CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-014/SE5-013	**SUBMISSION DATES:** December 13, 2004
	21-285/SE5-008	March 17, 2005
DRUG NAME:	Trileptal® (Oxcarbazepine)	March 29, 2005
DOSAGE STRENGTH:	Tablets (150, 300, 600 mg), oral suspension (60mg/mL)	
APPLICANT:	Novartis	
REVIEWER:	John Duan, Ph.D.	
TEAM LEADERS:	Ramana Uppoor, Ph.D., Jogarao Gobburu, Ph.D. (Pharmacometrics)	
TYPE OF SUBMISSION:	Pediatric supplement in response to pediatric written request	

EXECUTIVE SUMMARY

Trileptal is indicated as monotherapy and adjunctive therapy for the treatment of partial seizures in adults and in children 4-16 years of age. The current submission is in response to the Agency's formal Written Request of February 28, 2000, which requested the sponsor to conduct studies with oxcarbazepine in pediatric patients between the ages of 1 month to 16 years of age. The sponsor conducted one monotherapy trial (study 2339) and one adjunct therapy trial (study 2340) in pediatric patients with ages between 1 month and 16 years. While the monotherapy trial failed the primary endpoint, the adjunct therapy trial was successful. Comparison of results across trials indicated strongly that the monotherapy study 2339 was not adequately designed and conducted. The major deficiencies include the short duration of the study and lack of documentation of seizure rate at baseline. These deficiencies render the study results uninterpretable. However, this study did provide information for comparison of PK between children and adults. Adjunctive therapy study 2340 was a positive trial. Comparison between the current and previous studies indicates that similar concentrations are achieved among different studies. The dosing utilized in the pediatric adjunctive therapy study is considered adequate. Given the higher body weight adjusted clearance in 1 month to <4 years old children, a higher mg/kg dose should be considered in children with body weight under 20 kg. Considering the difficulties and ethical issues in conducting monotherapy in children, coupled with clinical experience in adjunctive therapy in children 1 month to <4 years old, a PK/PD bridging approach is recommended for monotherapy in this pediatric population.

RECOMMENDATIONS

Based on PK/PD information, proposed dosing for adjunctive therapy in children below 4 years of age seems generally reasonable. A higher starting dose should however be considered. A PK/PD bridging approach is recommended for extending the monotherapy indication to children below 4 years of age.

Comments to Medical Officer

1. Monotherapy study 2339 was not adequately designed and conducted. The major deficiencies include the following.

- **Missing of proper record of disease state (seizure rate) at the baseline.** The clinical end point used in this study (exit rate) was different from that of the previous PK/PD bridging study in children 4 -16 years (percent change of 28-day seizure frequency from baseline). In an effort to seek the comparison between the current study and previous study, the baseline data for study 2339 was requested. However, the sponsor indicated that the baseline seizure rate was not recorded. It is not clear how the inclusion/exclusion criteria were executed in the absence of such baseline information. Further, due to the lack of baseline disease information, it was not possible for probing whether the drug was efficacious or not.

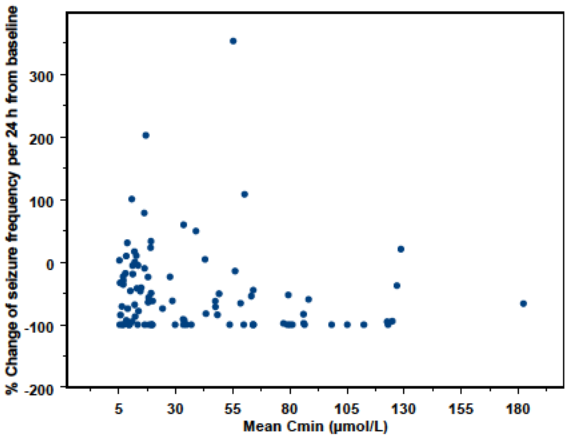
- **Short trial duration.** There were several monotherapy studies previously conducted mainly in adults which used exit rate as the end point, including studies 04, 25, 26 and 28, among which 04 and 25 used placebo control whereas 26 and 28 used lower dose as control similar to 2339. Study 2339 had shorter overall treatment duration of 5 days, compared to 10 days in study 04, 90 days in study 025, 56 days in study 026 and 96 days in study 028. The analyses conducted by this reviewer show that if the duration in studies 025, 026 and 028 had been cut down to 5 days, the effectiveness of trileptal would not be shown.

- **Potential carry-over effect of other AEDs.** In the 5-day short overall duration, 40% of time the patients were on other AEDs (100% of AED on Day 1 and 50% of AED on Day 2). From a pharmacokinetic perspective, the half-lives of AEDs are usually long and considerable amount of AEDs might have been left over during trileptal "monotherapy" period. If considering the usual delay compared to pharmacokinetics, the pharmacodynamic effect of these AEDs might have lasted even longer. At a minimum, this carry-over will confound the results/interpretation.

Although the short duration and short conversion period had understandable ethical reasons, these deficiencies render the study results not interpretable. (b) (4)

2. Based on population pharmacokinetic modeling and a comparison between the study in current submission and previous studies, the proposed dosing regimens for adjunctive therapy, which are similar to those in the clinical trials, are considered adequate.

3. An exploratory analysis of study 2340 indicates that for pediatric patients aged 1 month to <4 years old on adjunctive therapy, the responses (% change of seizure frequency per 24 hours from the baseline) and concentration (Cmin, μmol/mL) are correlated, as shown in the following figure. The analysis shows the possibility and feasibility of a PK/PD bridging approach for monotherapy.



Considering the scientific rationale and difficulties and ethical issues in conducting monotherapy in children, coupled with clinical effectiveness shown in adjunctive therapy in children 1 month to <4 years old, a PK/PD bridging approach is recommended for monotherapy in this pediatric age group. As the availability of anti-epileptic medications is limited, there is a public health need for more options in this age group. It is also believed that conducting more of such trials may be challenging. More importantly, given the positive trials for adjunctive therapy from 1 month children to adults and monotherapy approval above 4 years of age, scientifically it is appropriate to extrapolate to the 1 month to 4 years group using a PK/PD approach. The sponsor should make an attempt to integrate all available data across the epilepsy indications (b) (4)

LABELING RECOMMENDATIONS

(Reviewer's recommendations are in blue color, the additions are underlined)

1. In **CLINICAL PHARMACOLOGY**-**Special Populations**- ***Pediatric Use*** section, the following changes should be made.

(b) (4)

2. In **DOSAGE AND ADMINISTRATION** section, the following changes should be made.

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John Duan, Ph.D. Date
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Division of Pharmaceutical Evaluation I

Ramana Uppoor, Ph.D. Date
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cc: HFD-120 NDA 21-014
N. Hershkowitz
HFD-860 M. Mehta, A. Rahman, R. Uppoor, J. Gobburu, J. Duan

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SUMMARY OF THE SUBMISSION

Below is a summary of the submission with the items related to Clinical Pharmacology and Biopharmaceutics in the Written Request listed (in bold), followed by a brief description of the submitted studies addressing the requests.

1. Types of studies requested
Study 4: Pharmacokinetic Study (1 month to 16 years)

Study 2338: An open-label, age-stratified pilot-study to assess the tolerability and pharmacokinetics of ascending doses of oxcarbazepine oral suspension as adjunctive therapy in pediatric patients (1 month to < 4 years of age) with inadequately-controlled partial seizures. A supplemental pharmacokinetic report for study 2338 is submitted. This study served as a pilot study for justification of the titration and dosing schedule for the adjunctive therapy Study 2340.

Study 2341: An open-label, age-stratified pilot-study to assess the tolerability and pharmacokinetics of ascending doses of oxcarbazepine oral suspension as monotherapy in pediatric patients (1 month to <17 years of age) with inadequately-controlled partial seizures. This trial served as a pilot study for justification of the titration and dosing schedule for the monotherapy Study 2339.

In addition, a random PK sampling procedure was employed in studies 2339 and 2340 in order to obtain plasma concentrations to be used in constructing a population pharmacokinetic model..

2. Indications to be studied
Study 4: To determine the steady–state pharmacokinetics in pediatric subjects ages 1 month to 16 years.

The steady state pharmacokinetics was explored in the pilot studies 2338 and 2341. In addition, a random PK sampling procedure was employed in studies 2339 and 2340. All four studies were used in constructing a population pharmacokinetic model.

3. **Age group in which studies were performed**
Study 4: 1 month to 16 years

As can be seen from the table below, the studies covered all age groups in pediatric patients.

Demographic Variable	Study 2338 N=23	Study 2339 N=81	Study 2340 N=111	Study 2341 N=3	All studies N=218
Sex					
Male	13 (56.52%)	43 (53.09%)	63 (56.76%)	1 (33.33%)	120 (55.05%)
Female	10 (43.48%)	38 (46.91%)	48 (43.24%)	2 (66.67%)	98 (44.95%)
Race					
Caucasian	14 (60.87%)	53 (65.43%)	77 (69.37%)	3 (100.00%)	147 (67.43%)
Black	6(26.09%)	11 (13.58%)	7 (6.31%)	0 (0.00%)	24 (11.01%)
Other	3 (13.04%)	17 (20.99%)	27 (24.32%)	0 (0.00%)	47 (21.56%)
Age (years)					
1 month -<1 year	7 (30.43%)	15 (18.52%)	38 (34.23%)	2 (66.67%)	62 (28.44%)
1 year to <2 years	8 (34.78%)	11 (13.58%)	31 (27.93%)	0 (0.00%)	50 (22.94%)
2 years -<3 years	3 (13.04%)	7 (8.64%)	21 (18.92%)	1 (33.33%)	32 (14.68%)
3 years -<4 years	5 (21.74%)	8 (9.88%)	21 (18.92%)	0 (0.00%)	34 (15.60%)
≥4 years	0 (0.00%)	40 (49.38%)	0 (0.00%)	0 (0.00%)	40 (18.35%)

4. Study endpoints
Study 4: Pharmacokinetics measures as appropriate.

A descriptive assessment of the effect of age on pharmacokinetic parameters is presented in the submission. A population pharmacokinetic model that was previously used to describe the pharmacokinetics of MHD in children from an adjunctive therapy study of oxcarbazepine in pediatric patients with epilepsy was used to fit the data.

5. Drug information
Dosage form

Oxcarbazepine 300 mg/5 mL (60 mg/mL) was provided in brown (amber) glass bottles containing 250 mL of oral suspension and was used in the Pediatric Development Program. All data, reports and other pertinent information contained within the supplemental submission to NDA 21-014 for Trileptal® (oxcarbazepine) film coated tablets are included in NDA 21-285 for Trileptal® (oxcarbazepine) oral suspension.

Route of administration
Oral

Regimen
Study 2340: In the high dose group patients received 10 mg/kg/day of oxcarbazepine for the first five days and then were titrated up, in increments of 10 mg/kg/day at 5-day intervals, to a maximum of 60 mg/kg/day. In the low-dose group, patients received 10 mg/kg/day and were maintained on this dose through Day 9.
Study 2339: Patients in the low-dose group received 10 mg/kg/day of oxcarbazepine for 5 days. Patients in the high-dose group received 20 mg/kg/day on Day 1, dose increased to 40 mg/kg/day on day 3 and to 40-60 mg/kg/day on Days 4-5 based on the investigator's judgment and response by the patient.

