Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Licarbazepine

Therapeutic Area of Trial

Manic episodes of bipolar I disorder

Approved Indication

Investigational

Study Number

CLIC477D2303

Title

A randomized, double-blind, placebo-controlled, multi-center study to evaluate the efficacy, safety and tolerability of licarbazepine 750-2000 milligram/day (mg/d) as adjunctive therapy to lithium or valproate in the treatment of manic episodes of bipolar I disorder over six weeks.

Phase of Development

Phase III

Study Start/End Dates

21 Oct 2004 to 30 Aug 2007

Study Design/Methodology

This was a randomized, double-blind, placebo-controlled, parallel-group, multi-center 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 matching placebo administered twice daily orally. Licarbazepine dosage was gradually increased from 500 to 2000 mg/day based on tolerability. Patients received additional open-label treatment with lithium or valproate twice daily orally.

Centers

59 centers in North America, the European Union (EU), non-EU European countries, South America, Russia, Ukraine, India and South Africa.

Objectives

Primary objective(s)

To demonstrate the efficacy of licarbazepine 750-2000 mg/d added to lithium or valproate in patients with a manic episode of bipolar I disorder by testing the hypothesis that licarbazepine added to lithium or valproate is superior to placebo added to lithium or valproate in 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/d added to lithium or valproate in patients with manic episodes of bipolar I disorder by comparing with placebo added to lithium or valproate with respect to the rates of adverse events (AE) and serious adverse events (SAE), changes in laboratory values, ECGs and vital signs during the 6-week treatment.
- To compare the efficacy of licarbazepine 750-2000 mg/d added to lithium or valproate with placebo added to lithium or valproate, with respect to:
  1. reduction (≥50%)of the baseline Y-MRS at study endpoint
  2. the proportion of patients who achieve response at endpoint on the Global Improvement rating of the Clinical Global Impression (CGI-I)
  3. the mean reduction from baseline to endpoint in the total scores of the Brief Psychiatric Rating Scale (BPRS), the Clinical Anxiety Scale (CAS) and the Severity of Illness rating of the Clinical Global Impression (CGI-S).
- To compare licarbazepine 750-2000 mg/d added to lithium or valproate to placebo added to lithium or valproate in respect to the mean change from baseline to endpoint in the mean total score of the 21-item Hamilton Rating Scale for Depression (HAMD).
- To determine the efficacy of licarbazepine 750-2000 mg/d added to lithium or valproate compared to placebo added to lithium or valproate with respect to mean changes from baseline at 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 study the additional benefits of licarbazepine 750-2000 mg/d added to lithium or valproate in the treatment of manic episodes of bipolar I disorder by testing the hypothesis that licarbazepine added to lithium or valproate is superior to placebo added to lithium or valproate with respect to improvement in patients' sense of wellbeing from baseline to endpoint as measured by the Short Form Health Survey (SF-36).

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

Licarbazepine 250 mg and 500 mg tablets were administered orally twice a day. The patients received 750 – 2000 mg/day of licarbazepine, depending on tolerability. Additionally, they received either lithium or valproate orally twice a day.

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

Placebo matching licarbazepine 250 mg and 500 mg tablets were administered in addition to lithium or valproate twice a day orally.

Criteria for Evaluation

Primary variables

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 BPRS, CAS and HAMD was analyzed
- CGI-I and CGI-S scores were analyzed

Safety and tolerability

Frequency of the AEs and SAEs with severity grade, relationship to the study drug, duration, action taken and its seriousness; regular monitoring of hematology, blood chemistry, urinalysis, physical condition and body weight, vital signs and ECG.

Pharmacology: Pharmacokinetics (PK)

Licarbazepine concentrations in plasma were not measured. Plasma pre-dose concentrations of (either lithium or valproate) used in this study were determined to assess the effect of licarbazepine on the PK of these drugs. Serum levels were measured throughout the study and the dosage was adjusted only if the serum concentration fell outside the therapeutic window.

Other: Pharmacogenetics

In patients who signed the pharmacogenetic informed consent, blood samples for pharmacogenetic study were drawn. Pharmacogenetic analyses were 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 SAEs.

Statistical Methods

The analysis for the primary variable was carried out by testing the null hypothesis that there was no difference in 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 test was 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 seven "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.

