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 partial seizures	
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– CTRI476E2339	
Title– 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	
Phase of Development– Phase IIIb	
Study Start/End dates– 07-July-2002 through 26-Feb-2004	
Study Design/Methodology– This was a multicenter, rater-blind, randomized, parallel group monotherapy study comparing two doses of oxcarbazepine (low-dose 10 mg/kg/day vs. high-dose oxcarbazepine 40-60 mg/kg/day) in pediatric patients (1 month to <17 years of age) with either inadequately-controlled partial seizures or new-onset seizures who were hospitalized either for conversion to or initiation of treatment. Patients were randomized in a 1:1 ratio to high-dose or low-dose oxcarbazepine and stratified into age groups as follows: 1 month to <6 months, 6 months to <12 months, 12 months to <24 months, 24 months to <48 months, 4 to <8 years, and 8 to <17 years. Patients completed the study by either completing the 5-day treatment period or meeting one of the two specified exit criteria. Because oxcarbazepine is only available as a 6% oral suspension, with no placebo or lower strength formulations, it was not possible to securely blind the administration of the study drug. Therefore, this study used a "rater-blind" design in which video-EEG recorded seizures were assessed by an independent pediatric neurologist who was not involved in the conduct of the study and was blind to study treatment.	
Centres– Patients were enrolled from 42 centers: 31 in the USA, 4 in Germany, 3 in Brazil, 3 in Mexico, and 1 in Lithuania	
Publication – Ongoing	
Objectives– *Primary objective(s)–* • To evaluate the efficacy of high- vs low-dose oxcarbazepine as monotherapy based on time to meeting one of the exit criteria starting from the first dose of oxcarbazepine on Day 3. *Secondary outcome/efficacy objective(s)–* • To evaluate the efficacy of high- vs low-dose oxcarbazepine as monotherapy based on percentage of patients meeting one of the exit criteria and the electrographic partial seizure frequency per 24 hours during the treatment phase.	
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:* based on time to meeting one of the exit criteria starting from the first dose of oxcarbazepine on Day 3. The two video-EEG confirmed exit criteria were three SST-1 seizures with or without secondarily generalized seizures or an SST-1 lasting =5 minutes [seizures were characterized by	

(1) a recognizable focal ictal pattern on EEG involving at least two contiguous electrodes, which must have demonstrated a spatial and temporal evolution consistent with an ictal discharge and be distinct from the patient's background cerebral electrical activity; (2) an electrographic duration of at least 20 seconds; and (3) a behavioral correlate as observed on video or by trained site personnel or a parent)**]**.

Secondary efficacy: based on percentage of patients meeting one of the exit criteria and the electrographic partial seizure frequency (SST-1 + SST-2) per 24 hours during the treatment phase (SST-2 seizures were the same as the SST-1 seizures except that no behavioral correlate was observed).

Safety/tolerability: Safety assessments consisted of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, and blood chemistry laboratory parameters, urinalysis regular measurement of vital signs, and the performance of physical examinations and electrocardiograms.

Other: N/A

Pharmacology: Plasma sampling for determination of plasma levels of the active metabolite MHD.

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 treatment groups using the Cochran-Mantel-Haenzel 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 the descriptive summaries of adverse events frequencies, laboratory and vital sign values that fell outside of normal ranges, and clinically significant ECG abnormalities.

Study Population: Inclusion/Exclusion Criteria and Demographics – Pediatric patients 1 month to <17 years of age 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 had a diagnosis of partial seizures, an EEG prior to pre-randomization showing focal epileptiform discharges and/or a focal abnormality, and were to have experienced 2-30 partial seizures during the 7-day pre-randomization phase. Patients were either maintained on a stable dose of 1 concomitant AED for at least 7 days prior to baseline or were new-onset patients.

Patients with treatable etiology of seizures (eg, metabolic disturbance, toxic exposure or active infection), primary generalized epilepsy/generalized seizures, status epilepticus within 30 days prior to baseline, psychogenic or non-epileptic seizures, seizures in cluster patterns (multiple seizures within 30 minutes), benzodiazepine use within 1 week prior to randomization, barbiturate use within 1 month (patients <3 months of age) or 2 weeks (patients >3 months of age) prior to randomization, felbamate use within 6 months prior to randomization, serum sodium levels <135 mEq/L, history of hypersensitivity to carbamazepine or prior oxcarbazepine use were excluded.