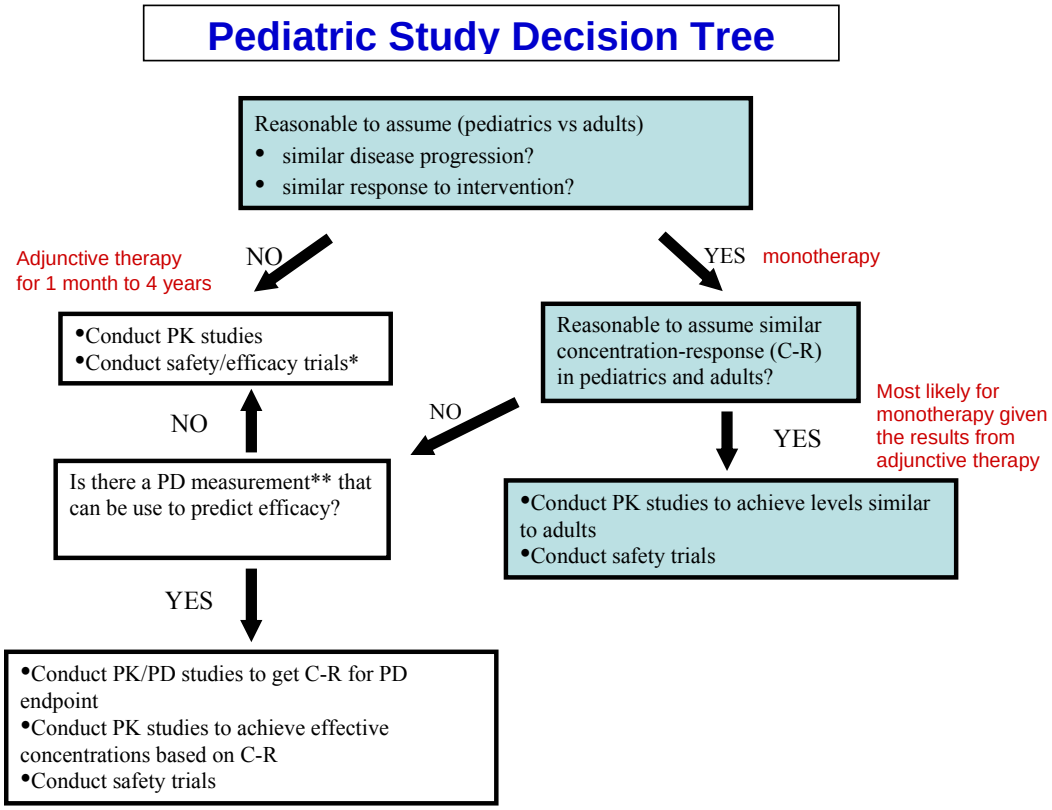
6. Drug specific safety concerns
Hepatic, hematologic and skin hypersensitivities reactions and hyponatremia.

Hepatic, hematologic and skin hypersensitivity reactions were assessed by monitoring and recording all adverse events and serious adverse events, monitoring of hematology, blood chemistry and urine values, measurement of vital signs, ECGs and the performance of physical examinations.

7. Statistical information, including power of study and statistical assessments
Study 4: Descriptive assessment of the effect of age on pharmacokinetic parameters.

Data were pooled from four studies: 2338, 2339, 2340, and 2341 to explore the population pharmacokinetics/pharmacodynamics of Trileptal® at doses up to 60 mg/kg/day as oral suspension as monotherapy or adjunctive therapy in pediatric patients 1 month to <17years of age with partial seizures. Data are presented in the report titled "Population pharmacokinetic/pharmacodynamic analysis for Trileptal® in patients 1 month to < 17 years of

age with partial seizures." A total of 218 subjects evaluable for pharmacology assessments were used for the population pharmacokinetic and pharmacodynamic modeling. Among them, 23 patients were from study 2338, 81 patients from study 2339, 111 patients from study 2340, and 3 patients from study 2341. Please see Appendix 2 for details of the population pharmacokinetic/pharmacodynamic study.



QUESTION BASED REVIEW

1. What is the regulatory history about this submission?

This submission is a supplement to NDA 21-014 and to NDA 21-285 as the sponsor's "**SUBMISSION OF PEDIATRIC STUDY REPORTS-PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED".** The submission was made in response to the FDA's formal Written Request dated February 28, 2000, issued pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act, which requested the applicant to conduct studies with oxcarbazepine in pediatric patients between the ages of 1 month to 16 years of age. With this submission, the applicant seeks to expand the currently approved indications of Trileptal for use as adjunctive therapy or monotherapy in the treatment of partial seizures in children with epilepsy (b) (4) and to qualify Trileptal for an additional 6-months exclusivity as established in §111 of the 1997 FDA Modernization Act (FDAMA) and as codified primarily in 21 CFR 201.23, 314.55, and 601.27. In addition, for the new indication resultant from the submission, the applicant requests an additional three years of exclusivity pursuant to 21 CFR 314.108(b)(5) if approval is based on new clinical investigations conducted by the applicant which are deemed essential for the approval.

In the US, Trileptal film-coated tablets were approved and marketing authorization was obtained on January 14, 2000 and Trileptal oral suspension 300 mg/5mL was approved on May 25, 2001. Oxcarbazepine is indicated for use as adjunctive therapy and monotherapy for the treatment of partial seizures (b) (4) in adults and in children 4 to <17 years of age. The monotherapy indication for children 4 to <17 years of age was obtained after the initial marketing authorization in the US through a pharmacokinetic/pharmacodynamic bridging approach on August 7, 2003.

2. Did the current submitted monotherapy study 2339 confirm the pharmacokinetic/ pharmacodynamic bridging?

Study 2339 is not interpretable. In the current submission, two clinical studies were provided. Trial 2339 was a monotherapy study and Trial 2340 was a study for adjunctive therapy. Although 2340 showed significant difference of effectiveness between lower dose and high dose groups, 2339 did not show the difference. The following table shows the situations for previous approvals and current application stratified by age groups.

	Adults	Children (4-16 years of age)	Children (1 mon-4 years)
Adjunctive	Trileptal approved on the basis of "positive" Phase 3 clinical trials	Trileptal approved on the basis of "positive" Phase 3 clinical trials	Current submission, Study 2340 showed "positive" results
Monotherapy	Trileptal approved on the basis of "positive" Phase 3 clinical trials	Trileptal approved on the basis of "PK-bridging" approach	Current submission: Study 2339 includes patients of 1 mon-4 yr,
		as well as4-16 yrs of age. Study 2339 did not show "positive" results.	

3. Why can we not use the previous model built for the pharmacokinetic/pharmacodynamic bridging to analyze the current data?

In the population pharmacokinetic study conducted by the applicant included in the current submission, the same PK model developed previously was used. However, from PD

perspective, the previous study and current study used different PD end point. The 28-day seizure frequency was the clinical end point for the previous study as well as for the previous model. On the other hand, the primary efficacy variable for Study 2339 was the time to meeting exit criteria based upon the type and number of video-EEG confirmed SST1 seizures. The primary efficacy variable for Study 2340 was the absolute change in video-EEG confirmed seizure frequency per 24 hours. Because the primary efficacy variables and the primary efficacy analyses of the current studies were different from previous studies utilized in the model building, the previous model can not be used for the current data analysis. Moreover, for study 2339, the record for the date, time and numbers of baseline seizures could not be found. When requested, as shown in the following Email, the applicant stated that the baseline disease information was not recorded.

> From: peter.mcardle@novartis.com [mailto:peter.mcardle@novartis.com]
> Sent: Tuesday, March 15, 2005 12:49 PM
> To: Griffis, Melina
> Subject: Re: N21-014/S-013; Request for Information
>
> Dear Melina:
>
> I've been provided with the following information regarding study 2339 by a member of the clinical team:
>
> "Study 2339 did not have baseline seizures assessed and documented in the CRF. There is no dataset available."
>
> Please let me know if this is a sufficient answer for the PK reviewer.
>
> Sincerely,
> Peter

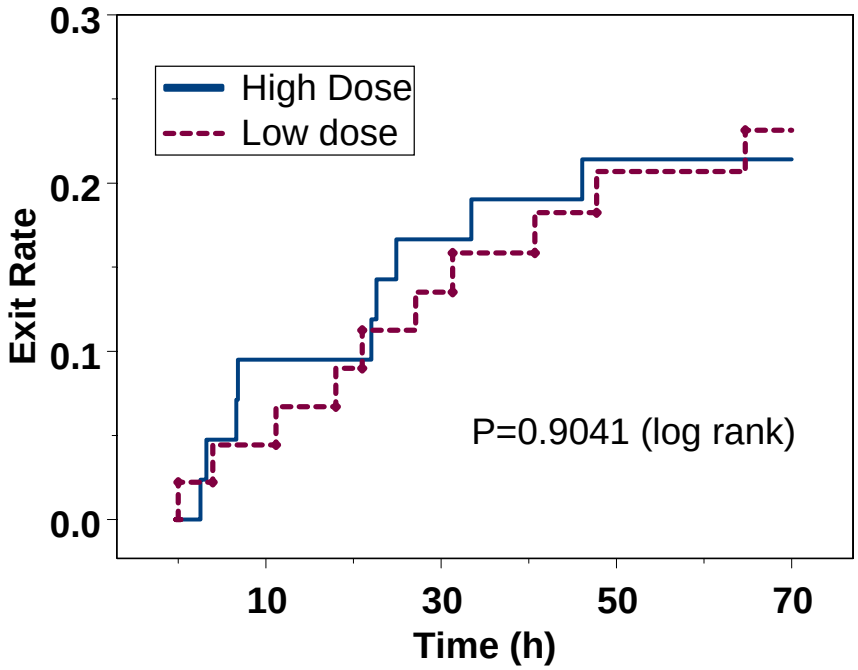
Due to lack of baseline disease information, it was not possible for further explorations by PK/PD modeling.

4. Why the results from currently submitted monotherapy study 2339 are not consistent with the results from PK/PD bridging study?

The possible reasons for this inconsistency include the following.

- Inadequacy of previous PK/PD bridging approach. However, based on currently available information, there is no evidence to support this.
- Inadequacy of the study design and conduct of monotherapy study 2339. Our analysis provides evidence to support this.

Our analysis begins with the confirming the applicant's analysis. The analysis of study 2339 is repeated and the following results are obtained.



The results are exactly the same as those of applicant. The high dose group does not show difference from the low dose group (p=0.9).

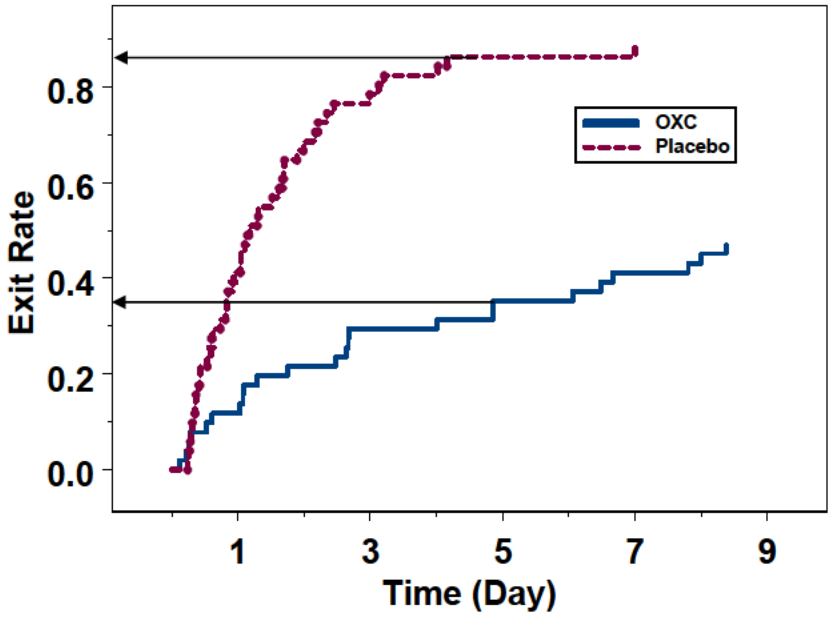
5. ***Was the exit rate in the monotherapy trial as expected by the applicant?***

No. The applicant expected 70% exit rate in the low dose group and 35% in the high dose group. However, the majority of patients from both dose groups completed the 5-day study without exiting. The rates of meeting exit criteria in both groups (21% and 22% for the High- and Low-dose OXC groups, respectively) were much lower than those that had been expected.

The reasoning for the expectation was not mentioned in the submission. When we look through the data in previous submissions, we find study 004 which had similar design with 2339. Protocol 004 was a multicenter, double-blind, **placebo-control**, randomized, parallel-group study designed to assess the safety and efficacy of oxcarbazepine as Monotherapy in patients with inadequately controlled partial seizures. The study consisted of three phases: a 48-hour Baseline Phase, a **10-day** Double-blind Phase, and a Long-term Extension Phase. The Double-blind Phase consisted of a 1 -day Titration Period and a 9-day Maintenance Period. Patients began treatment with a 1-day dose of 1500 mg/day oxcarbazepine or matching placebo and then received 2400 mg/day oxcarbazepine or matching placebo for the 9-day Maintenance Period. Participants were selected from male and female patients, 12 to 65 years of age who weighed at least 45 kilograms. Hospitalized patients were required to have undergone a presurgical evaluation for epilepsy and been **tapered off of all previous concomitant AEDs**. **Tapering off of benzodiazepine therapy was required 15 days prior to presurgical evaluation. Lorazepam was the only medication allowed for seizure**

control during the Baseline Phase. During the Baseline Phase, patients needed to experience two to 10 partial seizures of which a maximum of two seizures could be partial seizures evolving to secondarily generalized seizures. The primary efficacy variable was the time to meeting one of the exit criteria. The exit criteria were defined as: 1) experience of a fourth partial seizure with or without partial seizures evolving to secondarily generalized seizures (exclusive of seizures occurring during the 24-hour Titration Period); 2) experience of two new-onset partial seizures evolving to secondarily generalized seizures; and 3) experience of serial seizures or status epilepticus deemed by the investigator to require intervention.

