

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-764/S-011**

**20-241/S-017**

**MEDICAL REVIEW**

Review and Evaluation of Clinical Data  
Complete Response to the Action Letter

NDA #20-241 S-017 (and 20-764 S-011)

Sponsor: GlaxoSmithKline

Drug: Lamictal (lamotrigine)

Material submitted: Complete Response to 4/4/03 Approvable Letter  
Final Safety Update

Indication: Maintenance treatment of Bipolar I Disorder

Related INDs: 49,916

Correspondence date: 04/21/03

Date Review Completed: 06/06/03

**Background**

This supplemental NDA was originally submitted on June 5, 2002 for the indication "long-term management of Bipolar I Disorder to delay the relapse/recurrence of depressive episodes". Two pivotal trials were submitted to support this indication. Upon review of these studies it was concluded that the primary endpoint, which had been changed via amendment, was not an appropriate endpoint. The Division performed a reanalysis using a modified primary endpoint, TIME(BipEvent), that included TIME(Only), certain premature discontinuations (adverse events due to bipolar disorder and other = lack of efficacy), additional TIME(Only) events found in the review process, and did not include site #55466 (see Clinical Review and Statistical Review). Using the modified primary endpoint, lamotrigine separated from placebo; however lamotrigine did not separate from placebo for time to recurrence/relapse of depressive episode for one of the pivotal trials. For the combined analysis of the two pivotal trials, lamotrigine separated from placebo for both time to recurrence/relapse of depressive and manic episodes.

The Division issued an approvable action letter on April 4, 2003. This letter reiterated a request to the Sponsor to provide safety data to support the proposed dosing strategy to double the dose of lamotrigine during the first week after discontinuation of valproate. The Sponsor submitted a complete response to the approvable action letter on April 21, 2003 that included this additional safety data as well as labeling comments and the final safety update.

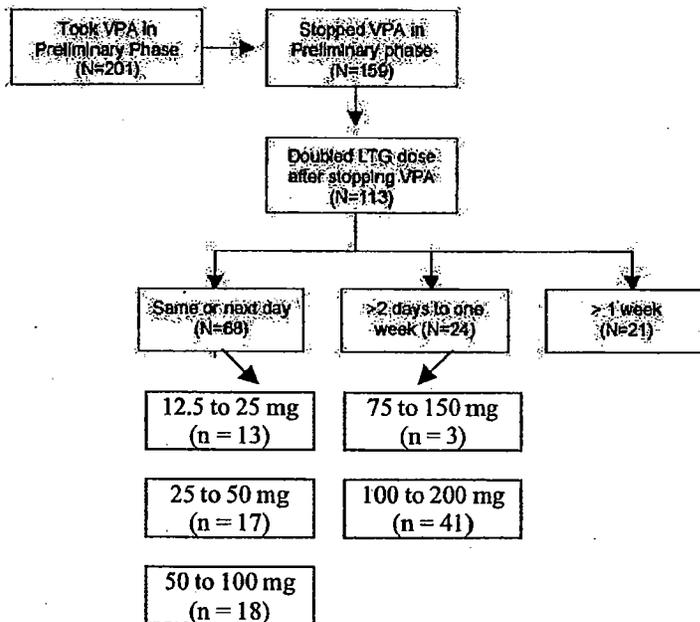
**Sponsor's Responses to Clinical Issues**

1. Safety data to support the proposed dosing strategy to double the dose of lamotrigine during the first week after discontinuation of valproate.

The two pivotal trials included a 8 to 16 week open-label preliminary phase in which lamotrigine was added to existing psychiatric medications (and other psychiatric medications could be added as well) targeting a lamotrigine dose of 200 mg/day. Concomitant medications were tapered off at the end of this preliminary phase and responders were randomized to lamotrigine, placebo, or lithium. These protocols included dosing guidelines for dosing lamotrigine when subjects were

taking medications known to interact with lamotrigine – specifically enzyme-inducing agents or valproate – in the preliminary phase. The protocols also specified how the dose of lamotrigine should be altered when these interacting medications were discontinued prior to randomization. In particular, when valproate was discontinued in the preliminary phase, the dose of lamotrigine was to be “immediately doubled”. In the proposed labeling in the original submission, the Sponsor proposed to double the dose of lamotrigine during the first week after discontinuation of valproate. However, the original submission did not provide any data to support the safety of this dose proposal and it was unclear how many subjects who received valproate during the preliminary phase had their lamotrigine dose “immediately doubled” or doubled within the first week after discontinuation of valproate. Due to the potential increased risk of lamotrigine-associated rash with valproate co-therapy, this reviewer was especially interested in the safety of this proposed dosage strategy as it relates to the incidence of rash.

