CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
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CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

Medical Division: Division of Neuropharmacological Drug Products (HFD-120)
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NDA NUMBER/SERIAL NUMBER:	20-241/S-017 & 20-764/S-011
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SPONSOR:	GlaxoSmithKline
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II. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1. Conclusions and Recommendations

The sponsor submitted two pivotal studies SCAB2003 and SCAB2006 in this submission to evaluate the safety and efficacy of lamotrigine in the long-term prevention of relapse and recurrence of depression and/or mania in subjects with bipolar I disorder. Two studies had similar designs except of different study populations and different dosage regimen. Study SCAB2006 was designed with flexible dose of lamotrigine but Study SCAB2003 was designed with fixed doses of lamotrigine (50mg, 200mg and 400mg).

After statistical review and evaluation, for Study SCAB 2003, the data indeed support the efficacy of lamotrigine 200mg. For Study SCAB2006, if the division decides to accept the sponsor's reason of termination, then the study provides support for the lamotrigine's efficacy. However, we should notice that the evidence is not dose specific because this study used flexible dose regimen.

2. Principal Findings

- In the sponsor's original protocols of two pivotal long term studies SCAB2003 and SCAB2006, the primary endpoint was prospectively specified as TIME, which was defined as "time from entry into the randomized phase to the time of the first prescription of any additional pharmacotherapy or electroconvulsive therapy determined by the investigator to be necessary for treatment of a relapse or recurrence of a depressive episode or recurrence of a manic, hypomanic, or mixed episode, whichever occurred first."

  Before the data were unblinded, the sponsor submitted the last amendments for each study to provide three different censoring schemes for dealing with subjects who discontinue prematurely from the study prior to reaching an event. They designated the first one as the principal analysis, which assumed the premature discontinuation of a subject prior to reaching TIME for reasons other than AEs not deemed related to bipolar symptomatology to be an event related to bipolar disorder. This censoring scheme was denoted as TIME(ABE).

  FDA did not agree with the proposed censoring scheme TIME(ABE) as the primary analysis because it treated almost all kinds of early drop-outs as events, which introduced an interpretation problem. Since the sponsor did not mention any way to deal with patients who prematurely discontinued prior to events or complete the study without reaching time in the original protocol, we should assume all patients without events were censored. That is the third analysis TIME(only) proposed in the sponsor's amendment.

  The medical division, however, also felt that considering TIME endpoint alone was not sensitive enough to capture all bipolar related events, so they decided to consider a different censoring scheme. They proposed that not only the patients who

reached TIME were counted as events, some patients who discontinued the study before reaching time due to lack of efficacy or some had adverse events clearly due to bipolar disorder were also counted as events. This reviewer reanalyzed the data by reversing the aforementioned patients' censoring status and for convenience denoted this new censoring scheme as TIME(BPD).

The principal statistical findings and analysis p-values for the two pivotal studies separately were summarized as follows.

Study SCAB2003

- The medical reviewer informed this reviewer that Site #55466 was closed for some safety problems but the sponsor still included the patients' data into the efficacy analyses. This reviewer reanalyzed the data by excluding that site. The p-values of TIME(only) for the comparisons between the combined lamotrigine 200 mg and 400mg treatment and the Placebo, and between the lamotrigine 200mg and the Placebo became 0.0594 and 0.0277 (Note: they were 0.029 and 0.013 for the original data), respectively.

- The medical reviewer also found six patients who had mood episodes treated but were not counted as events, so this reviewer reanalyzed the data after redefining those patient's TIMEs and their censoring status but without excluding Site #55466. The p-values of TIME(only) for the comparisons between the combined lamotrigine 200mg and 400mg treatment and the Placebo, and between the lamotrigine 200mg and the Placebo became 0.0297 and 0.0068, respectively.

- This reviewer also reanalyzed the data after both excluding Site #55466 and redefining the six patients as having an event. The p-values of TIME (only) for the comparisons between the combined lamotrigine 200mg and 400mg treatment and the Placebo, and between the lamotrigine 200mg and the Placebo became 0.0617 and 0.0156, respectively.

- For the aforementioned additional censoring scheme, TIME(BPD), this reviewer found that p-values for the comparisons between the combined lamotrigine 200mg and 400mg treatment and the Placebo, and between the lamotrigine 200mg and the Placebo were 0.0337 and 0.0104, respectively.

- Since we normally do not accept the sponsor's analysis results based on combining different dosage groups, this reviewer focuses on the results for the comparisons between each dosage group and the Placebo. Also, since there was no multiple comparison procedure planned in the protocol to deal with the multiplicity, this reviewer used the simple Bonferroni procedure to adjust for two dosage groups. It was found that after the problem site was removed and those six patients were re-defined, the difference between the lamotrigine 200mg and the Placebo was statistically significant since p-value of TIME (only) was 0.0156 (less than 0.025). For the additional newly defined censoring scheme TIME(BPD), the comparison

result between the lamotrigine 200mg and the Placebo also showed a statistically significant difference (p=0.0104).

Study SCAB2006

- Study SCAB2006 was terminated early before the planned number of patients was recruited. This reviewer questioned their reason of early termination. Although the sponsor provided the detailed internal letters to support their reason of early termination and assured us that no interim analysis was performed, this reviewer still questioned their reason of slow recruitment since the rate of recruitment seems to be similar by comparing Study SCAB2006 to Study SCAB2003.

- For Study SCAB2006, since TIME(only) shows statistically significant result ($p<0.05$), it is not necessary to look at the results by using the division proposed censoring scheme TIME(BPD), provided that the division accepts the sponsor's reason for terminating the trial early. It should be noted that this finding is not dose specific since the study used flexible dose regimen.

Other Supportive and Acute Efficacy Studies

- While the other non-pivotal studies were reviewed, this reviewer did not have any inconsistent findings.

III. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

1. Introduction and Background

The pivotal studies presented to support the proposed indication consist of two 76-week, multi-center, double-blind, parallel-group, placebo- and lithium-controlled, randomized studies of lamotrigine in the long-term treatment of adult patients diagnosed with Bipolar I Disorder (Studies SCAB2006 and SCAB2003). Patients who were currently or recently manic/hypomanic (SCAB2006) or depressed (SCAB2003) were stabilized while receiving a combination of lamotrigine and other medications or lamotrigine alone for up to 16 weeks and were then randomized to double-blind study medication. According to the significant analysis results, the sponsor concluded that lamotrigine significantly delayed the time to intervention for a mood episode. Especially, patients treated with lamotrigine remained stable and free of a depressive episode for a significantly longer time than those treated with placebo.

Two additional long-term studies in patients with rapid cycling bipolar disorder, the sponsor concluded that, provide supportive evidence of lamotrigine's efficacy in the long-term management of bipolar disorder (Studies SCAB2005 and SCAA2012) although the primary efficacy analyses [TIME(Only)] did not show statistically significant difference between the lamotrigine and placebo treatment groups.

There were also two completed controlled studies of acute treatment of bipolar depression: SCAB2001 and SCAA2010 in this submission. Both studies failed to show significant results on their primary efficacy analyses. The sponsor, however, considered the Study SCAB2001 a positive study in support of the efficacy of lamotrigine in the treatment of major depressive episodes in bipolar I disorder because of positive effects on important secondary efficacy endpoints indicative of a clinically relevant improvement in the lamotrigine group compared to placebo.

Another well controlled clinical study of acute treatment of bipolar depression was finished and the sponsor also submitted the final clinical study report just before this review was finished. Based on the sponsor's preliminary results shown in September 3, 2002's letter, they concluded that the outcome of SCA40910

This review mainly focused on evaluating two pivotal studies in detail. The review for two supportive studies and three failed acute studies are included in the Appendices.

2. Summary of the Sponsor's Results and Conclusions

According to the sponsor's study report, for both pivotal studies, i.e., Studies SCAB2003 and SCAB2006, the primary efficacy measure was TIME, defined as time from entry into the Randomized Phase to the time of the first prescription of any additional pharmacotherapy or electroconvulsive therapy (abbreviated as ECT) determined by the Investigator to be necessary for treatment of a relapse or recurrence of a depressive episode or recurrence of a manic, hypomanic, or mixed episode, whichever occurred first. Three different censoring schemes were provided to analyze the data (See Section 3.1.4.6). TIME(ABE) was determined by the sponsor as the principal analysis. TIME(Survival in Study) and TIME(only) were supportive analyses.

Secondary measures included (1) the time to the first prescription of any additional pharmacotherapy or ECT determined by the Investigator to be necessary for treatment of a present or impending depressive episode (TIDep) and (2) The time to the first prescription of any additional pharmacotherapy or ECT determined by the Investigator to be necessary for treatment of a present or impending manic, hypomanic, or mixed episode (TIMan). The original protocol also planned to perform some secondary analyses by comparing 'severity' categories of the various dose groups using data derived from the HAM-D, MRS from SADS-C, CGI-I, CGI-S and the clinician's assessment of the predominant state between visits. However, it was deleted by the sponsor's last amendments for both studies. The sponsor's study report showed the analyses for the GAMS between each visit and data collected from the following psychiatric rating scales: HAM-D, RS from SADS-C, CGI-S, CGI-I and GAS instead.

Table 3.1 shows the p-values reported by the sponsor for the primary endpoint by three different censoring schemes and the two primary endpoints of TIDep and TIMan for both pivotal studies.

Table 3.1 The Summary of P-values of Survival Analysis Results for Both Pivotal Studies

Study SCAB2003	Combined LTG 200mg and 400mg vs. Placebo	LTG 200mg vs. Placebo	LTG 400mg vs. Placebo
TIME(ABE)	0.004	0.003	0.240
TIME(SIS)	0.003	0.001	0.274
TIME(only)	0.029	0.013	0.571
TIDep	0.047	0.028	0.533
TIMan	0.339	0.237	0.937
Study SCAB2006	**LTG Flex vs. Placebo**		
TIME(ABE)	0.023		
TIME(SIS)	0.030		
TIME(only)	0.018		
TIDep	0.015		
TIMan	0.280		

According to the results, the sponsor made the following conclusions. For both Studies SCAB2003 and SCAB2006, the observations collected throughout the conduct of the study demonstrate that lamotrigine is well tolerated and effective in the long-term management of mood episodes in bipolar I subjects currently or recently experiencing depression at study entry. There results were observed when lamotrigine was administered in conjunction with other medications (Preliminary Phase) and when used at a maintenance dose up to 400mg daily under long term monotherapy. Compared with placebo, lamotrigine 200mg was the most effective lamotrigine dose in delaying mood episodes. The TIDep results indicate that the effects of lamotrigine in the management of bipolar disorder are primarily at the depressive pole. Therefore, these data support the use of lamotrigine in the long-term management of depression in bipolar I disorder.

3. Description of the Sponsor's Study and Statistical Methodologies

3.1 & 3.2 Pivotal Studies: Studies SCAB2003 and SCAB2006

Study SCAB2006 was an evaluation of the safety and efficacy of LAMICTAL in the long-term prevention of relapse and recurrence of mood symptoms in patients with bipolar I disorder who had recently experienced a manic or hypomanic episode. The study consisted of two phases. In the Preliminary Phase, patients received open-label LAMICTAL as monotherapy or with psychotropic medication as deemed clinically necessary to stabilize the patient. The duration of treatment in the Preliminary Phase was 8 to 16 weeks, depending upon time to response. Responders were discontinued from other psychotropic medications and randomized into one of three treatment groups: LAMICTAL (100 to 400mg/d), Lithium Carbonate (serum levels of 0.8 to 1.1mEq/L) or placebo for a maximum of 18 months of double-blind treatment. Randomized patients were maintained and followed on their respective monotherapy regimens until the investigator deemed it clinically necessary to intervene with additional pharmacotherapy or ECT for an emerging mood episode of either polarity.

Study SCAB2003 is similar to Study SCAB2006 except patients enter with an index episode of depression and that fixed doses of LAMICTAL (50, 200 and 400mg) rather than a flexible dose are being evaluated.

3.1.1 Study Objectives

The primary objective of these studies was:

- to compare the safety and efficacy of lamotrigine and placebo in preventing the relapse and recurrence of bipolar episodes over a long period (76 weeks) in subjects with bipolar I disorder who were experiencing or had recently experienced a manic or hypomanic episode (for Study SCAB2003)/ major depressive episode (for Study SCAB2006) which had responded to lamotrigine treatment in combination with other psychotropic medication or as monotherapy

The secondary objectives of the study were:

- to compare the treatments on measures of mood and global morbidity, including the Hamilton Depression Scale (HAM-D), Mania Rating Scale from the Schedule for Affective Disorders and Schizophrenia-Change Version (MRS from SADS-C), Clinical Global Impression of Severity and Improvement (CGI-S and CGI-I), General Assessment Scale (GAS) and a general assessment of mood state (GAMS) between visits
- to compare quality of life, medication impact and resource utilization between treatment groups within the Randomized Phase

3.1.2 Study Design

Study SCAB2003 was a multicenter, double-blind, double-dummy, parallel-group, placebo- and active treatment-controlled, randomized, fixed-dose study in subjects with bipolar I disorder who were experiencing or had recently experienced a depressive episode. Study SCAB2006 was a multicenter, double-blind, double-dummy, parallel-group, placebo- and active treatment-controlled, randomized, flexible-dose trial in subjects with bipolar I disorder who were experiencing or had recently experienced a manic or hypomanic episode. Both studies consisted of two phases: a Preliminary Phase and a Randomized Phase.

The Preliminary Phase of the study consisted of open-label treatment with lamotrigine, in addition to any other psychotropic agent (except fluoxetine) the Investigator considered to be necessary for treatment of the manic or hypomanic/depression episode in subjects with bipolar I disorder. Lithium treatment was not to be initiated during this period. Subjects receiving lithium at enrollment had their dose slowly tapered over at least 3 weeks and discontinued at least 1 week prior to the Randomized Phase. Other concurrent psychotropic medications, with the exception of lamotrigine, low doses of specified benzodiazepines, and oral chlorohydrate, were tapered (if necessary) and discontinued at

least 1 week prior to randomization. The duration of treatment in the Preliminary Phase was 8-16 weeks, depending on time to response.

Responders were defined as subjects who achieved a CGI-S of 3 or less during the Preliminary Phase, and maintained that score for the 4 continuous weeks immediately prior to Randomization. Responders were eligible to enter the Randomized Phase of the study for a maximum treatment duration of 76 weeks.

For Study SCAB2003, subjects were randomized into one of five treatment groups (prior to Amendment 12):

- lamotrigine 50mg/day and placebo (match for lithium)
- lamotrigine 200mg/day and placebo (match for lithium)
- lamotrigine 400mg/day and placebo (match for lithium)
- lithium, serum therapeutic level between 0.8 and 1.1mEq/L, and placebo (match for lamotrigine)
- placebo (match for lamotrigine) and placebo (match for lithium)

For Study SCAB2006, subjects were randomized into one of three treatment groups:

- lamotrigine, 100mg-400mg/day (starting dose 200mg/day), and placebo (match for lithium)
- lithium, serum therapeutic level between 0.8 and 1.1.mEq/L, and placebo (match for lamotrigine)
- placebo (match for lamotrigine) and placebo (match for lithium)

In both studies, subjects were stratified into groups based on adequate lithium treatment within 5 months prior to entry to the Randomized Phase of the study, as follows:

- no adequate course of lithium treatment
- a previous adequate course of lithium treatment

An adequate course of lithium treatment was defined as one in which serum levels ≥0.4mEq/L were maintained for a minimum period of at least 1 month. In the event that such lithium level determinations were not available, adequate documentation of at least 600mg lithium/day for at least 1 month was acceptable.

Once randomized, subjects were followed on the assigned monotherapy regimen until the investigator deemed it clinically indicated to prescribe additional pharmacotherapy (or ECT) in order to treat a present or impending relapse and recurrence of mania, or recurrence of depressive, hypomanic, or mixed episode. The time from entry into the Randomized Phase to the time of the first prescription of any additional treatment of the relapse or recurrence of a mood episode was identified as "TIME."

After TIME was reached, subjects were permitted to continue on their blinded medications plus other psychotropic drugs for up to 12 months. Although subjects had reached endpoint, they could continue to follow the study visit schedule. If TIME was not reached within the 12 months after randomization, subjects were to be continued in the trial until TIME occurred or for a total of 18 months, whichever came first.

After randomization, subjects were assessed at weekly intervals for 1 month, then every 2 weeks for 1 month, then at monthly intervals for up to 18 months (76 weeks) of double-blind treatment. Following the treatment period, there was a brief follow-up period, culminating in a follow-up clinic assessment visit.

3.1.3 Efficacy Measures

3.1.3.1 Primary Efficacy Measure

The primary efficacy measure was TIME, defined as time from entry into the Randomized Phase to the time of the first prescription of any additional pharmacotherapy or ECT determined by the Investigator to be necessary for treatment of a relapse or recurrence of a manic, hypomanic, depressive, or mixed episode, whichever occurred first.

