A Randomised, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Lamotrigine in the Maintenance Treatment of Chinese Adult Patients With Bipolar I Disorder

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Keywords: Maintenance, mood episode, prevention, recurrence, relapse, bipolar I disorder, lamotrigine

Posted Date: October 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-970763/v1

Abstract

Background: Lamotrigine is approved as a maintenance therapy for bipolar I disorder in many countries worldwide. It was approved in China in 2021. This study evaluated the efficacy and safety of lamotrigine in controlling relapse and/or recurrence of mood episodes in Chinese patients with bipolar I disorder.

Methods: Patients aged ≥18 years with bipolar I disorder who, during treatment with lamotrigine in a 6–16 week open-label (OL) phase, met response criteria (Clinical Global Impression–Severity [CGI-S] score of ≤3 for ≥4 consecutive weeks and lamotrigine 200 mg/day monotherapy maintained for ≥1 week) were randomised (1:1) to receive lamotrigine or placebo in a 36-week randomised double-blind (RD) phase. The primary endpoint was time to intervention for relapse and/or recurrence of a mood episode (TIME). Post hoc analyses assessed the impact of baseline mood severity on TIME. Safety assessments were conducted throughout the study.

Results: Of the 420 patients treated in the OL phase, 264 were randomised to receive lamotrigine (n=131) or placebo (n=133) in the RD phase. A total of 112 patients reached TIME (lamotrigine, n=50/130 [38.5%]; placebo, n=62/133 [46.6%]; adjusted hazard ratio [95% confidence interval (CI)]: 0.93 [0.64, 1.35]; p=0.701). Kaplan–Meier curves for TIME showed no significant difference between groups (p=0.432). Post hoc analyses demonstrated a significant benefit of lamotrigine versus placebo in delaying mood episodes in patients with baseline CGI-S score ≥4 (hazard ratio [95% CI]: 0.52 [0.30, 0.89]; p=0.018) and with baseline Hamilton Depression Rating Scale ≥18 or Young Mania Rating Scale ≥10 (0.44 [hazard ratio [95% CI]: 0.25, 0.78]; p=0.005). Lamotrigine was well tolerated with no new safety signals in Chinese patients with bipolar I disorder.

Conclusions: Lamotrigine was not significantly superior to placebo in preventing relapse and/or recurrence of mood episodes in Chinese patients with bipolar I disorder but post hoc analyses suggested a therapeutic benefit in patients with moderate/severe mood symptoms at baseline.

Clinical Trial Registration: ClinicalTrial.gov Identifier NCT01602510; 21st May 2012; https://clinicaltrials.gov/ct2/show/NCT01602510.

1. Introduction

Bipolar disorder is a severe and chronic psychiatric disorder, characterised by both depressive and manic/hypomanic episodes with a highly recurrent course [1]. As of 2017, bipolar disorder was estimated to affect 46 million people globally [2]. A recent meta-analysis of bipolar disorder I prevalence in China reported a lifetime prevalence of 0.09%, which is comparatively lower than observed in international populations [3]. On average, patients with bipolar I disorder experience two mood episodes per year [4], and maintenance treatment is aimed at preventing future episodes [1].

Lamotrigine, an inhibitor of voltage-sensitive sodium channels, is approved in the US (target dose 200 mg/day) for the maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes in patients treated with standard therapy for acute mood episodes [5]. It is also approved for the

prevention of bipolar depression in more than 30 countries worldwide [6, 7]. Major international and Chinese guidelines for the management of bipolar disorder recommend lamotrigine as a maintenance treatment to prevent relapse/recurrence of mood episodes [8–10]. However, lamotrigine was approved only recently for use in China as a maintenance treatment for the control of relapse and/or recurrence of mood episodes. Previously, the approved use of lamotrigine remained limited to the treatment of patients with epilepsy.

Several systematic reviews and meta-analyses have confirmed the beneficial effects of lamotrigine as maintenance therapy for prevention of depressive episodes in patients with bipolar disorder [11–13]. The efficacy of lamotrigine was found to be comparable to lithium [12]. Both lamotrigine and lithium have been shown to prevent relapse and/or recurrence of mood episodes in international clinical trials [14–17] and the control of relapse or recurrence of bipolar episodes in Chinese populations [18, 19].

In China, there are fewer treatment options for the prevention of depression compared with the treatment of mania, and a lack of treatments that can also offer an improved safety profile compared with lithium, valproate and anti-psychotics. The present placebo-controlled study evaluated the efficacy and safety of lamotrigine 200 mg/day for preventing relapse and/or recurrence of a manic, hypomanic, mixed or depressive episode in Chinese adult patients with bipolar I disorder.

2. Methods

2.1. Study design

This was a randomised, double-blind, placebo-controlled, parallel-group, multi-centre, fixed-dose study in adult patients (aged ≥18 years) with bipolar I disorder conducted from August 2012 to December 2015 at 21 centres in China. The study consisted of four phases: screening phase, open-label (OL) phase, randomised double-blind (RD) phase and a follow-up visit (**Supplemental Fig. 1**). Patients meeting the eligibility criteria entered the OL phase to receive lamotrigine monotherapy or combination therapy escalated to a target dose of lamotrigine 200 mg/day monotherapy for up to 16 weeks. When lamotrigine was used as an adjunctive therapy with valproate, the prespecified starting dose of lamotrigine and subsequent increases in dose were reduced to half; however, when used with carbamazepine the starting dose of lamotrigine and subsequent dose adjustment rates were doubled. Concomitant antiepileptic drugs and psychotropic medications (except fluoxetine) were permitted for the treatment of mood episodes during the OL phase but were discontinued at least 2 weeks (at least 3 weeks for lithium) prior to entering the RD phase. During the OL and RD phases, the short-term (two to three times/week, duration <2 weeks) use of chloral hydrate, lorazepam, clonazepam, estazolam or oxazepam was permitted as required for control of agitation, irritability, insomnia and hostile behaviour. Antidepressants, antipsychotics, benzodiazepines, anticonvulsants and mood stabilizers were permitted if the investigator deemed that the patient had reached time to intervention for relapse and/or recurrence of a mood episode (TIME). Concomitant medications for co-morbidities (including diabetes and hypertension) were permitted at the discretion of the investigator.

Beginning at Week 7 of the OL phase, patients who met the response criteria (Clinical Global Impressions of Severity [CGI-S] score ≤3 maintained for ≥4 continuous weeks and lamotrigine 200 mg/day monotherapy maintained for ≥1 week) while demonstrating compliance with the study treatment were enrolled in the RD

phase and randomised (1:1) to lamotrigine 200 mg/day or placebo. During the RD phase, patients were assessed at weekly intervals for the first month, biweekly intervals for the second month, and then at monthly intervals for up to 36 weeks. Patients who completed 36 weeks of randomised treatment, reached TIME or withdrew from the study early (including the OL phase and RD phase) were followed up for 14 days after the last dose. The scores on the Hamilton Depression Rating Scale (HAMD), Young Mania Rating Scale (YMRS), Clinical Global Impressions of Improvement (CGI-I), CGI-S and Global Assessment Scale (GAS) were used as indices for both intensity and duration of mood symptoms during this phase.