The subject disposition for those receiving valproate during the preliminary phase is given by the Sponsor’s figure below:



Source: Lamictal-VPA document, 4/21/03 submission, page 1; corrected in 5/16/03 correspondence

Of the 159 subjects who discontinued valproate during the preliminary phase, 71% (113) had their dose of lamotrigine doubled. Of the subjects who had their dose of lamotrigine doubled, 81% (92) had the dose doubled either on the same day, next day or >2 days to one week after valproate discontinuation.

### *Adverse Events - General*

The Sponsor provided adverse event data for those subjects for whom valproate was discontinued in the preliminary phase and the dose of lamotrigine was doubled either on the same day or the next day. The adverse event data is given for adverse events beginning within one week or within two weeks (separate listings) after discontinuation of valproate and doubling the dose of lamotrigine. Since the proposed labeling indicates that the dose of lamotrigine should be doubled *during the first week* of valproate discontinuation, the Sponsor was also asked to provide a combined listing of adverse events for subjects in the "same or next day doubling group (n = 68)" and the "> 2 days to one week group (n = 24)". Data regarding adverse events for the latter group were not included in the materials submitted on 4/21/03.

The Sponsor provided data for adverse events beginning within 1 week and within 2 weeks after the dose of lamotrigine was doubled after discontinuation of valproate. Providing this data up to two weeks after doubling the dose of lamotrigine is appropriate based on the pharmacokinetics of both valproate and lamotrigine. Valproate increases the half-life of lamotrigine from ~25-35 hours to ~70-75 hours. Since valproate was not continued throughout this two week period, it is likely that the half-life of lamotrigine decreased during this period after the discontinuation of valproate. Adverse events occurring within a two week period of time as the chosen reporting period is appropriate and should capture most treatment-emergent adverse events occurring after the doubling of lamotrigine dose after discontinuation of valproate.

The only comparison group that the Sponsor provided were subjects who had their lamotrigine dose doubled from 100 to 200 mg/day without any prior exposure to valproate or carbamazepine. These data were originally included in the 4/21/03 correspondence with data for subjects with the lamotrigine dose doubled from 100 to 200 mg/day who had prior exposure to valproate. However, due to errors in this table discussed by the Sponsor in the 5/16/03 correspondence, the Sponsor asked that this table be disregarded. The primary error appeared to be that the lamotrigine dose adjustment may have been made on more than one occasion and the tables did not account for this possibility. Despite this potential error, data from the subjects without prior exposure to valproate or carbamazepine are included in this review to serve as some type of comparison group (see Table 1). It is possible that this comparison group could underrepresent some adverse events especially adverse events that may occur more commonly during lamotrigine initiation since this comparison group includes only those subjects for whom the dose of lamotrigine was doubled from 100 to 200 mg/day (weeks after beginning lamotrigine). Excluding subjects with prior exposure to carbamazepine was important since drug interactions via induction mechanisms are longer-lasting and this could have underrepresented adverse events due to lower lamotrigine concentrations in that group.

Table 1. Adverse Events in > 2% of Subjects (in any group) Beginning Within 1 or 2 Weeks of Doubling Dose of Lamotrigine; Subjects Discontinuing Valproate versus Subjects with no Prior Exposure to Valproate

	LTG dose doubled on same day or next day after DC VPA (n = 68)		LTG dose doubled within one week of DC VPA (n = 92)*		LTG dose doubled (100 to 200 mg/d), no prior exposure to VPA (n = 607)	
	1 Week	2 Weeks	1 Week	2 Weeks	1 Week	2 Weeks
<b>General</b>						
Headache	7 (10%)	9 (13%)	10 (11%)	16 (17%)	31 (5%)	47 (8%)
Influenza	3 (4%)	5 (7%)	3 (3%)	5 (5%)	≤ 2%	≤ 2%
Back pain	2 (3%)	2 (3%)	≤ 2%	3 (3%)	≤ 2%	≤ 2%
Pain	≤ 2%	2 (3%)	3 (3%)	5 (5%)	≤ 2%	≤ 2%
<b>Nervous system</b>						
Insomnia	4 (6%)	5 (7%)	4 (4%)	5 (5%)	≤ 2%	≤ 2%
Somnolence	2 (3%)	2 (3%)	2 (2%)	≤ 2%	≤ 2%	≤ 2%
Migraine	≤ 2%	2 (3%)	3 (3%)	4 (4%)	≤ 2%	≤ 2%
Tremor	≤ 2%	2 (3%)	2 (2%)	3 (3%)	≤ 2%	≤ 2%
Agitation	-	-	-	3 (3%)	≤ 2%	≤ 2%
Anxiety	-	≤ 2%	≤ 2%	3 (3%)	≤ 2%	≤ 2%
<b>Digestive</b>						
Constipation	≤ 2%	2 (3%)	3 (3%)	4 (4%)	≤ 2%	≤ 2%
<b>Metabolic &amp; Nutritional</b>						
Edema of extremities	-	≤ 2%	≤ 2%	4 (4%)	≤ 2%	≤ 2%

