Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Licarbazepine

Therapeutic Area of Trial

Manic episodes of bipolar I disorder

Approved Indication

Investigational

Study Number

CLIC477D2302E1

Title

A 52-week, open-label extension study to evaluate the safety and tolerability of licarbazepine 750-2000 milligram/day (mg/d) in the treatment of manic episodes of bipolar I disorder.

Phase of Development

Phase III

Study Start/End Dates

04 Jan 2005 to 25 Jul 2007

Study Design/Methodology

This was a 52-week, multicenter, open-label extension study for patients completing the 6-week double-blind study CLIC477D2302. During this extension study, all patients received open-label treatment with licarbazepine 750-2000 mg/day, administered in morning and evening doses (b.i.d. dosing).

The baseline for this extension study was the final visit of study CLIC477D2302 (Visit 9). On Day 1, the dosage of licarbazepine was 500 mg and increased to 750 mg on Day 2. On Day 3, the dosage was to be raised to 1000 mg, and then maintained at this dosage through Day 7. On Day 7, (Visit 10), the dosage of study drug could be maintained at 1000 mg, or increased to 1500 mg. Patients who did not tolerate 1000 mg/day at Day 7 could receive 750 mg/day. In such cases, the investigator was required to consider increasing the dosage to 1000 mg/day as soon as possible. Patients who could not tolerate 750 mg/day were to be removed from the study.

On Day 14 (Visit 11) the dosage of study drug could be maintained, increased up to 2000 mg, or decreased to the previous dosage level. Thereafter, dosage changes could be made at the scheduled visits or, if necessary, between visits. Dosage changes were to be limited to one per week.

Centers

50 centers: North America (15), the European Union (EU) (7), South America (11), Ukraine (14), India (3).

Publication

Ongoing

Objectives

Primary objective(s)

To assess the tolerability and long-term safety of open-label treatment with licarbazepine 750-2000 mg/day over 52 weeks in patients who completed the 6-week double-blind study CLIC477D2302, with respect to the rates of adverse events (AE) and serious adverse events (SAE), as well as changes in laboratory values, ECGs and vital signs.

Secondary objective(s)

To monitor the efficacy of open-label treatment with licarbazepine 750-2000 mg/day over 52 weeks.

Test Product (s), Dose(s), and Mode(s) of Administration

Licarbazepine 750-2000 mg/day was administered orally to all the patient in morning and evening doses (b.i.d. dosing). Patients received 750-2000 mg/day of licarbazepine, depending on tolerability. The dosage changes could be made at the scheduled visits or, if necessary, between visits and were limited to one per week.

Reference Product(s), Dose(s), and Mode(s) of Administration

Not applicable.

Criteria for Evaluation

Primary variables

- Frequency, type, duration and intensity of AEs and SAEs
- Relationship of AE/SAE frequency and type to dosage of study drug
- The documented reasons for withdrawal from the study

Secondary variables

- Young Mania Rating Scale (Y-MRS)
- Brief Psychiatric Rating Scale (BPRS)
- Clinical Anxiety Scale (CAS)
- Global Improvement rating of the Clinical Global Impression (CGI-I)
- Severity of Illness rating of the Clinical Global Impression (CGI-S)
- 21-item Hamilton Depression Rating Scale (HAMD)

Safety and tolerability

Frequency of AE with severity grade, relationship to study drug, duration, action taken and seriousness, regular monitoring of hematology, blood chemistry, urinalysis, physical examination, vital signs, pregnancy tests for females of childbearing potential and electrocardiograms.

Pharmacology

None

Other

None

Statistical Methods

Summary statistics of Y-MRS and CGI-I were reported by visit for the safety population by double-blind treatment in the core study and overall. This was done for observed cases; no imputation for missing data was performed.

Treatment emergent AEs were summarized by presenting the number and percentage of patients having any AE, having an AE in each system organ class, and having each individual AE (preferred term). Treatment emergent AEs were defined as AEs which occurred after entering the open-label extension phase or those occurring in the core phase but worsened during the extension. Death, SAEs, suspected drug-related AEs, discontinuations due to AEs and suspected drug-related discontinuations due to AEs were also reported as appropriate.