Patients were randomised (1:1) sequentially (block of four) through GlaxoSmithKline's interactive voice response system, following a computer-generated randomisation schedule. Both investigators and patients were blinded, and matching placebo tablets were used to maintain the blinding.

The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practices, applicable country-specific requirements and the ethical principles outlined in the Declaration of Helsinki (2008). The study protocol was approved by an Independent Ethics Committee or Institutional Review Board at each study centre. Written informed consent was obtained from each participant prior to any study-specific procedures.

2.2. Participants

Patients of either gender (aged ≥18 years) were recruited from inpatient or outpatient clinics. Patients entering the OL phase were diagnosed (using medical records and clinical interviews) with bipolar I disorder and had either a current or most recent depressed (296.5x), hypomanic (296.40), manic (296.4x), or mixed (296.6x) episode (as defined by Diagnostic and Statistical Manual of Mental Disorders-IV [DSM-IV] criteria) within the last 60 days. Patients diagnosed with 296.5x must have had at least one well-documented manic, hypomanic or mixed episode, as defined by DSM-IV criteria, within 3 years of enrolment. Patients diagnosed with 296.40, 296.4x or 296.6x must have had at least one well-documented additional manic, hypomanic or mixed episode and one depressed episode, as defined by DSM-IV criteria, within 3 years of enrolment. Patients were excluded from the OL phase if they met DSM-IV criteria for rapid cycling and had more than four manic, hypomanic, mixed or depressive episodes in the 12-month period prior to enrolment; had significant DSM-IV Axis II diagnosis; had current or previous diagnosis of an Axis I disorder with the exception of bipolar disorder, had signs or symptoms of psychosis, were at suicidal risk; had a history of substance abuse or dependence; had received fluoxetine within 4 weeks prior to the OL phase, used oral contraceptives or other hormonal preparations containing oestrogen within 2 weeks prior to OL phase entry; or had a history or current diagnosis of epilepsy, were morbidly obese (body mass index >35 kg/m^2) or were pregnant or lactating women. Key exclusion criteria for the RD phase included signs or symptoms of psychosis, the need for treatment of a manic or mixed episode during the OL phase (with new courses of lithium, psychotropic drugs or other drugs with a half-life greater than 14 days), becoming actively suicidal and/or having a score ≥3 on item 3 of the HAMD, or testing positive for an illicit drug on laboratory analysis administered before randomisation or alcohol abuse/addiction.

Patients were withdrawn from the study if they required intervention for a relapse and/or recurrence of a mood episode (primary endpoint, TIME, reached); had a medically relevant adverse event (AE) or intercurrent

illness or were pregnant; demonstrated significant non-compliance with the protocol or investigational treatment; had an inability to tolerate the drug; developed a rash or hypersensitivity reaction, had a prolonged QT interval (QTc >500 msec or uncorrected QT >600 msec or, in cases with bundle branch block, QTc >530 msec based on average QTc value of triplicate electrocardiograms [ECGs]); or discontinued treatment.

2.3. Assessments

Demographic and baseline characteristics were assessed by study investigators at screening or baseline. The primary efficacy endpoint was TIME defined as the time from entry into the RD phase to the time of the first prescription of any additional pharmacotherapy or electroconvulsive therapy necessary for the treatment of a relapse and/or recurrence of a depressive, manic, hypomanic or mixed episode. If the investigator determined that a patient had reached TIME, one or more of the following psychotropic medications were prescribed: antidepressants, antipsychotics (with or without anticholinergic medications), benzodiazepines, and anticonvulsants/mood stabilisers. Secondary endpoints included: time to intervention for manic, hypomanic or mixed episode (TIMan); time to intervention for depressive episode (TIDep); overall survival in the study (TIME-SIS); changes from baseline to Week 36 in CGI-S [20], CGI-I [20], HAMD [21], YMRS [22], GAS [23]; and change in weight from baseline during the RD phase. Safety assessments included monitoring of AEs including treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, ECGs, physical examinations, and the Columbia Suicide Severity Rating Scale (C-SSRS). Quality of life was compared using mean changes at each visit from baseline Short Form - 36 (SF-36) score [24]. The eight domains of SF-36 were physical functioning, role physical, role emotional, bodily pain, vitality, mental health, social functioning and general health. The SF-36 was administered by well-trained personnel who passed the consistency evaluation with a certification record.

2.4. Statistical analysis

Based on previous studies [14, 15], the median time to intervention in the lamotrigine group and control group was 97 days and 58 days, respectively. A target sample size of 178 patients (89 patients in each group) was estimated to provide 90% power at the significance level of 0.05. The minimum regulatory requirement specified by the State Food and Drug Administration of China was 100 pairs of patients. Assuming a 20% dropout rate, at least 250 patients were required for the RD phase (125 patients in each group). Considering 60% of patients who entered the OL phase would be randomised to RD phase, the total number of patients to be included in the OL phase was determined to be 416.

The full analysis population (FAP) for the OL and RD phases included all patients who received at least one dose of the study medication and provided at least one post-baseline efficacy/health outcome assessment during the OL and RD phases, respectively. The safety population included all patients who received at least one dose of the study medication in the corresponding phase (OL or RD phase). No interim analyses were planned or performed for this study.

All analyses were conducted using SAS software (Version 9, SAS Inc., Cary, NC, USA). The superiority test was performed to compare efficacy between two groups. TIME (primary efficacy endpoint) was assessed using the Cox proportional hazards regression model, including site and CGI-S baseline score as covariates. TIME-SIS, TIDep and TIMan (secondary efficacy endpoints) were analysed in a similar way; p values were

also provided based on the log-rank tests to describe any significant distribution difference between treatment groups for these endpoints. The between-group comparisons for HAMD, YMRS, CGI-S, CGI-I and GAS scales and body weight (secondary efficacy endpoints) were performed using analysis of covariance (ANCOVA) or rank sum test. The hazard ratios (HR) with 95% (two-sided) confidence intervals (CI) and p values are presented. Kaplan–Meier plots of TIME are also presented by the treatment group during the randomisation phase.

Post hoc analyses were conducted on the FAP to compare the efficacy (TIME endpoint) of lamotrigine and placebo in a subgroup of patients with moderate/severe mood symptoms at baseline. One post hoc analysis defined symptoms by CGI-S score (CGI ≥4; moderate to severe symptoms), the second defined symptoms by HAMD (≥18)/YMRS (≥10) scores. Baseline characteristics, including past psychiatric conditions, and OL phase lamotrigine exposures were summarised for each RD treatment population. TIME in the RD phase was analysed using a Cox proportional hazards regression model with covariates of site, CGI-S baseline score and treatment; adjusted HR (95% CI) and p values were calculated for lamotrigine compared with placebo. Kaplan–Meier survival estimates were also generated.