3.1.3.2 Secondary Efficacy Measures

Secondary measures included:

- The time to the first prescription of any additional pharmacotherapy or ECT determined by the Investigator to be necessary for treatment of a present or impending manic, hypomanic, or mixed episode (TIMan)

- The time to the first prescription of any additional pharmacotherapy or ECT determined by the Investigator to be necessary for treatment of a present or impending depressive episode (TIDep)

Additional secondary outcome measures also consisted of GAMS between each visit and data collected from the following psychiatric rating scales: scores on the HAM-D, MRS from SADS-C, CGI-I, CGI-S, and GAS.

3.1.4 Data Analysis Methods

3.1.4.1 Sample Size Consideration

For Study SCAB2003, sample sizes were based on the percentage of subjects experiencing a relapse or recurrence of a depressive episode (PRD). A minimum of 75 subjects per group was determined sufficient to detect a statistically significant difference between lamotrigine and placebo treatment groups in PRD with 80% power. This assumed a PRD for the placebo population of 65% and a PRD of 40% for the lamotrigine population and a significance level of 0.025, using the Bonferroni adjustment for two comparisons: lamotrigine 200mg versus placebo, and lamotrigine 400mg versus placebo. Assuming an approximate 25% dropout rate, a total of 100 subjects per group were to be enrolled into the Randomized Phase. Note: Due to the termination of enrollment into the lamotrigine 50mg and lamotrigine 400mg treatment arms of the study, actual enrollment into the Randomized Phase for these treatment arms did not meet the targeted enrollment of 100 subjects per treatment group.

For Study SCAB2006, sample sizes were based on a consideration of the percentage of subjects experiencing a recurrence of a manic episode (PRM). A minimum of 62 subjects per group was determined sufficient to detect a statistically significant difference between lamotrigine and placebo treatment groups in PRM with 80% power. This assumed a PRM for the placebo population of 65% and a PRM of 40% for the lamotrigine population and a significance level of alpha=0.05. Assuming an approximate 30-35% drop out rate, a total of 100 subjects per treatment group were to be enrolled into the Randomized Phase. Note: Due to the termination of enrollment into the lithium treatment arm of the study, as well as the premature termination of the study itself, actual enrollment into the Randomized Phase did not meet the targeted enrollment of 100 subjects per treatment group.

3.1.4.2 General Consideration for Data Analyses

All significance tests and confidence intervals were two-sided, and performed or constructed at the alpha=0.05 significance level, unless otherwise identified. All primary analyses were performed on a combined-center basis. In the Randomized Phase, subjects were analyzed according to the treatment group assignment.

The primary statistical comparisons of interest throughout are those between the lamotrigine and placebo treatment groups (For study SCAB2003, two arms of lamotrigine 200mg and 400mg were combined). Comparisons of either of these groups against subjects treated with lithium are provided for completeness. The statistical power calculations carried out prior to study initiation were not done with any measure of consideration having been given to comparisons between the two active treatment arms of the study (i.e., lamotrigine vs. lithium). This, (coupled with the termination of enrollment into the lithium arm early in study SCAB2006) necessitates the exercise of caution prior to making any inferences between lithium and either of the remaining treatment arms.

3.1.4.3 Analysis Populations

Three subject populations were defined: an Intent-to-Treat (ITT) population, an Efficacy population and a safety population.

The ITT population consisted of all subjects who were randomized, regardless of whether or not study drug was taken and was used in the summaries of subject accountability, demography and baseline characteristics.

The Efficacy analysis population was defined for the Preliminary and Randomized Phases as follows:

- All subjects in the ITT population who received at least one dose of study drug and had at least one post-screen efficacy assessment were evaluated for efficacy measures in the Preliminary Phase.

- All subjects in the ITT population who received at least one dose of study drug and had at least one post-randomization efficacy assessment were evaluated for efficacy measures in the Randomized Phase. Subjects who did not have at least one post-randomization efficacy assessment but reached TIME, TIMan or TIDep were evaluated for all relevant survival analyses.

The Safety population included all subjects in the ITT population who received at least one dose of study drug. Evaluability for safety analyses were performed within study phases (Preliminary and Randomized).

3.1.4.4 Efficacy Analyses

Primary Efficacy Endpoint

The protocol-defined primary efficacy endpoint, TIME, was measured relative to the date of the first dose of double-blind study drug.

The primary analysis consisted of a pairwise comparison of TIME (ABE) between the lamotrigine treatment group and the placebo treatment group. Survival probabilities were calculated by the Kaplan-Meier method. The estimated survival distribution were compared between treatment groups using a Log-Rank test.

Secondary Efficacy Endpoints

Procedures for analyzing TIMan and TIDep were as outlined for the primary efficacy endpoint (TIME) above. The secondary efficacy measures of psychiatric rating assessments (HAM-D, MRS, CGI-S, CGI-I and GAS) were summarized by nominal assessment time using both observed data and LOCF data. Mean change from screen were compared between treatment groups using analysis of variance. Only absolute scores, and not change from screen scores, were produced for CGI-I.

For changes from Screen, change scores were calculated as score minus Screen score. For changes from RD1, change scores were calculated as score minus RD1 score.

Note: The above analyses for the rating scale assessments were not prospectively specified in the protocol. For the rating scale assessment, what the sponsor originally proposed in the protocol was to compare 'severity' categories of the various dose groups using data derived from the HAM-D, MRS from SADS-C, CGI-I, CGI-S and the clinician's assessment of the predominant state between visits. They planned to use the Wilcoxon Rank Sum Test to perform the tests but they did not since they later explained in their protocol amendment 13, it would be difficult to interpret the meaning of information gained by pooling the components due to the lack of validated methodology developed.

3.1.4.5 Examination of Subgroups

For the primary efficacy measure TIME, and secondary efficacy measure TIMan and TIDep, analyses were also conducted within the adequate course of lithium treatment within 5 months of enrollment subgroups.

It was planned to analyze the secondary efficacy measures of psychiatric rating assessments (HAM-D, MRS, CGI-S, CGI-I and GAS) for the enrollment relative to initiation of Protocol Amendment 12 subgroups for Study2003 (Amendment 6 for Study 2006). Those analyses were not performed because it was felt that examination of the time-to-event efficacy endpoints would more accurately convey subject outcome than would ratings assessments. So, Instead, the sponsor conducted analyses of the primary efficacy measure, TIME, and secondary efficacy measures TIMan, TIDep, and alteration in pharmacotherapy or ECT for the enrollment relative to initiation of Protocol Amendment 12 subgroups for Study 2003 (Amendment 6 for Study 2006).

Subsequent post-hoc analyses were performed in response to feedback from European regulatory agencies. For Study SCAB2003, these analyses included the following subgroups: rapid cycling status, previous psychotropic treatment, any previous lithium treatment, and wellness at entry subgroups. For Study SCAB2006, these analyses included the following subgroups: severity of illness, previous psychotropic treatment, and any previous lithium treatment subgroups (Note: The sponsor's above subgroup analysis results were not shown in this review.)

About the demographic subgroup analyses, like Sex, Age and Race, the sponsor only performed them for the combined study data set and shown results in their Integrated Summary of Efficacy (ISE).

3.1.4.6 Handling of Subjects Prematurely Discontinued or Missing Data

According to the sponsor's Protocol Amendment 13 for Study SCAB2003 and 9 for Study SCAB2006, for the analysis of the primary endpoint, subjects who discontinued prematurely from the study prior to reaching TIME were analyzed in three ways:

- In the principal analysis, the premature discontinuation of a subject prior to reaching TIME for reasons other than AEs not deemed related to bipolar symptomatology was assumed to be an event related to bipolar disorder. This analysis was abbreviated as TIME (ABE).

- In a supportive analysis to the principal analysis, the premature discontinuation of a subject prior to reaching TIME, for any reason, was treated as an event related to bipolar disorder. This analysis was abbreviated as TIME (Survival in Study).

- In another supportive analysis, all subjects who prematurely discontinued from the study for any reason before the TIME event were censored. This analysis was abbreviated as TIME (Only).

In each of these analyses, subjects discontinued from the study prior to reaching TIME due to the sponsor's termination of the study were censored at the time of discontinuation, as were all subjects who completed the study without reaching TIME.

4. Sponsor's Efficacy Results and Conclusions

4.1 Study SCAB2003

4.1.1 Population Analyzed

As mentioned in Section 3.1.4.3, three subject populations were defined: an Intent-to-Treat (ITT) population, an Efficacy population, and a Safety population. Table 4.1.1 summaries the number of subjects analyzed in each population.

Table 4.1.1 Summary of Population Analyzed for Study SCAB2003

Population	Number of Subjects						
	Preliminary Phase	Randomized Phase					
		Placebo	Lithium	Lamotrigine (combind [a])	By Lamotrigine group		
					LTG [b] 50	LTG 200	LTG 400
ITT	966	121	121	171	50	124	47
Safety	958	121	120	169	50	122	47
Efficacy	943	119	120	165	50	120	45

a. lamotrigine 200mg and lamotrigine 400mg treatment groups combined
b. lamotrigine was abbreviated as LTG

4.1.2 Demographic Characteristics

According to Table 4.1.2, the majority of subjects in the Preliminary Phase were female (61%), and most subjects were White (89%). Mean age was 42 years, mean height was 170cm, and mean weight was 79kg.

Randomized Phase treatment groups were comparable with respect to the demographic characteristics evaluated at Screen. There was a slightly higher percentage of females in the lithium and lamotrigine combined group than in the placebo group. Most subjects

were White. Across treatment groups, mean age ranged from 42-44 years, mean height ranged from 170-172cm, and mean weight was 79-82 kg. There were no apparent differences between the treatment groups for demographic characteristics at Screen and at Randomization.

Table 4.1.2 Summary of Subject Demography for Study SCAB2003

		Preliminary Phase	Randomized Phase			
		Lamotrigine	Placebo	Lithium	Lamotrigine (combined)	Total
Number of Subjects	N	958	121	120	169	410
Age (years)	Mean (SD)	42.2 (12.2)	42.1 (13.0)	43.6 (12.3)	44.1 (11.7)	43.4 (12.3)
Sex	Male (%)	370 (39%)	61 (50%)	48 (40%)	70 (41%)	179 (44%)
	Female (%)	588 (61%)	60 (50%)	72 (60%)	99 (59%)	231 (56%)
Race	White (%)	857 (89%)	109 (90%)	113 (94%)	153 (91%)	375 (91%)
	Black (%)	55 (6%)	5 (4%)	5 (4%)	8 (5%)	18 (4%)
	Asian (%)	14 (1%)	2 (2%)	2 (2%)	3 (2%)	7 (2%)
	American Hispanic (%)	24 (3%)	3 (2%)	0	3 (2%)	6 (1%)
	Others (%)	8 (<1%)	2 (2%)	0	2 (1%)	4 (<1%)
Height (cm)	Mean (SD)	169.7(11.1)	171.7 (10.2)	169.6 (10.7)	169.9 (10.4)	170.4 (10.4)
Weight (kg)	Mean (SD)	79.12(17.55)	82.15(18.59)	80.50(17.98)	79.48(17.02)	80.56(17.77)

		Randomized Phase			
		Lamotrigine 50mg	Lamotrigine 200mg	Lamotrigine 400mg	Total
Number of Subjects	N	50	122	47	219
Age (years)	Mean (SD)	44.0 (8.9)	44.9 (11.8)	42.0 (11.5)	44.1 (11.1)
Sex	Male (%)	22 (44%)	49 (40%)	21 (45%)	92 (42%)
	Female (%)	28 (56%)	73 (60%)	26 (55%)	127 (58%)
Race	White (%)	45 (90%)	112 (92%)	41 (87%)	198 (90%)
	Black (%)	4 (8%)	4 (3%)	4 (9%)	12 (5%)
	Asian (%)	0	2 (2%)	1 (2%)	3 (1%)
	American Hispanic (%)	0	2 (2%)	1 (2%)	3 (1%)
	Others (%)	1	2 (2%)	0	3 (1%)
Height (cm)	Mean (SD)	171.7 (10.7)	169.6 (10.3)	170.8 (10.8)	170.3 (10.5)
Weight (kg)	Mean (SD)	78.68 (18.12)	79.09 (16.90)	80.47 (17.46)	79.29 (17.24)

4.1.3 Efficacy Results

The primary statistical comparisons of interest throughout are those between the lamotrigine (combined lamotrigine 200mg and 400mg treatment arms) and placebo treatment groups.

4.1.3.1 Primary Efficacy Endpoint

Recall in Section 3.1.4.6, for the analysis of the primary endpoint, subjects who discontinued prematurely from the study prior to reaching Time were analyzed in three different ways: TIME (ABE), TIME (Survival in Study) and TIME (only). In each of

these analyses, subjects discontinued from the study prior to reaching TIME due to the early termination of the study by the sponsor were censored at the time of study discontinuation, as were all subjects who completed the study without reaching TIME.

A summary of subjects prematurely withdrawn from the study prior to reaching TIME is shown in Table 4.1.3. Of the subjects in the placebo, lithium, and lamotrigine combined groups (lamotrigine 200mg and 400mg groups), 147 (36%) were withdrawn from the study prior to reaching TIME. A total of 68 subjects (31%) in the lamorigine 50mg, 200mg, and 400mg treatment groups were withdrawn from the study prior to reaching TIME.

The primary reason for discontinuation prior to TIME was adverse events, followed by withdrawal of consent. The percentage of subjects who discontinued prior to TIME due to adverse events was higher in the lithium group than in the lamotrigine combined and placebo groups. Of the 51 subjects discontinued prior to TIME due to an AE, a total of 39 subjects (nine in the placebo group, 16 in the lithium group, and 14 in the lamotrigine groups) were withdrawn due to an AE not deemed related to bipolar disorder where applicable. Withdrawal prior to TIME due to consent withdrawn, loss to follow-up, other, protocol violation, and sponsor discontinuation were comparable across treatment groups. Fewer subjects in the lamotrigine 50mg group discontinued prior to TIME compared with the other treatment groups. Among the three lamotrigine groups, the percentages of discontinuations due to AEs was comparable.

Table 4.1.3 Summary of Subjects Discontinued from the Study Prior to Reaching TIME in ITT Population for Study SCAB2003

Subject Status	Placebo N=121	Li N=121	LTG Combined N=171	By LTG Treatment Group		
				LTG 50 N=50	LTG 200 N=124	LTG 400 N=47
Discontinued Prior to Reaching TIME	43 (36)	45 (37)	59 (35)	9 (18)	44 (35)	15 (32)
Adverse Event	12 (10)	19 (16)	16 (9)	4 (8)	11 (9)	5 (11)
Consent Withdrawn	13 (11)	13 (11)	15 (9)	4 (8)	12 (10)	3 (6)
Lost to Follow-up	7 (6)	5 (4)	13 (8)	0	9 (7)	4 (9)
Other	9 (7)	4 (3)	8 (5)	1 (2)	8 (6)	0
Protocol Violation	2 (2)	3 (2)	5 (3)	0	2 (2)	3 (6)
Sponsor Discontinued	0	1 (1)	2 (1)	0	2 (2)	0

4.1.3.1.1 TIME (ABE)

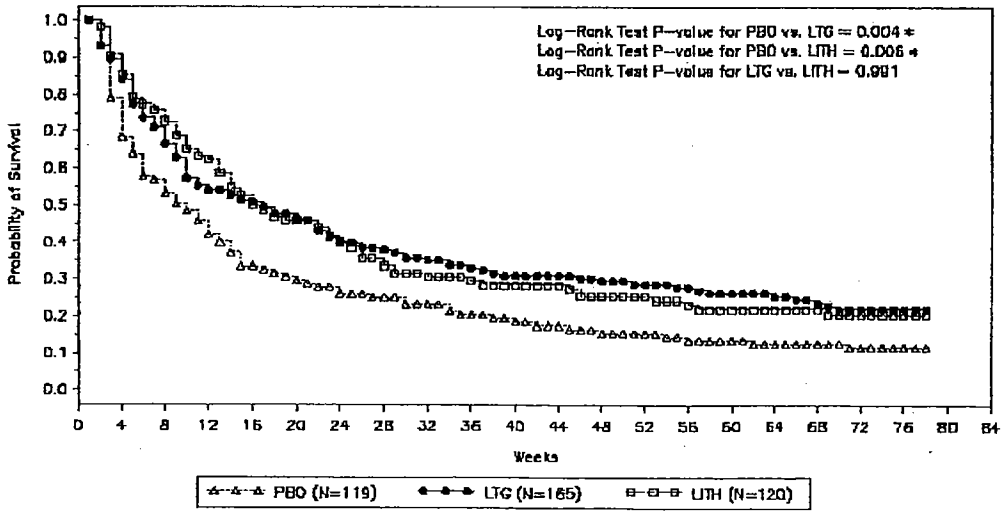
Median survival estimates for TIME (ABE) are shown in Table 4.1.4 and the survival curves are shown in Figure 4.1. As we observed from the table, there were significant differences in survival distribution in favor of the lamotrigine combined group (p=0.004), the lithium group (p=0.006), and the lamotrigine 200mg group (p=0.003) compared with placebo. There were no statistically significant differences in survival distribution between the lamotrigine combined group or the individual lamotrigine groups and the lithium group. A subsequent analysis employing the adequate lithium treatment within 5 months prior to entry into the Randomized Phase of the study as a stratification variable yielded consistent results.