The trial results are analyzed as shown below.



As can be seen, the oxcarbazepine treatment group has a clear separation from the placebo group. On Day 5, the exit rate is about 35% for oxcarbazepine group and 86% for placebo group. These study results might be the basis for the applicant to expect the exit rate 35% for the high dose group and 70% for the low dose group in the monotherapy study 2339 for children. However, this expectation failed.

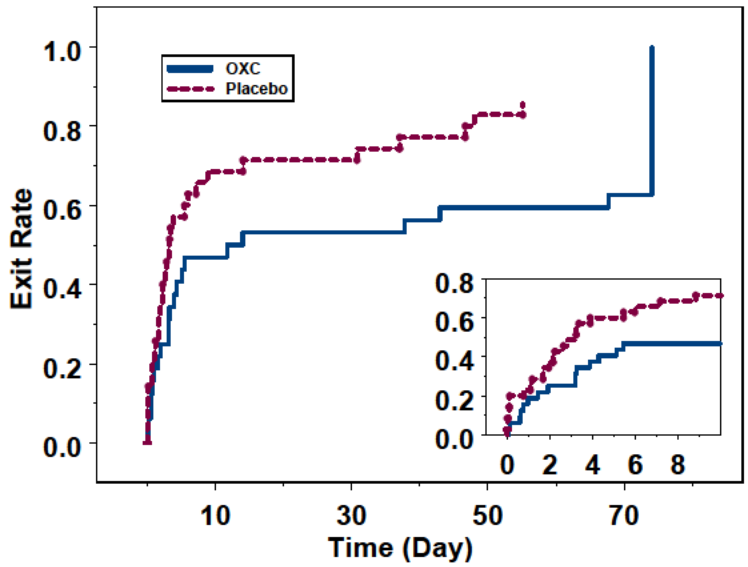
6. What are the potential reasons for a lower exit rate than expected, in study 2339?

In order to find the reasons of failure, we compared the study designs between studies of 004 and 2339. Among others, three differences should be noted.

First of all, the study duration is different. Whereas the duration of study 004 was 10 days, study 2339 only lasted 5 days. Although on fifth day, the exit rates had clear separation between oxcarbazepine treatment group and placebo group in study 004, could it be always the case? To answer this question, we analyzed study 025 submitted in the original NDA. Protocol 025 was a multicenter,

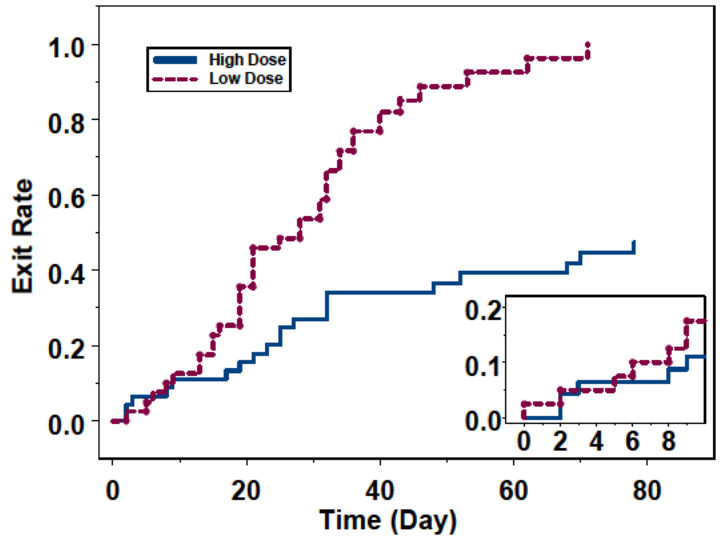
double-blind, placebo-control, randomized, parallel group study designed to evaluate the safety and efficacy of oxcarbazepine in patients with inadequately controlled partial seizures. The study consisted of three phases: a 56-day baseline phase (all or part of which could have been retrospective), a 90-day double-blind phase, and a long-term extension phase. During the baseline phase, patients were required to experience at least two seizures per month and were **not allowed to have received any AED treatment in the previous 3 months**. The double-blind phase consisted of a 6-day titration period and an 84-day maintenance period. Patients were randomized to receive either oxcarbazepine 1200 mg/day (**titrated over 6 days**) or placebo. Participants were selected from male and female patients, at least 10 years of age, who weighed at least 32 kg. **The primary efficacy variable was the time to first partial seizure.** The time to the occurrence of this event was computed from the date and time of first dose of double-blind study drug to the date and time of the occurrence of the first partial seizure.

Our analysis shows that if we consider the whole duration of the study, the exit rates have significant difference between oxcarbazepine treatment group and placebo group (log rank p=0.036) as shown in the following figure. However, if only the first five days are considered, the significance is lost (log rank p=0.16) as shown in the inlet of the following figure.



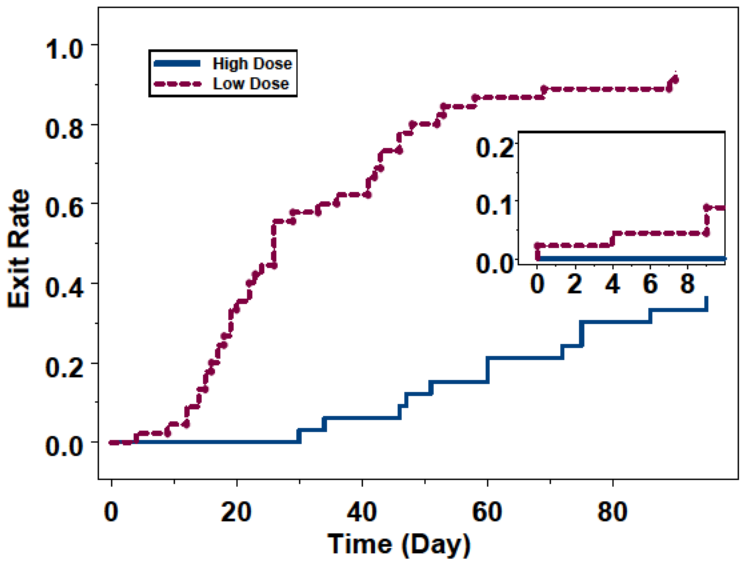
Therefore, if the duration of study 025 had been set to five days, it would be a negative study. This analysis also indicates that the separation on fifth day, such in the case of study 004, may not be always the case. If the applicant had taken the experience of both 004 and 025 into consideration, the duration of study 2339 would not be set to five days.

Secondly, compared to studies 004 and 025, low dose group was used in study 2339 as control instead of placebo. This difference might have made significant difference, because the low dose 10 mg/kg/day could be (partially) effective. If this had been the case, the differentiation between low dose group and high dose group would need longer time. Five days might not be enough. To examine this possibility, studies in previous submissions are analyzed, which include studies 026 and 028. In these two studies, low dose groups were used as controls. Following figure shows the results from study 026.



The separation does not begin until Day 12. On Day 5, not only do the curves overlap each other, but the exit rates are very low (less than 10%) as well (see inlet of the above figure). Although by looking at the whole duration, the two curves are separated with a p value less than 0.001 (log rank), they do not separate at all by the fifth day, which is the case in study 2339.

The analysis results for study 028 show the similar situation as illustrated in the following figure.



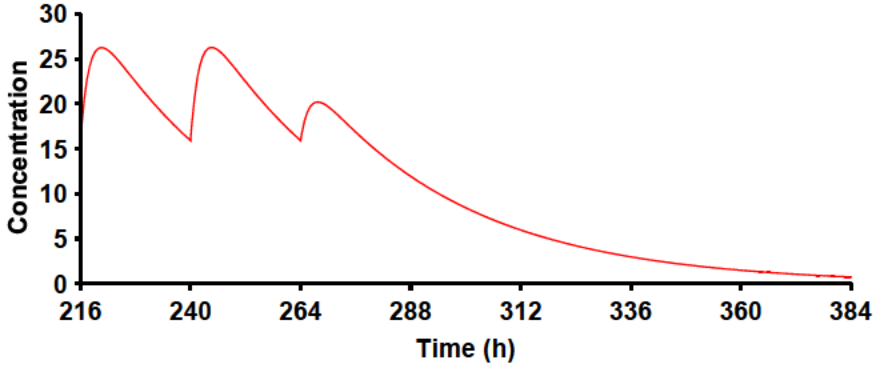
Thirdly, study 2339 had very short time for conversion from other AED to trileptal. The following table compares the reduction schedules for AEDs in three monotherapy studies. On Day 1 of a five-day study, patients still took 100% of the baseline dose of AED in study 2339. It was reduced to 0% until Day 3. Therefore, the effect of AEDs might still be available on Day 5.

Study day	%Baseline AED		
	Study 2339	Study 004	Study 025
Baseline	100%	tapered off of all concomitant AED. benzodiazepine therapy was stopped 15 days prior to baseline evaluation. Lorazepam was the only medication allowed for seizure control during the baseline phase.	not allowed to receive any AED treatment in the previous 3 months
1	100%	0%	0%
2	50%	0%	0%
3	0%	0%	0%
4-5	0%	0%	0%

From pharmacokinetic perspective, the half-lives of AEDs are usually long as shown in the following table which shows AEDs the patients took at the baseline stage in study 2339.

Antiepileptic Drugs	OXC Low N=46 N (%)	OXC High N=46 N (%)	Total N=92 n (%)	Half-lives (h)
CARBAMAZEPINE	14 (30.4)	18 (39.1)	32(34.8)	25-65 (12-17 after autoinduction)
VALPROATE SEMISODIUM	5 (10.9)	5 (10.9)	10(10.9)	16±3
PHENYTOIN	3 (6.5)	4 (8.7)	7(7.6)	22 (7-42)
CLONAZEPAM	1(2.2)	2(4.3)	3(3.3)	30-40
PHENOBARBITAL	0(0.0)	2(4.3)	2(2.2)	48-144
PHENYTOIN SODIUM	2(4.3)	2(4.3)	4(4.3)	22 (7-42)
VALPROATE SODIUM	2(4.3)	2(4.3)	4(4.3)	16±3
VALPROIC ACID	3(6.5)	2(4.3)	5(5.4)	16±3
CEREBREX (Vit B; glutamic acid; calcium glycerophosphate; calcium phosphate)	1(2.2)	1(2.2)	2(2.2)	
LEVETIRACETAM	5(10.9)	1(2.2)	6(6.5)	7±1
TOPIRAMATE	2(4.3)	1(2.2)	3(3.3)	21
ZONISAMIDE	0(0.0)	1(2.2)	1(1.1)	63
FOSPHENYTOIN	1(2.2)	0(0.0)	1(1.1)	Convert to phenytoin
LAMOTRIGINE	5(10.9)	0(0.0)	5(5.4)	25, 32
LORAZEPAM	1(2.2)	0(0.0)	1(1.1)	16
SULTIAME	1(2.2)	0(0.0)	1(1.1)	

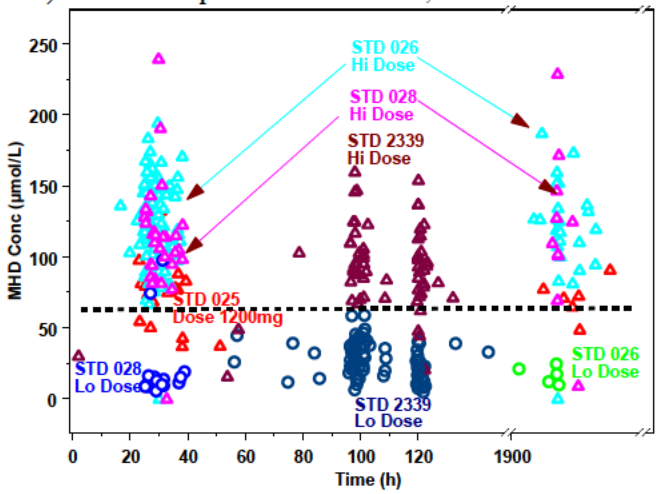
Following figure shows a simulated PK profile of a drug with 24-hour half life and with QD dosing, assuming a one-compartment model with first order absorption and first order elimination. At 240 hours, the drug is at steady state. It is counted as Day 1, on which 100% dose of AED is given. On Day 2 (264 hours), half of the regular dose is given. Although dose is not given on Day 3 and thereafter, the concentration at 288 hours (Day 3) is 74% and that at 312 hours (Day 4) is 38% of the trough concentration of the steady state. On Day 5 (336 hours), there is still 19%.