3. Results

A total of 421 patients were enrolled into the OL phase and 420 patients received at least one dose of the study medication. Of these 420 patients, 264 were randomised into the RD phase and 117 patients (44.3%) completed the study (Fig. 1). A total of 147 (55.7%) patients were withdrawn during the RD phase, most commonly because they had reached protocol-defined withdrawal criteria (n=106; 40.2%) and withdrawal because of an AE was reported for eight patients (3.0%). The demographic and baseline characteristics of both treatment groups in the RD phase were similar (Table 1). The most commonly used psychiatric concomitant medications during the OL phase were lithium carbonate (28.6%) and valproate sodium (28.3%), and during the RD phase were lamotrigine (11.0%) and valproate sodium (8.7%).

Table 1
Demographics and baseline characteristics

Characteristic	Open-label phase	Double-blind phase		
	Lamotrigine	Lamotrigine	Placebo	Total
	N=420	N=131	N=133	N=264
Age (years)	35.7 (11.7)	34.8 (10.9)	37.4 (12.5)	36.1 (11.8)
Gender, n (%)				
Women	220 (52.4)	75 (57.3)	62 (46.6)	137 (51.9)
Men	200 (47.6)	56 (42.7)	71 (53.4)	127 (48.1)
BMI (kg/m^2)	24.2 (3.8)	24.0 (3.9)	24.3 (3.8)	24.2 (3.9)
Weight (kg)	67.1 (12.8)	66.9 (13.8)	67.5 (11.9)	67.2 (12.8)
Duration of current episode (weeks)	7.6 (8.0)	7.8 (7.8)	7.7 (7.2)	7.8 (7.5)
Age at onset of first episode (years)				
Depression	29.5 (10.8)[a]	29.5 (9.7)[b]	30.7 (11.6)	30.1 (10.7)[c]
Mixed/manic	30.4 (11.1)[d]	30.4 (10.2)[e]	31.3 (12.1)[f]	30.9 (11.1)[c]
Number of episodes in past 3 years				
Mania	1.1 (0.73)[g]	1.2 (0.68)	1.1 (0.70)[f]	1.1 (0.69)[h]
Hypomania	0.1 (0.32)[g]	0.1 (0.24)	0.1 (0.44)[f]	0.1 (0.35)[h]
Depression	1.2 (0.76)[g]	1.3 (0.81)	1.2 (0.76)[f]	1.2 (0.79)[h]
Suicide attempts, n (%)	34 (8.1)	7 (5.3)	7 (5.3)	14 (5.3)

Data are presented as mean (SD), unless otherwise specified. BMI, body mass index; SD, standard deviation. [a]n=415; [b]n=129; [c]n=262; [d]n=416; [e]n=130; [f]n=132; [g]n=419; [h]n=263; [i]More than 5% in any group. Analysis population: Safety population

Characteristic	Open-label phase	Double-blind phase		
	Lamotrigine	Lamotrigine	Placebo	Total
	N=420	N=131	N=133	N=264
Concomitant psychiatric medications[i], n (%)	120 (28.6)	8 (6.1)	7 (5.3)	15 (5.7)
Lithium carbonate	119 (28.3)	12 (9.2)	11 (8.3)	23 (8.7)
Valproate sodium	78 (18.6)	8 (6.1)	9 (6.8)	17 (6.4)
Olanzapine	71 (16.9)	7 (5.3)	5 (3.8)	12 (4.5)
Quetiapine fumarate	69 (16.4)	8 (6.1)	7 (5.3)	15 (5.7)
Quetiapine				
Valproate magnesium				
Clonazepam				
Citalopram				
Alprazolam				
Aripiprazole				
	58 (13.8)	5 (3.8)	3 (2.3)	8 (3.0)
	48 (11.4)	1 (0.8)	6 (4.5)	7 (2.7)
	31 (7.4)	3 (2.3)	5 (3.8)	8 (3.0)
	23 (5.5)	2 (1.5)	2 (1.5)	4 (1.5)
	22 (5.2)	1 (0.8)	3 (2.3)	4 (1.5)
	22 (5.2)	1 (0.8)	0	1 (0.4)
Paroxetine				
Lamotrigine				
	4 (1.0)	13 (9.9)	16 (12.0)	29 (11.0)

Data are presented as mean (SD), unless otherwise specified. BMI, body mass index; SD, standard deviation. [a]n=415; [b]n=129; [c]n=262; [d]n=416; [e]n=130; [f]n=132; [g]n=419; [h]n=263; [i]More than 5% in any group. Analysis population: Safety population

3.1. Primary efficacy endpoint

Of the total 264 patients who entered the RD phase, 112 patients (lamotrigine, n=50 [38.5%]; placebo, 62 [46.6%]) reached the TIME event and received intervention for the treatment of a relapse and/or recurrence of a depressive, manic, hypomanic or mixed episode. This difference between lamotrigine and placebo arms was not statistically significant (adjusted HR [95% CI]: 0.93 [0.64, 1.35]; Cox model p=0.701). The difference is also not statistically significant when not adjusting for covariates (log-rank test p=0.432) (Fig. 2). The median survival times could not be estimated owing to <50% of patients reaching the TIME event.

3.2. Secondary efficacy endpoints

The Kaplan–Meier survival estimates for TIMan, TIDep and TIME-SIS for the RD phase showed no significant differences between treatment groups (p≥0.370) (Fig. 3). A total of 24 (18.5%) patients from the lamotrigine group and 27 (20.3%) patients from the placebo group reached TIMan events (adjusted HR [95% CI], 1.03 [0.59, 1.80]); 26 (20.0%) patients from the lamotrigine group and 35 (26.3%) patients from the placebo group reached TIDep events (adjusted HR [95% CI], 0.85 [0.51, 1.42]). Median survival times could not be estimated for TIMan and TIDep owing to <50% of patients experiencing events. For TIME-SIS in the RD FAP, a total of 72 patients (55.4%) in the lamotrigine group and 75 patients (56.4%) in the placebo group reached the event (HR [95% CI], 1.07 [0.77, 1.49]); the median survival time was 183 days for the placebo group and 188 days for the lamotrigine group.

The change from baseline in other secondary efficacy parameters (CGI-S, CGI-I, HAMD, YMRS, GAS and body weight) and quality of life (SF-36) parameters are presented in Table 2. The difference in the change from baseline to Week 36 between lamotrigine and placebo groups was not significant (p>0.05) for other secondary efficacy parameters, except for body weight where a larger decrease was observed amongst patients treated with lamotrigine (-0.84 [95% CI: -1.66, -0.01]; p=0.047) (Table 2). Similarly, the differences in the changes from baseline to Week 36 in measures of quality of life between lamotrigine and placebo groups were not significant (p>0.05), except for emotional role functioning (treatment difference, 0.3 [95% CI: 0.0, 0.6]; p=0.042).