Table 4.1.4 Summary of Analysis of TIME (ABE) for Study SCAB2003

Statistical Parameter	PBO N=119	Li N=120	LTG Comb. N=165	By LTG Treatment Group		
				LTG50 N=50	LTG200 N=120	LTG400 N=45
Subjects with Event, n (%)	98 (82)	83 (69)	123 (75)	38 (76)	89 (74)	34 (76)
Median Time to Event (days)	58	105	110	112	116	69
Confidence Interval	33, 85	85, 158	63, 150	60, 159	62, 176	45, 150
Survival Estimate, Week 76	0.115	0.206	0.220	0.191	0.225	0.207
p-value		0.006	0.004	Not sig.	0.003	Not sig.

An additional analysis of TIME (ABE) was performed in which subjects who relapsed to depression in the first 28 days of the Randomized Phase were excluded. TIME (ABE) was reached by 68 subjects in the placebo group, 70 subjects in the lithium group, and 99 subjects in the lamotrigine combined group. In the placebo group, the median time to TIME (ABE) occurred at 93 days on treatment, compared with 142 days for the lithium group, and 150 days for the lamotrigine combined group. For TIME (ABE) there were no significant differences in survival distribution between treatment groups, although the difference between the placebo and lamotrigine combined group approached statistical significance (p=0.055). TIME (ABE) was reached by 17/29 subjects in the lamotrigine 50mg group, 74/105 subjects in the lamotrigine 200mg group, and 25/36 subjects in the lamotrigine 400mg group. In the lamotrigine 50mg group, the estimated median time to TIME (ABE) was not calculable because the probability of not reaching TIME (ABE) remained greater than 0.50 throughout the study. The estimated median time to TIME (ABE) was 156 days on treatment in the lamotrigine 200mg group and 144 days in the lamotrigine 400mg group.

Figure 4.1 Survival Curves for TIME(ABE) for Study SCAB2003



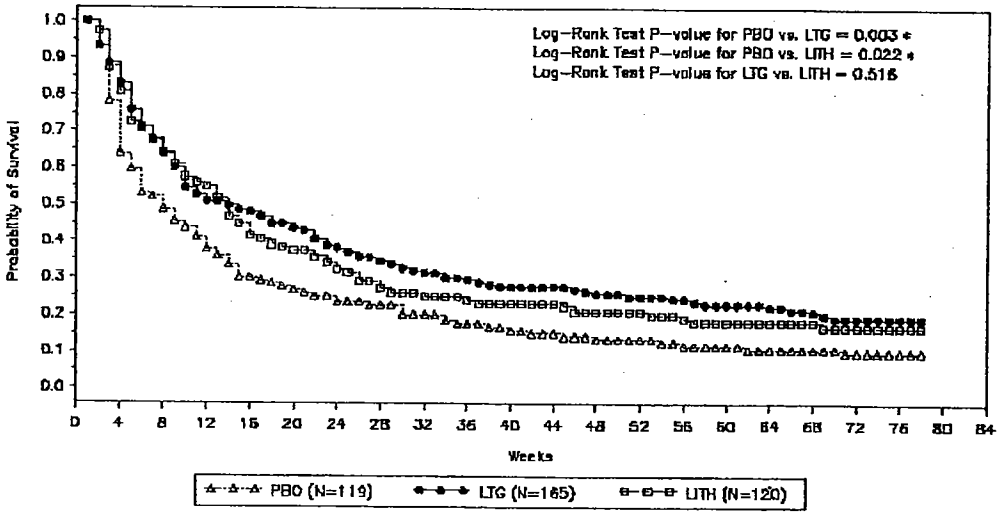
4.1.3.1.2 TIME (Survival in Study)

Median Survival Estimates are shown in Table 4.1.5 and the survival curves are shown in Figure 4.2. As we observed from the table, for TIME (Survival in Study), there were significant differences in survival distributions in favor of the lamotrigine combined group (p=0.003), the lithium group (p=0.022), and the lamotrigine 200mg group (p=0.001) compared with the placebo group; the difference between the lamotrigine 50mg and placebo groups approached statistical significance in favor of lamotrigine (p=0.059). There were no other statistically significant differences in survival distribution for TIME (Survival in Study) between groups.

Table 4.1.5 Summary of Analysis of TIME (Survival in Study) for Study SCAB2003

Statistical Parameter	PBO N=119	Li N=120	LTG Comb. N=165	By LTG Treatment Group		
				LTG50 N=50	LTG200 N=120	LTG400 N=45
Subjects with Event, n (%)	107 (90)	99 (83)	134 (81)	41 (82)	96 (80)	38 (84)
Median Time to Event (days)	46	86	92	88	105	68
Confidence Interval	30, 73	63, 111	59, 144	56, 151	59, 163	42, 144
Survival Estimate, Week 76	0.100	0.169	0.193	0.178	0.201	0.171
p-value		0.022	0.003	Not sig.	0.001	Not sig.

Figure 4.2 Survival Curves for TIME (SIS) for Study SCAB2003



An additional analysis of TIME (Survival in Study) was performed in which subjects who relapsed to depression in the first 28 days of the Randomized Phase were excluded. TIME (Survival in Study) was reached by 76 subjects in the placebo group, 85 subjects in the lithium group, and 110 subjects in the lamotrigine combined group. In the placebo group, the estimated median time to TIME (Survival in Study) occurred at 80 days on treatment, compared with 100 days for the lithium group, and 144 days for the lamotrigine combined group. There were significant differences in survival distribution in favor of the lamotrigine combined group compared with the placebo group (p=0.043).

There were no other significant differences between groups. For the individual lamotrigine groups, TIME (Survival in Study) was reached by 20 subjects in the lamotrigine 50mg group, 81 subjects in the lamotrigine 200mg group, and 29 subjects in the lamotrigine 400mg group. In the lamotrigine 50mg group, the median time to TIME (Survival in Study) was not calculable because the probability of not reaching TIME (Survival in Study) remained greater than 0.50 throughout the study. The estimated time to TIME (Survival in Study) occurred at 147 days on treatment in the lamotrigine 200 mg group and at 110 days in the lamotrigine 400 mg group.

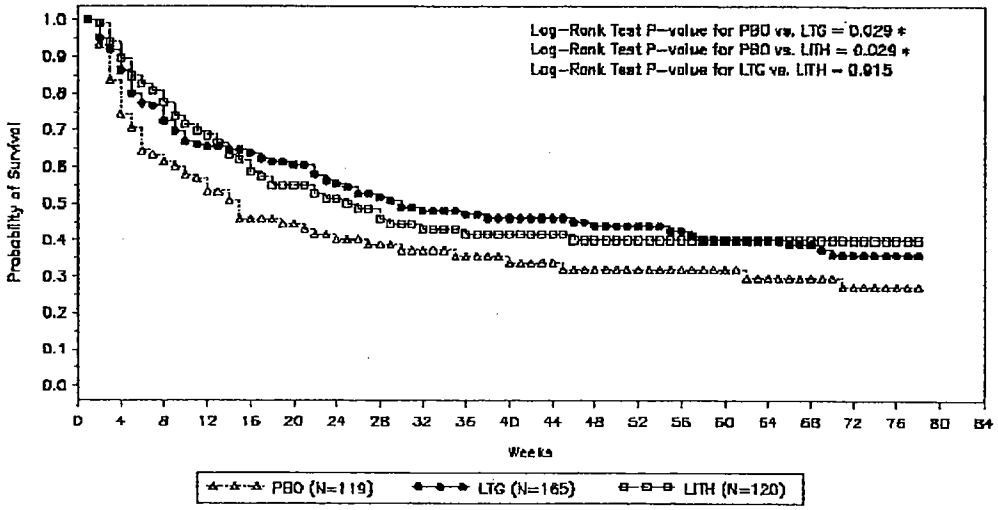
4.1.3.1.3 TIME (Only)

Median survival estimates for TIME (Only) are shown in Table 4.1.6 and the survival curves are in Figure 4.3. As we observed from the table, for TIME (only), there were significant differences in survival distribution in favor of the lamotrigine combined group (p=0.029), the lithium group (p=0.029), and the lamotrigine 200mg group (p=0.013) compared with placebo. There were no other statistically significant differences in survival distribution between groups.

Table 4.1.6 Summary of Analysis of TIME (Only) for Study SCAB2003

Statistical Parameter	PBO N=119	Li N=120	LTG Comb. N=165	By LTG Treatment Group		
				LTG50 N=50	LTG200 N=120	LTG400 N=45
Subjects with Event, n (%)	66 (55)	56 (47)	83 (50)	32 (64)	58 (48)	25 (56)
Median Time to Event (days)	93	170	200	118	256	144
Confidence Interval	58, 180	105, n/c	146, 399	64, 241	163, 482	49, 453
Survival Estimate, Week 76	0.272	0.400	0.360	0.245	0.374	0.326
p-value		0.029	0.029	Not sig.	0.013	Not sig.

Figure 4.3 Survival Curves for TIME(only) for Study SCAB2003



An additional analysis of TIME (only) was performed in which subjects who relapsed to depression in the first 28 days of the Randomized Phase were excluded. TIME (only) was reached by 40 subjects in the placebo group, 44 subjects in the lithium group, and 61 subjects in the lamotrigine combined group. In the placebo group, the estimated median time to TIME (only) occurred at 198 days on treatment, compared with 197 days for the lithium group, and 374 days for the lamotrigine combined group. There were no statistically significant differences in survival distribution between groups. For the individual lamotrigine groups, TIME (only) was reached by 12 subjects in the lamotrigine 50 mg group, 44 subjects in the lamotrigine 200 mg group, and 17 subjects in the lamotrigine 400 mg group. In the lamotrigine 50 mg group, the estimated median time to TIME (Only) was not calculable because the probability of not reaching TIME (Only) remained greater than 0.50 throughout the study. The estimated median time to TIME (Only) occurred at 388 days on treatment in the lamotrigine 200 mg group and at 202 days in the lamotrigine 400 mg group.

4.1.3.2 Secondary Efficacy Endpoints

4.1.3.2.1 TIMan

Nineteen subjects (16%) in the placebo group, ten subjects (8%) in the lithium group, and 26 subjects (16%) in the lamotrigine combined group reached TIMan. The median time to the event was not calculable in any treatment group because the probability of not reaching TIMan remained greater than 0.50 throughout the study. Survival estimates for TIMan at Week 76 were 0.665 for the placebo group, compared with 0.862 for the lithium group, and 0.700 for the lamotrigine combined group. There was a statistically significant difference (p=0.026) in survival distribution for TIMan in favor of the lithium group compared with placebo. There were no other statistically significant differences between groups.

Twelve subjects (24%) in the lamotrigine 50mg group, 18 subjects (15%) in the lamotrigine 200 mg group, and eight subjects (18%) in the lamotrigine 400 mg group reached TIMan. The median time to TIMan was 504 days for the lamotrigine 50 mg group, but was not calculable for the other individual lamotrigine treatment groups because the probability of not reaching TIMan remained greater than 0.50 throughout the study. Survival estimates for TIMan or premature withdrawal at Week 76 were 0.499 for the lamotrigine 50mg group, compared with 0.699 for the lamotrigine 200 mg group, and 0.713 for the lamotrigine 400mg group. There were no significant differences between lamotrigine treatment groups.

4.1.3.2.2 TIDep

Forty-seven subjects (39%) in the placebo group, 46 subjects (38%) in the lithium group, and 57 subjects (35%) in the lamotrigine combined group reached TIDep. The median time to the event was 162 days for the placebo group and 197 days for the lithium group, but was not calculable for the lamotrigine combined group because the probability of not reaching TIDep remained greater than 0.50 throughout the study. The survival estimates

for TIDep at Week 76 were 0.409 for the placebo group, compared with 0.464 for the elithium group, and 0.514 for the lamotrigine combined group. The survival distribution for TIDep was significantly different in favor of the lamotrigine combined group compared with placebo (p=0.047); there were no other significant differences between groups.

Twenty subjects (40%) in the lamotrigine 50mg group, 40 subjects (33%) in the lamotrigine 200mg group, and 17 subjects (38%) in the lamotrigine 400mg group reached TIDep. The median time to the event was 162 days in the lamotrigine 50mg group, was not calculable for the lamotrigine 200mg group because the probability of not reaching TIDep remained greater than 0.50 throughout the study, and was 453 days in the lamotrigine 400mg group. Survival estimates for TIDep at Week 76 were 0.492 for the lamotrigine 50mg group, compared with 0.535 for the lamotrigine 200mg group, and 0.458 for the lamotrigine 400mg group. There was a statistically significant difference in survival distribution for TIDep in favor of the lamotrigine 200mg group compared with placebo (p=0.028), but not between the other two individual lamotrigine groups and placebo. There were no significant differences between lamotrigine treatment groups.

4.1.3.2.3 General Assessment of Mood State (GAMS)

The GAMS was an assessment of the incidence and severity of mood episodes that occurred between scheduled study visits. The DSM-IV status and duration of each mood were also collected.

Moods were categorized as any moods and as moods that met DSM-IV criteria. Each of those mood categories were further categorized as those that occurred prior to reaching TIME and those that occurred up to the end of study (subjects completion or premature withdrawal).

An attempt was made to assess the frequency and intensity of moods experienced by subjects in all three treatment groups throughout the study. However, the GAMS assessment is an open-ended solicitation of information and is not a validated tool. The GAMS is therefore limited in its ability to inform on efficacy. Few differences were noted between treatment groups and the results were not considered to be clinically informative.

4.1.3.2.4 Hamilton Depression Scale (HAMD)

LOCF data for HAMD-17 total scores in the Efficacy population during the Randomized Phase are summarized in Table 4.1.7.

Table 4.1.7 HAMD-17:Mean LOCF Total Scores and Mean Change from RD1 During the Randomized Phase in Efficacy Population for Study SCAB 2003

Visit	Statistical Parameter	Placebo N=119	Lithium N=120	Lamotrigine Combined N=165
RD1	Mean Score ± SD	5.4 ± 4.0	5.6 ± 4.6	6.1 ± 4.3
Week 52	Mean Score ± SD	12.9 ± 8.5	11.8 ± 8.5	12.1 ± 8.9
	Mean Change from RD1 ± SD	7.4 ± 8.2	6.1 ± 8.1	6.0 ± 8.4
Week 76	Mean Score ± SD	13.0 ± 8.4	11.7 ± 8.6	12.0 ± 9.0
	Mean Change from RD1 ± SD	7.5 ± 8.2	6.1 ± 8.1	5.9 ± 8.6

As we observed from the above table, mean HAMD-17 scores were comparable among treatment groups on RD1. For all treatment groups, mean LOCF scores generally increased throughout the Randomized Phase, indicating a worsening of depressive symptoms. There were no significant differences between treatment groups in HAMD-17 scores at Week 52 or Week 76. There were no significant differences between any treatment groups in the mean change from RD1 at Week 52 or Week 76, although there were significant differences between the lamotrigine combined and placebo groups at Weeks 2 through 24.

LOCF data for the HAMD-31 total scores in the Efficacy population during the Randomized Phase are summarized in Table 4.1.8.

Table 4.1.8 HAMD-31: Mean LOCF Total Scores and Mean Changes from RD1 During the Randomized Phase in the Efficacy Population for Study SCAB 2003

Visit	Statistical Parameter	Placebo N=119	Lithium N=120	Lamotrigine Combined N=165
RD1	Mean Score ± SD	7.5 ± 5.8	7.8 ± 6.4	8.5 ± 6.1
Week 52	Mean Score ± SD	18.9 ± 12.9	17.2 ± 13.0	17.3 ± 13.2
	Mean Change from RD1 ± SD	11.4 ± 12.6	9.4 ± 12.1	8.9 ± 12.9
Week 76	Mean Score ± SD	19.0 ± 12.9	17.0 ± 13.1	17.3 ± 13.3
	Mean Change from RD1 ± SD	11.5 ± 12.5	9.2 ± 12.2	8.9 ± 13.0

As we observed from the above table, the pattern observed for the HAMD-31 rating scale was comparable to that of the HAMD-17 rating scale. Mean HAMD-31 scores were comparable among treatment groups on RD1. For all treatment groups, mean LOCF scores generally increased throughout the Randomized Phase, indicating a worsening of depressive symptoms. There were no significant differences between treatment groups in HAMD-31 scores at Week 52 or at Week 76, although significant differences were observed between the lamotrigine combined and placebo groups at Weeks 1 through 32.