Study Population: Inclusion Exclusion Criteria and Demographics

Inclusion Criteria

1. Male and females, 18 through 70 years of age
2. Diagnosed with 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
3. Total score of at least 20 on the Y-MRS at screening and at least 18 at baseline
4. Need of psychiatric treatment
5. Cooperation and willingness to complete all aspects of the study, including hospitalization
6. Written informed consent provided prior to participation in the study

Exclusion Criteria

1. Current DSM-IV Axis-I diagnosis other than bipolar I disorder
2. History of schizophrenia or schizoaffective disorder
3. Concomitant use of psychoactive medication other than lorazepam, lithium or valproate, whereby the washout time between the last dose of prior medication and the beginning of the Pre-randomization Treatment Phase (Day 7) was dependent on the medication
   - oral antipsychotics, mood stabilizers (carbamazepine, lamotrigine, etc.), antidepressants and sedatives (benzodiazepines, zolpidem, zopiclone): 5 half lives. The last dose of lorazepam must have been at least 12 hours before screening and baseline assessments
   - depot antipsychotics, MAOIs: 4 weeks
4. Use of warfarin, tolbutamide, iodide salts or zidovudine during the study
5. Drug dependence (DSM- IV criteria) during the one month prior to screening
6. Positive urine drug screen at screening visit for amphetamines, cocaine, hallucinogens, or opiates
7. History of suicide attempt within one month prior to the screening visit or immediate risk of harm to self or others at the time of screening
8. Mental retardation (DSM-IV criteria)
9. Female patients of childbearing potential not using effective contraception during the study, breast feeding, or having a positive pregnancy test (ß-hCG) at screening or baseline
10. Serum sodium =130 mmol/L at baseline or history of multiple episodes of hyponatremia` (defined as serum Na =125 mmol/L)
11. Any sensory or motor deficits that may have prevented the patient from completing any of the study assessments
12. Any unstable non-psychiatric coexistent illness (e.g., diabetes mellitus, hypothyroidism) for at least 3 months prior to baseline
13. Clinically significant abnormal conditions of the gastrointestinal system, liver, or kidneys,

which could have resulted in the possibility of altered absorption, excess accumulation, or impairment of metabolism or excretion of the double-blind or open label study drug

14. History of serious dermatological reaction while being treated with an anti-epileptic medication
15. Increased (at least twice the upper normal limit) values of SGOT, SGPT, LDH, alkaline phosphatase, or bilirubin; BUN values ≥30 mg/dL or creatinine clearance < 30 mL/min
16. Any other clinically significant abnormal laboratory findings at screening which remained 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)
17. Current diagnosis or recent past history of epilepsy, major head trauma, or progressive neurological disease (e.g., Parkinson's disease, ALS)
18. Known hypersensitivity to lithium or valproate or drugs chemically related to licarbazepine (e.g., oxcarbazepine, carbamazepine)
19. Exposure during the 30 days preceding screening to any drug not registered for use in the country where the study was being conducted
20. Electroconvulsive therapy (ECT) within the 3 months preceding baseline
21. Any form of psychotherapy within the 1 month preceding screening
22. Hospitalization for mania due to a court order
23. A documented history of non-response to lithium or valproate, whereby non-response was defined by the treating physician who documented the history
24. Patients who were under legal supervision or guardianship

Number of Subjects

Population	Licarbazepine N = 180 n (%)	Placebo N = 164 n (%)	Total N = 344 n (%)
Safety population	180 (100.0)	164 (100.0)	344 (100.0)
Intent-to-treat population (ITT)	177 (98.3)	159 (97.0)	336 (97.7)
Per protocol population (PP)	160 (88.9)	149 (90.9)	309 (89.8)

Percentages refer to the total number of patients randomized

Patient disposition

	Licarbazepine N = 180 n (%)	Placebo N = 164 n (%)	Total N = 344 n (%)
Completed	119 (66.1)	113 (68.9)	232 (67.4)
Discontinued	61 (33.9)	51 (31.1)	112 (32.6)
Main cause of discontinuation			
Adverse Event(s)*	20 (11.1)	16 (9.8)	36 (10.5)
Subject withdrew consent	11 (6.1)	13 (7.9)	24 (7.0)
Lost to follow-up	7 (3.9)	10 (6.1)	17 (4.9)
Protocol deviation	6 (3.3)	3 (1.8)	9 (2.6)
Unsatisfactory therapeutic effect	10 (5.6)	4 (2.4)	14 (4.1)
Abnormal laboratory value(s)	3 (1.7)	1(0.6)	4 (1.2)
Administrative problems	2 (1.1)	3 (1.8)	5 (1.5)