Table 2
Change from baseline in secondary efficacy and quality of life parameters

Parameter	Treatment	N	Change from baseline, LS mean (SE)	Treatment difference (95% CI)	P value
Secondary efficacy parameters					
CGI-S	Lamotrigine	130	0.5 (0.15)	-0.2 (-0.5, 0.1)	0.245
	Placebo	133	0.7 (0.15)		
CGI-I	Lamotrigine	130	2.7 (0.21)	0.0 (-0.4, 0.5)	0.833
	Placebo	133	2.6 (0.20)		
HAMD	Lamotrigine	130	1.8 (0.84)	-1.2 (-3.0, 0.5)	0.155
	Placebo	133	3.0 (0.83)		
YMRS	Lamotrigine	130	2.8 (0.88)	0.4 (-1.4, 2.2)	0.661
	Placebo	133	2.4 (0.87)		
GAS	Lamotrigine	130	-4.9 (1.77)	-0.1 (-3.7, 3.5)	0.945
	Placebo	133	-4.7 (1.75)		
Body weight	Lamotrigine	128	-1.56 (0.407)	-0.84 (-1.66, -0.01)	0.047
	Placebo	130	-0.72 (0.399)		
Quality of life parameters					
Physical functioning	Lamotrigine	127	-0.0 (0.09)	0.0 (-0.2, 0.2)	0.868
	Placebo	125	-0.1 (0.09)		
Physical role functioning	Lamotrigine	127	-0.2 (0.12)	0.1 (-0.2, 0.3)	0.566
	Placebo	125	-0.3 (0.12)		
Emotional role functioning	Lamotrigine	127	-0.2 (0.15)	0.3 (0.0, 0.6)	0.042
	Placebo	125	-0.5 (0.15)		
Social functioning	Lamotrigine	127	-0.1 (0.13)	0.2 (-0.1, 0.5)	0.180
	Placebo	125	-0.3 (0.13)		
Bodily pain	Lamotrigine	127	-0.2 (0.12)	0.1 (-0.2, 0.3)	0.585
	Placebo	125	-0.3 (0.12)		

Statistical analysis performed using ANCOVA with covariates of site, CGI-S baseline score and treatment.

CI, confidence interval; CGI-I, Clinical Global Impressions of Improvement; CGI-S, Clinical Global Impressions of Severity; GAS, Global Assessment Scale; HAMD, Hamilton Depression Rating Scale; SE, standard error; YMRS, Young Mania Rating Scale. Analysis population: RD full analysis population.

Parameter	Treatment	N	Change from baseline, LS mean (SE)	Treatment difference (95% CI)	P value
Mental health	Lamotrigine	127	-0.3 (0.15)	0.2 (-0.1, 0.5)	0.164
	Placebo	125	-0.5 (0.15)		
Vitality	Lamotrigine	127	-0.1 (0.13)	0.2 (-0.1, 0.5)	0.139
	Placebo	125	-0.3 (0.13)		
General health perception	Lamotrigine	127	0.0 (0.11)	0.1 (-0.1, 0.3)	0.355
	Placebo	125	-0.1 (0.12)		
Statistical analysis performed using ANCOVA with covariates of site, CGI-S baseline score and treatment.					
CI, confidence interval; CGI-I, Clinical Global Impressions of Improvement; CGI-S, Clinical Global Impressions of Severity; GAS, Global Assessment Scale; HAMD, Hamilton Depression Rating Scale; SE, standard error; YMRS, Young Mania Rating Scale. Analysis population: RD full analysis population.					

3.3. Safety endpoints

No deaths were reported in either the OL or RD phases of the study. Overall, 177 (42.1%) patients during the OL phase and 84 (31.8%) patients during the RD phase experienced one or more TEAEs (RD phase: lamotrigine, n=40; placebo, n=44) (Table 3). During the RD phase, the overall incidence of any TEAEs and treatment-related TEAEs were similar in the two treatment groups. The most common TEAEs during the OL phase were rash (4.8%), headache (4.3%) and dizziness (4.0%), and the most common TEAEs during the RD phase were nasopharyngitis (2.7%), headache, upper respiratory tract infection and urinary tract infection (2.3% each). The majority of the TEAEs reported during the RD phase in the lamotrigine (22.1%) and placebo (26.3%) groups were mild in intensity.

Table 3
Overall adverse events

Characteristic	Open-label phase	Double-blind phase	
	Lamotrigine	Lamotrigine	Placebo
	N=420	N=131	N=133
Any AE	177 (42.1)	41 (31.3)	47 (35.3)
TEAEs related to study treatment	111 (26.4)	19 (14.5)	20 (15.0)
AEs leading to discontinuation of study treatment	40 (9.5)	5 (3.8)	5 (3.8)
Any TEAE adverse events[1]	177 (42.1)	40 (30.5)	44 (33.1)
Rash	20 (4.8)	2 (1.5)	2 (1.5)
Headache	18 (4.3)	4 (3.1)	2 (1.5)
Dizziness	17 (4.0)	2 (1.5)	1 (0.8)
Constipation	15 (3.6)	-	1 (0.8)
Fatigue	15 (3.6)	-	2 (1.5)
Nasopharyngitis	14 (3.3)	3 (2.3)	4 (3.0)
Somnolence	10 (2.4)	1 (0.8)	1 (0.8)
Hepatic function abnormal	9 (2.1)	-	1 (0.8)
Upper respiratory tract infection	9 (2.1)	2 (1.5)	4 (3.0)
Urinary tract infection	3 (0.7)	3 (2.3)	3 (2.3)
Nausea	6 (1.4)	3 (2.3)	1 (0.8)
Poor quality sleep	5 (1.2)	1 (0.8)	3 (2.3)
Weight decreased	1 (0.2)	3 (2.3)	1 (0.8)
Serious adverse events			
Any serious adverse events	12 (2.9)	2 (1.5)	3 (2.3)
Mania	5 (1.2)	-	2 (1.5)
Rash	2 (0.5)	-	-
Bipolar disorder	1 (0.2)	-	-
Ankle fracture	1 (0.2)	-	-

Data are presented as n (%). [1]Data for adverse events is presented for events ≥2% in any group, any phase.

TEAE, treatment-emergent adverse event. Analysis population: Safety population

Characteristic	Open-label phase	Double-blind phase	
	Lamotrigine	Lamotrigine	Placebo
	N=420	N=131	N=133
Face injury	1 (0.2)	-	-
Head injury	1 (0.2)	-	-
Intentional product misuse	1 (0.2)	-	-
Hepatic function abnormal	1 (0.2)	-	-
Suicide attempt	-	1 (0.8)	-
Brain stem infarction	-	1 (0.8)	-
Concussion	-	-	1 (0.8)
Contusion	-	-	1 (0.8)
Laceration	-	-	1 (0.8)
Data are presented as n (%). [1]Data for adverse events is presented for events ≥2% in any group, any phase.			
TEAE, treatment-emergent adverse event. Analysis population: Safety population			

Serious AEs (SAEs) were reported for 12 patients (2.9%) in the OL phase, the most common of which was mania (n=5; 1.2%). Five patients reported SAEs during the RD phase (placebo, n=3 [2.3%]; lamotrigine, n=2 [1.5%]). The SAEs in the placebo group were mania (n=2 [1.5%]), concussion (n=1 [0.8%]), contusion (n=1 [0.8%]) and laceration (n=1 [0.8%]). For the lamotrigine group, the SAEs were suicide attempt (n=1 [0.8%]) and brain stem infarction (n=1 [0.8%]).

