.1 PRIMARY ENDPOINT:

The Kaplan-Meier curves for the primary objective are presented in Figure 5 (from sponsors exhibit 8.1.-1). An ITT log rank analysis revealed a significant but borderline p value of 0.0457.

Figure 5 Kaplan-Meier SurvivalCurves for Trial 025



When the center that deviated from the standards of Good Clinical Practice and Compliance, Hasegawa/M0274P, was excluded from this analysis the p value improved to 0.0295. Analysis of all data using Cox's regression model revealed a significant effect of treatment (p=0.043) when treatment-by-baseline interaction was factored in. No statistical significance (p=0.134) was observed without the interaction factor included.

A factor that should be noted is that this monotherpy trial's treatment dose (1200mg/day) is half that of all other monotherpy trials (2400 mg/day).

5.1.2.9.2 SECONDARY ENDPOINTS:

Percent Change in Seizure frequency: The design of the study, as noted above, was altered to allow patients to enter into the extension phase following the first seizure if deemed appropriate by the investigator. As already noted, because of this design flaw the significance of the secondary measure of seizure frequency cannot be clearly analyzed. As a result this reviewer feels that it is best to ignore this measure. Notwithstanding this, comparison of the percent change from baseline of seizure frequency in OXC with Placebo groups revealed a significant (Wilcoxin-rank sum) reduction in the OXC group when an intent to treat analysis was performed (p=0.033). An analysis that included only those patients completing the double blind phase (p= 0.036) was also found statistically significant. The documentation of baseline seizures frequency however was not rigorous and when only those patients with at least 28 day seizure diary was analyzed a p value of only 0.065 was obtained. Although it appears that the sponsor feels that this data might support the sponsor's contention of efficacy these data at best should be considered as non-contributory.

Poisson examination of seizure frequency data did not reveal significance. The sponsor argues that this is an inappropriate model (it was considered an "exploratory" analysis in the original protocol).

Percent of seizure-free patients: A greater percent of patients in the OXC group were seizure free when compared to the Placebo group (values in the intent to treat population was 34% compared to 14 % respectively). This value, however, was not statistically significant when calculations were performed using a variety of methods of handling early withdrawals (see Table 9). The sponsors wish to argue that efficacy is supported by statistical analysis that demonstrates significance is "approached" (p=0.073) when dropouts are considered seizure free. As this measure is quite directly dependent on time to fist seizure (the primary objective) it is no surprise that the result was not significant when considering the borderline significance of the latter measure.

Table 9 Analysis of Seizure Free Patients Using Different Methods of Handling Dropouts in Trial 025

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

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

[2] Based on Mantel-Haenszel test.

[3] Excluding seizure-free dropouts.

5.1.2.10 ADVERSE AFFECTS AS IT MAY INFLUENCE MEASURES OF EFFICACY:

There were no withdrawals due to deaths or abnormal laboratories. There were three withdrawals from adverse events in the OXC group and 2 in the Placebo group. One patient in the OXC groups was withdrawn as a result of pregnancy. There was no meaningful difference between the toxicity experienced in both groups nor was there a clearly significant relationship between serum MHD concentrations and toxicity. These observations are likely the result of the low dose used in the present study.

There was an option for dose (or placebo) reduction if subjects were unable to tolerate the 1200 mg/day test dose (or placebo). A disparity between placebo and OXC reductions has the potential to compromise the blind. Information on the number of patients requiring reductions could not be found in the application and was requested by phone on 8/31/99. The sponsor noted that 2 in drug and 2 in placebo group required "reductions" in dosage. This should have not had any adverse effect on the study.

5.1.2.11 PHARMACOKINETICS AS IT MAY EFFECT MEASURES OF EFFICACY:

The failure to find a robust treatment effect in the present study may have resulted from the fact as noted above, that doses were rather low compared to