4.1.3.2.5 Mania Rating Scale

LOCF data for MRS-11 total scores in the Efficacy population during the Randomized Phase are summarized in Table 4.1.9. As we observed from the table, Mean MRS-11 scores were comparable among treatment groups on RD1. For all treatment groups, mean LOCF scores generally increased throughout the Randomized Phase, indicating a worsening of manic symptoms.

Table 4.1.9 MRS-11: Mean LOCF Total Scores and Mean Change from RD1 During the Randomized Phase in the Efficacy Population for Study SCAB2003

Visit	Statistical Parameter	Placebo N=119	Lithium N=120	Lamotrigine Combined N=165
RD1	Mean Score ± SD	1.6 ± 2.8	1.7 ± 2.7	1.5 ± 2.8
Week 52	Mean Score ± SD	4.4 ± 7.3	2.6 ± 5.1	3.8 ± 7.3
	Mean Change from RD1 ± SD	2.8 ± 7.1	1.0 ± 4.9	2.3 ± 7.4
			0.019*	Not Sig.
Week 76	Mean Score ± SD	4.5 ± 7.5	2.6 ± 5.1	3.8 ± 7.5
	Mean Change from RD1 ± SD	2.9 ± 7.3	1.0 ± 4.9	2.3 ± 7.5
			0.015*	Not Sig.

*Significantly different from placebo

Differences between placebo and lithium were significantly different from Week 32 through Week 76. There were no significant differences between placebo and the lamotrigine combined groups or between the lamotrigine combined and lithium groups at any treatment week.

LOCF data for the MRS-16 scores in the Efficacy population during the Randomized Phase are summarized in Table 4.1.10.

Table 4.1.10 MRS-16: Mean LOCF Total Scores and Mean Change from RD1 During the Randomized Phase in the Efficacy Population for Study SCAB2003

Visit	Statistical Parameter	Placebo N=119	Lithium N=120	Lamotrigine Combined N=165
RD1	Mean Score ± SD	1.9 ± 3.0	2.0 ± 3.0	2.0 ± 3.3
Week 52	Mean Score ± SD	6.0 ± 8.9	3.9 ± 6.5	5.2 ± 8.7
	Mean Change from RD1 ± SD	4.1 ± 8.8	1.9 ± 5.9	3.2 ± 8.6
	p-value		0.024*	Not Sig.
Week 76	Mean Score ± SD	6.2 ± 9.2	3.9 ± 6.5	5.3 ± 8.9
	Mean Change from RD1 ± SD	4.3 ± 9.2	1.9 ± 5.9	3.3 ± 8.7
	p-value		0.017*	Not Sig.

*Significantly different from placebo

As we observed from the above table, the pattern observed for the MRS-16 rating scale was comparable to that of the MRS-11 rating scale. Mean MRS-16 scores were comparable on RD1. For all treatment groups, mean LOCF scores generally increased throughout the Randomized Phase, indicating a worsening of manic symptoms.

Changes in MRS-16 scores were significantly ($p<0.05$) lower in the lithium group compared with the placebo group from Week 32 through Week 76, with the exception of Week 36 when the difference approached statistical significance ($p=0.054$). There were no statistically significant differences between the placebo and lamotrigine combined groups or between the lamotrigine combined and lithium groups at any treatment week.

4.1.3.2.6 Clinical Global Impression of Improvement

LOCF data for CGI-I scores in the Efficacy population during the Randomized Phase are summarized in Table 4.1.11.

Table 4.1.11 Mean LOCF Total Scores During the Randomized Phase in the Efficacy Population for Study SCAB2003

Visit	Statistical Parameter	Placebo N=119	Lithium N=120	Lamotrigine Combined N=165
RD1	Mean Score ± SD	1.7 ± 0.6	1.7 ± 0.6	1.7 ± 0.7
Week 52	Mean Score ± SD	3.2 ± 1.6	3.1 ± 1.6	3.1 ± 1.7
Week 76	Mean Score ± SD	3.3 ± 1.6	3.1 ± 1.6	3.1 ± 1.7

As we observed from the above table, there were no statistically significant differences between treatment groups in scores at RD1. For all treatment groups, mean LOCF scores generally increased throughout the Randomized Phase. There were no consistent significant differences among treatment groups in mean LOCF CGI-I scores.

4.1.3.2.7 Clinical Global Impression of Severity

LOCF data for CGI-S scores in the Efficacy population during the Randomized Phase are summarized in Table 4.1.12.

Table 4.1.12 CGI-S: Mean LOCF Total Scores and Mean Change From RD1 During the Randomized Phase in the Efficacy Population for Study SCAB2003

Visit	Statistical Parameter	Placebo N=119	Lithium N=120	Lamotrigine Combined N=165
RD1	Mean Score ± SD	2.0 ± 0.7	2.0 ± 0.8	2.0 ± 0.7
Week 52	Mean Score ± SD	3.2 ± 1.4	2.9 ± 1.2	2.9 ± 1.3
	Mean Change from RD1 ± SD	1.2 ± 1.4	0.9 ± 1.3	0.9 ± 1.4
Week 76	Mean Score ± SD	3.2 ± 1.3	2.9 ± 1.2	2.9 ± 1.3
	Mean Change from RD1 ± SD	1.2 ± 1.4	0.8 ± 1.3*	0.9 ± 1.4

* Statistically significant from placebo

As we observed from the above table, mean CGI-S scores were comparable among treatment groups on RD1. For all treatment groups, mean LOCF scores increased throughout the Randomized Phase, indicating a worsening of illness. There were no statistically significant differences among treatment groups in change from RD1 scores at Week 52. The difference between the placebo and lithium groups approached statistical significance (p=0.059) at Week 52 and was statistically significant at Weeks 2, 4, 6, 12, 48 and 60 through 76 of the randomized phase.

4.1.3.2.8 Global Assessment Score

LOCF data for the GAS scores in the Efficacy population during the Randomized Phase are summarized in Table 4.1.13.

Table 4.1.13 GAS: Mean LOCF Total Scores and Mean Change from RD1 During the Randomized Phase in the Efficacy Population for Study SCAB2003

Visit	Statistical Parameter	Placebo N=119	Lithium N=120	Lamotrigine Combined N=165
RD1	Mean Score ± SD	76.4 ± 11.4	76.0 ± 10.4	75.3 ± 11.7
Week 52	Mean Score ± SD	64.1 ± 16.2	67.2 ± 13.9	67.1 ± 14.9
	Mean Change from RD1 ± SD	-12 ± 16.2	-8.8 ± 14.9	-8.2 ± 16.5
	p-value		Not Sig.	0.041*
Week 76	Mean Score ± SD	63.9 ± 16.2	67.2 ± 14.0	67.1 ± 15.3
	Mean Change from RD1 ± SD	-12 ± 16.2	-8.7 ± 15.0	-8.2 ± 16.8
	p-value		Not Sig.	0.035*

*Significantly different from placebo

As we observed from the above table, mean GAS scores were comparable among treatment groups on RD1. For all treatment groups, mean LOCF scores generally decreased throughout the Randomized Phase, indicating a worsening of illness. Differences between the placebo and lamotrigine combined groups were significantly different ($p<0.05$) beginning at Week 2 and continuing throughout the remainder of the study. While statistically significant differences between the placebo and lithium groups were sporadically observed during the first 4 weeks of treatment, these differences were not sustained throughout the Randomized Phase.

4.1.4 Relationship Between Response and Drug Dose

Protocol Amendment 12 terminated enrollment into the 50mg and 400mg lamotrigine treatment arms of the study and at the same time the inclusion criteria were broadened to allow for an index episode of depression within 60 days of enrollment. Data from the 279 subjects enrolled into the placebo (n=60), lithium (n=63), lamotrigine 50mg (n=50), lamotrigine 200mg (n=61) and lamotrigine 400 mg (n=45) dose groups prior to initiation of Amendment 12 were analyzed to evaluate whether there was a dose-response relationship for this range of lamotrigine doses in subjects with bipolar disorder.

The following endpoints were evaluated: TIME(ABE), TIME(Survival in Study), TIME(Only), TIDep, TIMan, HAMD-17 and MRS-11.

4.1.4.1 TIME(ABE)

The Analyses of TIME(ABE) for all subjects enrolled prior to Amendment 12 in Efficacy Population are summarized in Table 4.1.14. As we observed from the table, there were no significant differences in survival distribution for any of the lamotrigine groups or the lithium group compared with placebo. The differences in survival distribution between the lamotrigine 200mg and the placebo groups approached significance in favor of lamotrigine. For TIME(ABE), the median time to event were longer in all three lamotrigine groups than in the placebo group; the 200mg group had the longest median time to event. There were no significant differences in survival distribution between lamotrigine treatment groups.

Table 4.1.14 Summary of Analysis of TIME(ABE) for all Subjects Enrolled Prior to Amendment 12 in Efficacy Population for Study SCAB2003

Statistical Parameter	Placebo N=60	Li N=63	LTG 50 N=50	LTG 200 N=61	LTG 400 N=45
Subjects with Event, n (%)	47 (78)	43 (68)	38 (76)	45 (74)	34 (76)
Median Time to Event (days)	56	142	112	116	69
Confidence Interval	30, 93	88, 187	60, 159	58, 240	45, 150
p-value*		Not Sig.	Not Sig.	Not Sig.	Not Sig.

* Difference in survival distribution between treatments tested using a Log-Rank test

4.1.4.2 TIME(Survival in Study)

Table 4.1.15 shows the summary of analysis of TIME(Survival in Study) for all subjects enrolled prior to Amendment 12 in the efficacy population. There were significant differences in survival distribution in favor of the lamotrigine 200mg group (p=0.033) compared with placebo. There were no statistically significant differences in survival distribution between the placebo group and the lamotrigine 50mg, lamotrigine 400mg, or the lithium groups. For TIME(Survival in Study) the median times to event were longer in all three lamotrigine groups than in the placebo group; the 200mg group had the longest median time to event. There were no significant differences in survival distribution between lamotrigine treatment groups.

Table 4.1.15 Summary of Analysis of TIME(Survival in Study) for all Subjects Enrolled Prior to Amendment 12 in Efficacy Population for Study SCAB2003

Statistical Parameter	Placebo N=60	Li N=63	LTG 50 N=50	LTG 200 N=61	LTG 400 N=45
Subjects with Event, n (%)	52 (87)	53 (84)	41 (82)	48 (79)	38 (84)
Median Time to Event (days)	42	100	88	105	68
Confidence Interval	26, 85	64, 150	56, 151	55, 190	42, 144
p-value*		Not Sig.	Not Sig.	0.033	Not Sig.

* Difference in survival distribution between treatments tested using a Log-Rank test

4.1.4.3 TIME(Only)

Table 4.1.16 show the summary of analysis of TIME(Only) for all subjects enrolled prior to Amendment 12 in the Efficacy population.

Table 4.1.16 Summary of Analysis of TIME(Only) for all Subjects Enrolled Prior to Amendment 12 in Efficacy Population for Study SCAB2003

Statistical Parameter	Placebo N=60	Li N=63	LTG 50 N=50	LTG 200 N=61	LTG 400 N=45
Subjects with Event, n (%)	31(52)	30 (48)	32 (64)	28 (46)	25 (56)
Median Time to Event (days)	93	166	118	256	144
Confidence Interval	34, 303	111, n/c	64, 241	150, n/c	49, 453
p-value*		Not Sig.	Not Sig.	Not Sig.	Not Sig.

* Difference in survival distribution between treatments tested using a Log-Rank test

There were no significant differences in survival distribution between treatment groups. For TIME(Only), all three lamotrigine treatment group had longer median times to event than the placebo group; the 200mg group had the longest median time to event. There were no significant differences in survival distribution between lamotrigine treatment groups.

4.1.4.4 TIMan

For TIMan (See Table 4.1.17), there were significant differences in survival distribution in favor of the lithium group (p=0.020) compared with placebo. There were no statistically significant differences in survival distribution between the placebo group and the lamotrigine 50mg, lamotrigine 200mg, or lamotrigine 400mg groups. There were significant differences in survival distribution in favor of the lithium group (p=0.019) compared with the lamotrigine 50 mg group. In addition, the difference between the lithium and lamotrigine 400mg group approached significance (p=0.053). There were no significant differences in survival distribution between lamotrigine treatment groups.

Table 4.1.17 Summary of Analysis of TIMan for all Subjects Enrolled Prior to Amendment 12 in Efficacy Population for Study SCAB2003

Statistical Parameter	Placebo N=60	Li N=63	LTG 50 N=50	LTG 200 N=61	LTG 400 N=45
Subjects with Event, n (%)	11 (18)	4 (6)	12 (24)	7 (11)	8 (18)
Median Time to Event (days)	n/c	n/c	504	n/c	n/c
Confidence Interval			241, n/c		
p-value[a]		0.020[b], 0.019[c]	Not Sig.	Not Sig.	Not Sig.

a. Difference in survival distribution between treatments tested using a Log-Rank test
b. Significantly different from placebo
c. Significantly different from LTG 50mg

4.1.4.5 TIDep

For TIDep, there were no significant differences in survival distribution between treatment groups. Specifically, there were no significant differences in survival distribution between lamotrigine treatment groups.

4.1.4.6 HAMD-17

Table 4.1.18 shows the summaries of mean change from RD1 during the Randomized Phase for all subjects enrolled prior to Amendment 12 in the efficacy population for Study SCAB2003. For all treatment groups, mean LOCF scores generally increased throughout the Randomized Phase, indicating a worsening of depressive symptoms. The lamotrigine 50mg, lamotrigine 200mg, and lithium dose groups had smaller increases from the RD1 values than the placebo and lamotrigine 400mg groups. The magnitude of the mean change from RD1 was lowest and comparable for the lamotrigine 50mg and lamotrigine 200mg groups, and higher for the lamogrigine 400mg group.

There were no significant differences between the lithium and placebo groups in the mean change from RD1 at Week 52 or Week 76. Statistical comparisons of the individual lamogrigine treatment groups to the placebo group were not performed.

Table 4.1.18 HAMD-17: Mean Change from RD1 During the Randomized Phase for All Subjects Enrolled Prior to Amendment 12 in the Efficacy Population for Study SCAB2003

Visit	Change from RD1	Placebo N=60	Li N=63	LTG 50 N=50	LTG 200 N=61	LTG 400 N=45
Week 52	Mean ± SD	7.2 ± 8.0	5.4 ± 7.4	5.4 ± 7.4	5.8 ± 8.3	7.5 ± 10.0
Week 76	Mean ± SD	7.2 ± 8.0	5.4 ± 7.4	5.5 ± 7.8	5.6 ± 8.4	7.6 ± 10.1

4.1.4.7 MRS-11

LOCF data for MRS-11 total scores for the efficacy population during the Randomized Phase are summarized in Table 4.1.19. For all treatment groups, mean LOCF scores increased throughout the Randomized Phase, indicating a worsening of manic symptoms. The lithium dose group had smaller increases from the RD1 values than all other dose groups. The magnitude of the man change from RD1 was smallest for the lamotrigine 200mg group. The lamotrigine 50mg group had a greater change from RD1 than the placebo group.

Table 4.1.19 MRS-11: Mean Change from RD1 During the Randomized Phase for All Subjects Enrolled Prior to Amendment 12 in the Efficacy Population for Study SCAB2003

Visit	Change from RD1	Placebo N=60	Li N=63	LTG 50 N=50	LTG 200 N=61	LTG 400 N=45
Week 52	Mean ± SD	3.2 ± 7.8	0.3 ± 4.8	3.3 ± 7.8	2.0 ± 6.9	2.6 ± 8.1
	p- value		0.015*	Not Sig.	Not Sig.	Not Sig.
Week 76	Mean ± SD	3.2 ± 7.8	0.3 ± 4.8	3.7 ± 8.2	2.0 ± 7.0	2.7 ± 8.1
	p-value		0.017*	Not Sig.	Not Sig.	Not Sig.

* Significantly different from placebo

There were significant differences in the mean change in MRS-11 scores from RD1 between the lithium and placebo groups from Week 8 through the end of the study (Week 76). Statistical comparisons of the individual lamotrigine treatment groups to the placebo group were not performed.