A total of 40 (9.5%) patients in the OL phase and 10 (3.8%) patients in the RD phase had TEAEs leading to withdrawal from the study. The most common TEAE leading to withdrawal was rash during the OL phase (n=17; 4.0%). During the RD phase, rash (placebo, n=1 [0.8%]; lamotrigine, n=1 [0.8%]) and mania (placebo, n=2 [1.5%]) were the most common TEAE leading to withdrawal.

No clinically significant changes were observed in vital signs, ECG values, haematology, clinical chemistry, or urinalysis during both the OL and RD phases. The C-SSRS assessment showed that a total of 31 (7.7%) patients reported suicidal events (ideation or behaviour) during the OL phase and 18 (7.1%) patients during the RD phase. The proportion of patients in C-SSRS Suicide Categories during the RD phase was marginally higher in the placebo group (n=12, 9.2%) compared with that in the lamotrigine group (n=6, 4.8%).

3.4. Post hoc analyses

Despite similar inclusion/exclusion criteria in the China study and pivotal trials, patients in this study were seen to have a milder bipolar I disorder history and milder mood symptoms at baseline (mean number of mood episodes in 3 years prior to study entry, lower HAMD and CGI-S scores) [15, 14]. Given that patients with a milder history and milder symptoms are considered to have a lower risk of relapses and/or recurrences of mood episodes, post hoc analyses were conducted to investigate the primary efficacy endpoint (TIME) in subgroups of patients with moderate/severe mood symptoms at baseline, a population more similar to those included in the previous international lamotrigine studies. The subgroup allocation by baseline mood symptom severity is shown in **Supplementary Table 1**. A total of 150 (57.0%) and 156 (59.3%) patients in the RD phase met the CGI-S and HAMD/YMRS threshold of moderate/severe baseline mood symptoms, respectively. The post hoc analyses using CGI-S or HAMD/YMRS scores both showed a greater efficacy response with lamotrigine versus placebo in patients who had more severe bipolar disorder at screening/baseline with respect to TIME.

Of the 156 patients with baseline CGI-S ≥4, 60 (lamotrigine, n=22 [28.9%]; placebo n=38 [51.4%]) reached the TIME events. The difference between lamotrigine and placebo groups was statistically significant (HR [95% CI]: 0.52 [0.30, 0.89]; p=0.018). For the 156 patients with baseline HAMD ≥18 or YMRS ≥10, 57 (lamotrigine n=20 [25.3%]; placebo n=37 [48.1%]) reached the TIME events. This difference was also statistically significant (HR [95% CI] 0.44 [0.25, 0.78]; p=0.005). Kaplan–Meier survival estimates for TIME in patients with moderate/severe baseline mood symptoms, defined using CGI-S and HAMD/YMRS scores, showed significant differences between the treatment groups (p≤0.01) (Fig. 4).

4. Discussion

This randomised double-blind study was conducted to explore the efficacy of lamotrigine for the prevention of relapse and/or recurrence of manic, hypomanic, mixed or depressive episodes in Chinese patients with bipolar I disorder. The current study was based on two earlier pivotal studies [14, 15], which led to the approval of lamotrigine in the global markets including US and EU (at a target dose of 200 mg/day) [5, 7].

The number of patients who reached TIME (primary endpoint) was slightly lower in the lamotrigine group than in the placebo group; however, this difference was not significant. In addition, median survival time was slightly higher for the lamotrigine group (188 days) than that of the placebo group (183 days) but superiority of lamotrigine was not demonstrated. Similarly, all secondary efficacy endpoints except for body weight (TIMan, TIDep, TIME-SIS, CGI-S, CGI-I, HAMD, YMRS and GAS) did not show significant differences between the lamotrigine and placebo groups. Body weight showed a significantly greater decrease among the lamotrigine group. These findings contrast with those from the previous pivotal studies in international

populations. In both of these studies, lamotrigine was superior to placebo in prolonging TIME and TIDep but not TIMan [14, 15]. The differences in the changes from baseline in HAMD between the lamotrigine and placebo groups in pivotal studies were also significant and the median survival time was significantly longer with lamotrigine versus placebo (85 vs 58 days [p=0.03] and 200 vs 93 days [p=0.003]) [14, 15]. The possible reasons for the differences between these results from the pivotal studies and the current findings merit consideration.

The lack of significant efficacy in the current study population could be because the patients included had milder disease compared with the previous study populations despite mostly similar inclusion and exclusion criteria [17, 16, 14]. There is evidence in the literature that disease characteristics at baseline have a strong impact on the treatment outcome of patients with bipolar I disorder. Patients who have more prior mood episodes are known to have a slower response to treatment and a higher risk of relapse/recurrence of further episodes than patients who have fewer prior mood episodes [25–27]. Patients who present with severe mood symptoms at baseline generally respond slowly to treatment and are likely to present with residual mood symptoms during recovery after the initial treatment; the presence of residual symptoms is a major risk factor for relapses/recurrences during maintenance treatment [28–31, 25, 32]. The patients in this Chinese study had a shorter bipolar I disorder disease history and milder mood symptoms at baseline compared with previous pivotal studies. In the present study, the mean CGI-S score at screening was 3.6, which is lower than reported in the pivotal trials (4.3 and 4.4) [14, 15].

Furthermore, patients in the present study also had a lower number of depression and mania/mixed episodes in the preceding 3 years and a lower rate of suicide attempts compared with the pivotal studies [14, 15]. Therefore, the current study population could be expected to have a lower risk of relapse/recurrence of mood episodes during the RD phase than the populations in the pivotal studies based on the severity of disease at baseline.

Additional factors may also have contributed to the lack of a significant effect of lamotrigine in the main study population. Patients in both the lamotrigine and placebo groups experienced a low number of mood episodes during the 36-week RD phase, as expected as a consequence of their relatively mild disorder. The dropout rate was also higher than anticipated (56% compared with the assumed 20%) further reducing the number of patients available to experience an event. Consequently, superiority of lamotrigine over placebo in preventing the relapse/recurrence of mood episodes could not be demonstrated. The duration of the RD phase within the present study was also comparatively shorter (36 weeks) compared with the previous studies (approximately 78 weeks) [14, 15]; a longer duration of study may have resulted in a higher number of mood episodes allowing estimation of time to an event and potential demonstration of a significant effect. In a previous phase I study in healthy Chinese volunteers, lamotrigine demonstrated a comparable pharmacokinetic profile to that in the international population [5, 33]. Therefore, differences in genetics and ethnicity are not thought to play a major role in the differences in results between this study in Chinese patients and the studies conducted in international populations.

The post hoc analyses aimed to explore the potential impact of disease severity at baseline on the lack of a significant effect of lamotrigine by evaluating the response i.e. the primary endpoint (TIME) in a subgroup of patients with moderate/severe disease at baseline using the criteria of CGI-S or HAMD/YMRS thresholds.

