Sponsor

Novartis

Generic Drug Name

Licarbazepine

Therapeutic Area of Trial

Manic episodes of bipolar I disorder

Approved Indication

Investigational

Study Number

CLIC477D2302

Title

A randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety and tolerability of licarbazepine 750 – 2000 milligram (mg)/day as adjunctive therapy to an atypical antipsychotic (AA) in the treatment of manic episodes of bipolar I disorder over 6 weeks

Phase of Development

Phase III

Study Start/End Dates

09 Nov 2004 to 04 Apr 2007

Study Design/Methodology

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter

study in patients with a manic episode of bipolar I disorder. Patients were randomized in a ratio of 1:1 to receive licarbazepine 250 and 500 mg tablets or placebo matching to the 250 and 500 mg tablets administered twice daily orally. Licarbazepine dosage was gradually increased from 500 to 2000 mg/day. Patients received additional open-label treatment with AA (either risperidone, olanzapine, quetiapine, ziprasidone, or aripiprazole) once or twice a day orally.

Centers

70 centers in 8 countries: Argentina (9), Chile (2), France (9), Hungary (3), India (4), Spain (7), Ukraine (15), United States (21)

Publication

Objectives

Primary objective(s)

To compare the efficacy of licarbazepine 750 – 2000 mg/day added to an AA with placebo added to an AA in the treatment of manic episodes of bipolar I disorder by the reduction of the mean total score of the Young Mania Rating Scale (Y-MRS) from baseline to endpoint (Week 6)

Secondary objective(s)

- To study the safety and tolerability of licarbazepine 750 – 2000 mg/day added to an AA in patients with manic episodes of bipolar I disorder by comparing with placebo added to an AA with respect to the rates of adverse events (AEs), serious adverse events (SAEs), changes in laboratory values, ECGs and vital signs during the 6-week treatment
- To compare the efficacy of licarbazepine 750 – 2000 mg/day added to an AA with placebo added to an AA with respect to:
  1. reduction (= 50%) of the baseline Y-MRS at endpoint
  2. proportion of patients who achieved response at endpoint, where response is defined as a score of 1 or 2 on the Global Improvement Rating of the Clinical Global Impression (CGI-I)
- To compare licarbazepine 750 – 2000 mg/day added to an AA to placebo added to an AA with respect to the mean change from baseline to endpoint in the total score of 21-item Hamilton Depression Rating Scale (HAMD)
- To determine the efficacy of licarbazepine 750 – 2000 mg/day added to an AA compared to placebo added to an AA with respect to mean changes from baseline to each assessment time point in the total scores of the Y-MRS, HAMD, BPRS, CGI-I, CGI-S and CAS during the 6-week treatment
- To evaluate the effect of licarbazepine 750 – 2000 mg/day on the steady-state pharmacokinetics of AAs by comparing changes from baseline of trough plasma concentrations of each AA at study Day 14

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

Licarbazepine 250 and 500 mg tablets were administered orally twice a day. Additionally, the patients were treated with AA (either risperidone, olanzapine, quetiapine, ziprasidone, or aripiprazole) once or twice in a day orally. Patients received 750 – 2000 mg/day of licarbazepine, depending on tolerability.

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

Placebo matching licarbazepine 250 and 500 mg tablets were administered orally twice a day. Additionally, the patients were treated with AA (either risperidone, olanzapine, quetiapine, ziprasidone, or aripiprazole) once or twice in a day orally.

Criteria for Evaluation

Primary variable

Change from baseline to endpoint (week 6) in the total Y-MRS score

Secondary variables

- Responder rates for the Y-MRS score were compared between the two treatment groups
- Change from baseline to the endpoint in the HAMD was analyzed
- CGI-I scores were analyzed

Safety and tolerability

Frequency of adverse event (AE) with severity grade, relationship to study drug, duration, action taken and seriousness, regular monitoring of hematology, blood chemistry, urinalysis, physical examination, vital signs and ECG. Laboratory evaluations included also a hepatitis screen, thyroid function tests, urine drug screen, and pregnancy test.

Pharmacology: Pharmacokinetics (PK)

Licarbazepine concentrations in plasma were not measured. Plasma pre-dose concentrations of the five AA (either risperidone, olanzapine, quetiapine, ziprasidone, or aripiprazole) used in this study were determined to assess the effect of licarbazepine on the PK of these drugs. Blood samples were taken just before the morning dose of the AA at Visit 2 (baseline) and Visit 5 (Study Day 14).