4.1.5 The Sponsor's Efficacy Conclusions

Treatment with lamotrigine (the combined 200mg and 400mg) treatment group was superior to placebo in delaying mood episodes in subjects with bipolar I disorder for all three analyses of the primary efficacy measure. Differences between lamotrigine 200mg and placebo were also statistically significant for the three analyses of the primary efficacy measure. The TIDep results indicate that the effects of lamotrigine in the

management of bipolar disorder are primarily at the depressive pole. Therefore, these data support the use of lamotrigine in the long-term management of depression in bipolar I disorder. Moreover, the TIMan and TIDep anayses demonstrated that lamotrigine treatment delayed the occurrence of mood episodes at the depressive polarity without a concomitant worsening of the other pole of the illness (manic/hypomanic/mixed episodes).

About the dose-response, the sponsor concluded that the 50mg and 400mg lamotrigine doses were less efficacious than the 200mg dose of lamotrigine for most efficacy measures analyzed. In aggregate, the data suggest that the 200mg dose of lamotrigine had the greatest effectiveness in delaying mood episodes.

4.2 Study SCAB2006

4.2.1 Population Analyzed

As mentioned in Section 3.1.4.3, three subject populations were defined: an Intent-to-Treat population, an Efficacy population, and a Safety population. Table 4.2.1 summaries the number of subjects analyzed in each population.

Table 4.2.1 Summary of Population Analyzed for Study SCAB2006

Population	Number of Subjects				
	Preliminary Phase	Randomized Phase			
		Placebo	Lithium	Lamotrigine	Total
ITT	349	70	46	59	175
Safety	347	69	46	58	173
Efficacy	334	69	44	58	171

4.2.2 Demographic and Baseline Characteristics

As it was shown in Table 4.2.2, the population enrolled into the Preliminary Phase was equally divided between males and females. Most subjects were White (90%). The mean age was 41 years, the mean height was 170cm, and the mean weight was 78kg. Randomized Phase treatment groups were comparable with respect to the demographic characteristics evaluated at Screen. The distribution of males and females was similar for the three treatment groups. Most subjects were White (range 90-98% across treatment groups). Across treatment groups, the mean age ranged from 41-42 years, the mean height ranged from 170-172cm, the mean weight was 78-79kg. There were no apparent differences between the treatment groups for demographic characteristics at Screen and at Randomization.

Table 4.2.2 Summary of Subject Demography for Study SCAB2006

		Preliminary Phase	Randomized Phase			
		Lamotrigine	Placebo	Lithium	Lamotrigine	Total
Number of Subjects	N	347	69	46	58	173
Age (years)	Mean (SD)	40.7 (11.8)	40.9 (11.0)	41.9 (11.3)	40.6 (12.6)	41.1 (11.6)
Sex	Male (%)	172 (50%)	34 (49%)	22 (48%)	26 (45%)	82 (47%)
	Female (%)	175 (50%)	35 (51%)	24 (52%)	32 (55%)	91 (53%)
Race	White (%)	311 (90%)	62 (90%)	45 (98%)	52 (90%)	159 (92%)
	Black (%)	18 (5%)	4 (6%)	0	3 (5%)	7 (4%)
	Asian (%)	3 (<1%)	2 (3%)	0	0	2 (1%)
	American Hispanic (%)	13 (4%)	0	1 (2%)	3 (5%)	4 (2%)
	Others (%)	2 (<1%)	1 (1%)	0	0	1 (<1%)
Height (cm)	Mean (SD)	170.3 (11.4)	170.1 (10.4)	170.6 (9.6)	171.5 (10.2)	170.7 (10.1)
Weight (kg)	Mean (SD)	78.10(16.84)	79.29(17.62)	79.11(17.74)	78.48(17.7)	78.97(17.58)

4.2.3 Efficacy Results

Table 4.2.3 shows a by-treatment group summary of subjects prematurely withdrawn from the Randomized Phase of the study prior to reaching TIME.

A total of 76 subjects were withdrawn from the study prior to reaching TIME. The primary reason for discontinuation prior to TIME was sponsor termination of the study, followed by discontinuation due to AEs. The percentage of subjects that discontinued due to AEs that occurred prior to TIME was higher in the lithium group compared with the lamotrigine and placebo groups. Of the 17 subjects discontinued prior to TIME due to an AE, a total of 15 subjects (three in the placebo group, nine in the lithium group, and three in the lamotrigine group) were withdrawn due to an AE not deemed related to bipolar disorder. The treatment groups were similar in the percentages of subjects discontinued prior to TIME due to sponsor discontinuation, consent withdrawn, loss to follow-up, protocol violation, and other. Note that, in the three different analyses for TIME, subjects discontinued from the study prior to reaching TIME due to the early termination of the study by the Sponsor were censored at the time of study discontinuation, as were all subjects who completed the study without reaching TIME.

Table 4.2.3 Summary of Subjects Discontinued from the Study Prior to Reaching TIME in the ITT Population for Study SCAB2006

Subject Status	PBO N=70	Li N=46	LTG N=59	Total N=175
Discontinuation Prior to Reaching TIME, n(%)	21 (30)	27 (59)	28 (47)	76 (43)
Sponsor Discontinuation, n (%)	11 (16)	9 (20)	15 (25)	35 (20)
Adverse Event, n (%)	3 (4)	11 (24)	3 (5)	17 (10)
Consent Withdrawn, n(%)	3 (4)	2 (4)	4 (7)	9 (5)
Lost to Follow Up, n(%)	1 (1)	3 (7)	1 (2)	5 (3)
Other, n(%)	2 (3)	1 (2)	3 (5)	6 (3)
Protocol Violation, n(%)	1 (1)	1 (2)	2 (3)	4 (2)

4.2.3.1 Primary Efficacy Endpoint

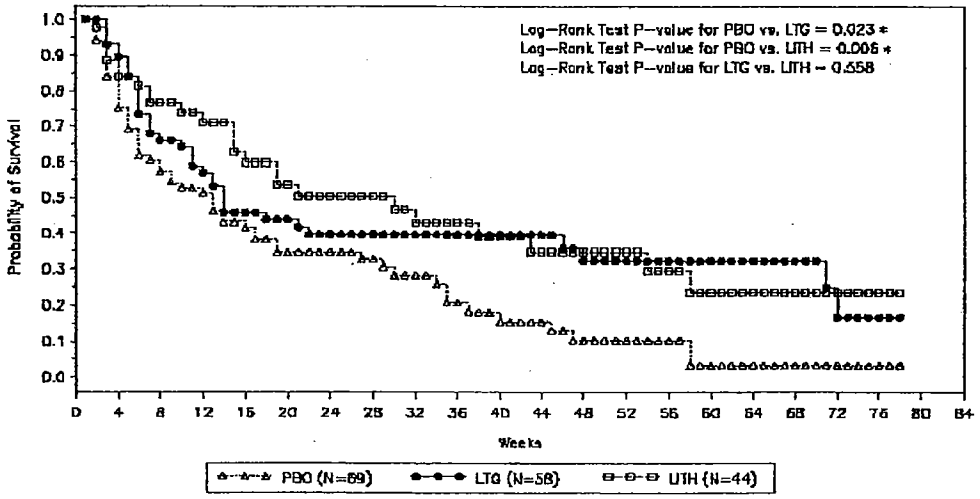
4.2.3.1.1 TIME(ABE)

Table 4.2.4 shows the summary of analysis of TIME(ABE) in the efficacy population and Figure 4.4 shows the survival curves. As we observed from the table, there were significant differences in survival distribution in favor of lamotrigine compared with placebo (p=0.023) and in favor of lithium compared with placebo (p=0.006). There were no statistically significant differences in survival distribution between the lamotrigine and lithium groups. The other analysis employing the adequate lithium treatment within 5 months prior to entry to the Randomized Phase of the study as stratification variable yielded consistent results.

Table 4.2.4 Summary of Analysis of TIME(ABE) in Efficacy Population for Study SCAB2006

Statistical Parameter	PBO N=69	Li N=44	LTG N=58
Number(%) of Subjects with Event	55 (80)	25 (57)	37 (64)
Median Time to Event (days)	82	202	86
Confidence Interval	37, 111	98, 366	66, 315
Survival Estimate at Week 76	0.035	0.236	0.168
p-value		0.006	0.023

Figure 4.4 Survival Curves of TIME(ABE) for Study SCAB2006



An additional analysis of TIME(ABE) was performed in which subjects who relapsed to mania in the first 28 days of the study were excluded. The results showed that TIME(ABE) was reached by 30 subjects in the lamotrigine group, 22 subjects in the lithium group, and 41 subjects in the placebo group. In the lamotrigine group, TIME(ABE) occurred at a median of 141 days on treatment, compared with 111 days for the placebo group and 212 days for the lithium group. For TIME(ABE), there were significant differences in survival distribution in favor of lithium compared with placebo

(p=0.034). There were no statistically significant differences in survival distribution between the lamotrigine and placebo or lamotrigine and lithium groups.

4.2.3.1.2 TIME(Survival)

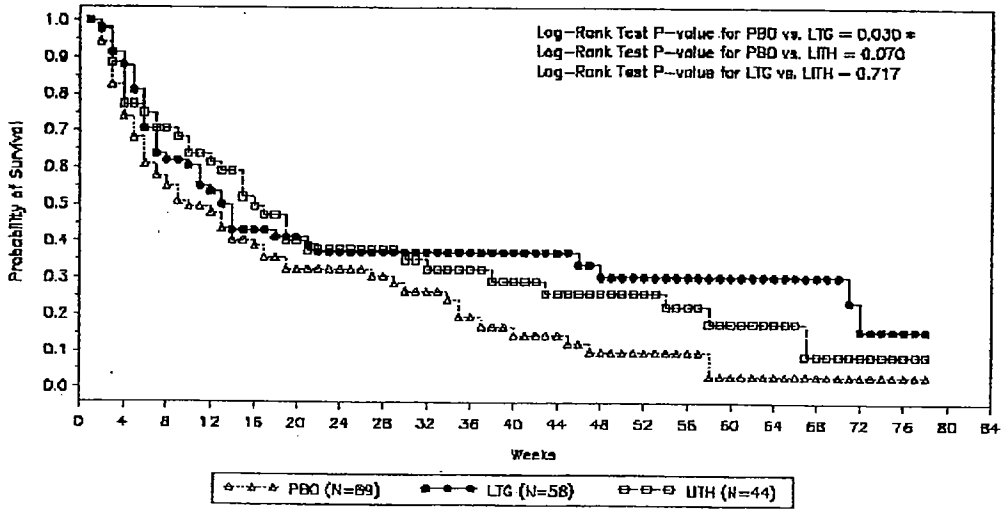
Table 4.2.5 shows the summary of analysis of TIME(Survival in Study) in the efficacy population and Figure 4.5 shows the survival curves. As we observed from the table, there were significant differences in survival distribution in favor of lamotrigine compared with placebo (p=0.030). There were no statistically significant differences in survival distribution for TIME(Survival in Study) between the lamotrigine and lithium groups or between the lithium and placebo groups.

Table 4.2.5 Summary of Analysis of TIME(Survival in Study) in the Efficacy Population for Study SCAB2006

Statistical Parameter	PBO N=69	Li N=44	LTG N=58
Number(%) of Subjects with Event	58 (84)	34 (77)	40 (69)
Median Time to Event (days)	58	101	85
Confidence Interval	34, 108	59, 202	44, 142
Survival Estimate at Week 76	0.032	0.088	0.158
p-value		Not Sig.	0.030

An additional analysis of TIME(Survival in Study) was performed in which subjects who relapsed to mania in the first 28 days of the study were excluded. The results showed that TIME(Survival in Study) was reached by 33 subjects in the lamotrigine group, 30 subjects in the lithium group, and 44 subjects in the placebo group. In the lamotrigine group, TIME(Survival in Study) occurred at a median of 91 days on treatment, compared with 104 days for the placebo group and 122 days for the lithium group. There were no statistically significant differences in survival distribution between the treatment groups.

Figure 4.5 Survival Curves of TIME(SIS) for Study SCAB2006



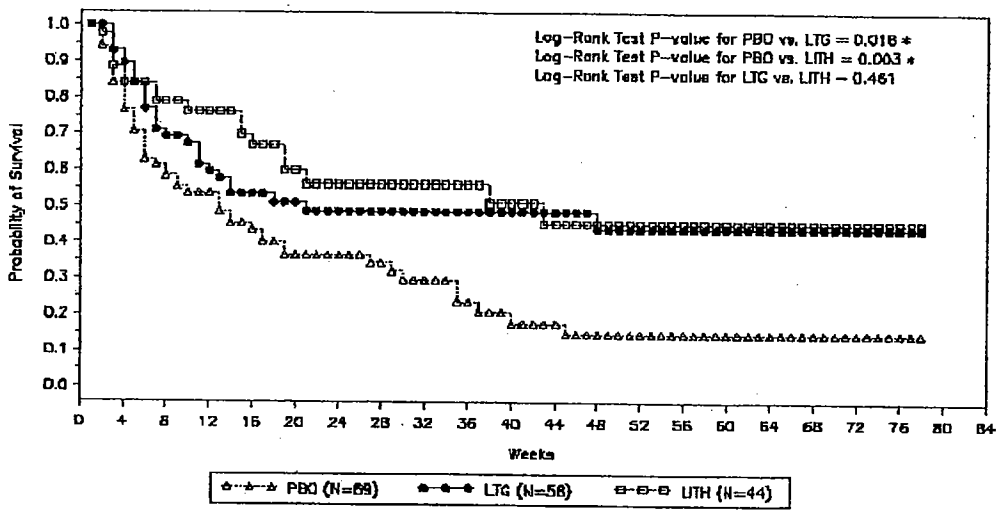
4.2.3.1.3 TIME(Only)

Table 4.2.6 shows the summary of analysis of TIME(Only) in the efficacy population and Figure 4.6 shows the survival curves. As we observed from the table, there were significant differences in survival distribution in favor of lamotrigine compared with placebo (p=0.018) and in favor of lithium compared with placebo (p=0.003). There were no statistically significant differences in survival distribution between the lamotrigine and lithium groups.

Table 4.2.6 Summary of Analysis of TIME(Only) in Efficacy Population for Study SCAB2006

Statistical Parameter	PBO N=69	Li N=44	LTG N=58
Number(%) of Subjects with Event	49 (71)	18 (41)	28 (48)
Median Time to Event (days)	85	292	141
Confidence Interval	37, 121	123, n/c	71, n/c
Survival Estimate at Week 76	0.149	0.454	0.438
p-value		0.003	0.018

Figure 4.6 Survival Curves of TIME(only) for Study SCAB2006



An additional analysis of TIME(Only) was performed in which subjects who relapsed to mania in the first 28 days of the study were excluded. The results showed that TIME(Only) was reached by 21 subjects in the lamotrigine group, 15 subjects in the lithium group, and 35 subjects in the placebo group. In the lamotrigine group, TIME(Only) occurred at a median of 324 days on treatment, compared with 121 days for the placebo group and 292 days for the lithium group. For TIME(Only), there were significant differences in survival distribution in favor of lithium compared with placebo (p=0.019). There were no statistically significant differences in survival distribution between the lamotrigine and placebo or lamotrigine and lithium groups. However, the

difference in survival distribution between the lamotrigine and placebo groups approached statistical significance (p=0.050) in favor of lamotrigine.

4.2.3.2 Secondary Efficacy Endpoints

4.2.3.2.1 TIMan

Twenty subjects in the lamotrigine group, eight subjects in the lithium group, and 28 subjects in the placebo group reached TIMan. The median time to TIMan was 203 days for the placebo group, but was not calculable for the lamotrigine or lithium groups because the probability of survival remained greater than 0.50 throughout the study. The survival estimates for TIMan at Week 76 were 0.532 for the lamotrigine group, compared with 0.635 for the lithium group and 0.371 for the placebo group. The survival distribution for TIMan was not significantly different between the lamotrigine and placebo or lamotrigine and lithium groups. There were significant differences in survival distribution in favor of lithium compared with placebo.

4.2.3.2.2 TIDep

Eight subjects in the lamotrigine group, 10 subjects in the lithium group, and 21 subjects in the placebo group reached TIDep. The median time to the event was 269 days for the placebo group, but was not calculable for the lamotrigine or lithium groups because the probability of survival remained greater than 0.50 throughout the study. The survival estimates for TIDep at Week 76 were 0.824 for the lamotrigine group, compared with 0.714 for the lithium group and 0.401 for the placebo group. For TIDep, there were significant differences in survival distribution in favor of lamotrigine compared with placebo (p=0.015). The survival distribution for TIDep was not significantly different between the lamotrigine and lithium groups, or between the lithium and placebo groups.

4.2.3.2.3 General Assessment of Mood State (GAMS)

An attempt was made to assess the frequency and intensity of moods experienced by subjects in all three treatment groups throughout the study. However, the GAMS assessment is not a validated tool. The GAMS is therefore limited in its ability to inform on efficacy. Few differences were noted between treatment groups and the results were not considered to be clinically informative.

