Sponsor– Novartis	**Web Page/Link to Prescribing/Label Information**– www.pharma.us.novartis.com/product/pi.jsp
Generic Drug Name– Oxcarbazepine	
Therapeutic Area of Trial– Epilepsy	
Approved Indication– Oxcarbazepine is indicated for adjunctive therapy and monotherapy for treatment of partial seizures (with and without secondarily generalized tonic-clonic seizures) in adult and pediatric patients (US: monotherapy ≥4 years; adjunctive therapy ≥2 years; EU: > 6 years) with epilepsy.	
Study Number– CTRI476E2340	
Title– 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	
Phase of Development– IIIb	
Study Start/End dates– First patient enrolled: 24-Jun-2002 Last patient completed: 11-Jun-2004	
Study Design/Methodology– Multicenter, rater-blind, randomized, parallel group study, stratified by age, using High- vs. Low-dose oxcarbazepine (60 vs. 10 mg/kg/day). Patients were stratified by age as follows: 1-<6, 6-<12, 12-<24, or 24-<48 months and randomized in a 1:1 ratio to receive either low- (10 mg/kg/day) or high-dose (60 mg/kg/day) oxcarbazepine (OXC) as adjunctive therapy. Patients randomized to low-dose oxcarbazepine received 10 mg/kg/day for a total of 9 days. Patients randomized to high-dose oxcarbazepine initially received 10 mg/kg/day for 5 days, titrated up 10 mg/kg/day at 5-days intervals to a maximum dose of 60 mg/kg/day and were maintained on this dose for 9 days.	
Centres– USA (37), Argentina (4), France (4), Germany (4), Brazil (3), Mexico (3), Lithuania (1)	
Publication– JE Piña-Garza, MD; R Espinoza, MD; D Nordli, MD; et al. Neurology (In press)	
Objectives– *Primary outcome/efficacy objective(s)–* 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 outcome/efficacy objective(s)–* To explore the population pharmacokinetics of oxcarbazepine at steady-state in pediatric patients 1 month to <4 years of age.	
Test Product, Dose, and Mode of Administration– Oxcarbazepine oral suspension (60 mg/ml) administered orally.	
Reference Product(s), Dose(s), and Mode(s) of Administration– None	
Criteria for Evaluation– *Primary 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 efficacy:* Percentage change in SST1 seizure frequency per 24 hours; absolute change in SST1 + SST2 seizure frequency per 24 hours; 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/tolerability:* Physical and neurological exams with vital signs and ECG, adverse events, hematology, blood chemistry and urinalysis. *Other:* N/A	

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).

Study Population: Inclusion/Exclusion Criteria and Demographics–

Inclusion criteria

To enter this study, patients must have:

- been 1 month to <4 years of age at Visit 1.
- had a minimum weight of 3kg (6.6 lbs.) at Visit 1.
- had a diagnosis of partial seizures, which may include seizure subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures (based on the International League Against Epilepsy (ILAE) Classification, as modified in 1981 (Commission on Classification and Terminology of the International League Against Epilepsy 1981. Epilepsia;22:489-501).
- had an EEG prior to baseline showing focal epileptiform discharges and/or a focal abnormality.
- been willing to be hospitalized for both the Baseline Period (up to 72 hours) and the final 72 hours of the Maintenance Period.
- been maintained on stable doses of one to two concomitant AEDs for at least 7 days prior to the Baseline Period and continued to be maintained on these dosages during both the Baseline Period and Treatment Phase.
- had non-allowed medication discontinued at least 7 days prior to the Baseline Period.
- had at least 24 hours, with a maximum of 72 hours, of continuous video-EEG monitoring during the Baseline Period (prior to randomization).
- experienced at least two SST1 seizures during the Baseline Period. If the patient experienced at least two SST1 seizures by the end of the first 24 hours of required EEG monitoring the patient was randomized. If the patient did not experience at least two SST1 seizures by the end of the first 24 hours of EEG monitoring, the EEG monitoring was continued (up to a maximum of 72 hours) until the second SST1 seizure was experienced, at which point the patient was randomized. Patients who failed screening because they did not meet the seizure entry criteria following completion of the Baseline Period were allowed to enter the Open-label Extension Phase of the study Protocol Amendment 2 (10-June-2003).
- had a previous computed tomography or magnetic resonance imaging scan that confirmed the absence of evolving space occupying lesions or progressive neurological diseases. (No physical examination changes suggestive of such lesions or diseases should have occurred since that imaging procedure).
- had routine clinical laboratory values within a normal range. Minor deviations in clinical laboratory values considered clinically insignificant were allowed.
- had a parent or legal guardian's written consent for the patient to enter the study once the nature of the study had been fully explained.