\*includes subjects with LTG dose doubled on same day or next day

Table 2. Rash/Pruritis Adverse Events Beginning Within 1 or 2 Weeks of Doubling Dose of Lamotrigine; Subjects Discontinuing Valproate versus Subjects with no Prior Exposure to Valproate

	LTG dose doubled on same day or next day after DC VPA (n = 68)		LTG dose doubled within one week of DC VPA (n = 92)*		LTG dose doubled (100 to 200 mg/d), no prior exposure to VPA (n = 607)	
	1 Week	2 Weeks	1 Week	2 Weeks	1 Week	2 Weeks
<b>Skin</b>						
Rash	0	0	1 (1%)	1 (1%)	5 (<1%)	12 (2%)
Pruritis	0	1 (1%)	1 (1%)	2 (2%)	7 (1%)	7 (1%)

Adverse events occurring more frequently in the subjects who had their lamotrigine dose doubled on the same or next day after discontinuation of valproate compared to the comparison group included headache, influenza, and insomnia (Table 1). Similar trends were observed for subjects who had their lamotrigine dose doubled within one week after discontinuation of valproate. Reports of rash and pruritis occurred in ≤ 2% of subjects in each group (Table 2). The rate of insomnia appears to be higher in the groups who doubled the dose of lamotrigine after discontinuing valproate (4 – 7%), however, this rate is similar to the 5% rate of insomnia occurring in a study evaluating the conversion to lamotrigine monotherapy from adjunctive therapy with carbamazepine or phenytoin in adults with partial seizures (Table 6 in labeling). It is also possible that insomnia could be a component of the underlying mood disorder that may be more apparent during the transition from valproate to lamotrigine as well as being an adverse

event due to lamotrigine. Again, the available comparison group for subjects not exposed to prior valproate evaluated adverse events for lamotrigine dose doubling from 100 to 200 mg/day. If insomnia is an early adverse event that subsides with increases in dose, this comparison group would underestimate the rate of insomnia occurring with initiation of lamotrigine.

#### Adverse Events – Rash

The development of rash can be a delayed adverse event (2 – 8 weeks after lamotrigine initiation or longer) and might not be reflected in the data the Sponsor submitted on 4/21/03 since the listing only includes adverse events occurring within 2 weeks of lamotrigine dose doubling. The Sponsor was asked to provide an analysis for all subjects who developed rash in the preliminary and randomized phases of the pivotal trials (n = 141 preliminary phase, n = 15 randomized phase – corrected via 6/5/03 correspondence) with regard to prior valproate exposure. Of special interest to this reviewer was an analysis evaluating risk of rash after the dose of lamotrigine was doubled within a week after valproate was discontinued.

In response to this request, the Sponsor provided the following table to the Division on 6/5/03 for subjects who had a rash occurring after discontinuation of valproate and doubling of the lamotrigine dose. This table also includes the number of days to rash onset after the lamotrigine dose was doubled. Eight subjects in this category had rash, most occurring during the preliminary phase – two of these eight subjects experienced a second rash during the randomized phase. Of note, it would appear that for one of these cases the lamotrigine dose was increased from 25 to 100 mg/day. None of these rashes were serious rashes. As discussed in the protocols for the pivotal trials, the threshold for discontinuing subjects from the trial due to rash was fairly low.