Other: Pharmacogenetics

In patients who signed the pharmacogenetic informed consent, blood samples for pharmacogenetic study were drawn. Pharmacogenetics analysis was planned as a part of this study with the objective of identifying inherited genetic factors which may (1) be related to bipolar I disorder, (2) predict response to treatment with licarbazepine, (3) predict relative susceptibility to drug-drug interactions, or (4) predict genetic predisposition to serious adverse events (SAE).

Statistical Methods

The analysis for the primary variable was carried out by testing the null hypothesis that there was no difference between the primary variable in the two treatment groups against a two-sided alternative, namely, there was a difference in the primary variable in the two treatment groups. The tests were performed at the 5% significance level. The primary analysis was performed on the Intent to treat (ITT) population using last observation carried forward (LOCF). It was based on an analysis of covariance model, with treatment and center as factors and the baseline Y-MRS as the covariate. The 95% confidence interval for the difference in the mean change of Y-MRS from baseline to endpoint between treatment groups and p-value of the hypothesis testing were provided. A center pooling strategy was used based on the geographical proximity to form 15

"pooled centers". This decision was made before database lock and after all patients were randomized. In the above analyses and for the additional analyses, the pooled new centers were used in the model.

Analysis of pharmacokinetics: All patients with valuable PK data were included in the analysis. Atypical antipsychotic PK data was considered valuable for a patient if one sample was taken at baseline and one sample was taken at visit 5 and if the patient had been stable on stable licarbazepine total daily dose for at least 3 consecutive days before visit 5 and on stable AA total daily dose for at least 7 consecutive days (3 consecutive days for ziprasidone and quetiapine) before baseline and visit 5.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

- Males and females of 18 to 70 years of age
- Diagnosis of bipolar disorder type I, manic or mixed episodes according to Diagnostic and Statistical Manual of Mental disorders (DSM-IV) criteria (i.e., 296.0, 296.4, or 296.6), including patients with/without psychotic features or with/without a history of rapid cycling
- Total score of at least 20 on the Y-MRS at screening and at least 18 at baseline
- Need of psychiatric treatment
- Co-operation and willingness to complete all aspects of the study
- Written informed consent provided prior to participation in the study

Exclusion Criteria

- Current DSM-IV Axis-I diagnosis other than bipolar I disorder
- History of schizophrenia or schizoaffective disorder
- Concomitant use of psychoactive medication, except lorazepam use as described below and the AA which the patient will be taking during the study. The time between the last dose of prior medication and the beginning of the Pre-Randomization Treatment Phase (Day -7) is dependent on the medication: oral antipsychotics, mood stabilizers, antidepressants and sedatives/hypnotics: 5 half lives; depot antypsychotics, monoamine oxidase inhibitors (MAOIs): 4 weeks
- Drug dependence during the month prior to screening
- Positive urine drug screen at screening visit (or at repeat screening within 1 week of initial drug screen failure) for amphetamines, cocaine, hallucinogens, or opiates
- History of suicide attempt within the past one month prior to the screening visit or immediate risk of harm to self or others at the time of screening, as judged by the investigator
- Mental retardation according to DSM-IV criteria
- Female patients of childbearing potential who are not using effective contraception during the study, are breast feeding, or have a positive pregnancy test at screening or baseline
- Serum sodium = 130 mmol/L or history of multiple episodes of hyponatremia
- Any sensory or motor deficits that may prevent the patient from completing any of the study assessments
- Any non-psychiatric coexistent illness (e.g., diabetes mellitus, hypothyroidism) that has not