Percentages refer to the total number of patients randomized

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 = 180	Placebo N = 164	Total N = 344
Age (years)			
n	180	164	344
Mean	40.2	38.4	39.3
SD	11.60	11.65	11.64
Minimum	19	18	18
Median	39.5	37.5	39.0
Maximum	67	68	68
Sex - n (%)			
Male	83 (46.1)	69 (42.1)	152 (44.2)
Female	97 (53.9)	95 (57.9)	192 (55.8)
Race - n (%)			
Caucasian	135 (75.0)	127 (77.4)	262 (76.2)
Black	18 (10.0)	13 (7.9)	31 (9.0)
Oriental	0	1 (0.6)	1 (0.3)

Other	27 (15.0)	23 (14.0)	50 (14.5)
Weight (kg)			
n	178	162	340
Mean	82.73	81.85	82.31
SD	20.796	22.230	21.463
Minimum	42.2	45.8	42.2
Median	81.00	79.50	79.85
Maximum	162.3	211.0	211.0
Mood Stabilizer - n (%)			
Lithium	86 (47.8)	70 (42.7)	156 (45.3)
Valproate	94 (52.2)	93 (56.7)	187 (54.4)
Missing	0	1 (0.6)	1 (0.3)

AA = atypical antipsychotic

Primary Objective Result(s)

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

	Statistics	Licarbazepine N = 177	Placebo N = 159
Baseline	n	177	159
	Mean (SD)	22.8 (4.08)	23.5 (4.51)
	Median	22.0	23.0
Endpoint	n	177	159
	Mean (SD)	11.6 (9.07)	12.7 (9.36)
	Median	10.0	12.0
Change from baseline at endpoint (visit 9)	n	177	159
	Mean (SD)	11.3 (8.63)	10.8 (9.31)
	Median	12.0	12.0
	95% CI*	(10.01, 12.57)	(9.38, 12.30)
	p-value*	<0.001	<0.001
Comparison with placebo at endpoint (LIC – placebo)	Adjusted mean difference**		0.84
	95% CI**		(-0.91, 2.60)
	p-value**		0.345

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)

Y-MRS responders

The summary statistics and regression analysis at endpoint (ITT population with LOCF) are summarized in the table below.

	Licarbazepine N = 177	**Placebo N = 159**
n	177	159
Number of responders (%)	99 (55.9)	80 (50.3)
Number of non-responders (%)	78 (44.1)	79 (49.7)
Odds ratio*		1.32
95% CI for odds ratio*		(0.82, 2.13)
p-value*		0.258

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.

BPRS

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): Improvement of BPRS was seen in both groups. Mean change from baseline in BPRS score at visit 9 (end of study) was comparable in both groups (4.4 vs. 4.6). The adjusted mean treatment difference at visit 9 was 1.03 (p=0.215).

CAS

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): Improvement of CAS score was seen in both groups. Mean change from baseline in CAS score at visit 9 (end of study) was comparable in both groups (2.1 vs. 1.8). The adjusted mean treatment difference at Visit 9 was 0.78 (p=0.46).

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 also improvement of HAMD was seen in both treatment groups. The comparison of licarbazepine and placebo showed a significant difference, at the end of study (Visit 9), the adjusted mean treatment difference was statistically significant in favor of licarbazepine (p=0.024).

CGI-I responders (ITT population with LOCF)

	Licarbazepine N = 177	**Placebo N = 159**
n	174	153
Number of responders (%)	110 (63.2)	80 (52.3)
Number of non-responders (%)	64 (36.8)	73 (47.7)
p-value for the CMH test*		0.030

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.

CGI-S

Mean change from baseline in CGI-S scores to study endpoint was similar in the licarbazepine treatment group and the placebo group (1.4 vs. 1.2 points, respectively)

Safety Results

The adverse events were mostly mild and transient and did not seem to be dose-related and gave no indication of organ toxicity. The overall incidence of patients experiencing treatment-emergent AEs was similar in the two treatment groups (approximately 67%). A slightly higher proportion of licarbazepine treated patients discontinued due to AEs (11.1% vs. 9.9%). Study drug dose interruption or adjustment occurred in a substantially greater proportion in licarbazepine-treated patients than placebo-treated patients (29.4% and 9.3%, respectively). No effect on blood pressure, pulse, weight, or ECGs was evident.