Therefore, the AEDs used before Day 2 have considerable amount left over during trileptal treatment period. When the drug half-lives are longer than 24 hours, this effect may be more pronounced. Further, if assuming a certain delay of the antiepileptic effect relative to its concentration, the pharmacodynamic effects might have even longer duration. Under this situation, it added another layer of complexity for differentiating the antiepileptic effects between trileptal and these AEDs.

7. *What do the results of study 2339 indicate?*

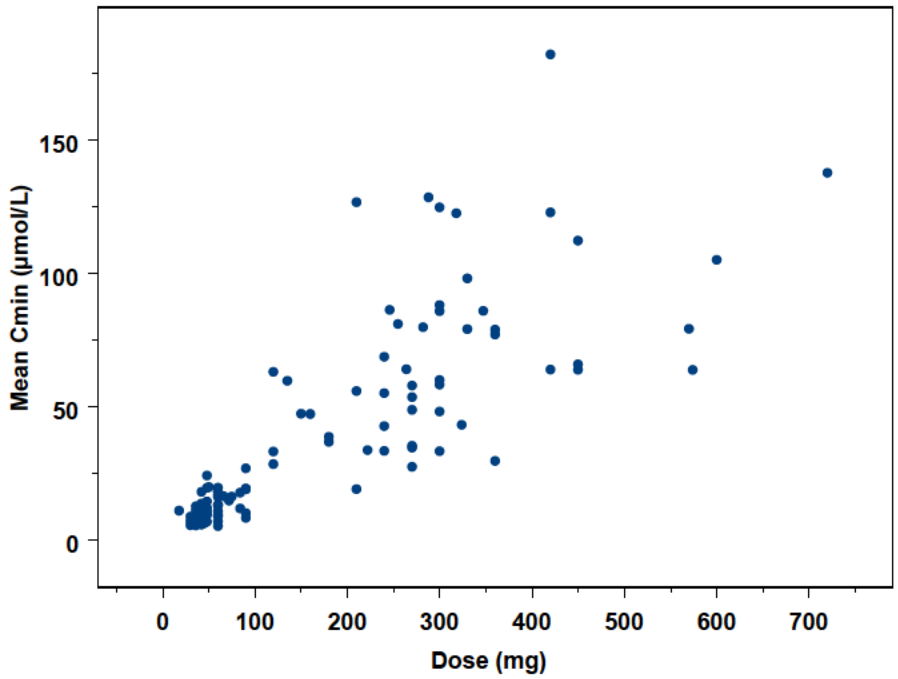
The design and conduct of study 2339 are inadequate. The evidence of effectiveness of trileptal in children aged 1 month to 4 years has not been shown by this study. However, could this study have been able to show the effectiveness of trileptal in children aged 1 month to 4 years if the design and conduct of study were adequate? From pharmacokinetic perspective, the possibility is explored by examining the clinically achieved concentrations in monotherapy studies conducted in adults and in children. Following figure shows the concentrations achieved at different time points in several monotherapy studies (including 2339, 25, 26 and 28). Most of the patients in studies 25, 26 and 28 are adults.

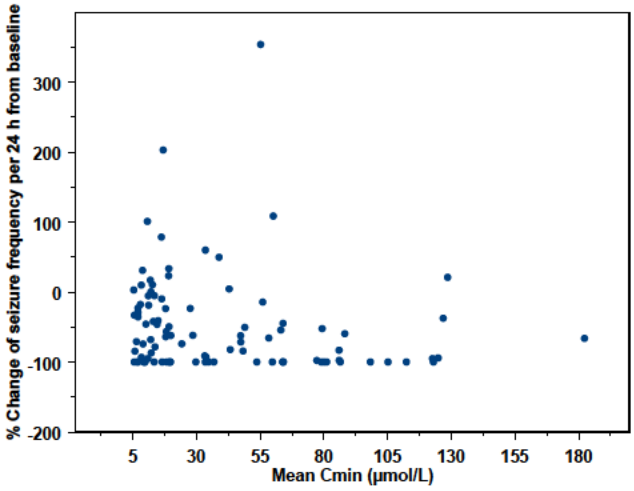


As can be seen, the concentrations achieved in the monotherapy study 2339 in children are similar to the concentrations obtained in monotherapy studies in adults. Also similar among

these monotherapy studies, the high dose and low dose groups are separated by an arbitrarily drawn line. Most of the concentration points from high dose group fall above this line whereas those from low dose group fall below it. The concentrations of study 025 fall between because the dose used in this study (1200 mg/day) was less than that of studies 026 and 028 (2400 mg/day). This indicates that the dose of 40-60 mg/kg used for the high dose group in children in study 2339 produced concentrations similar to those from 2400 mg/day in adults. On the other hand, there seems a trend that the dose of 10 mg/kg used for the low dose group in study 2339 generates higher concentrations than those from the low dose group (300mg/day) in studies 026 and 028 (This may partially explain why the exit rate is low in the low dose group in study 2339).

Considering the scientific bases (and ethical issues) in pediatric monotherapy studies, we recommend a PK/PD bridging approach to establish the effectiveness in children aged 1 month to <4 years for trileptal monotherapy. A preliminary analysis is conducted in this regard in adjunctive therapy study 2340. As shown in the following figures, the dose and concentrations (Cmin) have a linear relationship and the response (percent change of seizure frequency per 24 hours compared to baseline) seems to correlate with concentrations (Cmin). If the PK/PD relationship in the younger age group is similar to the older children and adults, PK/PD approach can be used to obtain a monotherapy indication in 1 month to <4 years group.





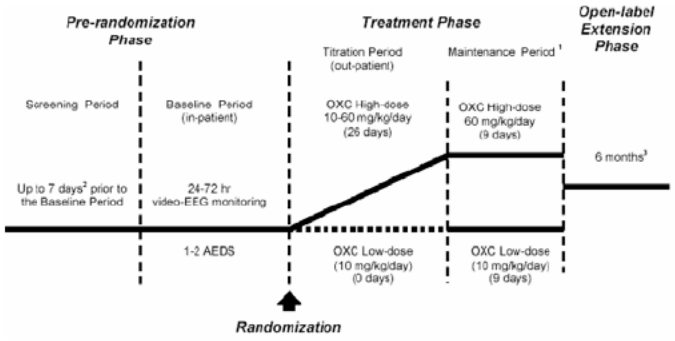
Therefore, for a PK/PD bridging study, there is not only possibility, but feasibility as well (please see below for details of adjunctive study 2340).

8. *What are the results of study 2340?*

Although the basic difference between study 2340 and 2339 is that 2340 was an adjunctive therapy study whereas 2339 was monotherapy study, there are several other differences between these two studies.

The primary end point in Study 2340 was the absolute change in SST1 seizure frequency per 24 hours (during the last 72 hours of continuous video-EEG monitoring in the Treatment Phase compared to the seizure frequency at Baseline). On the other hand, exit rate was the end point for study 2339.

The duration of treatment for study 2340 is up to 9 days for the low-dose OXC group and up to 35 days for the high-dose OXC group. Therefore, study 2340 had more time to differentiate the high dose and low dose groups. The design of 2340 was as follows.

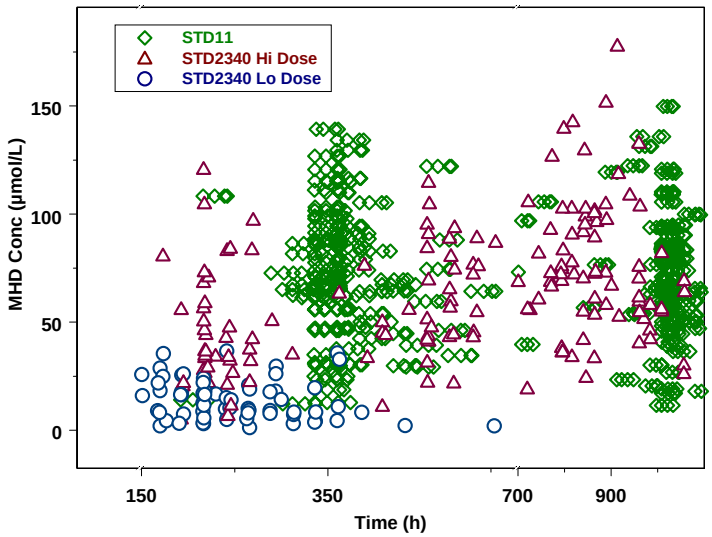


The primary efficacy variable, absolute reduction in SST1 seizure frequency per 24 hours, was statistically significantly greater in the High-dose OXC group than in the Low-dose OXC group (median 2.00 and 1.37 for High-dose OXC and Low-dose OXC groups respectively; p=0.043). The percent reduction in SST1 seizure frequency per 24 hours also was statistically significantly greater in the High-dose OXC group than in the Low-dose OXC group (83.3% and 46.2% for High-dose OXC and Low-dose OXC groups respectively, p=0.047). Similarly, the absolute reduction in seizure frequency (SST1 + SST2) per 24 hours was statistically significantly greater in the High-dose OXC group than in the Low-dose OXC group (median 2.32 and 1.64 for High-dose OXC and Low-dose OXC groups respectively; p=0.020). The percentage of patients who were categorized as responding to treatment (i.e., experienced at least a 50% reduction in SST1 seizure frequency per 24 hours) was greater in the High-dose OXC group compared with the OXC Low-dose group, although the difference did not reach statistical significance (64.4% and 47.4% for High-dose OXC and Low-dose OXC groups respectively; p=0.088).

9. In adjunctive therapy, is PK in children of 1 month to <4 years similar to that of other age group?

In study 2340, blood samples for plasma MHD determination were available from 119 patients and 291 plasma concentrations were determined. Descriptive statistics were performed on 274 plasma concentrations from 116 patients. The median trough MHD concentration clearly differentiated: 58.4 µmol/L and 9.76 µmol/L for the High-dose OXC and Low-dose OXC groups, respectively. For trough sampling, the dose ranges for the last dose given to patients prior to sampling for the High- and Low-dose groups did not overlap (dose range 9.6 to 33.8 mg/kg and 2.3 to 6.0 mg/kg, respectively) but the plasma concentration ranges did show some overlap (7.13 – 152 µmol/L and 1.95 – 36.6 µmol/L, respectively). Similar differentiation was obtained for the other sampling times.

The comparison across studies is conducted in the adjunctive setting. Following figure shows the concentration achieved in studies conducted in different age groups. Study 011 was conducted in children aged 4 to 17 years old whereas study 2340 was in pediatric patients 1 month to <4 years of age.



The concentrations achieved in older children in study 011 were based on the following dosing regimen.

Body weight	Target randomized daily dose (given bid)
20 to 29 kg	900 mg (31 mg/kg to 45 mg/kg)
29.1 to 39 kg	1200 mg (31 mg/kg to 41 mg/kg)
39.1 to 60 kg	1800 mg (30 mg/kg to 46 mg/kg)

Patients with body weight >60 kg were randomized to 1800 mg/day dose.

On the other hand, the dosing scheme for study 2340 in the treatment phase is shown below.

Study day (24-hour periods)	Low dose (mg/kg/day)	High dose (mg/kg/day)
1-5	10	10
6-10	10*	20
11-15	-	30
16-20	-	40
21-25	-	50
26-35	-	60
* For low-dose group – Day 6-9		

As shown, the body weight based doses for younger children tended to be higher to result in similar concentrations between younger and older children. However, this body weight based difference results from the fact that the clearance is proportional to body surface area (BSA) as shown in the following model.

CL/F =

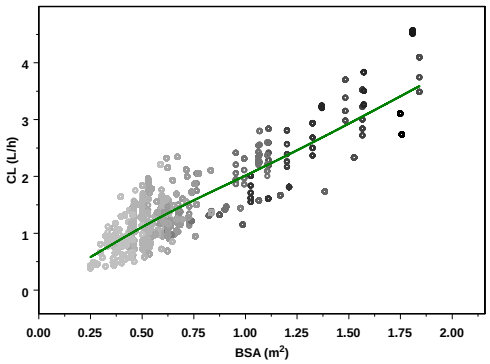
$$\theta_9\left(\frac{BSA}{1.3}\right)^{\theta_2}\left[1+(\theta_3-1)e^{-\frac{\log 2}{\theta_4}T_{CBZ}}\right]^{CBZ}\left[1+(\theta_5-1)e^{-\frac{\log 2}{\theta_6}T_{PB}}\right]^{PB}\left[1+(\theta_7-1)e^{-\frac{\log 2}{\theta_8}T_{PHT}}\right]^{PHT}e^{\eta_1}\ \text{L/h}$$

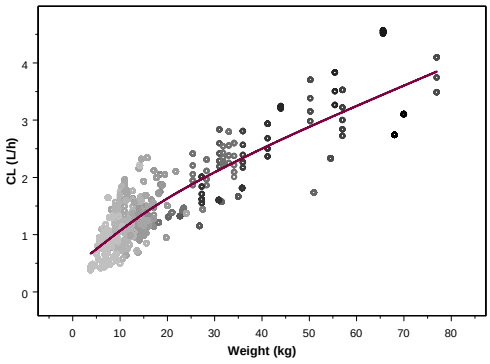
where θ^2 is 0.962 in the final model.