Number of Subjects	**Oxcarbazepine Low**	**Oxcarbazepine High**
Planned N	40	40
Randomized n	46	46
Completed n (%)	42 (91.3)	44 (95.7)
Withdrawn n (%)	4 (8.7)	2 (4.3)
Included in the primary analysis n (%)	45 (97.8)	42 (91.3)
Withdrawn due to adverse events n (%)	1 (2.2)	2 (4.3)
Withdrawn due to lack of efficacy n (%)	0	0
Withdrawn for other reasons n (%)	3 (6.5)	0

Demographic and Background Characteristics		
N (ITT)	45	42
Females:males	18:28	25:21
Baseline age, n (%)		
1 to <6 months	4 (8.7)	4 (8.7)
6 to <12 months	7 (15.2)	6 (13.0)
12 to <24 months	6 (13.0)	6 (13.0)
24 to <48 months	9 (19.6)	9 (19.6)
4 to < 8 years	10 (21.7)	11 (23.9)
8 to <17 years	10 (21.7)	10 (21.7)
Mean weight, kg (SD)		
Race White n (%) Black n (%) Other n (%)	 30 (65.2) 8 (17.4) 8 (17.4)	 26 (56.5) 4 (8.7) 16 (34.8)
Initiation of monotherapy		
Yes	5 (10.9)	10 (21.7)
No	41 (89.1)	36 (78.3)
ILAE Classification		
Simple partial	13 (28.3)	13 (28.3)
Complex partial	35 (76.1)	35 (76.1)
Partial seizures with secondary GTC	22 (47.8)	23 (50.0)
Other seizures	13 (28.3)	12 (26.1)

Primary Efficacy Result(s)–intent to treat population

Number (%) of patients meeting exit criteria based on SST1 seizure data – All

	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

* p-value based on comparison between the High-dose OXC group and the Low-dose OXC group using Cochran-Mantel-Haenszel (CMH) test blocking on age groups.

Number of patients meeting exit criteria based on SST1 seizure data - patients <4 years old

	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=25)	3	12.0	4	16.0	5	20.0
OXC High (N=22)	4	18.2	6	27.3	6	27.3

Number of patients meeting exit criteria based on SST1 seizure data - patients =4 years old

Treatment	By Day 3 (1st day of EEG) n	%	By Day 4 (1st-2nd day of EEG) n	%	By Day 5 (1st-3rd day of EEG) n	%
OXC Low (N=20)	2	10.0	5	25.0	5	25.0
OXC High (N=20)	2	10.0	3	15.0	3	15.0

Secondary efficacy result(s)–intent to treat population

Electrographic partial seizure frequency (SST-1 + SST-2) per 24 hours

	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 Results

Patients with Adverse Events and Adverse Events by System Organ Class

	OXC Low N = 46 n (%)	OXC High N = 46 n (%)	Total N = 92 n (%)
Total number of patients with AEs	22 (47.8)	28 (60.9)	50 (54.3)
Nervous system disorders	3 (6.5)	19 (41.3)	22 (23.9)
Gastrointestinal disorders	11 (23.9)	13 (28.3)	24 (26.1)
General disorders and administration site conditions	4 (8.7)	5 (10.9)	9 (9.8)
Psychiatric disorders	1 (2.2)	3 (6.5)	4 (4.3)
Eye disorders	0 (0.0)	2 (4.3)	2 (2.2)
Cardiac disorders	1 (2.2)	1 (2.2)	2 (2.2)
Infections and infestations	3 (6.5)	1 (2.2)	4 (4.3)
Investigations	3 (6.5)	1 (2.2)	4 (4.3)
Skin and subcutaneous tissue disorders	5 (10.9)	1 (2.2)	6 (6.5)
Injury, poisoning and procedural complications	1 (2.2)	0 (0.0)	1 (1.1)
Metabolism and nutrition disorders	4 (8.7)	0 (0.0)	4 (4.3)
Renal and urinary disorders	1 (2.2)	0 (0.0)	1 (1.1)
Respiratory, thoracic and mediastinal disorders	7 (15.2)	0 (0.0)	7 (7.6)

10 Most Frequently Reported AEs Overall by Preferred Term	Oxcarbazepine Low	Oxcarbazepine High
Somnolence	0	**8 (17.4)**
Dizziness	0	**6 (13.0)**
Nausea	0	**5 (10.9)**
Vomiting	**6 (13.0)**	5 (10.9)
Ataxia	0	**2 (4.3)**
Conclusion	1 (2.2)	**2 (4.3)**
Abnormal gait	0	**2 (4.3)**
Headache	1 (2.2)	**2 (4.3)**
Status epilepticus	0	**2 (4.3)**
Abdominal pain	0	**1 (2.2)**

Serious Adverse Events and Deaths

	OXC Low N = 46 n (%)	OXC High N = 46 n (%)	Total N = 92 n (%)
Death	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	1 (2.2)	2 (4.3)	3 (3.3)
Premature discontinuation due to AEs	1 (2.2)	2 (4.3)	3 (3.3)
Premature discontinuation due to SAEs	0 (0.0)	0 (0.0)	0 (0.0)
Premature discontinuation due to lab abnormalities	0 (0.0)	0 (0.0)	0 (0.0)

Includes 1 patient from the Low-dose group and 2 patients from the High-dose group with SAEs: Low-dose group: 1 patient experienced a 5-sec episode of apnea, cardiac arrest, and abnormal EEG with subsequent bradycardia; High-dose group: 2 patient had status epilepticus.

Other Relevant Findings–

Date of Clinical Trial Report–	29-Sep-2004	
Date Inclusion on Registry–	31-August-2005	
Date of Latest Update–	1-March-2006	