been maintained in a stable condition for at least 3 months prior to baseline

- Clinically significant abnormal conditions of the gastrointestinal system, liver, kidneys, which could have resulted in the possibility of altered absorption, excess accumulation, or impairment of metabolism or excretion of the study drug
- History of serious dermatological reaction while being treated with an antiepileptic medication
- Twice the upper normal limit at screening and upon repeated measurement for any one of the following laboratory parameters: SGOT, SGPT, LDH, alkaline phosphatase, bilirubin, BUN values = 30 mg/dL or creatinine clearance < 30 mL/min
- Any other clinically significant abnormal laboratory findings at screening which remain abnormal upon repeated measurement
- Any of the following serological findings: positive hepatitis A antibody (IgM); positive hepatitis B surface antigen (HBsAg); positive hepatitis B core antibody (Anti-HBcAb), along with a negative hepatitis B surface antibody (Anti-HBsAb), in the setting of abnormal liver enzymes or recent clinical symptoms of hepatitis (within the last 2 months)
- Current diagnosis or recent past history of epilepsy, major head trauma, or progressive neurological disease (e.g., Parkinson's disease, amyotrophic lateral sclerosis)
- Any condition that required treatment with levodopa or any dopaminergic agonist
- Known hypersensitivity to atypical antipsychotic that will be used during the study and drugs chemically related to licarbazepine (e.g., oxcarbazepine, carbamazepine)
- Exposure during the 30 days preceding screening to any drug not registered for use in the country where the study is being conducted
- Electroconvulsive therapy (ECT) within the three months preceding baseline
- Any form of psychotherapy within the months preceding screening
- Hospitalization for mania due to a court order
- Patients who are under legal supervision or guardianship
- Use of an atypical antipsychotic to which there is a documented history of non-response

Number of Subjects

A total of 449 patients were recruited of whom 222 were randomized to licarbazepine and 227 to placebo as shown in the table below

Population	Licarbazepine N = 222 n (%)	Placebo N = 227 n (%)	Total N = 449 n (%)
Safety population	221 (99.5)	227 (100.0)	448 (99.8)
Intent-to-treat population (ITT)	218 (98.2)	226 (99.6)	444 (98.9)
Per protocol population (PP)	201 (90.5)	212 (93.4)	413 (92.0)

Percentages refer to the total number of patients randomized.

Patient disposition

Details of patient disposition are mentioned in the table below.

	Licarbazepine N = 222 n (%)	Placebo N = 227 n (%)	Total N = 449 n (%)
Completed	157 (70.7)	171 (75.3)	328 (73.1)
Discontinued	65 (29.3)	56 (24.7)	121 (26.9)
Main cause of discontinuation			
Adverse Event(s)*	20 (9.0)	13 (5.7)	33 (7.3)
Subject withdrew consent	13 (5.9)	15 (6.6)	28 (6.2)
Lost to follow-up	12 (5.4)	9 (4.0)	21 (4.7)
Protocol deviation	10 (4.5)	5 (2.2)	15 (3.3)
Unsatisfactory therapeutic effect	7 (3.2)	12 (5.3)	19 (4.2)
Abnormal laboratory value(s)	2 (0.9)	2 (0.9)	4 (0.9)
Administrative problems	1 (0.5)	0 (0.0)	1 (0.2)

Percentages refer to the total number of patients randomized.
Reasons for discontinuation are presented in order of descending frequency in the licarbazepine group.
* Of the 20 licarbazepine and 13 placebo patients discontinued for AEs, 6 licarbazepine and 1 placebo discontinuations were for AEs related to laboratory abnormalities.

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	Licarbazepine N = 222	Placebo N = 227	Total N = 449
Age (years)			
n	222	227	449
Mean	41.1	40.8	41.0
SD	12.78	12.87	12.81
Minimum	18.0	18.0	18.0
Median	41.0	40.0	41.0
Maximum	69.0	70.0	70.0
Sex – n (%)			
Male	98 (44.1)	110 (48.5)	208 (46.3)
Female	124 (55.9)	117 (51.5)	241 (53.7)
Race – n (%)			
Caucasian	184 (82.9)	184 (81.1)	368 (82.0)
Black	29 (13.1)	31 (13.7)	60 (13.4)
Oriental	2 (0.9)	1 (0.4)	3 (0.7)
Other	7 (3.2)	11 (4.8)	18 (4.0)
Weight (kg)			
n	222	227	449
Mean	80.2	80.3	80.2
SD	20.37	20.24	20.28
Minimum	40.5	39.5	39.5
Median	76.5	78.8	78.0
Maximum	159.7	156.5	159.7
AA type – n (%)			
Risperidone	80 (36.0)	87 (38.3)	167 (37.2)
Ziprasidone	14 (6.3)	8 (3.5)	22 (4.9)
Quetiapine	42 (18.9)	51 (22.5)	93 (20.7)
Olanzapine	58 (26.1)	67 (29.5)	125 (27.8)
Aripiprazole	28 (12.6)	14 (6.2)	42 (9.4)

AA = atypical antipsychotic

Primary Objective Result(s)

A significant improvement from baseline at endpoint in Y-MRS was observed in both the licarbazepine and the placebo group ($p < 0.001$). The two groups did not differ regarding this effect ($p = 0.139$). Significant differences between the two groups were not found at any of the assessed time points (visits).