Therefore, the clearance of children 1 month to <4 years old is related to the clearance of older children by BSA while on the body weight basis, the clearance in the two age groups has some differences (see below).

10. How should the children in adjunctive therapy be dosed?

Although the clearance has an almost linear relationship with BSA, body weight does not have a linear relationship with clearance. In the following figures, the clearance of MHD in patients of studies 2338, 2339, 2340, and 2341 are plotted against their weight and BSA, respectively, smoothed by spline smoother (To discern the age effect, the colors of data points in the figures are changed with the age of the patients. The darker the color, the higher the age of the patients). As shown, although CL and BSA show an almost linear relationship, the relationship between CL and weight seems to have more phases with different slopes. This is why the studies conducted by the applicant showed clearance difference among different age groups.





BSA is the best predictor for clearance in the model developed by the applicant. Theoretically, therefore, the dosing in children should be generated based on BSA.

Practically, however, body weight based dosing was used in the clinical trials. Following results are provided in the submission.

In monotherapy (or adjunctive therapy with non-enzyme inducing AEDs), for the children with 1 month to <4 years of age, whose mean body weight was 11 kg (range 4 kg – 24 kg), the mean overall apparent body-weight normalized MHD clearance was 0.081 L/hr/kg (range 0.048 L/hr/kg – 0.133 L/hr/kg). This clearance was similar among the different clinical studies. For the children 4 years to ≤12 years of age with a mean body weight of 26 kg (range 13 kg – 55 kg), the mean apparent body-weight normalized clearance was 0.060 L/hr/kg (range 0.034 L/hr/kg – 0.088 L/hr/kg). For children 16 to <17 years of age with a mean body weight of 69 kg, the mean apparent body-weight normalized clearance was 0.042 L/hr/kg, similar to that of adults (about 3 L/hr, or 0.043 L/hr/kg for a 70 kg adult). These data are in agreement with previous study 011 (an estimated bodyweight normalized apparent clearance of 0.083 L/hr/kg and 0.060 L/hr/kg for children 3 to 4 years of age and at about 11 years, respectively).

Although the BSA should have been considered responsible for the clearance difference, body weight has been practically used. Due to its usage in the clinical trials and comparable concentrations found in pediatric studies compared with those of previous trials (both in adults and children), the conclusion made regarding the clearance differences and subsequent dosing recommendations among different age groups are considered adequate.

The applicant's conclusion that for children 1 month to <4 years the influence of enzyme-inducing AEDs on apparent clearance may be higher compared to older children, lacks sufficient evidence. There were no pediatric patients aged between 4 to 12 years, who were classified as Group 1 (referred to the patients with concomitant AEDs). The comparison made (in 1 month to 16 years age range) between Group 2 (monotherapy patients or non-inducing AEDs) and Group 3 (18 patients in study 2339 who stopped to take AEDs before participating in monotherapy period) does not necessarily support the interpretation.

11. How should the pediatric dosing in adjunctive therapy be addressed in the labeling?

The pediatric dosing in adjunctive therapy proposed by the applicant is as follows.

Adjunctive Therapy

(b) (4)

(b) (4)

The specific dosing is not recommended although it is indicated that the due to the differences in body weight normalized clearance among different age groups different dose per body weight should be given to each age group. Based on the following considerations, we recommend the starting dose 16-20 mg/kg for patients below 4 years of age.

- Based on the fact that the mean weight-adjusted clearance in children 1 month - <4 years of age is approximately 93% higher on average than that of adults, the dose per body weight in this group should be doubled compared to adults.
- In the high dose group of monotherapy trial 2339, the dose on Day 1 is 20 mg/kg/day and 100% baseline AEDs were used simultaneously (could be considered as adjunctive therapy). Based on discussion with the medical officer, there were no unusual safety concerns with this starting dose.

In addition, the language in this section is recommended to be changed as follows, focusing on dosing instructions.

Adjunctive Therapy

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APPENDIX 2. SUMMARY OF THE SPONSOR'S POPULATION PK/PD ANALYSIS

Study title: Population pharmacokinetic/pharmacodynamic analysis for Trileptal® in pediatric patients (age 1 month to <17years) with partial seizures.

Objectives: To explore the population pharmacokinetics/pharmacodynamics of Trileptal at doses up to 60 mg/kg/day as oral suspension as monotherapy or adjunctive therapy in pediatric patients 1 month to <17years of age with partial seizures.

Study design: The following studies were included in the population PK/PD analysis.

Study CTRI476E2338 was an open-label, age-stratified pilot study of oxcarbazepine (OXC) as adjunctive therapy in pediatric patients 1 month to <4 years of age with new onset or inadequately-controlled partial seizures who were taking no antiepileptic drugs (AEDs) or up to two concomitant AEDs.

Study CTRI476E2339 was a multicenter, rater-blind, randomized, age-stratified, parallel-group monotherapy study comparing two doses of OXC in pediatric patients 1 month to <17 years of age with inadequately-controlled or new-onset partial seizures who were hospitalized either for conversion to alternative OXC monotherapy or for initiation of treatment.

Study CTRI476E2340 was a multicenter, rater-blind, randomized, age-stratified, parallel-group, adjunctive therapy study comparing two doses of OXC in pediatric patients 1 month to <4 years of age with inadequately-controlled partial seizures who were taking up to two concomitant AEDs.

Study CTRI476E2341 was an open-label, age-stratified pilot study of oxcarbazepine as monotherapy in pediatric patients 1 month to <4 years of age with inadequately-controlled partial seizures who were hospitalized for alternative OXC monotherapy treatment.

Number of subjects evaluable for pharmacology assessments: Overall 218 patients, 23 patients from Study 2338, 81 patients from Study 2339, 111 patients from Study 2340, and 3 patients from Study 2341 were used for the population pharmacokinetic and pharmacodynamic modeling.

Investigational drug and duration of treatment: Trileptal oral suspension 300 mg/5ml (60 mg/ml) administered orally. Duration of treatment was 30 days in Study 2338, 5 days in Study 2339, 9 days or 35 days in Study 2340, and 4 days in Study 2341.

Methods:
Bioanalytical methods: Part of the plasma samples from the pilot Study 2338, and all the study samples from Studies 2339 and 2340 were analyzed using an LC-MS/MS method. Part of the plasma samples from the pilot Study 2338, and all the study samples from Study 2341were analyzed using an HPLC-UV method.

Pharmacokinetic evaluation: NONMEM was used for the population pharmacokinetic analysis.

Exposure-response evaluations: In Study 2339, OXC treatment group and MHD clearance were used as indicators of MHD exposure in a proportional hazards model for time to exit. In Study 2340, the average MHD trough concentration during the final video-EEG monitoring was used as a predictor of percent change from baseline in seizure frequency. In both studies, OXC treatment group and MHD clearance were used as indicators of MHD exposure in logistic regression models for the risk of an adverse event.

Results:

Pharmacokinetics: The population pharmacokinetic model that was previously developed on data from pediatric patients 3-17 years of age in Study 011 was fit to the new data from patients 1 month to <17years of age in Studies 2338, 2339, 2340, and 2341. Under monotherapy or adjunctive therapy without any enzyme-inducing AEDs, the mean estimated MHD apparent clearance normalized by the body weight was 35% higher in children 1 month to <4 years of age (0.081 L/hr/kg) compared to children 4 to ≤12 years of age (0.060 L/hr/kg), suggesting a higher rate of elimination of MHD in younger children. Compared to adults (0.043 L/kg/hr), the mean body-weight-normalized apparent estimated clearance was 93% and 43% higher for the younger and older children, respectively. There were only three patients >12 years of age in the pharmacokinetic analysis. The mean estimated body-weight-normalized MHD apparent clearance increased by 57% and 35% after co-administration with enzyme-inducing AEDs in patients 1 month to <4 years and 4 to ≤12 years of age, respectively.

Exposure-response relationships: In Study 2339, the time to exit was not found to be related to OXC treatment group, MHD clearance, or age. This conclusion was valid not only for all patients together, but also for patients 1 month to <4 years of age. In Study 2340, the percent change in seizure frequency from baseline was greater with higher trough concentrations, and the effect was more pronounced for patients with higher baseline seizure frequencies. In Study 2339, the risk of adverse events (AEs) increased with decreasing clearance and increasing age in the patients <4 years of age. In Study 2340, the risk of AEs increased with decreasing clearance in the Low-dose OXC group. The High-dose OXC group had more AEs than the Low-dose OXC group, but within the High-dose OXC group there was no relationship between the risk of AEs and clearance.

Comments:

1. The population pharmacokinetic model of epilepsy patients 1 month to <17 years of age was similar to the model found previously for patients 3 years to <17years of age.

2. In the monotherapy study, no relation was found between MHD exposure and the time to meet exit criteria in Study 2339. This is because no effectiveness of trileptal treatment was shown. When the effects of treatment were demonstrated in Study 2340, the seizure frequency during the final video-EEG measurement relates to the average trough MHD concentration during the video-EEG.

3. In both Study 2339 and Study 2340, the number of adverse events in general was found to increase with MHD exposure.

4. Based on the study results, children 1 month to <4 years of age may require twice the oxcarbazepine dose per body weight compared to adults, and children 4 to ≤12 years of age may require a 50% higher oxcarbazepine dose per body weight compared to adults for both mono and adjunctive therapy.

5. For children 1 month to <4 years of age, the influence of enzyme-inducing AEDs on their weight-normalized MHD apparent clearance was investigated by comparison between the monotherapy patients or non-inducing AEDs and patients who stopped to take AEDs before participating in monotherapy period. Therefore, the conclusion, that for children 1 month to <4 years the influence of enzyme-inducing AEDs on apparent clearance may be higher compared to older children, lacks sufficient evidence.

APPENDIX 3. SUMMARY OF STUDIES USED IN PK/PD ANALYSIS

1. Monotherapy in children: Study 2339

Title of study: A multicenter, rater-blind, randomized, age-stratified, parallel-group study comparing two doses of oxcarbazepine as monotherapy in pediatric patients with inadequately-controlled partial seizures.

Investigators: Arthur Cukiert, et al.

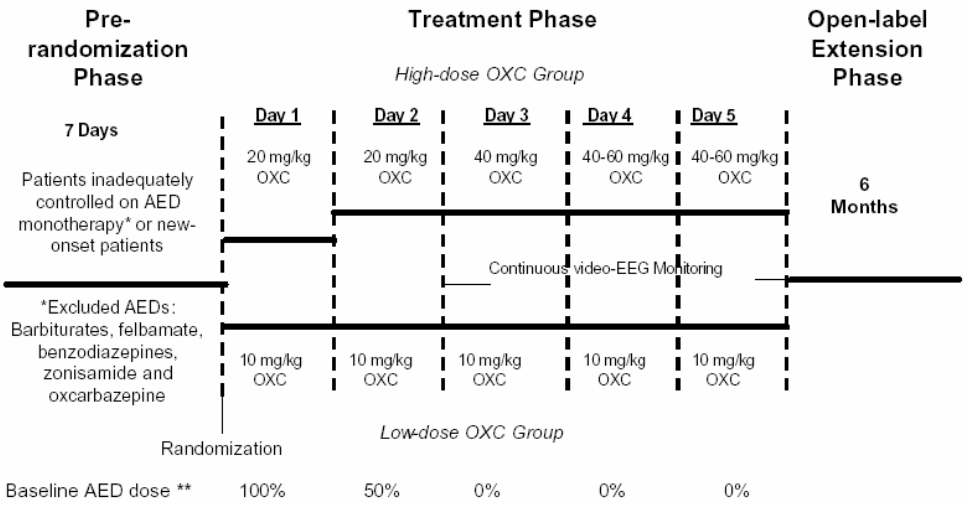
Study center(s): USA (31), Germany (4), Brazil (3), Mexico (3), Lithuania (1)

Study period: First patient enrolled: 07-Jul-2002 Last patient completed: 26-Feb-2004

Development phase: Phase III

Objectives: Primary objective – to evaluate the efficacy and safety of high- versus low-dose oxcarbazepine as monotherapy in pediatric patients 1 month to <17 years of age with inadequately-controlled partial seizures or new-onset partial seizures.
Secondary objective – to explore the population pharmacokinetics of oxcarbazepine at steady-state in pediatric patients 1 month to <17 years of age.