All clinically notable laboratory, ECG and vital sign abnormalities were summarized using the same clinically notable criterion as for the core phase. All AE, laboratory, ECG and vital sign

data were listed as appropriate.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

- Written informed consent provided prior to participation in the extension study
- Successful completion of study CLIC477D2302
- Willingness and ability to comply with all study requirements

Exclusion Criteria

- Premature discontinuation from study CLIC477D2302
- Failure to comply with the study CLIC477D2302 protocol

Number of Subjects

From the group of patients who received licarbazepine during the core study, 117 entered the extension study and from the group who received placebo, 134 patients entered the extension study. Details of patient disposition are mentioned in the table below:

	DB LIC N=117 n (%)	DB Placebo N=134 n (%)	Total N=251 n (%)
Disposition Reason			
Entered extension	117 (100.0)	134 (100.0)	251 (100.0)
Completed	19 (16.2)	26 (19.4)	45 (17.9)
Discontinued	98 (83.8)	108 (80.6)	206 (82.1)
Main cause of discontinuation			
Administrative problems	53 (45.3)	49 (36.6)	102 (40.6)
Subject withdrew consent	20 (17.1)	22 (16.4)	42 (16.7)
Adverse Event(s)	10 (8.5)	17 (12.7)	27 (10.8)
Lost to follow-up	9 (7.7)	13 (9.7)	22 (8.8)
Unsatisfactory therapeutic effect	4 (3.4)	5 (3.7)	9 (3.6)
Protocol violation	1 (0.9)	2 (1.5)	3 (1.2)
Death	1 (0.9)	0 (0.0)	1 (0.4)

Demographic and Background Characteristics

Demography (age, sex, race etc.) and baseline characteristics (weight, etc) were summarized by treatment group for all patients using mean, standard deviation (SD), median and others as shown in the table below:

Variable	DB-licarbazepine N=116	DB-placebo N=128	Total N=244
Age* (years)			
n	116	128	244
Mean	39.4	41.5	40.5
SD	12.82	12.96	12.90
Minimum	18.0	18.0	18.0
Median	40.0	41.0	41.0
Maximum	66.0	70.0	70.0
Sex* - n (%)			
Male	49 (42.2)	59 (46.1)	108 (44.3)
Female	67 (57.8)	69 (53.9)	136 (55.7)
Race* - n (%)			
Caucasian	99 (85.3)	110 (85.9)	209 (85.7)
Black	9 (7.8)	9 (7.0)	18 (7.4)
Oriental	2 (1.7)	1 (0.8)	3 (1.2)
Other	6 (5.2)	8 (6.3)	14 (5.7)
Weight (kg)**			
n	116	128	244
Mean	79.75	81.23	80.53
SD	21.52	21.36	21.41
Minimum	42.0	39.8	39.8
Median	78.0	77.5	78.0
Maximum	166.8	158.2	166.8

*Data were collected at the baseline of the double-blind study (LIC2302)

** Weight was collected from the OL baseline visit

Primary Objective Result(s)

Serious adverse events and deaths

One death due to completed suicide occurred.

	Total N=244 n (%)
Death	1 (0.4)*
Treatment emergent SAE(s)	36 (14.8)
Discontinued due to treatment emergent AE(s)	27 (11.1)

* An additional death due to completed suicide occurred 8 days after the last dose of study medication and was therefore not included in the clinical database

The table below depicts SAEs by system organ class (SOC) and preferred terms

	Total N=244 n (%)
Patients with at least one SAE	36 (14.8)
Psychiatric disorders	22 (9.0)
Mania	8 (3.3)
Bipolar disorder	3 (1.2)
Depression	3 (1.2)
Major depression	3 (1.2)
Anxiety	2 (0.8)
Aggression	1 (0.4)
Bipolar I disorder	1 (0.4)
Delirium	1 (0.4)
Homicidal ideation	1 (0.4)
Psychotic disorder	1 (0.4)
Suicidal ideation	1 (0.4)
Gastrointestinal disorders	3 (1.2)
Ileus	1 (0.4)
Pancreatitis	1 (0.4)
Vomiting	1 (0.4)
Injury, poisoning and procedural complications	3 (1.2)
Contusion	1 (0.4)
Lower limb fracture	1 (0.4)
Overdose	1 (0.4)
Road traffic accident	1 (0.4)
Nervous system disorder	3 (1.2)
Psychomotor hyperactivity	2 (0.8)
Syncope	1 (0.4)