These post hoc data showed a statistically significant difference in favour of lamotrigine versus placebo in patients with moderate/severe mood symptoms (baseline CGI-S score ≥4 or HAMD ≥18/YMRS ≥10). Although the data from the post hoc analyses need to be interpreted with caution, these results are more consistent with the observations from previously mentioned international studies [14, 15].

Overall, lamotrigine 200 mg/day showed a comparable safety and tolerability profile to placebo and led to a lower number of AEs compared to the prior studies outside China [14, 15, 34, 17]. The number of patients who experienced serious TEAEs and AEs leading to withdrawal from the study were similar in both placebo and lamotrigine groups. No new or unexpected safety signals emerged based on the AEs, laboratory analyses, and monitoring of vital signs and ECGs.

This study has a number of limitations. The study may have benefitted from longer lead-in requiring patients to be stable for longer than 4 weeks. Diagnosis of bipolar disorder in this study was made without using standardised measures (e.g. Structured Clinical Interview for DSM Disorders). Moreover, there was no active comparator. The use of concomitant medications during the treatment phase, including lamotrigine and valproate sodium in the RD phase, may have impacted the results.

5. Conclusion

This study demonstrated that treatment with lamotrigine 200 mg/day over 36 weeks was not superior to placebo in preventing relapse and/or recurrence of mood episodes in the adult Chinese patients with bipolar I disorder who were recruited. However, post hoc analyses suggested a benefit of lamotrigine over placebo in patients with moderate/severe mood symptoms at baseline, a finding consistent with the results from previous pivotal studies. Lamotrigine was well-tolerated with no new safety signals in Chinese patients with bipolar I disorder.

Abbreviations

AE, adverse event; CGI-I, Clinical Global Impressions of Improvement; CGI-S, Clinical Global Impression of Severity; CI, confidence interval; C-SSRS, Columbia Suicide Severity Rating Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; ECG, Electrocardiogram; EU, European Union; FAP, full analysis population; GAS, Global Assessment Scale; GSK, GlaxoSmithKline; HAMD-17, Hamilton Depression Scale 17 Items; HR, hazard ratio; Kg, kilogram; LTG, lamotrigine; OL, open-label; PBO, placebo; QTc, corrected QT interval; RD, randomised double-blind; SAE, serious adverse event; SD, standard deviation; TIDep, Time to Intervention for Depressive Episode; TIMan, Time to Intervention for Manic, Hypomanic or Mixed Episode; TIME, Time to intervention for a relapse or recurrence of a mood episode; TIME-SIS, Time to Intervention for Manic, Hypomanic or Mixed Episode; US, United States; YMRS, Young Mania Rating Scale.

Declarations

Ethics approval and consent to participate:

The study protocol was approved by an Independent Ethics Committee or Institutional Review Board at each study centre. Written informed consent was obtained from each participant prior to any study-specific procedures.

Consent for publication:

[to be completed prior to submission]

Availability of data and material:

Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com

Competing interests:

Lu Zi is an employee of GlaxoSmithKline. James Cooper and Abhay Phansalkar are employees of, and hold stocks in, GlaxoSmithKline. All other authors declare that they have no conflicts of interest.

Funding:

This study was supported by GlaxoSmithKline (China) R&D Company Limited, Shanghai, China. Medical writing assistance for the manuscript was also funded by GSK.

Authors contributions:

Ling Zhang, Honggeng Zhang, Lu-xian Lv, Qingrong Tan, Xiufeng Xu, Jian Hu, Gang Wang contributed to conception or design, acquisition and interpretation of data. Lu Zi, James Cooper and Abhay Phansalkar contributed to analysis and interpretation of data. The first draft was written by a medical writer under the guidance of authors. All authors critically reviewed the drafts and provided important intellectual suggestions. All authors read and approved the final manuscript before submission.

Acknowledgements:

Editorial support (in the form of writing assistance, including collating authors' comments for each draft, assembling tables and figures, grammatical editing and referencing) was provided by Robert Bloxham at Fishawack Indicia Ltd, part of Fishawack Health UK. The authors would like to thank other investigators: Fude Yang, Hongyan Zhang, Shiping Xie, Tao Li, Huichun Li, Xi Xu, Jinbei Zhang, Jingping Zhao, Huafang Li, Yi Li, Fujun Jia, Xueyi Wang for their contribution in the study conduct.