Methodology: This was a multicenter, rater-blind, randomized, parallel group study, stratified by age, using Low- vs. High-dose oxcarbazepine (10 vs. 40-60 mg/kg/day).



Number of patients: Planned – 80; Randomized – 92; Analyzed for efficacy – 87 total (42 High-dose OXC, 44 Low-dose OXC); Analyzed for safety – total 92 (46 High-dose OXC, 46 Low-dose OXC). The patient distribution is shown below.

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

Indication and main criteria for inclusion: Pediatric patients 1 month to <17 years with inadequately-controlled partial seizures who were hospitalized for conversion to alternative oxcarbazepine monotherapy or who were new-onset patients beginning treatment with oxcarbazepine. Patients were to have a diagnosis of partial seizures and were to have experienced 2 to 30 partial seizures during the 7-day pre-randomization phase. Patients were either maintained on a stable dose of one concomitant AED for at least 7 days prior to baseline or were new-onset patients.

Investigational drug: Trileptal oral suspension [300 mg/5 mL (60 mg/mL); 250 ml bottle was administered orally. Two batches were used: batch number H1005, formulation number KN#3750510.01.006 and re-supply batch number H3901, formulation number KN#3750510.006.

Duration of treatment: Up to 5 days

Criteria for evaluation:

Efficacy: Primary variable: time to meeting exit criteria based upon video-EEG confirmed SST1 seizures as determined by the Central Reader. The EEG-confirmed exit criteria were defined as: 1) three SST1 seizures with or without secondarily generalized seizures or 2) a prolonged SST1 seizure. The exit criteria became effective following the first dose of oxcarbazepine on Day 3 (seizures occurring on Days 1 and 2 did not count toward the exit criteria). Any other seizure types did not count toward the exit criteria. Exit criterion #2 ("prolonged SST1 seizure") was defined as a single seizure with the following characteristics:

- A consistent and recognizable focal ictal pattern on EEG involving at least two contiguous electrodes, which must demonstrate a spatial and temporal evolution consistent with an ictal discharge and be distinct from the patient's background cerebral electrical activity, and
- An electrographic duration of at least 5 minutes, and
- A behavioral correlate as observed on video or by a parent/trained site personnel.

Secondary variables: SST1 seizures are EEG-defined seizures of at least 20 second duration which have an accompanying behavioral correlate. SST2 seizures are EEG-defined seizures of at least 20 second duration which do not have an accompanying behavioral correlate.

- The percentage of patients meeting exit criteria based on SST1 seizure data was compared between the two dose groups using Cochran-Mantel-Haenszel (CMH) test blocking on age groups. The percentage of patients meeting exit criteria was also analyzed using a logistic regression model with treatment and age group as explanatory variables. Age was divided into <4 years and 4 years or older.
- Electrographic partial seizure frequency (i.e., SST1+SST2) per 24-hours during the Treatment Phase. Electrographic partial seizure frequency was computed as the number of SST1+SST2 seizures experienced during the continuous video-EEG monitoring in the Treatment Phase, divided by the length of the period in hours and multiplied by 24. Uninterpretable EEG minutes were subtracted from the total period. SST1+SST2 seizure frequencies per 24-hours were compared between treatment groups using the Rank Analysis of Covariance (Stokes, Davis, Koch 1995) with age as the covariate.

Safety: Physical and neurological exams with vital signs and ECG, adverse events, hematology, blood chemistry and urinalysis.

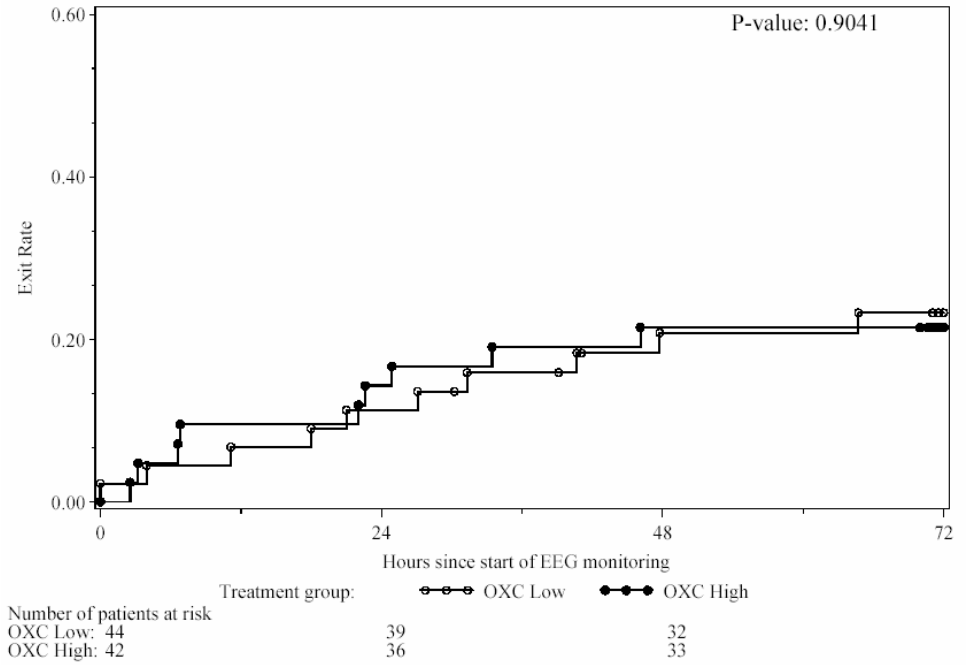
Pharmacokinetics: Plasma samples for the determination of MHD plasma concentrations were scheduled to be obtained for each patient before the morning dose of oxcarbazepine on Day 5. The sampling time was either 0.5, 2, or 5 hours post-dose and was distributed with the patient's IVRS randomization assignment. A second plasma sample was scheduled to be obtained at the Termination Visit (Day 6), 12 hours after the evening dose of oxcarbazepine on Day 5 for those patients who completed all 5 days of the study. For patients who exited the study, a sample was scheduled to be obtained at the time of meeting one of the exit criteria. Patients who prematurely discontinued were also to have a sample obtained at the Termination Visit. Complete dosing information, including the date and time of the actual blood draw and times of the last three study drug doses prior to the sampling, was recorded on the appropriate laboratory requisition form.

Statistical methods: Primary efficacy variable: The time to meeting exit criteria was tested for equality between the two groups (ITT efficacy population) using a log-rank test with evaluable video-EEG data. Secondary efficacy variables: The percentage of patients meeting exit criteria based on SST1 seizure data was compared between the two dose groups using Cochran-Mantel-Haenszel (CMH) test blocking on age groups. Electrographic partial seizure frequency (SST1+SST2) per 24-hours during the Treatment Phase was compared between treatment groups using the Rank Analysis of Covariance with age as the covariate. Safety was assessed using descriptive summaries of adverse events frequencies, laboratory and vital sign values that fell outside of pre-specified ranges, and clinically significant ECG abnormalities. Plasma MHD levels are presented by time point for individual patients and for each dose group (summary statistics).

Results:

Efficacy: There was no significant difference between the High-dose OXC and Low-dose OXC groups (p=0.904) for the primary efficacy variable, time to meeting exit criteria (based upon

video-EEG confirmed seizures as determined by the Central Reader) as shown in the following figure.



The groups were also similar for the secondary efficacy variables: 1) percentage of patients meeting the exit criteria based on SST1 seizure data (21.4% and 22.2% for High-dose OXC and Low-dose OXC groups respectively, p = 0.939 as shown in the following table).

	By Day 3 (1st day of EEG)	By Day 4 (1st - 2nd day of EEG)	By Day 5 (1st - 3rd day of EEG)
Treatment	**n (%)**	**n (%)**	**n (%)**
OXC Low (N=45)	5 (11.1)	9 (20.0)	10 (22.2)
OXC High (N=42)	6 (14.3)	9 (21.4)	9 (21.4)
p-value*			0.939

2) Electrographic partial seizure frequency per 24 hours during the Treatment Phase (mean of 1.3 and 1.0 for the High-dose OXC and Low-dose OXC groups respectively, p = 0.371) as shown in the following table.

	OXC Low	OXC High
N	45	42
Mean	1.0	1.3
SD	2.16	4.33
Median	0.0	0.0
Minimum	0.0	0.0
Maximum	10.1	25.6
p-value*	0.371	

Safety: The overall incidence of AEs was 60.9% and 47.8% in the High-dose OXC and the Low-dose OXC groups, respectively. The difference was mainly due to a higher frequency of nervous system disorders in the High-dose OXC group (41%) than in the Low-dose OXC group (7%). The most frequent (≥ 10% in either treatment group) AEs were somnolence, dizziness, nausea, and vomiting. These AEs occurred only in the High-dose OXC group with the exception of vomiting, which was reported in both groups (11% and 13% in the High-dose OXC and Low-dose OXC groups, respectively). No deaths occurred in this study. The drug was well tolerated by patients in both dose groups, as demonstrated by the low incidence of SAEs and discontinuation due to AEs. There were no unexpected findings identified for laboratory and vital sign parameters.

Pharmacokinetics: Blood samples for plasma MHD determination were available from 87 patients and 152 plasma concentrations were determined. Descriptive statistics were performed on the plasma concentrations. Patients who were inappropriately dosed or who had inappropriate PK sampling were excluded from the analysis (n=7). The trough MHD concentration range (minimum-maximum) obtained in the High-dose OXC group clearly differentiated from that of the Low-dose OXC group: 44.7 – 160 μmol/L and 4.64 – 40.2 μmol/L, respectively with no overlapping. Similar differentiation was obtained for the other sampling times.

Comments:
1. There was no significant difference between the exit rates in the two dose groups. The majority of patients from both dose groups completed the 5-day study without exiting.
2. No statistically significant difference was noted in secondary efficacy variables.
3. There was a clear differentiation between the groups for the MHD concentration ranges with no overlapping. However, this distinction did not separate the two groups by exit rate.

2. Adjunctive Therapy in children: Study 2340

Title of study: A multicenter, rater-blind, randomized, age-stratified, parallel-group study comparing two doses of oxcarbazepine as adjunctive therapy in pediatric patients with inadequately-controlled partial seizures

Investigators: J. Eric Pina-Garza, et al.

Study center(s): USA (37), Argentina (4), France (4), Germany (4), Brazil (3), Mexico (3), Lithuania (1)

Study period
First patient enrolled: 24-Jun-2002. Last patient completed: 11-Jun-2004

Development phase: IIIb

Objectives: Primary objective – to evaluate the efficacy and safety of high-versus low-dose of oxcarbazepine (OXC) as adjunctive therapy in pediatric patients, 1 month to <4 years of age with inadequately controlled partial seizures.
Secondary objective – to explore the population pharmacokinetics of oxcarbazepine at steady-state in pediatric patients 1 month to <4 years of age.

Methodology: This was a multicenter, rater-blind, randomized, parallel group study, stratified by age, using High vs. Low-dose oxcarbazepine (60 vs. 10 mg/kg/day).

Number of patients: Planned – 128; Randomized – 128 (64 in each group); Analyzed for efficacy – 116 total (59 High-dose OXC, 57 Low-dose OXC); Analyzed for safety – total 128 (64 High-dose OXC, 64 Low-dose OXC).

Indication and main criteria for inclusion: Pediatric patients 1 month to <4 years of age with inadequately-controlled partial seizures who were taking up to two concomitant antiepileptic drugs (AEDs) were hospitalized for continuous video-EEG monitoring during both the Baseline Period and the final 72 hours of the Maintenance Period. Patients were to have experienced at least two study seizure type 1 (SST1) seizures during the Baseline Period and were maintained on stable doses of one to two concomitant AEDs for at least 7 days prior to the Baseline Period.

Investigational drug: Oxcarbazepine oral suspension [300 mg/5 mL (60 mg/mL); 250 ml bottle administered orally. An initial batch and a resupply were used: batch number H1008, formulation number KN#3750510.01.006; batch number H3902, formulation number KN#3750510.006.

Duration of treatment: Up to 9 days for the Low-dose OXC group and up to 35 days for the High-dose OXC group.