Infection and infestations	2 (0.8)
Gastroenteritis	1 (0.4)
Urinary tract infection	1 (0.4)
General disorders and administration site conditions	2 (0.8)
Non-cardiac chest pain	1 (0.4)
Pyrexia	1 (0.4)
Metabolism and nutrition disorder	2 (0.8)
Hyponatremia	2 (0.8)
Vascular disorders	2 (0.8)
Hypotension	1 (0.4)
Orthostatic hypotension	1 (0.4)
Cardiac disorders	2 (0.8)
Atrial fibrillation	1 (0.4)
Myocardial infarction	1 (0.4)
Eye disorders	1 (0.4)
Cataract	1 (0.4)
Hepatobiliary disorders	1 (0.4)
Cholelithiasis	1 (0.4)

A subject with multiple occurrences of an AE is counted only once in the AE category

A subject with multiple adverse events within a primary system organ class is counted only once in the total row

Adverse events

Most frequent affected system organ class is summarized in the table below

	Total N=244 n (%)
Total no. of patients with at least one treatment emergent AE	169 (69.3)
Primary system organ class	
Psychiatric disorders	76 (31.1)
Nervous system disorders	74 (30.3)
Gastrointestinal disorders	60 (24.6)
Infections and infestations	38 (15.6)
Investigations	23 (9.4)
Musculoskeletal and connective tissue disorders	21 (8.6)
General disorders and administration site conditions	19 (7.8)
Metabolism and nutrition disorders	18 (7.4)
Injury, poisoning and procedural complications	14 (5.7)
Respiratory, thoracic and mediastinal disorders	14 (5.7)
Skin and subcutaneous tissue disorders	13 (5.3)

A subject with multiple AEs within a primary system organ class is counted only once in the total row.

The table below depicts the most frequent treatment emergent AEs by preferred terms

	Total N=244 n (%)
Total no. of patients with at least one treatment emergent AE	91 (68.9)
Treatment emergent adverse event	
Somnolence	29 (11.9)
Dizziness	27 (11.1)
Headache	27 (11.1)
Insomnia	22 (9.0)
Anxiety	15 (6.1)
Depression	15 (6.1)
Vomiting	15 (6.1)

A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category

Discontinuation due to treatment emergent AEs

The table below summarizes adverse events that led to discontinuation of study drug by SOC and preferred term

	Total N=244 n (%)
Patients who discontinued due to AEs	27 (11.1)
Psychiatric disorders	19 (7.8)
Major depression	6 (2.5)
Depression	5 (2.0)
Bipolar disorder	2 (0.8)
Mania	2 (0.8)
Anxiety	1 (0.4)
Completed suicide	1 (0.4)
Homicidal ideation	1 (0.4)
Suicidal ideation	1 (0.4)
Nervous system disorders	2 (0.8)
Dizziness	2 (0.8)
Headache	1 (0.4)
Somnolence	1 (0.4)
Gastrointestinal disorders	2 (0.8)
Nausea	2 (0.8)
Eye Disorders	2 (0.8)
Diploplia	1 (0.4)
Vision blurred	1 (0.4)
Cardiac disorders	1 (0.4)
Myocardial infarction	1 (0.4)
Metabolism and nutrition disorders	1 (0.4)

Hyponatremia	1 (0.4)*
Investigations	1 (0.4)
Alanine aminotransferase increased	1 (0.4)
Gamma-glutamyltransferase increased	1 (0.4)
Injury, poisoning and procedural complications	1 (0.4)
Overdose	1 (0.4)

A subject with multiple occurrences of an AE is counted only once in the AE category for that treatment.

A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

* One patient, discontinued from the study due to asymptomatic hyponatremia. Due to a data error, this event was not captured in the clinical database

Clinical laboratory evaluation

The number of patients with clinically notable abnormal hematology values were low and were not considered clinically meaningful. The table below summarizes the numbers of patients with clinically notable biochemistry abnormalities

TEST		Total N=244 n (%)
Bicarbonate	Total	238
	Low	17 (7.1)
	High	0 (0.0)
	Low/high	0 (0.0)
Calcium	Total	239
	Low	1 (0.4)
	High	0 (0.0)
	Low/high	0 (0.0)
Chloride	Total	239
	Low	3 (1.3)
	High	0 (0.0)
	Low/high	0 (0.0)
Cholesterol (total)	Total	239
	Low	0 (0.0)
	High	6 (2.5)
	Low/high	0 (0.0)
Creatinine	Total	239
	Low	0 (0.0)
	High	1 (0.4)
	Low/high	0 (0.0)