4.2.3.2.4 Hamilton Depression Scale (HAMD)

The LOCF data for the HAMD-17 total scores in the Efficacy population during the Randomized Phase are summarized in Table 4.2.7. As we observed from the table, the mean HAMD-17 scores were comparable on RD1. For all treatment groups, the mean LOCF scores increased throughout the Randomized Phase, indicating a worsening of depressive symptoms. There were no significant differences between treatment groups in HAMD-17 scores at Week 52. At Week 76, the mean change from RD1 was significantly (p=0.044) lower for the lamotrigine group compared with the placebo group. There were

no significant differences between the lamotrigine and lithium groups or the lithium and placebo groups.

Table 4.2.7 HAMD-17: Mean LOCF Total Scores and Mean Change from RD1 During the Randomized Phase in Efficacy Population for Study SCAB2006

Visit	Statistical Parameter	Placebo N=69	Lithium N=44	Lamotrigine N=58
RD1	Mean Score ± SD	3.0 ± 3.2	2.7 ± 3.5	2.8 ± 3.5
Week 52	Mean Score ± SD	9.7 ± 8.7	8.1 ± 9.3	7.2 ± 7.1
	Mean Change from RD1 ± SD	6.7 ± 7.7	5.4 ± 8.4	4.4 ± 6.1
	p-value		Not Sig.	Not Sig.
Week 76	Mean Score ± SD	9.8 ± 8.6	8.4 ± 9.2	7.1 ± 7.1
	Mean Change from RD1 ± SD	6.8 ± 7.6	5.6 ± 8.4	4.3 ± 6.2
	p-value		Not Sig.	0.044

The LOCF data for the HAMD-31 total scores in the efficacy population during the Randomized Phase are summarized in Table 4.2.8. As we observed from the table, the mean HAMD-31 scores were comparable on RD1. For all treatment groups, the mean LOCF scores increased throughout the Randomized Phase, indicating a worsening of depressive symptoms. There were no significant differences between treatment groups in HAMD-31 scores at Week 52. At Week 76, the mean change from RD1 was significantly (p=0.050) lower for the lamotrigine group compared with the placebo group. There were no differences between the lamotrigine and lithium groups or the lithium and placebo groups.

Table 4.2.8 HAMD-31: Mean LOCF Total Scores and Mean Change from Screen During the Randomized Phase in Efficacy Population for Study SCAB2006

Visit	Statistical Parameter	Placebo N=69	Lithium N=44	Lamotrigine N=58
RD1	Mean Score ± SD	4.2 ± 4.8	3.6 ± 4.3	4.2 ± 5.1
Week 52	Mean Score ± SD	13.3 ± 12.3	11.8 ± 13.0	10.1 ± 10.4
	Mean Change from RD1 ± SD	9.1 ± 10.7	8.2 ± 12.0	5.9 ± 8.9
	p-value		Not Sig.	Not Sig.
Week 76	Mean Score ± SD	13.4 ± 12.2	12.0 ± 13.0	10.0 ± 10.5
	Mean Change from RD1 ± SD	9.3 ± 10.6	8.4 ± 12.0	5.8 ± 9.0
	p-value		Not Sig.	0.050

4.2.3.2.5 Mania Rating Scale

The LOCF data for the MRS-11 total score in the Efficacy population during the Randomized Phase are summarized in Table 4.2.9. As we observed from the table, the mean MRS-11 scores were comparable on RD1. For all treatment groups, the mean LOCF scores increased throughout the Randomized Phase, indicating a worsening of manic symptoms. There were no statistically significant differences between treatment groups at Week 52; however the differences between the lamotrigine and lithium groups approached significance (p=0.055), as did the difference between the lithium and placebo groups (p=0.053). There were no statistically significant differences between treatment groups at Week 76.

Table 4.2.9 MRS-11: Mean LOCF Total Scores and Mean Change from RD1 During the Randomized Phase in Efficacy Population for Study SCAB2006

Visit	Statistical Parameter	Placebo N=69	Lithium N=44	Lamotrigine N=58
RD1	Mean Score ± SD	2.3 ± 3.0	2.7 ± 3.9	2.9 ± 3.7
Week 52	Mean Score ± SD	7.0 ± 9.2	4.6 ± 7.5	8.1 ± 9.5
	Mean Change from RD1 ± SD	4.8 ± 8.6	1.9 ± 5.8	5.2 ± 10.1
Week 76	Mean Score ± SD	7.0 ± 9.2	4.7 ± 7.5	8.0 ± 9.4
	Mean Change from RD1 ± SD	4.8 ± 8.6	2.0 ± 5.8	5.1 ± 10.0

The LOCF data for the MRS-16 scores for the Efficacy population during the Randomized Phase are summarized in Table 4.2.10. The mean MRS-16 scores were comparable on RD1. For all treatment groups, the mean LOCF scores increased throughout the Randomized Phase, indicating a worsening of manic symptoms. Changes in MRS-16 scores were significantly lower in the lithium group at Week 52 compared with the lamotrigine group. There were no statistically significant differences between the lamotrigine and placebo or lithium and placebo groups at Week 52. There were no statistically significant differences between treatment groups at Week 76.

Table 4.2.10 MRS-16: Mean LOCF Total Scores and Mean Change from RD1 During the Randomized Phase in Efficacy Population for Study SCAB2006

Visit	Statistical Parameter	Placebo N=69	Lithium N=44	Lamotrigine N=58
RD1	Mean Score ± SD	2.8 ± 3.7	3.0 ± 4.2	3.4 ± 4.2
Week 52	Mean Score ± SD	8.6 ± 10.6	5.6 ± 8.3	9.9 ± 10.8
	Mean Change from RD1 ± SD	5.7 ± 9.8	2.6 ± 6.5	6.4 ± 11.5
	p-value		Not Sig.	Not Sig
Week 76	Mean Score ± SD	8.6 ± 10.6	5.8 ± 8.4	9.8 ± 10.7
	Mean Change from RD1 ± SD	5.8 ± 9.8	2.7 ± 6.5	6.3 ± 11.4
	p-value		Not Sig.	Not Sig.

4.2.3.2.6 Clinical Global Impression of Improvement

The LOCF data for the CGI-I scores in the Efficacy population during the Randomized Phase are summarized in Table 4.2.11.

Table 4.2.11 CGI-I Mean LOCF Total Scores During the Randomized Phase in Efficacy Population for Study SCAB2006

Visit	Statistical Parameter	Placebo N=69	Lithium N=44	Lamotrigine N=58
RD1	Mean Score ± SD	1.6 ± 0.7	1.3 ± 0.5	1.6 ± 0.5
Week 52	Mean Score ± SD	3.2 ± 1.7	2.9 ± 1.7	3.2 ± 1.8
Week 76	Mean Score ± SD	3.2 ± 1.6	3.0 ± 1.7	3.2 ± 1.8

For all treatment groups, the mean LOCF scores increased throughout the Randomized Phase. However, there were no statistically significant differences between treatment groups in the scores at Week 52 or Week 76.

4.2.3.2.7 Clinical Global Impression of Severity

The LOCF data for the CGI-S scores in the Efficacy population during the Randomized Phase are summarized in Table 4.2.12.

Table 4.2.12 CGI-S Mean LOCF Total Scores During the Randomized Phase in Efficacy Population for Study SCAB2006

Visit	Statistical Parameter	Placebo N=69	Lithium N=44	Lamotrigine N=58
RD1	Mean Score ± SD	1.8 ± 0.8	1.6 ± 0.7	1.8 ± 0.7
Week 52	Mean Score ± SD	3.0 ± 1.5	2.7 ± 1.4	2.8 ± 1.3
	Mean Change from RD1 ± SD	1.2 ± 1.4	1.1 ± 1.4	1.0 ± 1.4
Week 76	Mean Score ± SD	3.1 ± 1.4	2.8 ± 1.4	2.8 ± 1.3
	Mean Change from RD1 ± SD	1.2 ± 1.3	1.1 ± 1.4	1.0 ± 1.3

The mean CGI-S scores were comparable across treatment groups on RD1. For all treatment groups, the mean LOCF scores increased throughout the Randomized Phase, indicating a worsening of illness. There were no statistically significant differences between treatment groups at Week 52 or Week 76.

4.2.3.2.8 Global Assessment Score

The LOCF data for the GAS scores in the Efficacy population during the Randomized Phase are summarized in Table 4.2.13.

Table 4.2.13 GAS Mean LOCF Total Scores During the Randomized Phase in Efficacy Population for Study SCAB2006

Visit	Statistical Parameter	Placebo N=69	Lithium N=44	Lamotrigine N=58
RD1	Mean Score ± SD	77.5 ± 9.7	80.0 ± 10.7	76.9 ± 11.5
Week 52	Mean Score ± SD	66.7 ± 15.8	69.9 ± 17.3	66.1 ± 17.6
	Mean Change from RD1 ± SD	-11 ± 14.3	-10 ± 17.3	-11 ± 18.8
Week 76	Mean Score ± SD	66.4 ± 15.6	69.9 ± 17.2	66.3 ± 17.6
	Mean Change from RD1 ± SD	-11 ± 14.0	-10 ± 17.5	-11 ± 18.8

The mean GAS scores were comparable on RD1. For all treatment groups, the mean LOCF scores decreased throughout the Randomized Phase, indicating a worsening of illness. There were no statistically significant differences between treatment groups at Week 52 or Week 76.

4.2.4 The Sponsor's Efficacy Conclusions

Subjects with bipolar I disorder who received lamotrigine treatment remained stable for a significantly longer time than those who received placebo. This was observed for all three analyses of the primary efficacy measure. The TIDep results indicate that the effects of lamotrigine in the management of bipolar disorder are primarily at the depressive pole. Therefore, these data support the use of lamotrigine in the long-term management of

depression in bipolar I disorder. Moreover, the TIMan and TIDep analyses demonstrate that lamotrigine treatment resulted in an improvement in one pole of the illness (depressive episodes), without a concomitant worsening of the other pole of the illness (manic/hypomanic/mixed episodes).

5. Statistical Issues and Collective Evidence

5.1 Statistical Reviewer's Findings and Comments

(1) The sponsor submitted the Amendment 13 which was finalized on August 28, 2001 to the protocol of Study SCAB2003 (same as the Amendment 9 for Study SCAB2006, which was finalized on October 24, 2000) to provide three different censoring schemes for the primary endpoint TIME and designated the first one TIME (ABE) as the primary analysis. It assumed the premature discontinuation of a subject prior to reaching TIME for reasons other than AEs not deemed related to bipolar symptomatology to be an event related to bipolar disorder.

Since Study SCAB2003 was completed on August 9 of 2001 and Study SCAB2006 was early terminated on December 10 of 1999, which were earlier than the last amendment of each study, the validity of these final amendments for both studies was questioned although the sponsor did mention in their study report that data were authorized for release on October 26 of 2001 and October 31 of 2000 for Study SCAB2003 and Study SCAB2006, respectively. If, like the sponsor mentioned in the amendments that 'Several sources of information support the hypothesis that the inclusion of premature discontinuations in the survival analysis may provide a more sensitive measure of efficacy than TIME alone' is the reason, they should have had the protocols to both studies amended simultaneously when the studies were still ongoing.

FDA did not agree with the use of TIME(ABE) as the primary analysis, because this TIME(ABE) censoring scheme captured almost all kinds of early drop-out events, which introduced an interpretation problem. Since the sponsor did not mention any way to deal with patients who prematurely discontinued prior to events or complete the study without reaching time in the original protocol, we should assume all patients without events were censored. That is the third analysis TIME(only) proposed in the sponsor's amendment.

However, since our medical division also felt considering the protocol specified TIME endpoint alone was not sensitive enough to capture all bipolar related events, they decided to consider another endpoint. So, not only the patients who reached TIME were counted as events, some patients who discontinued the study before reaching time due to lack of efficacy or some had adverse events clearly due to bipolar disorder were also counted as events. This reviewer reanalyzed the data by reversing the aforementioned patients' censoring status and for convenience denoted this new censoring scheme as TIME(BPD). The principal statistical findings and analysis results for two studies were in the following comments.

(2) For Study SCAB2003, the medical reviewer informed this reviewer that Site #55466 was closed for some safety problems by the sponsor during the study. As a result of it, the efficacy data from that site should not be included into the study. This reviewer re-analyzed the data after excluding that site and showed the results in Tables 5.1 and 5.2. Since p-values for TIME (only) and TIDep were greater than 0.05, it was concluded that the difference between the combined 200mg and 400mg of lamotrigine and the placebo became insignificant for these two endpoints. Moreover, the p-value for TIME (only) for the comparison between LTG 200mg and Placebo became 0.0277 which was greater than 0.025. If we use the simple Bonferroni procedure, the difference from this comparison became statistically insignificant (See Comment #6).

Table 5.1 The Log-Rank Test Results after Deleting Patients in Study Site #55466 for Study SCAB2003

Study SCAB2003	Combined LTG 200mg and 400mg vs. Placebo	LTG 200mg vs. Placebo	LTG 400mg vs. Placebo
TIME(ABE)	0.0098	0.0063	0.2886
TIME(SIS)	0.0066	0.0032	0.3235
TIME(only)	**0.0594**	**0.0277**	0.6826
TIDep	**0.0970**	0.0578	0.6612
TIMan	0.3650	0.2639	0.9377

Table 5.2 The Detailed Estimats from the Survival Distributions for the Original Data Set and the Site 55466 Removed Data for Study SCAB2003

	The Original Data Set			After Site 55466 Was Removed		
For TIME (only) Statistical Parameter	**PBO N=119**	**LTG 200 N=120**	**LTG 400 N=45**	**PBO N=116**	**LTG 200 N=117**	**LTG 400 N=45**
Subjects with Event, n (%)	66 (55)	58 (48)	25 (56)	63 (54)	57 (49)	25 (56)
Median Time to Event (days)	92	255	144	92	255	144
Confidence Interval	57, 179	172, 481	48, 452	68, 197	162, 471	48, 452
Survival Estimate, Week 76	0.2730	0.3751	0.3251	0.2803	0.3719	0.3251
For TIDep Statistical Parameter						
Subjects with Event, n (%)	47 (39)	40 (33)	17 (38)	44 (38)	39 (33)	17 (38)
Median Time to Event (days)	161	NA	452	269	NA	452
Confidence Interval	92, NA	255, NA	119, NA	96, NA	255, NA	119, NA
Survival Estimate, Week 76	0.4099	0.5353	0.4565	0.4211	0.5335	0.4565
For TIMan Statistical Parameter						
Subjects with Event, n (%)	19 (16)	18 (15)	8 (18)	19 (16)	18 (15)	8 (18)
Median Time to Event (days)	NA	NA	NA	NA	NA	NA
Confidence Interval	NA	NA	NA	NA	NA	NA
Survival Estimate, Week 76	0.6677	0.7007	0.7122	0.6672	0.6972	0.7122

(3) According to the sponsor's data analysis attachment, the date of reaching the patients' primary endpoint was not specifically recorded in the CRF, so their TIME endpoint was derived based on an algorithm defined prior to the unblinding and subsequent analysis of the database. The medical reviewer checked each patient in both pivotal studies to see if the sponsor correctly determined the patients' TIMEs and found 6 patients in Study SCAB2003 and 5 patients in Study SCAB2006, who did receive the

concomitant medication to treat their mood episode in their randomized phase, but however, were not counted the events and recorded their TIMEs. This reviewer was asked to reanalyze the data by updating these patients' TIMEs and censoring status but without excluding Site #55466. It was found that for Studies SCAB2006, there were no p-values changed big enough to affect the conclusions. However, for Study SCAB2003, the test for TIDep for LTG 200mg vs. Placebo became significant (p=0.0127 <0.025, See Comment #6). Table 5.3 shows the detailed p-values for this re-analysis and Table 5.4 shows the detailed estimates from the survival distributions.

Table 5.3 The Log-Rank Test Results after Changing the Following Patients' TIMEs and Censoring Status.

- For Study SCAB2003, redefining patients #4103, 4104, 12790, 4231, 57035, and,57038's TIMEs and censoring status.
- For Study SCAB2006, redefining patients #20765, 20768, 6075, 6565, and 6575's TIMEs and censoring status.

Study SCAB2003	**Combined LTG 200mg and 400mg vs. Placebo**	**LTG 200mg vs. Placebo**	**LTG 400mg vs. Placebo**
TIME(ABE)	0.0041	0.0011	0.4958
TIME(SIS)	0.0035	0.0007	0.5898
TIME(only)	0.0297	0.0068	0.9209
TIDep	0.0416	0.0127	0.8651
TIMan	0.3938	0.2577	0.9342
Study SCAB2006	**LTG Flex vs. Placebo**		
TIME(ABE)	0.0221		
TIME(SIS)	0.0286		
TIME(only)	0.0138		
TIDep	*		
TIMan	*		

*: not being calculated since the last two patients didn't have their mood episodes determined as either mania or depression (noted as "bipolar" in subject listing).