Adverse Events by System Organ Class (SOC)

	Licarbazepine N = 180 n (%)	**Placebo N = 161 n (%)**	**Total N = 341 n (%)**
Total no. of patients with treatment emergent AE	129 (71.7)	101 (62.7)	230 (67.4)
Primary system organ class			
Nervous system disorders	72 (40.0)	35 (21.7)	107 (31.4)
Gastrointestinal disorders	70 (38.9)	35 (21.7)	105 (30.8)
General and administration site disorders	27 (15.0)	10 (6.2)	37 (10.9)
Psychiatric disorders	15 (8.3)	32 (19.9)	47 (13.8)
Infections and infestations	20 (11.1)	21 (13.0)	41 (12.0)
Musculoskeletal and connective tissue disorders	10 (5.6)	12 (7.5)	22 (6.5)
Skin and subcutaneous tissue disorders	20 (11.1)	6 (3.7)	26 (7.6)
Eye disorders	19 (10.6)	2 (1.2)	21 (6.2)
Metabolism and nutrition disorders	10 (5.6)	5 (3.1)	15 (4.4)
Investigations	17 (9.4)	15 (9.3)	32 (9.4)
Respiratory, thoracic and mediastinal disorders	10 (5.6)	2 (1.2)	12 (3.5)

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 = 180 n (%)	**Placebo N = 161 n (%)**	**Total N = 341 n (%)**
Total no. of patients with treatment emergent AE	129 (71.7)	101 (62.7)	230 (67.4)
Treatment emergent AE			
Dizziness	23 12.8)	3 (1.9)	26 (7.6)
Headache	17 (9.4)	22 (13.7)	39 (11.4)
Nausea	38 (21.1)	9 (5.6)	47 (13.8)
Somnolence	19 (10.6)	6 (3.7)	25 (7.3)
Tremor	15 (8.3)	8 (5.0)	23 (6.7)
Vomiting	15 (8.3)	5 (3.1)	20 (5.9)

Fatigue	14 (7.8)	7 (4.3)	21 (6.2)
Vision blurred	12 (6.7)	1 (0.6)	13 (3.8)
Diarrhea	7 (3.9)	13 (8.1)	20 (5.9)

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 = 180 n (%)	**Placebo N = 161 n (%)**	**Total N = 341 n (%)**
Death	0 (0.0)	0 (0.0)	0 (0.0)
Other treatment emergent SAE(s)	4 (2.2)	10 (6.2)	14 (4.1)
Discontinued due to treatment emergent SAE(s)	3 (1.7)	9 (5.6)	12 (3.5)
Discontinued due to treatment emergent AE(s)	20 (11.1)	16 (9.9)	36 (10.6)
Treatment emergent AE(s) leading to study drug dose interruption/adjustment	53 (29.4)	15 (9.3)	68 (19.9)

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 = 180 n (%)	**Placebo N = 161 n (%)**	**Total N =341 n (%)**
Patients with at least one SAE	4 (2.2)	10 (6.2)	14 (4.1)
Cardiac disorders	1 (0.6)	0 (0.0)	1(0.3)
Supraventricular tachycardia	1 (0.6)	0 (0.0)	1 (0.3)
Gastrointestinal disorders	1 (0.6)	0 (0.0)	1 (0.3)
Hematemesis	1 (0.6)	0 (0.0)	1 (0.3)
Musculoskeletal and connective tissue disorders	1 (0.6)	0 (0.0)	1 (0.3)
Joint swelling	1 (0.6)	0 (0.0)	1 (0.3)
Nervous system disorders	1 (0.6)	0 (0.0)	1 (0.3)
Tremor	1 (0.6)	0 (0.0)	1 (0.3)
Psychiatric disorders	1 (0.6)	6 (3.7)	7 (2.1)
Depression	1 (0.6)	1 (0.6)	2 (0.6)
Bipolar disorder	0 (0.0)	1 (0.6)	1 (0.3)
Major depression	0 (0.0)	1 (0.6)	1 (0.3)
Mania	0 (0.0)	3 (1.9)	3 (0.9)
Infections and infestations	0 (0.0)	1 (0.6)	1 (0.3)
Hepatitis C	0 (0.0)	1 (0.6)	1 (0.3)
Injury, poisoning and procedural complications	0 (0.0)	3 (1.9)	3 (0.9)
Alcohol poisoning	0 (0.0)	2 (1.2)	2 (0.6)
Jaw fracture	0 (0.0)	1 (0.6)	1 (0.3)

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

None

Date of Clinical Trial Report

07 April 2008

Date Inclusion on Novartis Clinical Trial Results Database

27 August 2008

Date of Latest Update

13 August 2008