Gamma Glutamyltransferase	Total	239
	Low	0 (0.0)
	High	19 (7.9)
	Low/high	0 (0.0)
Glucose	Total	238
	Low	1 (0.4)
	High	34 (14.3)
	Low/high	1 (0.4)
Phosphate (Inorganic Phosphorus)	Total	239
	Low	0 (0.0)
	High	6 (2.5)
	Low/high	0 (0.0)
Potassium	Total	239
	Low	0 (0.0)
	High	1 (0.4)
	Low/high	0 (0.0)
SGOT (AST)	Total	236
	Low	0 (0.0)
	High	2 (0.8)
	Low/high	0 (0.0)
SGPT (ALT)	Total	238
	Low	0 (0.0)
	High	6 (2.5)
	Low/high	0 (0.0)
Sodium	Total	239
	Low	11 (4.6)
	High	2 (0.8)
	Low/high	0 (0.0)
Triglycerides	Total	239
	Low	0 (0.0)
	High	32 (13.4)
	Low/high	0 (0.0)
Uric Acid	Total	239
	Low	4 (1.7)
	High	1 (0.4)
	Low/high	0 (0.0)

Total = number of subjects with evaluable OL-baseline and post OL baseline measurements for the test and is the denominator for the percentage
n = number of subjects meeting the criterion (i.e., notably abnormal)
Subjects are counted only once for each test
The categories of low, high and low/high are mutually exclusive
This table displays only those tests with at least one patient meeting the notable criterion

Vital signs

Except for weight, for which notable increases were reported in 14.2% and notable decreases in 6.7% of patients, the incidence rates for clinically notable abnormalities in vital sign values were very low and not considered to be clinically meaningful.

Urinalysis

Clinically notable high values were observed for RBC/HPF in 31 (13.1%) patients and WBC/HPF in 22 (9.3%) patients. A low percentage of patients were reported to have clinically notable high values for specific gravity (3.4%), urine protein (1.7%) and urine pH (0.4%). Overall, the urinalysis findings were not considered to be clinically meaningful.

ECG

The total number of patients experiencing any ECG abnormality was 23.2%. The most commonly observed conduction abnormality was first degree atrioventricular block, seen in 5.2% of the patients. Flat T-wave abnormalities were the most frequently occurring T-wave abnormality (3.4%). The most prevalent rhythm disorder was sinus tachycardia, observed in 5.2% of the patients. Treatment emergent arrhythmias (atrial premature conduction or ventricular premature conduction were reported in 1.7% and 1.3% of patients, respectively. Two (0.9%) patients were reported to have a depressed ST-segment abnormality and one patient experienced an elevated ST-segment abnormality. Overall the ECG findings in this study were not considered to be clinically meaningful.

Secondary Objective Result(s)

Summary statistics of Y-MRS, HAMD, BPRS, CGI-I, CGI-S and CAS were planned. However, because the primary objective of demonstrating the superiority of licarbazepine over placebo in the mean reduction in the total score of the Y-MRS from baseline to endpoint was not achieved in the core double-blind study, only summary statistics for Y-MRS and CGI-I are presented.

Y-MRS

At the end of study visit (Week 52), the improvement in mean Y-MRS score of 7.3 ± 7.47 points from OL baseline was observed for patients who had been randomized to licarbazepine in the DB core study (n=23). In the group of patients who switched from DB placebo treatment to OL licarbazepine treatment (n=29), there was an improvement from OL baseline in mean Y-MRS score of 7.1 ± 7.06 points. Overall, the mean improvement was 7.2 ± 7.18 points (n=52).

CGI-I

At the end of study visit (Week 52), the percentage of patients who were evaluated as "very much improved" on the CGI-I scale score was 41.4% in the group of patients treated with licarbazepine and 50% in the group who received placebo during the DB core study. The percentage of patients who were evaluated as "very much improved" or "much improved" was 86.2% and 84.4% in the DB licarbazepine and DB placebo groups respectively.

Summary statistics showed improvement on both the Y-MRS and CGI-I scale scores. However, no meaningful interpretation of the efficacy results was possible due to the lack of a placebo control group, a significant improvement in the placebo-treated group in the core double blind study (CLIC477D2302) and early termination of the study resulting in a small number of patients completing the study.

Safety Results

Same as primary objective results mentioned above.

Adverse Events by System Organ Class

Same as primary objective results mentioned above.

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

Same as primary objective results mentioned above.

Serious Adverse Events and Deaths

Same as primary objective results mentioned above.

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