Table 5.4 The Detailed Estimates from the Survival Distributions after Changing the Aforementioned Patients' TIMEs and Censoring Status

For TIME (only) Statistical Parameter	**Study SCAB 2003**			**Study SCAB 2006**	
	PBO N=119	**LTG 200 N=120**	**LTG 400 N=45**	**PBO N=69**	**LTG Flex N=58**
Subjects with Event, n (%)	67 (56)	58 (48)	27 (60)	50 (72)	28 (48)
Median Time to Event (days)	92	239	119	84	140
Confidence Interval	57, 145	172, 481	44, 201	36, 120	69, NA
Survival Estimate, Week 76	0.2748	0.3756	0.2694	0.1488	0.4389

Statistical Parameter	**Study SCAB 2003 For TIDep**			**Study SCAB 2003 For TIMan**		
	PBO N=119	**LTG 200 N=120**	**LTG 400 N=45**	**PBO N=119**	**LTG 200 N=120**	**LTG 400 N=45**
Subjects with Event, n (%)	48 (40)	39 (33)	19 (42)	19 (16)	19 (16)	8 (18)
Median Time to Event (days)	145	NA	153	NA	NA	NA
Confidence Interval	92, NA	255, NA	119, NA	421, NA	NA	NA
Survival Estimate, Week 76	0.4197	0.5502	0.3817	0.6564	0.6828	0.7059

(4) For Study SCAB2003, this reviewer also reanalyzed the data by combining the medical reviewer's two findings and showed the results in Tables 5.5 and 5.6. That is,

reanalyzing the data after removing the safety problem Site #55466 and redefining those six patients. The p-values for TIME(only), TIDep and TIMan all became greater than 0.05 for the comparisons between the combined lamotrigine 200mg and 400mg treatment and the Placebo. Specifically, the p-value of TIME(only) became 0.0617. However, we noticed that the p-value for TIME (only) for the lamotrigine 200mg versus the Placebo comparison became 0.0156 (<0.025), which means they were statistically significantly different.

Table 5.5 The Log-Rank Test Results after Deleting Patients in Study Site #55466 and Redefining Patients Mentioned in Table 5.3 for Study SCAB2003

Study SCAB2003	Combined LTG 200mg and 400mg vs. Placebo	LTG 200mg vs. Placebo	LTG 400mg vs. Placebo
TIME(ABE)	0.0098	0.0029	0.5735
TIME(SIS)	0.0084	0.0019	0.6692
TIME(only)	**0.0617**	**0.0156**	0.9560
TIDep	**0.0883**	0.0287	0.9847
TIMan	**0.4192**	0.2826	0.9430

Table 5.6 The Detailed Estimates from the Survival Distributions for Data after Removing Site #55466 and Redefining Patients Mentioned in Table 5.3 for Study SCAB2003

	Data After Site 55466 Removed and Some Redefinings		
For TIME (only) Statistical Parameter	**PBO N=116**	**LTG 200 N=117**	**LTG 400 N=45**
Subjects with Event, n (%)	64 (55)	57 (49)	27 (60)
Median Time to Event (days)	92	239	119
Confidence Interval	57, 161	162, 471	44, 201
Survival Estimate, Week 76	0.2822	0.3724	0.2694
For TIDep			
Subjects with Event, n (%)	45 (39)	38 (32)	19 (42)
Median Time to Event (days)	161	NA	153
Confidence Interval	92, NA	255, NA	119, NA
Survival Estimate, Week 76	0.4313	0.5484	0.3817
For TIMan			
Subjects with Event, n (%)	19 (16)	19 (16)	8 (18)
Median Time to Event (days)	NA	NA	NA
Confidence Interval	NA	NA	NA
Survival Estimate, Week 76	0.6558	0.6793	0.7059

(5) For the aforementioned additional endpoint TIME(BPD) (See Comment #1), this reviewer performed the analysis and showed the results in Tables 5.7. More specifically, among the lamotrigine 200mg, 400mg and the Placebo groups, in addition to the patients who reached the TIMEs, this reviewer reversed nine patients' censoring status to events. Those nine patients' IDs were 3827, 4284, 12714, 4861, 4929, 12753 who discontinued the study due to lack of efficacy and 4555, 3858 and 12654 who discontinued the study due to some adverse events related to bipolar disorder. (Note that this analysis was performed after combining the medical reviewer's findings in Comments #2 and #3.) As it was shown in the table, the p-values were 0.0337 and 0.0104 for the comparisons between the combined

lamotrigine 200mg and 400mg group and the Placebo, and between the lamotrigine 200mg and the Placebo. So, both comparisons showed statistically significantly different.

Table 5.7 Survival Analysis for the Additional Endpoint TIME(BPD) for Study SCAB2003

Statistical Parameter	PBO N=116	LTG Comb. N=162	By LTG Treatment Group	
			LTG200 N=117	LTG400 N=45
Subjects with Event, n (%)	69 (59)	88 (54)	61 (52)	27 (60)
Median Time to Event (days)	92	177	217	119
Confidence Interval	57, 137	129, 323	149, 398	44, 201
Survival Estimate, Week 76	0.2280	0.3312	0.3564	0.2694
p-value		**0.0337**	**0.0104**	0.7664

(6) Normally, we FDA do not accept the sponsor's analysis results based on the combining data from different dosage groups, so this reviewer focused on the analysis results for the comparisons between each dosage group and the Placebo.

For Study SCAB2003, since there was no any multiple comparison method planned in the protocol for dealing with separate treatment dosage group versus the placebo comparisons, this reviewer performed the simple Bonferroni procedure, i.e, comparing the LTG 200mg and LTG400mg with the placebo separately, by α=0.025.

It is clear that the differences between the LTG 400mg versus Placebo were not significant on any of the endpoints (TIME(only), TIDep and TIMan) in any scenarios mentioned above. For the comparison between the LTG 200mg and the Placebo, results showed statistically significantly different on the primary endpoint TIME(only), but not on the secondary endpoints of TIDep and TIMan by either the sponsor's original data, or the data after Site #55466 was removed and the six patients were redefined. For the Division newly defined censoring scheme, TIME(BPD), the result also showed they were statistically significantly different.

(7) Study SCAB2006 was terminated early before the planned number of patients was recruited. According to the sponsor's study report, the reason why they terminated the study was because they had trouble in recruitment. The medical reviewer noticed that 20% of patients who didn't complete the study was due to the sponsor's early termination. So, this reviewer questioned if the reason of termination was mainly due to the recruitment problem, why didn't they allow the patients who were already in the study to complete their 76 week trials? Was there any interim analysis involved? If the study was monitored at that time point and the sponsor decided to whether to continue the study after analyzing the data, then we should not use alpha equal to 0.05 to perform the test any more. Thus, we sent a letter to the sponsor to clarify these points.

They provided us their reasons and two internal communication letters to support their argument. In their response to our questions, they stated "The decision to discontinue ongoing subjects was made primarily because of internal budget constraints during that period." and "In addition, because enrollment in the study had been terminated and 80% of patients had already completed or reached endpoint, it was also believed to be in the remaining patients' best interest to minimize their further exposure to the clinical trial process." About the question of interim analysis, they answered that 'No interim analyses were planned or conducted for study SCAB2006.'

Since Study SCAB2003 was initiated on July 12, 1997 and completed on August 9, 2001, which lasted for more than 4 years, but Study SCAB2006 was initiated on August 14, 1997 and completed on December 10 of 1999, which only lasted for two years plus about 4 months, this reviewer had a question about the acceptability of the sponsor's reason of termination. Especially, they didn't inform the agency their decision before the trial was terminated. For simplicity, this reviewer compared the numbers of patients in the placebo groups for both studies. We notice that 69 patients randomized in the placebo groups for Study SCAB2006 are more than 50% of 119 patients randomized in the placebo groups for Study SCAB2003 in the Efficacy population. So, the slow recruitment seems not to be a good reason. Moreover, their response about internal budget constraints and patients' best interests for completing the trial also seem to be unreasonable to this reviewer.

(8) Closely observing from the Figures 4.1 to Figure 4.6, it is interesting to find that for Study SCAB2003, the curves between the lamotrigine combined group and the placebo group for TIME(ABE), TIME(SIS) and TIME(only) analyses seem to have the bigger differences among the earlier period of the study than the later period. On the contrary, for Study SCAB2006, the differences between the curves of lamotrigine group and the placebo group seem to be smaller in the earlier period of the study. To further explore this phenomena, this reviewer performed the Fleming-Harrington G^{ρ} family of tests by specifying different weights $\rho = 1, 0$, and -1. Notice that when $\rho=1$ is specified, this test is more sensitive to the early differences in the survival distributions. When $\rho=0$ is specified, this test is exactly the well-known Log-rank test, which was the sponsor applied. Moreover, when $\rho=-1$ is specified, this test is able to pick up the later differences.

Table 5.5 shows the test results by this reviewer. The results basically confirmed our observance. Now we also noticed that for Study SCAB2003, the test for TIME(only) showed p-value of 0.083 ($\geq$0.05) by $\rho=-1$ and for Study SCAB2006, the tests for TIME(ABE) and TIME(SIS) showed p-values of 0.066 ($\geq$0.05) and 0.092 ($\geq$0.05), respectively.

Table 5.5 The Fleming-Harrington G^{ρ} Tests between Lamotrigine and Placebo for TIME(ABE), TIME(SIS) and TIME(only) for Both Pivotal Studies

Study SCAB2003	**$\rho = 1$**	**$\rho = 0$ (Logrank Test)**	**$\rho = -1$**
TIME(ABE)	0.002	0.004	0.040
TIME(SIS)	0.001	0.003	0.051
TIME(only)	0.015	0.029	**0.083**
Study SCAB2006	**$\rho = 1$**	**$\rho = 0$ (Logrank Test)**	**$\rho = -1$**
TIME(ABE)	**0.066**	0.023	0.003
TIME(SIS)	**0.092**	0.030	0.003
TIME(only)	0.033	0.018	0.010

(9) The sponsor presented the combined analysis results for the comparisons between the lamotrigine and placebo from two pivotal studies for the endpoints of TIME (ABE), TIME (SIS), TIME (only), TIDep and TIMan. The p-values were 0.0004, 0.0004, 0.0007, 0.0089 and 0.0339, respectively.

Since the p-values for the endpoint TIMan were both greater than 0.05 in the two pivotal studies, we told the sponsor in February of 2002's pre-sNDA meeting that 'FDA's review will examine the initial hypothesis as tested to determine, if possible, the source of the treatment effect seen; in this context, the fact that the combined studies show a statistically significant effect vs. emergence of mania is reassuring.' This reviewer wishes to point out that although the p-values from the combined study analyses were less than 0.05, which does not imply the differences between the lamotrigine and placebo were significant. This combined data analysis, which is a meta-analysis may be overpowered, so we should not use alpha=0.05 to draw the conclusions. No well-known and generally acceptable rules for alpha in the meta-analysis were developed so far.

(10)Since the sponsor only performed the demographic subgroup analyses for the combined study data set, this reviewer performed the sub-group analysis for TIME (only) by the Log Rank test for each pivotal study separately (See Tables 5.6 and 5.7). Since more than 90% of patients were white, this subgroup analysis for race was not performed. According to the results, this reviewer noticed that the male patients with lamotrigine showed much better performance than the male patients with Placebo, but this did not happen on female patients, where they had better placebo responses.

Table 5.6 Subgroup Analyses for Gender and Age for Study SCAB2003

Female			LTG	By LTG Treatment Group		
Statistical Parameter	PBO N=59	Li N=72	Comb. N=96	LTG50 N=28	LTG200 N=72	LTG400 N=24
Subjects with Event, n (%)	31 (53)	34 (47.2)	50 (52)	17 (60.7)	35 (48.6)	15 (62.5)
Median Time to Event (days)	96	149	155	114	239	109
Confidence Interval	(68, NA)	(71, 309)	(107, 323)	(59, 268)	(129, NA)	(44, 201)
Survival Estimate, Week 76	0.3526	0.345	0.355	0.297	0.389	0.271
p-value		0.5387	0.3893	0.9390	0.2205	0.757

Male Statistical Parameter	PBO N=60	Li N=48	LTG Comb. N=69	By LTG Treatment Group		
				LTG50 N=22	LTG200 N=48	LTG400 N=21
Subjects with Event, n (%)	35 (58.3)	22 (45.8)	33 (47.8)	15 (68.2)	23 (47.9)	10 (47.6)
Median Time to Event (days)	85	211	373	158	373	452
Confidence Interval	(42, 236)	(101, NA)	(189, NA)	(63, 379)	(189, NA)	(15, NA)
Survival Estimate, Week 76	0.2183	0.4670	0.3804	0.1948	0.372	0.408
p-value		0.016	0.0303	0.5180	0.026	0.3010
Age≤40 Statistical Parameter	PBO N=53	Li N=49	LTG Comb. N=59	By LTG Treatment Group		
				LTG50 N=18	LTG200 N=41	LTG400 N=18
Subjects with Event, n (%)	28 (53)	18 (37)	30 (51)	11 (61)	21 (51)	9 (50)
Median Time to Event (days)	120	NA	175	114	175	146
Confidence Interval	(68, 302)	(110, NA)	(107, NA)	(29, NA)	(59, NA)	(61, NA)
Survival Estimate, Week 76	0.31	0.54	0.36	0.32	0.34	0.39
p-value		0.09	0.4825	0.9374	0.6825	0.4214
Age>40 Statistical Parameter	PBO N=66	Li N=71	LTG Comb. N=106	By LTG Treatment Group		
				LTG50 N=32	LTG200 N=79	LTG400 N=27
Subjects with Event, n (%)	38 (58)	38 (54)	53 (50)	21 (66)	37 (47)	16 (59)
Median Time to Event (days)	86	118	217	117	373	109
Confidence Interval	(22, 236)	(85, 211)	(149, 471)	(70, 240)	(162, NA)	(31, 201)
Survival Estimate, Week 76	0.2611	0.323	0.36	0.20	0.40	0.29
p-value		0.1149	0.023	0.5119	0.0061	0.8627

Table 5.7 Subgroup Analyses for Gender and Age for Study SCAB2006

Female Statistical Parameter	PBO N=35	Li N=24	LTG Flex N=32
Subjects with Event, n (%)	23 (66)	10 (42)	14 (44)
Median Time to Event (days)	107	291	NA
Confidence Interval	(55, 232)	(97, NA)	(70, NA)
Survival Estimate, Week 76	0.18	0.42	0.53
p-value		0.1313	0.1390
Male Statistical Parameter	PBO N=34	Li N=20	LTG Flex N=26
Subjects with Event, n (%)	26 (76)	8 (40)	14 (54)
Median Time to Event (days)	36	258	85
Confidence Interval	(18, 182)	(124, NA)	(43, NA)
Survival Estimate, Week 76	0.1119	0.50	0.34
p-value		0.0081	0.058
Age≤40 Statistical Parameter	PBO N=35	Li N=20	LTG Flex N=29
Subjects with Event, n (%)	25 (71)	10 (50)	10 (34)
Median Time to Event (days)	44	258	NA
Confidence Interval	(23, 232)	(100, 291)	(113, NA)
Survival Estimate, Week 76	0.1585	0.1883	0.5463
p-value		0.1326	0.0059

Age>40 Statistical Parameter	PBO N=29	Li N=24	LTG Flex N=29
Subjects with Event, n (%)	24 (71)	8 (33)	18 (62)
Median Time to Event (days)	89	NA	70
Confidence Interval	(52, 192)	(97, NA)	(37, NA)
Survival Estimate, Week 76	0.1547	0.6050	0.3403
p-value		0.0203	0.6567

(11)While the other non-pivotal studies were reviewed, this reviewer did not have any inconsistent findings.

5.2 Summary of Statistical Reviewer's Principal Findings and Conclusions

The sponsor submitted two pivotal long term studies SCAB2003 and SCAB2006 with the primary endpoint, TIME, defined as "time from entry into the randomized phase to the time of the first prescription of any additional pharmacotherapy or ECT determined by the investigator to be necessary for treatment of a relapse or recurrence of a depressive episode or recurrence of a manic, hypomanic, or mixed episode, whichever occurred first."

Before the data were unblinded, the sponsor submitted the last amendments for each study to provide three different censoring schemes for dealing with subjects who discontinue prematurely from the study prior to reaching an event. They designated the first one as the principal analysis, which assumed the premature discontinuation of a subject prior to reaching TIME for reasons other than AEs not deemed related to bipolar symptomatology to be an event related to bipolar disorder. This censoring scheme was denoted as TIME(ABE).

FDA did not agree with the use of TIME(ABE) as the primary analysis because this TIME(ABE) censoring scheme treated almost all kinds of early drop-out as events, which introduced interpretation problem. Since the sponsor did not mention any way to deal with patients who prematurely discontinued prior to events or complete the study without reaching time in the original protocol, we should assume all patients without events were censored. That is the third analysis TIME(only) proposed in the sponsor's amendment.