Exclusion criteria

To enter this study, a patient must not have had:

- a diagnosed treatable etiology of seizures, such as metabolic disturbance, toxic exposure, or an active infection.

- a primary diagnosis of a generalized epilepsy/generalized seizures (e.g., Lennox Gastaut syndrome, severe infantile myoclonus, or infantile spasms with or without hypsarrhythmia), with the exception of secondarily generalized seizures.
- a history of status epilepticus within 30 days prior to Baseline Period.
- psychogenic or non-epileptic seizures.
- seizures only occurring in cluster patterns, defined as multiple seizures occurring in less than a 30-minute period.
- used intermittent rectal diazepam, or any other acute seizure treatment medication, within 30 days prior to the Baseline Period, or used felbamate within 6 months prior to randomization.
- serum sodium levels <135 mEq/L.
- evidence upon physical examination, or a history of any clinically significant cardiac, respiratory, hepatic, gastrointestinal, renal, hematological, or oncologic disorder requiring current medical intervention/therapy likely to have a significant impact on the outcome of this study.
- a history of known or suspected chronic infection(s) (e.g., hepatitis, HIV).
- clinically significant ECG abnormalities.
- a history of parents or legal guardians who are noncompliant to medical regimens or who were considered potentially unreliable (as judged by the principle investigator).
- a nursing mother who was taking AEDs or currently had an alcohol/drug abuse problem.
- participated in another study of an investigational drug/device within 30 days prior to the Baseline Period.
- a history of hypersensitivity to carbamazepine treatment.
- a history of oxcarbazepine treatment. This was changed to a history of oxcarbazepine treatment that would be described by any of the following: (Protocol Amendment 1 [14-April-2003])
    - treatment for more than a total of 4 weeks (continuous or accumulated),
    - treatment with doses greater than or equal to 20 mg/kg/day,
    - treatment discontinued due to AEs possibly caused by oxcarbazepine,
    - treatment within 4 weeks of entering the Screening Period.

Deviations from the inclusion/exclusion criteria were allowed if approved by Novartis. Written confirmation acknowledging approved deviations form the inclusion/exclusion criteria were sent from the sponsor to the investigator; this confirmation letter was kept on file at the study site.

Number of Subjects	**OXC low-dose (10 mg/kg/day)**	**OXC high-dose (60 mg/kg/day)**
Planned N	64	64
Randomized, n	64	64
Completed, n (%)	59 (92.2)	56 (87.5)
Withdrawn, n (%)	5 (7.8)	8 (12.5)
Included in the primary analysis , n (%)	57 (89.1)	59 (92.2)
Withdrawn due to adverse events, n (%)	2 (3.1)	3 (4.7)
Withdrawn due to unsatisfactory therapeutic effect, n (%)	1 (1.6)	3 (4.7)
Withdrawn for other reasons , n (%)	2 (3.1)	2 (3.1)

Demographic and Background Characteristics		
N (All randomized patients)	**OXC low-dose N=64**	**OXC high-dose N=64**
Females:males, n	29:35	26:38
Baseline age, n (%) 1-<6 months 6 - <12 months 12 - <24 months 24 - <48 months	 10 (15.6) 12 (18.8) 19 (29.7) 23 (35.9)	 11 (17.2) 12 (18.8) 19 (29.7) 22 (34.4)
Race, n (%) White Black Other	 42 (65.6) 3 (4.7) 19 (29.7)	 47 (73.4) 5 (7.8) 12 (18.8)
ILAE Classification Simple partial seizures Complex partial seizures Partial seizures, secondarily generalized Other	 20 (31.3) 46 (71.9) 24 (37.5) 18 (28.1)	 23 (35.9) 50 (78.1) 35 (54.7) 22 (34.4)
Primary Efficacy Result(s)–intent to treat population (defined as all randomized patients who received oxcarbazepine and had video-EEG data from both baseline and final treatment visit)		
Absolute change in partial seizure frequency (SST1) per 24-hours (ITT population)	**OXC low-dose N=57**	**OXC high-dose N=59**
Baseline Mean (SD)	13.29 (22.34)	10.27 (17.82)
Treatment Mean (SD)	10.50 (24.08)	2.67 (4.40)
Absolute Change Mean (SD)	-2.79 (16.02)	-7.60 (17.38)
Median Absolute Change	-1.37	-2.00
p-value (based on median absolute change between the high- and low-dose OXC groups from the Rank Analysis of Covariance model stratifying by age groups with the SST1 seizure frequency/24 hours at baseline as covariate)	0.043	