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Figures

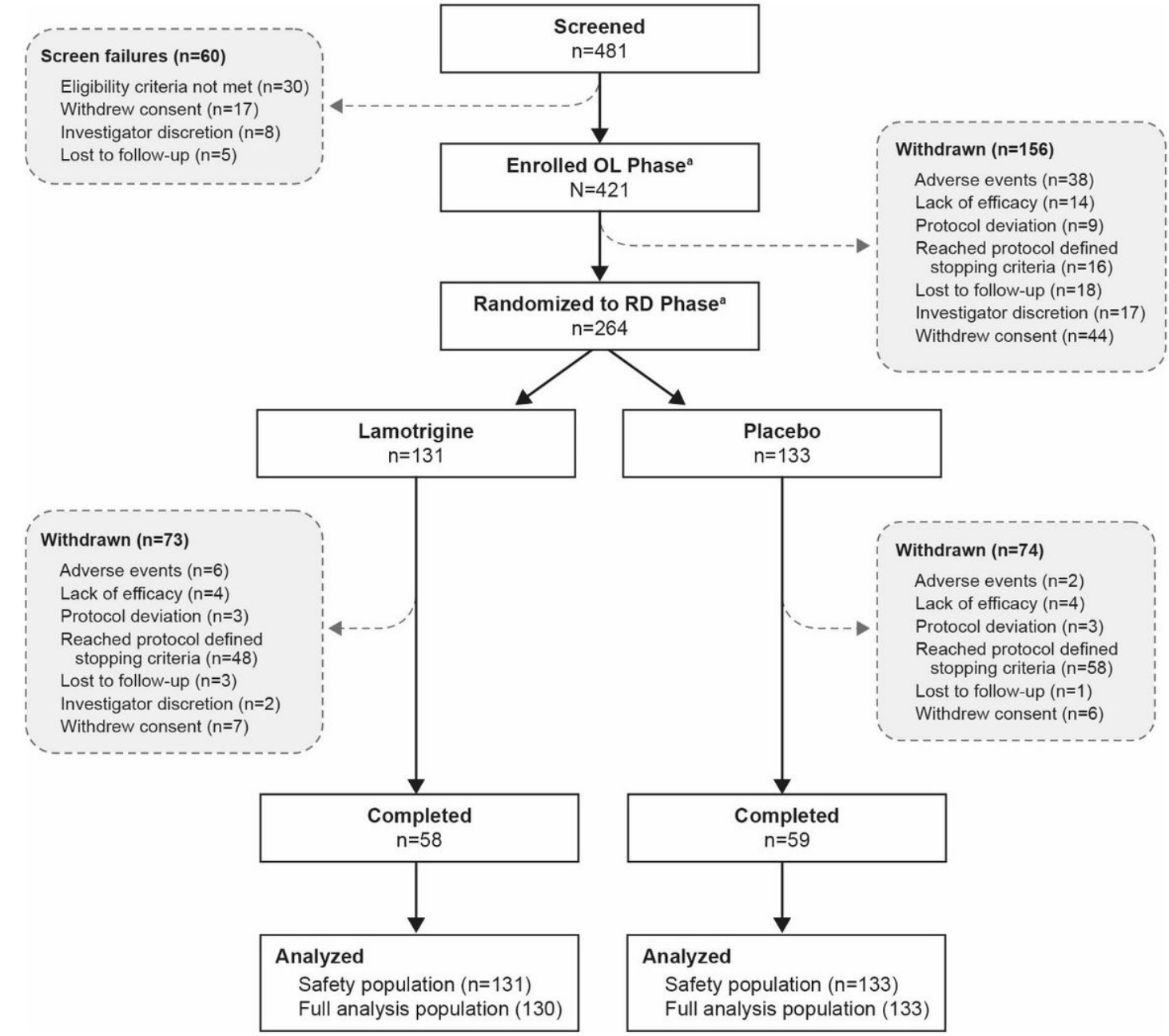

Figure 1

CONSORT flow diagram. aOne patient was enrolled to open-label phase but did not receive any treatment. The stopping criteria was defined as a CGI-S score of ≤3 for at least 6 consecutive weeks. CGI-S, Clinical Global Impression–Severity; RD, double-blind; OL, open-label.

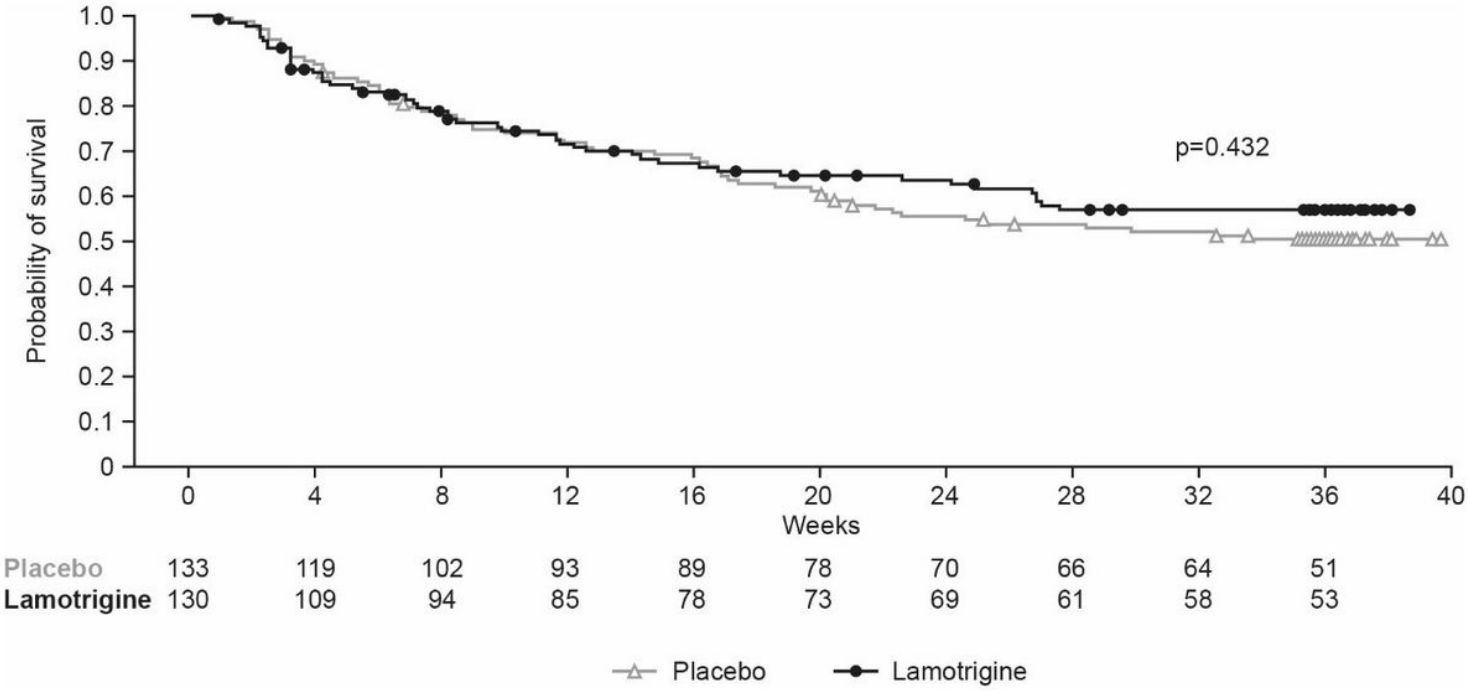

Figure 2

Kaplan–Meier survival estimates depicting time to intervention for mood episode (TIME). The p value was calculated using the log-rank test and is for the PBO versus LTG comparison. Marks represent censored events. Estimates are for the RD FAP. FAP, full analysis population; LTG, lamotrigine; PBO, placebo; RD, randomised double-blind; TIME, time to intervention for mood episode.