Analysis of Y-MRS change from baseline at endpoint is summarized in the table below.

	Statistics	**Licarbazepine N = 218**	**Placebo N = 226**
Baseline	n	218	226

	Mean (SD)	24.2 (4.57)	24.0 (4.56)
	Median	23.0	23.0
Endpoint	n	218	226
	Mean (SD)	11.2 (8.08)	12.0 (8.19)
	Median	11.0	11.0
Change from baseline at endpoint (visit 9)	n	218	226
	Mean (SD)	13.1 (7.59)	12.0 (8.49)
	Median	13.0	13.0
	95% CI*	(12.0, 14.1)	(10.9, 13.1)
	p-value*	< 0.001	< 0.001
Comparison with placebo at endpoint (LIC – placebo)	Adjusted mean difference**		1.0
	95% CI**		(-0.3, 2.3)
	p-value**		0.139

Change is calculated as baseline – endpoint. A positive value in change indicates improvement.
* from paired t-test.
** from comparisons of LS Means from the ANCOVA model: change = baseline + treatment + center.

Secondary Objective Result(s)

The percentage of Y-MRS responders (by at least 50%) was similar in the licarbazepine and the placebo groups, with a slight tendency for more responders in the licarbazepine treated patients. The two groups did not differ significantly regarding Y-MRS responders (p = 0.359) as shown in the table below.

Y-MRS responders (ITT population with LOCF)

	Licarbazepine N = 218	**Placebo N = 226**
n	218	226
Number of responders (%)	128 (58.7)	124 (54.9)
Number of non-responders (%)	90 (41.3)	102 (45.1)
Odds ratio*		1.21
95% CI for odds ratio*		(0.81,1.81)
p-value*		0.359

Responder is defined as subject with a reduction of the baseline Y-MRS total scores by at least 50% at endpoint.
* Based on logistic regression: log(odds) = baseline + treatment + center.

More licarbazepine-treated patients tended to respond than placebo-treated patients regarding the CGI-I score, but this difference did not reach statistical significance (p = 0.159) as depicted in the table below.

CGI-I responders (ITT population with LOCF)

	Licarbazepine N = 218	**Placebo N = 226**
n	217	222
Number of responders (%)	137 (63.1)	126 (56.8)
Number of non-responders (%)	80 (36.9)	96 (43.2)
p-value for the CMH test*		0.159

Responder is defined as subject with CGI-I score of 1 or 2 at endpoint.
Based on CMH test for association between the CGI-I responders and treatment after adjusting for center.

Hamilton Depression Rating Scale data (HAMD)

The change from baseline was significant in both treatment groups and at all time points assessed (visits 3, 4, 5, 6, 7, 8, 9) (LOCF and observed cases) and improvement of HAMD was seen in both treatment groups. The comparison of licarbazepine and placebo showed a significant difference at visit 9 with observed cases analysis: p = 0.034 (for LOCF: p = 0.061): Mean change from baseline in HAMD score at visit 9 was 3.9 in the licarbazepine group and 2.7 in the placebo group. No significance was reached at all the other time points assessed.

Safety Results

The percentage of patients experiencing treatment-emergent AEs was similar in the two treatment groups (approximately 60%). Treatment-emergent AEs were mainly nervous system disorders, gastrointestinal disorders, general disorders and administration site conditions and psychiatric conditions. More patients in the placebo group had AEs of psychiatric disorders. No deaths occurred on study. The number of patients discontinuing the study due to SAEs or AEs was similar in the two treatment groups, but more patients in the licarbazepine group had dose interrup-

tions or adjustments. The number of patients in the licarbazepine group with at least one SAE was slightly higher than in the placebo group. More licarbazepine-treated patients had high GGT values than patients in the placebo group (7.4% and 3.6% of the patients, respectively). The incidence of high ALT and AST values was low, with high ALT values observed in a higher proportion of the placebo group. Hyponatremia was observed in twelve patients (5.5%) of the licarbazepine group and in none of the placebo group.