Criteria for evaluation

Efficacy: Primary variable: absolute change in SST1 seizure frequency per 24 hours (during the last 72 hours of continuous video-EEG monitoring in the Treatment Phase compared to the seizure frequency at Baseline). Secondary variables: (1) percentage change in SST1 seizure frequency per 24 hours; (2) absolute change in SST1 + SST2 seizure frequency per 24 hours; (3) Response to treatment, characterized by at least a 50%, 75%, or 100% reduction in SST1 seizure frequency per 24 hours. SST1 seizures are EEG-defined seizures of at least 20 second duration which have an accompanying behavioral correlate. SST2 seizures are EEG-defined seizures of at least 20 second duration which do not have an accompanying behavioral correlate. Video-EEG confirmed SST1 and SST2 seizures were determined by the Central Reader.

Safety: Physical and neurological exams with vital signs and ECG, adverse events, hematology, blood chemistry and urinalysis.

Pharmacology: Plasma sampling for analysis of plasma levels of the active 10-monohydroxy derivative (MHD) of oxcarbazepine.

Statistical methods: Primary efficacy variable: The absolute change in SST1 seizure frequency per 24 hours was compared between the treatment groups using the Rank Analysis of Covariance.
Secondary efficacy variables: The percentage change in SST1 seizure frequency per 24 hours and the absolute change in SST1 + SST2 seizure frequency per 24 hours were compared between the treatment groups using the Rank Analysis of Covariance. The proportion of patients having a response to treatment was compared between the two dose groups using Cochran-Mantel-Haenszel (CMH) test blocking on age groups.
Safety was assessed using descriptive summaries of adverse events frequencies, laboratory and vital sign values that fell outside of pre-specified ranges, and clinically significant ECG abnormalities.
Plasma MHD levels are presented by time point for individual patients and for each dose group (summary statistics).

Results

Efficacy: The primary efficacy variable, absolute reduction in SST1 seizure frequency per 24 hours, was statistically significantly greater in the High-dose OXC group than in the Low-dose OXC group (median 2.00 and 1.37 for High-dose OXC and Low-dose OXC groups respectively; p=0.043). The percent reduction in SST1 seizure frequency per 24 hours also was statistically significantly greater in the High-dose OXC group than in the Low-dose OXC group (83.3% and 46.2% for High-dose OXC and Low-dose OXC groups respectively, p=0.047). Similarly, the absolute reduction in seizure frequency (SST1 + SST2) per 24 hours was statistically significantly greater in the High-dose OXC group than in the Low-dose OXC group (median 2.32 and 1.64 for High-dose OXC and Low-dose OXC groups respectively; p=0.020). The percentage of patients who were categorized as responding to treatment (i.e., experienced at least a 50% reduction in SST1 seizure frequency per 24 hours) was greater in the High-dose OXC group compared with the OXC Low-dose group, although the difference did not reach statistical significance (64.4% and 47.4% for High-dose OXC and Low-dose OXC groups respectively; p=0.088).

Safety: The overall incidence of AEs was 73.4% and 40.6% in the High-dose OXC and Low-dose OXC groups, respectively. The difference was mainly due to a higher frequency of infections and infestations, nervous system disorders, gastrointestinal disorders, general disorders and administration site conditions, respiratory and thoracic and mediastinal disorders in the High-dose group compared to the Low-dose group.. The most frequent AEs (≥10% in either treatment group) were pyrexia and somnolence. Pyrexia was reported in 17.2% of patients in the High-dose OXC group and 9.4% in the Low-dose OXC group. Somnolence was reported in 17.2% of patients in the High-dose OXC group and 4.7% in the Low-dose OXC groups. No deaths occurred during study treatment. One patient died due to pneumopathy 2 days after being tapered off study drug; according to the investigator, the death was not suspected to be related to study drug. Fifteen patients had SAEs, 10 in the High-dose OXC group and five in the Low-dose OXC group. Overall, most of the SAEs involved infections and/or seizures. Two of the 15 patients with SAEs (both in the Low-dose OXC group) discontinued permanently due to the events (SAEs of somnolence and convulsions in one patient, status epilepticus in the other). Three of the 15 patients with SAEs (two in the High-dose OXC group, one in the Low-dose OXC group) had SAEs with a suspected study drug relationship. In the High-dose OXC group, one patient had an SAE of vomiting and one patient had SAEs of somnolence and increased transaminases that were suspected to be study drug related. One patient in the Low-dose OXC group had SAEs of somnolence and convulsions that were suspected to be study drug related.

Overall, five patients discontinued prematurely due to adverse events, three in the High-dose OXC group and two in the Low-dose OXC group. In the High-dose OXC group, one patient discontinued due to convulsions, one due to status epilepticus, and one due to ataxia, tremor, and vomiting. As previously noted, two patients in the Low-dose OXC group discontinued due to SAEs (somnolence and convulsions in one patient, status epilepticus in the other). No patient discontinued due to laboratory, vital sign or ECG abnormalities. There were no unexpected findings identified for laboratory, vital sign or ECG parameters.

Pharmacokinetics: Blood samples for plasma MHD determination were available from 119 patients and 291 plasma concentrations were determined. Descriptive statistics were performed on 274 plasma concentrations from 116 patients. The median trough MHD concentration clearly differentiated: 58.4 μmol/L and 9.76 μmol/L for the High-dose OXC and Low-dose OXC groups, respectively. For trough sampling, the dose ranges for the last dose given to patients prior to sampling for the High- and Low-dose groups did not overlap (dose range 9.6 to 33.8 mg/kg and 2.3 to 6.0 mg/kg, respectively) but the plasma concentration ranges did show some overlap (7.13 – 152 μmol/L and 1.95 – 36.6 μmol/L, respectively). Similar differentiation was obtained for the other sampling times.

Comments

1. High-dose oxcarbazepine (60 mg/kg/day) adjunctive therapy was significantly more effective in controlling partial seizures than treatment with low-dose oxcarbazepine (10 mg/kg/day) in pediatric patients (ages 1 month to < 4 years).

2. The median trough MHD concentration clearly differentiated: 58.4 μmol/L and 9.76 μmol/L for the High-dose OXC and Low-dose OXC groups, respectively whereas the concentration ranges showed overlapping.

3. Pilot adjunctive therapy in children: study 2338

Title of study: An open-label, age-stratified, pilot study to assess the tolerability and pharmacokinetics of ascending doses of oxcarbazepine oral suspension in pediatric patients with inadequately-controlled partial seizures.

Investigators: Ralph Northam, M.D., Angel Hernandez, M.D., Marcia Litzinger, M.D., Daniela Menican, M.D., Tracy Glauser, M.D., Blanca Vazquez, M.D. Arie Weinstock, M.D.

Study center(s): Seven US centers. Five out of seven centers recruited patients into the study.

Study period: September 25, 2001 to February 25, 2003

Objectives: The objectives of this study were: (1) To evaluate the tolerability and safety of oxcarbazepine as adjunctive therapy in pediatric patients 1 month to <4 years of age with inadequately-controlled partial seizures. (2) To determine the pharmacokinetic profile of oxcarbazepine as adjunctive therapy in patients receiving enzyme-inducing AEDs, or no AEDs or receiving non-enzyme-inducing AEDs (mimicking monotherapy).

Study design: This was an open-label, age-stratified study of oxcarbazepine as adjunctive therapy in pediatric patients with inadequately-controlled partial seizures. The study consisted of three phases: Baseline, Open-label Treatment and Open-label Extension.

Baseline Phase: The study was conducted using a total of 24 patients divided into two groups of 12 patients each. **Group-1** patients were receiving up to two concomitant AEDs, one of which must have been an enzyme-inducing AED. If a second AED was being taken, it could have been either an enzyme-inducing AED or a non-enzyme-inducing AED. **Group-2** patients were either new-onset patients (currently receiving no AED treatment) or patients receiving up to two non enzyme-inducing AEDs (mimicking monotherapy). The 12 patients in each group were stratified into three age categories: 1 to <12 months of age, 12 to <24 months of age, and 24 to <48 months of age. Each age category had four patients.

Open-label Treatment Phase: The Open-label Treatment Phase lasted for up to 30 days. All patients initiated treatment with 10 mg/kg/day of oxcarbazepine for the first 5 days (Days 1-5) and were then titrated up to a maximum of 60 mg/kg/day in increments of 10 mg/kg/day at 5-day intervals. Oxcarbazepine was administered twice daily in the morning and the evening. In the event of poor tolerability, dosage reductions of 5 mg/kg/day were permitted.

Open-label Extension Phase: Patients who completed the Open-label Treatment Phase were eligible to enter the Open-label Extension Phase.

Number of subjects available for pharmacokinetic assessments: Twenty-four male or female patients 1 month to <4 years of age were divided into two groups with 12 patients in each group. Group-I patients received up to two concomitant AEDs, one of which should have been an enzyme-inducing AED. Group-II patients were either new onset patients (currently receiving no AED treatment) or patients receiving up to two non enzyme-inducing concomitant AEDs.

Investigational drug and duration of treatment: Oxcarbazepine 300 mg/5 mL (60 mg/mL) was provided in brown (amber) glass bottles containing 250 mL of oral suspension. Treatment duration was up to 30 days.

Methods: Bioanalytical methods: The MHD and DHD plasma concentrations were determined by either an HPLC or a LC-MS method.

Population Pharmacokinetic Analysis: Observed MHD concentrations were compared with predictions from Model 011. The model was refitted to the current data.

Results: Eighty-two MHD concentration measurements from 23 patients were obtained and compared with the predicted MHD concentrations from Model 011. Model 011 was able to predict the observed MHD concentrations fairly well. When Model 011 was refitted to the present data, that bias was eliminated. Pharmacokinetic parameter estimates for Clearance in the two fits were similar, while the typical Volumes were different. However, standard errors of the Volume parameters were large, indicating imprecision in their estimation. The mean estimated apparent Clearances (±SD) normalized by the body weight were 0.096 ± 0.024 and 0.071 ± 0.015 L/hr/kg for Group-I and 2, respectively. The mean estimated Volumes (± SD) normalized by the body weight were 1.39 ± 0.23 and 1.45 ± 0.11 L/kg. Higher Clearances were found in children from Group-I compared to Group-II but Clearance did not show any trend within groups whereas Volumes seemed to be not affected by co-administration of enzyme-inducing AEDs.

Conclusions: A linear, one-compartment, population-PK model with first-order absorption was established to describe the pharmacokinetic profile of MHD in pediatric patients 1 month to 4 years of age. The model has the same structure as a model determined previously for older pediatric patients (3 years – 17 years of age). Pharmacokinetic parameter estimates for Clearance were similar for the two studies.

4. Monotherapy in adults and children: Study 004

Study Design: Protocol 004 was a multicenter, double-blind, placebo-control, randomized, parallel-group study designed to assess the safety and efficacy of oxcarbazepine as Monotherapy in patients with inadequately controlled partial seizures (including the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures). The study consisted of three phases: a 48-hour Baseline Phase, a 10-day Double-blind Phase, and a Long-term Extension Phase. During the Baseline Phase, patients completing an inpatient presurgical evaluation, who had been taken off all AED(s), were required to have two to 10 partial seizures within 48 hours of randomization. The Double-blind Phase consisted of a 1 -day Titration Period and a 9-day Maintenance Period. Patients began treatment with a 1-day dose of 1500 mg/day oxcarbazepine or matching placebo and then received 2400 mg/day oxcarbazepine or matching placebo for the 9-day Maintenance Period. Patients completing the entire Double-blind Phase, or meeting one of the exit criteria were eligible to enter the Long-term Extension Phase.

Selection Criteria: Participants were selected from male and female patients, 12 to 65 years of age who weighed at least 45 kilograms. Hospitalized patients were required to have undergone a presurgical evaluation for epilepsy and been tapered off of all previous concomitant AEDs. Tapering off of benzodiazepine therapy was required 15 days prior to presurgical evaluation. Lorazepam was the only medication allowed for seizure control during the Baseline Phase. During the Baseline Phase, patients needed to experience two to 10 partial seizures of which a maximum of two seizures could be partial seizures evolving to secondarily generalized seizures.

Efficacy Criteria: The primary efficacy variable was the time to meeting one of the exit criteria. The time to this event was computed from Day 2 at 8 a.m. (the beginning of the Maintenance Period) to the date and time one of the exit criteria was met. When meeting one of these exit criteria, a patient was considered to have completed the Double-blind Phase and was then eligible for the Long-term Extension Phase. The exit criteria were defined as: I) experience of a fourth partial seizure with or without partial seizures evolving to secondarily generalized seizures (exclusive of seizures occurring during the 24-hour Titration Period); 2) experience of two new-onset partial seizures evolving to secondarily generalized seizures; and 3) experience of serial seizures or status epilepticus deemed by the investigator to require intervention. Any patient who finished the entire Double-blind Phase or prematurely discontinued for any reason was classified as a censored patient for these analyses.