The medical division, however, also felt considering the original protocol specified TIME endpoint alone was not sensitive enough to capture all bipolar related events, so they decided to consider a different censoring scheme. They proposed that not only the patients who reached TIME were counted as events, some patients who discontinued the study before reaching time due to lack of efficacy or some had adverse events clearly due to bipolar disorder were also counted as events. This reviewer reanalyzed the data by reversing the aforementioned patients' censoring status and for convenience denoted this new censoring scheme as TIME(BPD).

For Study SCAB2003 since the medical reviewer found a site, which was closed due to some safety problems but the data were still included into the efficacy analyses, and also some patients who had mood episodes treated but not being counted as events, this

reviewer was asked to reanalyze the data by excluding that site and redefining the six patients who had events but were not counted. The p-values of TIME(only) became 0.0617 and 0.0156 for the comparisons between the combined lamotrigine 200mg and 400mg group and the Placebo, and between lamotrigine 200mg and the Placebo, respectively. Moreover, for the aforementioned additional endpoint TIME(BPD), the p-values were 0.0337 and 0.0104 for the comparisons between the combined lamotrigine 200mg and 400mg group and the Placebo, and between the lamotrigine 200mg and the Placebo, respectively.

For Study SCAB2006, since TIME(only) shows statistically significant results ($p<0.05$), it is not necessary to look at the results by using the division proposed censoring scheme TIME(BPD), provided that the division accepts the sponsor's reason for terminating the study.

In conclusion, for Study SCAB 2003, the data indeed support the efficacy of lamotrigine 200mg. Although the p-value of TIME (only) for the comparison between the combined dosage group and the Placebo was 0.0617, the p-value of TIME (only) for the comparison between lamotrigine 200mg and the Placebo was 0.0156. Since we do not generally accept the sponsor's analysis results based on the combined dosage group data, this reviewer focused on the comparisons between different dosage group and placebo, separately. Now that the p-value of TIME (only) for the comparison between lamotrigine 200mg and the Placebo was 0.0156, which was less than 0.025,-if we use the simple Bonferroni procedure to adjust for the two different dosage groups, and also the statistically significant results shown for the additional censoring scheme TIME(BPD), the lamotrigine 200mg indeed showed efficacy. For Study SCAB2006, the study provides support for the lamotrigine's efficacy provided that the division accepts the sponsor's reason for terminating the study early. However, we should notice that the evidence is not dose specific because this study used flexible dose regimen.

Yeh-Fong Chen, Ph.D.
Mathematical Statistician

Concurrence:

Dr. Jin Dr. Chi

cc: NDA 20-241 (S-017) & 20-764 (S-011)
HFD-120/Dr. Katz
HFD-120/Dr. Laughren
HFD-120/Dr. Alfaro
HFD-120/Dr. Ware
HFD-700/Dr. Anello
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Dr. Chen
This review consists of 62 pages. MS Word: C:/yfchen/nda20764/review.doc

6. Appendices

6.1 Review for Study SCAB2005

Title: A Multicenter, Double-Blind, Placebo-Controlled, Flexible-Dose Evaluation of the Safety and Efficacy of LAMICTAL in the Long Term Treatment of Subjects who have Bipolar Disorder with Rapid Cycling)

6.1.1 Study Objectives

The objectives of this study were to compare the efficacy and safety of lamotrigine (LTG) with that of placebo (PBO) as either monotherapy or adjunctive therapy in long term treatment of mood episodes in subjects with bipolar disorder (I or II) with rapid cycling.

6.1.2 Study Design

This study was a multicenter, double-blind, PBO-controlled, flexible dose, parallel trial with 2 traetment groups, LTG and PBO. The subject population included adults with a diagnosis of rapid cycling bipolar disorder. A total of 137 subjects were randomized to receive either LTG (50-400mg per day, depending upon current regimen) or PBO as monotherapy or add-on therapy in a randomized manner using a balanced design. A Screening Visit determined eligibility of the subject into the trial. Following confirmation of eligibility, subjects were entered into a 32-week Treatment Phase followed by a 2-week Follow-up Phase.

At randomization, all subjects were either psychotropic drug free or on a regimen of medication without restriction (pre-Amendment 7) or up to a total of three psychotropic drugs with a maximum of two in any one class, i.e., mood stabilizers, antidepressants or neuroleptics (post-Amendment 7).

6.1.3 Efficacy Analysis Methods

6.1.3.1 Primary Endpoint

The primary measure of efficacy was based on time to intervention for treatment of a mood episode (TIME). TIME was defined as the elasped time from randomization to the first alteration of pharmacotherapy, including study drug, or ECT, for the treatment of a mood episode (depression, mania, hypomania or mixed) or one that, in the investigator's opinion, appeared to be emerging.

A subject's overall survival time, if lost to follow-up or prematurely discontinued from the study, was censored from the time of the last dose of study drug. TIME was measured relative to the date of the first dose of study drug, if recorded, and randomization date otherwise.

Survival probabilities were calculated by the Kaplan-Meier method, and tabulated by one-week intervals. The estimated survival functions were compared between lamotrigine and placebo using a Log Rank test. The null hypothesis was that the distribution of time to treatment intervention was not different for lacebo and lamotrigine.

6.1.3.2 Secondary Endpoints

Secondary efficacy measures included: a comparison of the number of mood episodes irrespective of intervention (depression, mania, hypomania or mixed) experienced over the treatment period between the two groups: the efficacy of long term treatment with LTG versus PBO in reducing the overall morbidity associated with bipolar disorder by reducing the frequency; duration and intensity of recurrences using measures of mood and global morbidity including the HAM-D, MRS from SADS-C, IVPE, CGI-S, CGI-I and GAS; the time from randomization to the time and incidence of first alteration of pharmacotherapy or decision to administer ECT, for an "all depressed" or an "all manic" episode (TID or TIM); the use of concomitant psychotropic medication between the two groups throughout the treatment period; and the utilization of health care resources between the two treatment groups.

For Rating Scales, missing data were imputed using the LOCF method. For the HAM-D scale, mean changes were compared between lamotrigine and placebo treatment groups using ANOVA adjusted for investigator. Similarly, the MRS total scores and the mean changes from Baseline were summarized for all subjects who entered the study with "all mania". The numbers of mood episodes were tabulated, and the distributions compared between treatment groups using Wilcoxon rank sum tests, adjusted for investigator using the van Elteren procedure. Moreover, procedures for analyzing TID and TIM are as outlined for the primary efficacy endpoint.

6.1.3.3 Analysis Population

The ITT population consisted of subjects who were randomized, regardless of whether or not study drug was taken. The safety population consisted of all subjects who were randomized and received at least one dose of study drug. The efficacy population consisted of all subjects in the safety population who provided at least one post-Baseline assessment. Notice that this was the primary population for all analyses of efficacy data, with the exception of the primary endpoint (TIME).

6.1.4 The Summary of the Sponsor's Study Results and Efficacy Conclusions

This study was conducted from May 31 of 1997 to Jan 6 of 2000. The subjects were enrolled at 27 sites located in Australia, Germany, Hungary, Ireland, Italy, UK, Yugoslavia and USA.

Table 6.1 summarizes demographics of the ITT population. The majority of the randomized subjects were female (57%) and caucasian/white (98%). Subjects had a mean

6.2.2 Study Design

This study was a multicenter, double-blind, PBO-controlled, flexible-dose, parallel-group evaluation of the safety and efficacy of LTG in the prevention of mood episodes in adult subjects with bipolar (I or II) disorder with rapid cycling. The study was conducted in two phases. Subjects could enter the Preliminary Phase euthymic or experiencing a mood episode (manic, hypomanic, depressed or mixed), as defined by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for a current bipolar mood state. Open-label treatment with LTG was started and progressively escalated at doses dependent on the subject's current regimen of psychotropic medication. The target dose of LTG (depending on the current regimen) during the Preliminary Phase was 200mg/day; the maximum dose was 300mg/day. After four weeks of exposure to LTG, all other psychotropic medications were tapered over 4-8 weeks if the subject had reached the minimum dose of 100mg/day of LTG (50 and 200mg/day with valproic acid or carbamazepine, respectively), and had a current Hamilton Depression Rating Scale, 17 item (HAMD-17) score of ≤ 14 and a Mania Rating Scale from Schedule for Affective Disorders and Schizophrenia-Change Version (MRS from SADS-C) score of ≤ 12. Any subject meeting the minimum criteria for wellness (defined as a HAMD-17 of ≤ 14 and a MRS from SADS-C of ≤ 12 maintained for the last 2 continuous weeks of the taper) and having successfully completed the taper to LTG monotherapy, was then to be immediately randomized into a monotherapy continuation and maintenance phase (Randomized Phase) in a 1:1 ratio of LTG and PBO. During the Randomized Phase, subjects were randomized into 1 of 2 treatment groups for a maximum of 26 weeks of double-blind treatment with flexible dose LTG (100mg-500mg/day) or PBO. Randomization to either treatment (LTG or PBO) was stratified according to a diagnosis of bipolar I or bipolar II disorder.

6.2.3 Efficacy Analysis Methods

6.2.3.1 Primary Endpoint

The predefined primary efficacy measure was the time from entry into the Randomized Phase to the first dose of any additional pharmacotherapy (other than study medication or lorazepam up to 2mg/day) or electroconvulsive therapy (ECT) determined by the investigator to be necessary for treatment of a manic, hypomanic, depressive or mixed episode or one that appeared to be emerging (TIME). Survival probabilities were calculated by the Kaplan-Meier method. The estimated survival distributions were compared between treatment groups using the Log Rank test.

6.2.3.2 Secondary Endpoints

After reviewing the study results, external experts in bipolar disorder research proposed that supportive analyses of the primary endpoint be performed in order to gain a more complete understanding of the efficacy of LTG in subjects with rapid cycling bipolar disorder. Additional post-hoc analyses that were performed included an evaluation of the

primary efficacy measure with the assumption that all premature discontinuations were "treatment failures" and an evaluation of the primary endpoint by severity of disease.

Secondary efficacy measures that were prospectively defined were:

- The time from entry into the Randomized phase to the first prescription of any additional pharmacotherapy or ECT for the treatment of "all mania" (TIM)
- The time from entry into the Randomized phase to the first prescription of any additional pharmacotherapy or ECT for the treatment of "all depression" (TID)
- Proportion of subjects completing the study without any additional pharmacotherapy (monotherapy completers)
- Number and percent of subjects reaching TIME by all mood at study entry
- Number and percent of subjects who were diagnosed as depressed at entry and reached TID
- Change from Baseline (Preliminary Day 1 and Randomized Day 1 for the Prelimianry and Randomized Phases, respectively) scores for the Hamilton Depression Rating Scale, 17 item (HAMD-17), Mania Rating Scale, 11 item (MRS-11), Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Improvement (CGI-I), and Global Assessment Scale (GAS) scores in the Preliminary and Randomized Phases
- Analyses of the life-chart data (frequency of mood episodes, percentage of time at each mood severity, number of functional polarity changes, mean daily hours of sleep, number and percent of days with dysphoric mania, mean mood score, and number of subjects with functional impairment scale score changes greater than 2 points from one day to the next day in the Preliminary and Randomized Phases)

The time from entry into the Randomized Phase to the first prescription of any additional pharmacotherapy or ECT for "all mania" (TIM) and for "all depression" (TID) was also tested using the Log Rank Test. Both observed and LOCF analyses were performed for the secondary efficacy assessment parameters (HAMD-17, MRS-11, CGI-S, CGI-I and GAS) in the Preliminary and Randomized Phases. LOCF was defined as the final on-therapy value for an individual subject irrespective of duration of therapy. Change from Baseline scores was used as the response variable for these efficacy parameters, with the exception of CGI-I for each study phase. For CGI-I, mean scores, as opposed to change from Baseline scores, were analyzed. Analysis of variance (ANOVA) was used to test for significant differences between treatment groups. Moreover, LCMsev (an illness index based on the severity and duration of mood episodes from life-chart), LCMfreq (the frequency of mood episodes based on the data from prosepctive life-chart) and percent of days euthymic were analyzed. Proportions of subjects completing the study without any additional pharmacotherapy or ECT by treatment were compared.

6.2.3.3 Analysis Populations

The Intent-to-Treat Population in the Randomized Phase was comprised of all subjects who were randomized to study medication.

The Safety Population in the Preliminary Phase was comprised of all subjects who received at least one dose of open-label LTG. The Safety Population in the Randomized Phase was comprised of all subjects who were randomized to study drug and received at least one dose of double-blind study drug.

The Efficacy Population in the Preliminary Phase was comprised of all subjects who received at least one dose of open-label LTG and had a Baseline efficacy assessment and at least one post-Baseline efficacy assessment during the Preliminary Phase. The Efficacy Population in the Randomized Phase was comprised of all subjects who received at least one dose of study drug and, had at least one post-Baseline efficacy assessment during the Randomized Phase or reached TIME.

6.2.4 The Summary of the Sponsor's Study Results and Efficacy Conclusions

This study was conducted from September 15 of 1997 to October 8 of 1999. The subjects were enrolled at 27 sites, where 24 were in the U.S. and 3 were in Canada.

The Intent-to-Treat Population in the Preliminary Phase consisted of 326 subjects and in the Randomized Phase consisted of 182 subjects. The Safety Population in the Preliminary Phase consisted of 324 subjects and in the Randomized Phase consists of 180 subjects. The Efficacy Population in the Preliminary Phase consisted of 313 subjects and in the Randomized Phase consisted of 177 subjects. Table 6.2 summarizes demographics of the Safety Population for the Preliminary and Randomized Phases. In the Randomized Phase, three patients (1 in PBO and 2 in LTG) were excluded from the Safety Population because they did not have a Baseline and a post-Baseline efficacy assessment.

Table 6.2 Summary of Subject Demography in the Safety Population for Study SCAA2012

		Preliminary Phase	Randomized Phase		
		Lamotrigine (N=324)	Placebo (N=88)	Lamotrigine (N=92)	Total (N=180)
Age (years)	Mean (SD)	38.6 (10.3)	37.5 (10.5)	38.3 (9.2)	37.9 (9.9)
Sex	Male	134 (41%)	36 (41%)	41 (45%)	77 (43%)
	Female	190 (59%)	52 (59%)	51 (55%)	103 (57%)
Race	White	297 (92%)	86 (98%)	79 (86%)	165 (92%)
	Black	15 (5%)	2 (2%)	6 (7%)	8 (4%)
	Asian	2 (<1%)	0	2 (2%)	2 (1%)
	American Hispanic	7 (2%)	0	3 (3%)	3 (2%)
	Oriental	0	0	0	0
	Other	3 (<1%)	0	2 (2%)	2 (1%)
Height (cm)	Mean (SD)	170.6 (9.9)	169.6 (10.5)	171.4 (10.3)	170.6 (10.4)
Weight (kg)	Mean (SD)	81.10 (19.19)	79.84 (22.36)	82.60 (18.52)	81.25 (20.47)

The survival analysis for the primary endpoint, time to intervention for a mood episode or one that was emerging, indicated that subjects treated with LTG were able to continue in the study without needing additional treatment for a mood episode longer than subjects treated with PBO. The difference in median survival between the two treatment groups

was approximately 6.7 weeks. However, the difference between treatment groups on the survival analysis was not statistically significant.

In the supportive analysis of the primary endpoint, time to intervention for a mood episode (or one that was emerging) or study withdrawal, LTG was statistically significantly more effective than PBO for the prevention of mood episodes (p=0.036). The difference in median survival between treatment groups was approximately 6.2 weeks. About the proportions completing study without additional pharmacotherapy or ECT, there was a statistically significantly bigger percentage of subjects in the LTG treatment group (41%) than that in the PBO treatment group (26%, p=0.028). Subjects with bipolar II disorder who were randomized to LTG (n=24) consistently demonstrated increased survival on monotherapy compared to those who were randomized to PBO (n=28); however, there were no differences in survival between treatment groups for the subgroup of subjects with bipolar I disorder (n=60 for PBO and n=68 for LTG).

Although the response to lamotrigine was similar in subjects with bipolar I and II disorder, there were differences in the two subgroups with respect to placebo, with the bipolar II placebo subgroup showing greater decline. The treatment difference in the bipolar II subgroup trended toward statistical significance on the primary endpoint analysis (p=0.073) and was statistically significant in the supportive analysis of the primary endpoint, time to intervention for a mood episode or study withdrawal (p=0.015). Subjects with bipolar II disorder who were randomized to LTG were more statistically significantly likely to complete the study on monotherapy compared to those who were randomized to PBO (p=0.040). However, comparisons between LTG and PBO were not statistically significant for the bipolar I subgroup.

6.3 Review for Study SCAB2001

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