Adverse Events by System Organ Class (SOC)

	Licarbazepine N = 221 n (%)	**Placebo N = 227 n (%)**	**Total N = 448 n (%)**
Total no. of patients with treatment emergent AE	139 (62.9)	133 (58.6)	272 (60.7)
Primary system organ class			
Nervous system disorders	82 (37.1)	52 (22.9)	134 (29.9)
Gastrointestinal disorders	48 (21.7)	41 (18.1)	89 (19.9)
General and administration site disorders	25 (11.3)	13 (5.7)	38 (8.5)
Psychiatric disorders	25 (11.3)	25 (11.0)	50 (11.2)
Infections and infestations	20 (9.0)	31 (13.7)	51 (11.4)
Musculoskeletal and connective tissue disorders	17 (7.7)	17 (7.5)	34 (7.6)
Skin and subcutaneous tissue disorders	15 (6.8)	7 (3.1)	22 (4.9)
Eye disorders	13 (5.9)	5 (2.2)	18 (4.0)
Metabolism and nutrition disorders	13 (5.9)	9 (4.0)	22 (4.9)
Investigations	7 (3.2)	14 (6.2)	21 (4.7)

Primary system organ classes are presented in descending order based on LIC group.
A subject with multiple AEs within a primary system organ class is counted only once in the total row.

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

	Licarbazepine N = 221 n (%)	Placebo N = 227 n (%)	Total N = 448 n (%)
Total no. of patients with treatment emergent AE	139 (62.9)	133 (58.6)	272 (60.7)
Treatment emergent AE			
Dizziness	29 (13.1)	11 (4.8)	40 (8.9)
Headache	27 (12.2)	19 (8.4)	46 (10.3)
Nausea	20 (9.0)	9 (4.0)	29 (6.5)
Somnolence	20 (9.0)	15 (6.6)	35 (7.8)
Sedation	12 (5.4)	5 (2.2)	17 (3.8)

Preferred terms are presented in descending order based on LIC group.
A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Serious Adverse Events and deaths

	Licarbazepine N = 221 n (%)	Placebo N = 227 n (%)	Total N = 448 n (%)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Other treatment emergent SAE(s)	9 (4.1)	6 (2.6)	15 (3.3)
Discontinued due to treatment emergent SAE(s)	5 (2.3)	5 (2.2)	10 (2.2)

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

Serious adverse events by primary SOC and preferred term (Safety population) are shown in the table below.

	Licarbazepine N = 221 n (%)	Placebo N = 227 n (%)	Total N = 448 n (%)
Patients with at least one SAE	9 (4.1)	6 (2.6)	15 (3.3)
Psychiatric disorders	5 (2.3)	5 (2.2)	10 (2.2)
Mania	2 (0.9)	1 (0.4)	3 (0.7)
Bipolar disorder	1 (0.5)	1 (0.4)	2 (0.4)
Conversion disorder	1 (0.5)	0 (0.0)	1 (0.2)
Major depression	1 (0.5)	1 (0.4)	2 (0.4)
Bipolar I disorder	0 (0.0)	1 (0.4)	1 (0.2)
Homicidal ideation	0 (0.0)	1 (0.4)	1 (0.2)
Suicidal ideation	0 (0.0)	3 (1.3)	3 (0.7)
Gastrointestinal disorders	1 (0.5)	0 (0.0)	1 (0.2)
Anal fissure	1 (0.5)	0 (0.0)	1 (0.2)
Infections and infestations	0 (0.0)	1 (0.4)	1 (0.2)
Tonsillitis	0 (0.0)	1 (0.4)	1 (0.2)
Investigations	1 (0.5)	0 (0.0)	1 (0.2)
Blood creatine phosphokinase increased	1 (0.5)	0 (0.0)	1 (0.2)
Metabolism and nutrition disorders	1 (0.5)	0 (0.0)	1 (0.2)
Hyponatremia	1 (0.5)	0 (0.0)	1 (0.2)

Skin and subcutaneous tissue disorders	1 (0.5)	0 (0.0)	1 (0.2)
Erythema multiforme	1 (0.5)	0 (0.0)	1 (0.2)

Primary system organ classes are presented in descending frequency; preferred terms are sorted within primary system organ class in descending frequency by licarbazepine column.
A subject with multiple occurrences of an AE under one treatment 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.

Other Relevant Findings

Bioanalytical results: PK data showed a lowering effect of licarbazepine on the pre-dose concentrations of the active moiety of risperidone, olanzapine and quetiapine by about one half in a dose-independent manner. Therefore, the bioavailability of these antipsychotics was decreased.

Date of Clinical Trial Report

09 October 2007

Date Inclusion on Novartis Clinical Trial Results Database

03 April 2008

Date of Latest Update

02 April 2008