Secondary efficacy variable evaluated was the percentage of patients meeting one of the exit criteria.

Pharmacokinetic Assessments: Blood samples for the analysis of oxcarbazepine and its metabolites were collected before the first dose of the study drug and thereafter as trough samples before the morning dose on selected days during the Double-blind Phase (or when a patient complained of adverse experiences or prematurely discontinued).

5. Monotherapy in adults and children: Study 025

Study Design: Protocol 025 was a multicenter, double-blind, placebo-control, randomized, parallel group study designed to evaluate the safety and efficacy of oxcarbazepine in patients with inadequately controlled partial seizures (including the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures). The study consisted of three phases: a 56-day Baseline Phase (all or part of which could have been retrospective), a 90-day Double-blind Phase, and a Long-term Extension Phase. During the Baseline Phase, patients were required to experience at least two seizures per month and were not allowed to have received any AED treatment in the previous 3 months. The Double-blind Phase consisted of a 6-day Titration Period and an 84-day Maintenance Period. Patients were randomized to receive either oxcarbazepine 1200 mg/day (titrated over 6 days) or placebo. Patients completing the entire Double-blind Phase or who experienced their first seizure and were allowed to leave the study, were eligible to enter the Long-term Extension Phase.

Selection Criteria: Participants were selected from male and female patients, at least 10 years of age, who weighed at least 32 kg. Patients were required to have an onset of partial seizures within 2 years and experience at least two partial seizures per month during the Baseline Phase. In addition, each patient was required to have at least 1 seizure-free year prior to the current onset of partial seizures and could not have received treatment from standard AED(s) within 90 days of randomization.

Efficacy Criteria: The primary efficacy variable was the time to first partial seizure. The time to the occurrence of this event was computed from the date and time of first dose of double-blind study drug to the date and time of the occurrence of the first partial seizure. A secondary efficacy variable evaluated the percentage of seizure-free patients.

Pharmacokinetic Assessments: Blood samples for the analysis of oxcarbazepine and the MHD plasma levels were collected as trough levels at one center and according to the following schedule at all other centers: blood collection times at selected visits during the Double-blind Phase distributed over three time slots of 8:00 am to 11:00 am, 11:01 am to 2:00 p m. and 2:01 p.m. to 6:00 p.m..

6. Monotherapy in adults and children: Study 026

Study Design: Protocol 026 was a multicenter, double-blind, randomized, parallel group study that compared high and low dose trileptal (OXC) monotherapy in patients who were considered refractory on carbamazepine (CBZ) treatment. The study was divided into 5 phases: screening (on Day -56), open-label conversion (Day 1 to 27, from CBZ to OXC), open-label baseline (Day 28 to 83), double-blind treatment (including down-titration from Day 84 to 139 and maintenance from Day 140 to 210) and open label long-term extension. During open label baseline phase, OXC 2400 mg/day was administrated and in down titration period, one group kept 2400 mg/day whereas the other group went through gradual down-titration to OXC 300 mg/day.

Selection Criteria: Participants were selected from male and female patients, aged 12 years or older. Patients were required to have 2-40 partial seizures per 28 day period during the 56 day screening phase.

Efficacy Criteria: The primary efficacy variable was the time to meet the exit criteria. The exit criteria include: (1) A two-fold increase in the number of seizures, as compared to the frequency during the open label baseline phase, during 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 the exit criteria. (2) A two-fold increase in the highest consecutive 2-day seizure frequency that occurred during baseline. (3) Occurrence of a single generalized seizure if none occurred during baseline. (4) A prolonged generalized seizure of any seizure subtype to require intervention.

7. ***Monotherapy in adults and children: Study 028***

Study Design: Protocol 028 was a multicenter, double-blind, randomized, parallel group study that compared high (2400mg/day) and low dose (300mg/day) trileptal (OXC) monotherapy in patients with inadequately controlled partial seizure. The study was divided into 3 phases: baseline (from Day -56 to 0), double-blind treatment (including titration from Day 1 to 27 and maintenance from Day 28 to 126), and open label extension. During baseline phase, one or two AEDs could be used. In double-blind phase, OXC 300 mg/day or gradual titration to OXC 2400 mg/day were administrated. AEDs were withdrawn over the first 42 days.

Selection Criteria: Participants were selected from male and female patients, aged 12 years or older with a minimum body weight of 41 kg. Patients were required to have 2-40 partial seizures per 28-day period during the 56 day baseline phase.

Efficacy Criteria: The primary efficacy variable was the number of patients who meet exit criteria and the secondary endpoint was the time to meet the exit criteria. The exit criteria include: (1) A two-fold increase from baseline in partial onset seizure frequency during any 28-day interval. (2) A two-fold increase in the frequency of seizures from the highest 2-day baseline frequency except were the highest 2-da seizure count was 1. In the later case the patient had to have a 2-day seizure count of 3. (3) Occurrence of a single generalized seizure if none occurred 6 month prior to randomization. (4) A prolongation or worsening of generalized seizure to require intervention.

8. ***Adjunctive Therapy in children: Study 011***

Study Design: Protocol 011 was a multicenter. multinational, double-blind, placebo-control, randomized, parallel-group study designed to evaluate the safety and efficacy of oxcarbazepine as adjunctive therapy in pediatric patients with inadequately controlled partial seizures (including the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures). The study consisted of three phases: an 8-week Baseline Phase, a 16-week Double-blind Phase, and a Long-term Extension Phase. During the Baseline Phase, patients were required to have a minimum of eight seizures, with at least one seizure occurring in each 28-day period, and to remain on stable doses of one to two AEDs. The Double-blind Phase consisted of a 2-week Titration Period and a 14-week Maintenance Period. Patients were randomized to either oxcarbazepine (900-1800 mg/day based upon body weight) or placebo. Treatment in the oxcarbazepine group was initiated at 10 mg/kg/day. Patients who did not achieve their assigned dose levels during the Titration Period were titrated to their maximum tolerated dose. This dose was to remain constant during the 14-week Maintenance Period. There was some flexibility of dose allowed during the Maintenance Period if necessary and approved by a Novartis monitor. The dose of the concomitant AED(s) was to remain constant during the entire Double-blind Phase. Patients who completed the Double-blind Phase were eligible to enter the Long-term Extension Phase or a Tapering Period during which they were withdrawn from study drug.

The trial consisted of a baseline phase, double-blind treatment and an open label extension. The population pharmacokinetic analysis consists of data collected during the double blind treatment phase. The double blind phase consisted of a titration phase (14 days) and a maintenance phase (98 days). The titration scheme is shown below in Table 1. Based on body weight, patients' target randomized trial drug doses were determined on a mg/kg basis as shown below in Table 2.

Table 1

Days	Dose (mg/kg/day) given bid
1 to 2	10
3 to 6	20
7 to 10	30
11 to 14	Randomized dose or maximum tolerated dose (whichever was less)

Table 2

Body weight	Target randomized daily dose (given bid)
20 to 29 kg	900 mg (31 mg/kg to 45 mg/kg)
29.1 to 39 kg	1200 mg (31 mg/kg to 41 mg/kg)
39.1 to 60 kg	1800 mg (30 mg/kg to 46 mg/kg)

Patients with body weight >60 kg were randomized to 1800 mg/day dose.

Plasma concentrations of MHD and concomitant antiepileptic drugs were measured on Study days 42, 56, 84 and 112 during the maintenance period. At least one plasma sample was obtained on each of these days in each of the following time periods: 0800-1100 hrs, 1101-1400 hrs, 1401 to 1800 hrs. MHD was analyzed in plasma using a validated HPLC method (Note: the analytical methods section was reviewed as part of the original NDA for Trileptal tablets).

The patient population for the population pharmacokinetic analysis consisted of 109 patients contributing a total of 376 blood samples. Of the 109 patients, 58 were male and 51 were female; 93 were Caucasian, 7 were Black, 1 was Oriental and the remaining were other races. Patients ranged in age from 3 to 17 years (one patient was aged 3 years). (Note: n=5 at 4 years, n=5 at 5 years, n=7 at age 6 years, n=7 at age 7 years). Baseline demographic characteristics are shown below in Table 3. The frequency of coadministered antiepileptic drugs for patients in the pharmacokinetic analysis is shown below (out of n=109) in Table 4.

Table 3

Demographic	N	Mean	SD	Min	Max
Age (years)	109	11.0	3.9	3	17
BSA (m^2)	108	1.31	0.39	0.68	2.59
CrCL (ml/min)	108	79	30	30	150
Height (cm)	108	143	21	98	186
Baseline Seizure Freq (per 28 days)	109	50.1	151	3	1470
SGOT (U/L)	109	23.6	15.1	9	160
SGPT (U/L)	109	16.4	9.5	0	58
Weight (kg)	109	43.3	20.7	15.9	134.5

Table 4:

Coadministered antiepileptic drug	Number of patients on the drug
Carbamazepine	58
Diazepam	4
Gabapentin	14
Lamotrigine	17
Phenobarbital	14
Phenytoin	15
Valproic Acid	33

Selection Criteria: Participants were selected from male and female patients 4 to 17 years of age, (two 3-year olds were allowed entry in the study), who weighed at least 20 kg. Patients were required to experience at least eight seizures during the Baseline Phase with at least one partial seizure occurring during each 28-day period. Patients were required to remain on stable doses of one to two concomitant AEDs that were approved in the country in which they were participating in the study. All other non-allowed AED medications needed to be discontinued at least 30 days prior to starting the Baseline Phase except felbamate which needed to be discontinued at least 90 days prior to starting the Baseline Phase.

Efficacy Variables: The primary efficacy variable was the percentage change (PCH) in partial seizure frequency per 28 days of the Double-blind Phase relative to the Baseline Phase.Patients who provided double-blind seizure diary data over a longer time period than specified in the protocol had their partial seizure frequency per 28 days adjusted to include data from the time period immediately after randomization to the time point where the Double-blind Phase was intended to end as specified in the protocol. This variable was calculated as the number of partial seizures per 28 days in the Double-blind Phase minus the number of partial seizures per 28 days

in the Baseline Phase all divided by the number of partial seizures per 28 days in the Baseline Phase, all multiplied by 100. The partial seizure frequency per 28 days for any study phase was calculated as the total number of partial seizures reported during the phase divided by the number of days in the phase. all multiplied by 28.

Secondary efficacy variables included the number and percentage of responders to treatment (defined as a 50% or greater reduction in partial seizure frequency per 28 days from baseline) and the percentage change in secondarily generalized seizure frequency per 28 days from baseline.

Pharmacokinetic Assessments: Blood samples for the analyses of MHD derivative and DHD levels were obtained at selected visits during the double-blind phase (or when a patient terminated from the study).

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-014/SE5-013 21-285/SE5-008	Brand Name	Trileptal
OCPB Division (I, II, III)	I	Generic Name	Oxcarbazepine
Medical Division	Neuropharm	Drug Class	Anti-epileptics
OCPB Reviewer	John Duan	Indication(s)	Partial seizures
OCPB Team Leader	Ramana Uppoor Jogarao Gobburu	Dosage Form	Tablets
		Dosing Regimen	adults: 600-2400 mg/day, bid children (b) (4) (adjunctive) : 8-60 mg/kg/day, bid children 4 -16 years of age (monotherapy): (b) (4) increased by 5 mg/kg/day every third day to the body weight based recommended doses, not to exceed 2100 mg/day
Date of Submission	12/13/04	Route of Administration	Oral
Estimated Due Date of OCPB Review	5/20/05	Sponsor	Novartis
PDUFA Due Date	6/13/05	Priority Classification	Priority
Division Due Date	5/30/05		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e g , Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	4	4	
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	X	4	4	
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	**1**	**1**	
Data sparse:	X	**1**	**1**	
II Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		5	5	

Filability and QBR comments

	"X" if yes	**Comments to be sent to firm**
Application filable?	X	
Comments sent to firm?		

QBR questions (key issues to be considered)	1 Is the application for monotherapy of trileptal in children (b) (4) approvable from CPB perspective? 2 Is the application for adjunctive therapy of trileptal in children (b) (4) approvable from CPB perspective? 3 If so, what should the dosing regimens be?
Other comments or information not included above	
Primary reviewer Signature and Date	John Duan, PhD
Secondary reviewer(s) Signature and Date	Ramana Uppoor, PhD Jogarao Gobburu, PhD

CC: NDA 21-014, HFD-850 (Lee), HFD-120 (Griffis), HFD-860 (Duan, Uppoor, Gobburu, Mehta, Rahman), CDR

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Jogarao Gobburu
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