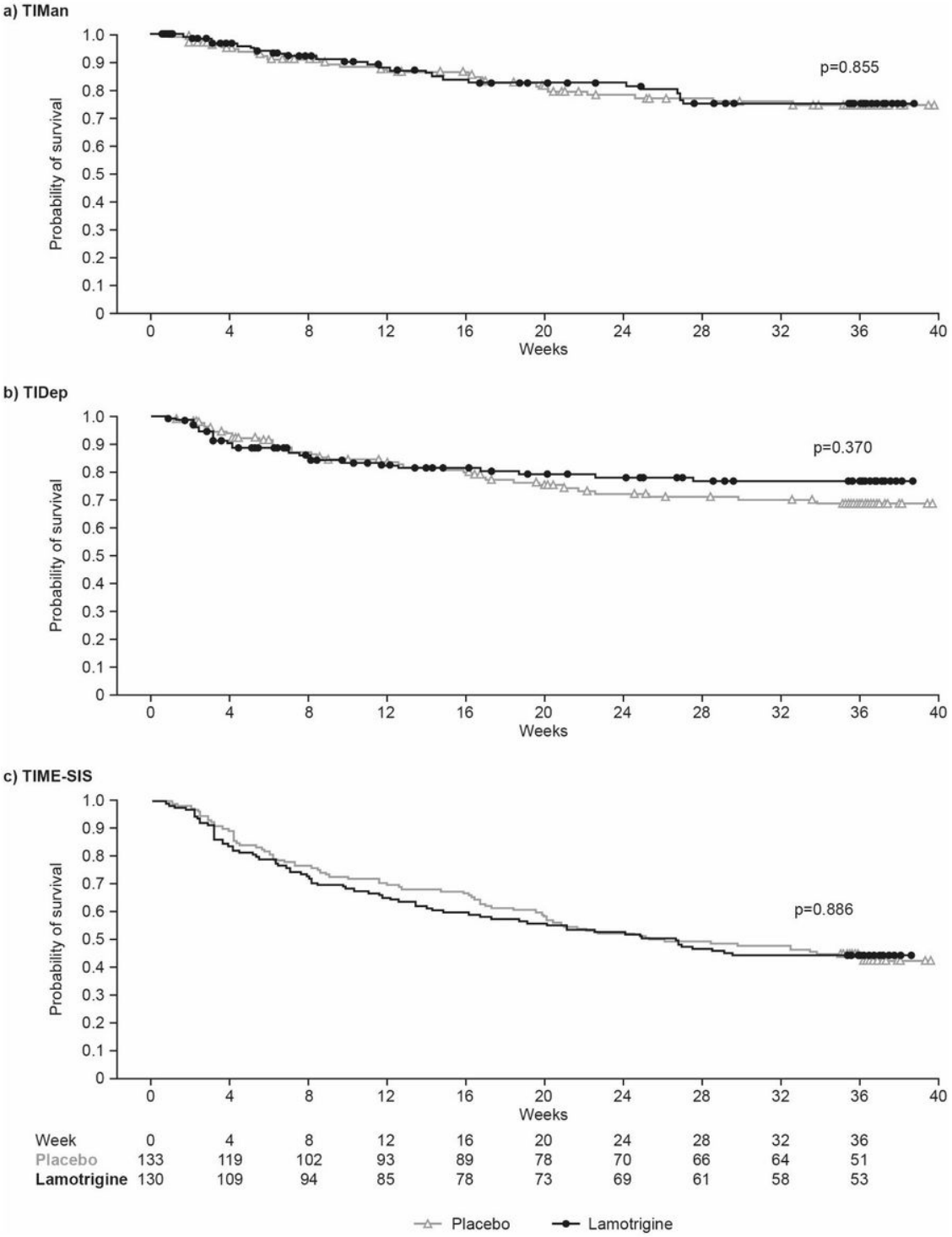

Figure 3

Kaplan–Meier survival estimates depicting (a) TIMan, (b) TIDep and (c) TIME-SIS. The p-values were calculated using the log-rank test and is for the PBO versus LTG comparison. Marks represent censored events. Estimates are for the RD FAP. FAP, full analysis population; LTG, lamotrigine; PBO, placebo; RD, randomised double-blind; TIMan, time to intervention for manic, hypomanic or mixed episode; TIDep, time to intervention for depressive episode; TIME-SIS, overall survival in study.

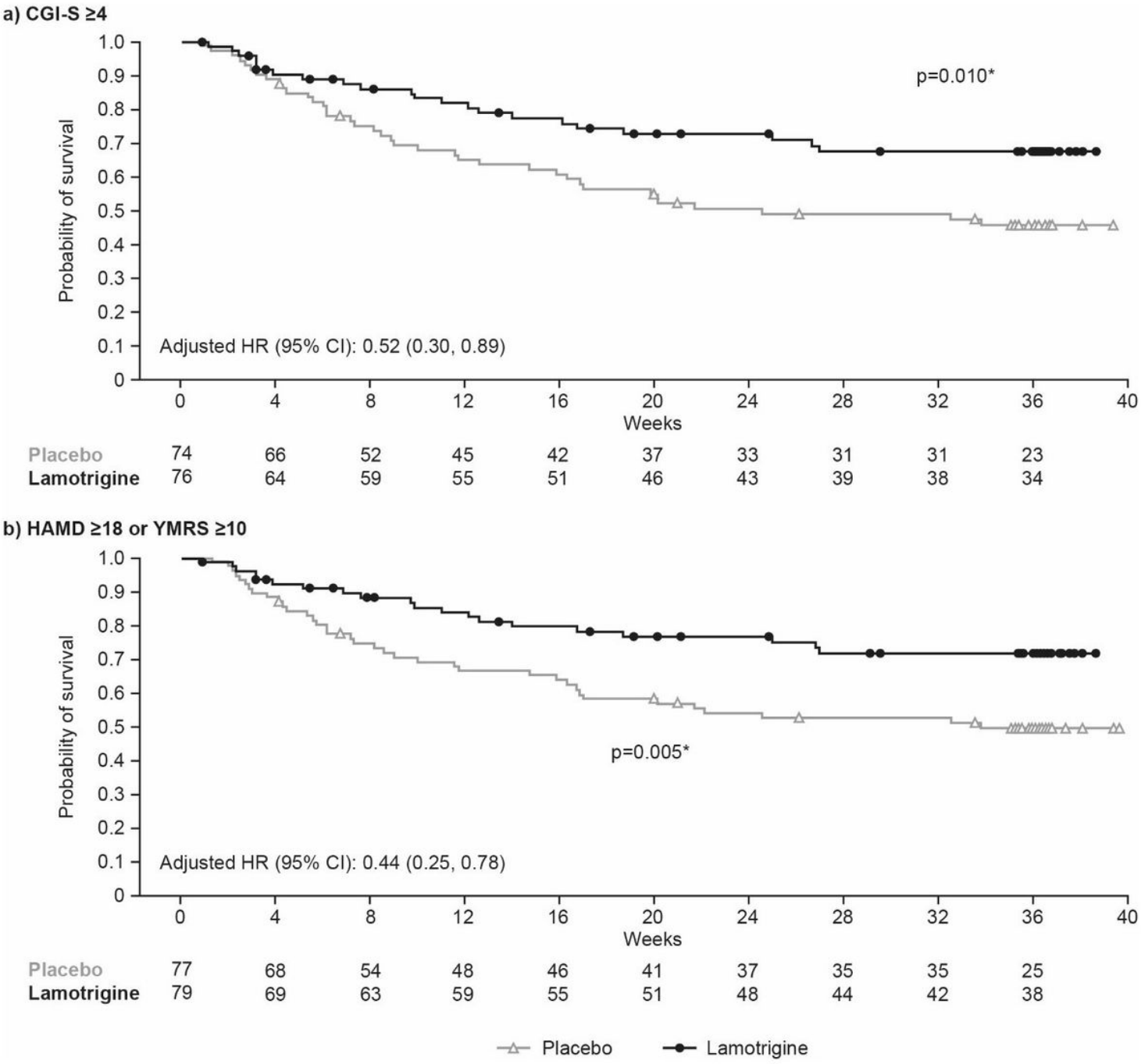

Figure 4

Kaplan–Meier survival estimates for TIME in patients with moderate/severe baseline mood symptoms. *The p values were calculated using the log-rank test and is for the PBO versus LTG comparison. Marks represent censored events. Estimates are for the RD FAP (excluding patients without baseline CGI-S or HAMD/YMRS scores). CGI-S, Clinical Global Impressions of Severity; FAP, full analysis population; HAMD, Hamilton Depression Rating Scale; HR, hazard ratio; LTG, Lamotrigine; PBO, Placebo; RD, randomised double-blind; TIME, time to intervention for a mood episode; YMRS, Young Mania Rating Scale.

Supplementary Files

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- SupplementaryTableAndFigure.docx