Secondary efficacy result(s)–intent to treat population (defined as all randomized patients who received oxcarbazepine and had video-EEG data from both baseline and final treatment visit)		
Percent change in partial seizure frequency (SST1) per 24-hours (ITT population)	**OXC low-dose N=57**	**OXC high-dose N=59**
Baseline Mean (SD)	13.29 (22.34)	10.27 (17.82)
Treatment Mean (SD)	10.50 (24.08)	2.67 (4.40)
Percent Change Mean (SD)	-12.80 (114.66)	-45.73 (90.36)
Median Percent Change	-46.18	-83.33
P-value (based on median percent change between high- and low-dose OXC groups from the Rank Analysis of Covariance model stratifying by age groups with the SST1 seizure frequency/24 hours at baseline as covariate)	0.047	
Absolute change in electrographic partial seizure frequency (SST1+SST2) per 24-hours (ITT population)	**OXC low-dose N=57**	**OXC high-dose N=59**
Baseline Mean (SD)	14.03 (23.23)	10.82 (18.06)
Treatment Mean (SD)	10.77 (24.11)	3.07 (5.11)
Percent Change Mean (SD)	-3.26 (16.78)	-7.76 (17.13)
Median Percent Change	-1.64	-2.32
P-value based on comparison for the median absolute change between the high- and low-dose OXC groups from the Rank Analysis of Covariance model stratifying by age groups with the SST1+SST2 seizure frequency per 24 hours at baseline as covariate.	0.020	
Response to treatment (ITT population)	**OXC low-dose N=57**	**OXC high-dose N=59**
= 50% Reduction	27 (47.37)	38 (64.41)
= 75% Reduction	19 (33.33)	32 (54.24)
100% Reduction	10 (17.54)	19 (32.20)
P-value based on comparison between the high- and low-dose OXC groups using the Cochran-Mantel-Haenszel (CMH) test.	0.088	

Safety Results

Patients with Adverse Events and Adverse Events by System Organ Class	OXC low-dose N=64 n (%)	OXC high-dose N=64 n (%)
Total no. of patients with AEs	26 (40.6)	47 (73.4)
Infections and infestations	9 (14.1)	25 (39.1)
Nervous system disorders	6 (9.4)	24 (37.5)
Gastrointestinal disorders	4 (6.3)	14 (21.9)
General disorders and administration site conditions	6 (9.4)	13 (20.3)
Respiratory, thoracic and mediastinal disorders	1 (1.6)	10 (15.6)
Psychiatric disorders	3 (4.7)	6 (9.4)
Investigations	2 (3.1)	4 (6.3)
Metabolism and nutrition disorders	0 (0.0)	4 (6.3)
Skin and subcutaneous tissue disorders	4 (6.3)	4 (6.3)
Injury, poisoning and procedural complications	0 (0.0)	2 (3.1)
Vascular disorders	0 (0.0)	2 (3.1)
Blood and lymphatic system disorders	0 (0.0)	1 (1.6)
Eye disorders	0 (0.0)	1 (1.6)

10 Most Frequently Reported AEs by preferred term and treatment	OXC low-dose N=64 n (%)	OXC high-dose N=64 n (%)
Pyrexia	6(9.4)	11(17.2)
Somnolence	3(4.7)	11(17.2)
Convulsion	1(1.6)	6(9.4)
Cough	0(0.0)	6(9.4)
Vomiting	1(1.6)	6(9.4)
Ataxia	0(0.0)	5(7.8)
Otitis media	1(1.6)	4(6.3)
Pneumonia	0(0.0)	4(6.3)
Status epilepticus	3(4.7)	4(6.3)
Diarrhoea	1(1.6)	3(4.7)

Serious Adverse Events and Deaths	OXC low-dose N = 64 n (%)	OXC high-dose N = 64 n (%)
Death	0 (0.0)	0 (0.0)
SAEs	5 (7.8)	10 (15.6)
Premature discontinuation due to AEs	2 (3.1)	3 (4.7)
Premature discontinuation due to SAEs	2 (3.1)	0 (0.0)

No deaths occurred during study treatment. Fifteen patients had serious adverse events (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 SAEs (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.

Other Relevant Findings– No patients in either group had a clinically notable sodium value.

Date of Clinical Trial Report– 06-Oct-2004
Date Inclusion on Registry– 31-August-2005
Date of Latest Update– 1-March-2006