Patients Whose Rash Occurred After Discontinuation of VPA (that was taken Concomitantly with Lamotrigine*)					
Study Phase in which rash occurred	Subject Number	Number of Days from VPA Stop Date to Next LTG dose change (if applicable)	Dose Change (daily dose)		Number of Days from Next LTG Dose Change to Rash Onset
			From	To	
Preliminary	5028	15	25mg	50mg	32
	5199**	7	100mg	200mg	40 (1 <sup>st</sup> rash)
	6447	6	12.5mg	25mg	1
	12729	11	25mg	50mg	9
	13097	0	12.5mg	50mg	94
	13298**	1	25mg	100mg	86 (1 <sup>st</sup> rash)
Randomized	5199**	7	100mg	200mg	220 (2 <sup>nd</sup> rash)
	13298**	1	25mg	100mg	105 (2 <sup>nd</sup> rash)
	4804	1	25mg	50mg	144
	13144	1	12.5mg	25mg	At least 127***

\* Excludes subjects whose VPA was stopped prior to Preliminary Day 1  
 \*\* Subjects 5199 and 13298 each had two rashes (one in the Preliminary Phase and one in the Randomized Phase), both of which occurred subsequent to the discontinuation of VPA in the Preliminary Phase  
 \*\*\* Start date for rash was listed as Jan 1999 (no specific day provided)  
 Sources: Listings 1-4 of Attachment 2, Listing 6.20 of the SCAB2003 study report, and Listing 6.20 of the SCAB2006 study report

A total of 156 subjects had the adverse event "all rash" in both the preliminary and randomized phases of the two pivotal trials: 141/1305 (11%) in the preliminary phases and 15/227 (7%) in the randomized phases. Of these 156 subjects, only 5 (3%) subjects fit the criteria for having the dose of lamotrigine doubled within the first week after discontinuation of valproate – as per proposed labeling (this excludes 3/8 cases: in two cases, the dose of lamotrigine was doubled 11 and 15 days after discontinuation of valproate, in another case the dose of lamotrigine was more than doubled). As expected by this reviewer, most of these cases of rash were delayed occurring from 1 day (n = 1) out to 144 days after the dose of lamotrigine was doubled. It is difficult to ascertain causality of delayed rash with doubling the dose of lamotrigine especially since lamotrigine dose titration continued after the doubling of the dose, therefore it could be a cumulative exposure and not necessarily related to the original dose doubling.

Among the cases of rash occurring in the preliminary phase only, a phase likely to be associated with higher rates due to the initiation of lamotrigine, the rate for subjects who had their dose doubled within the first week after discontinuation of valproate is 3% (4 out of 141 cases of rash).

If one evaluates the rate of rash only for those subjects for whom the dose of lamotrigine was doubled within a week after valproate was discontinued, the rate is 5% (5 cases out of 92 subjects who had their dose doubled within one week). If one evaluates the rate of rash for only those subjects for whom the dose of lamotrigine was doubled within one week from 12.5 to 25 and 25 to 50 mg/d (early initiation of lamotrigine), the rate appears to be higher at 13% (4 out of 30 subjects with these doses doubled). However, due to the small numbers of subjects and the difficulties in ascertaining delayed causality, it is difficult to make firm conclusions about the accuracy of this rash rate in this subpopulation.

Though data from the randomized phase (compared to the preliminary phase) may underestimate the rate of rash, the rate in subjects receiving placebo was 5%. No placebo comparator is available for the open-label preliminary phase.

It would appear that very few of the cases of "all rash" were due to a doubling of the lamotrigine dose after discontinuation of valproate. This data, along with the data regarding adverse events occurring within 2 weeks after lamotrigine dose doubling, suggests that this approach does not significantly increase risk of adverse events in subjects.

## 2. Final Safety Update

The following safety information was submitted for this supplement:

ISS: Submitted 6/5/02. Data cut-off date = 10/31/01 (except SCAB2003 = 11/26/01).

120-day Safety Update: Submitted 10/04/02. Dates covered 11/1/01 – 3/31/02. Three ongoing studies (SCA40910 – DB and open label phases, LAM30046, SCA40912).

Second Safety Update: Submitted 2/26/03. Dates covered 4/1/02 – 8/31/02. Five ongoing studies (SCA40910 – open label continuation phase, LAM30046, SCA40912, SCA30905, SCA30923).

Final Safety Update: Submitted 4/21/03. Dates covered 9/01/02 – 2/28/03. Six ongoing studies (SCA40910 – open label continuation phase, LAM30046, SCA30905, SCA30923, SCA10908, SCA10910).

Ongoing Studies*Clinical Pharmacology Studies*

SCA10908 Single center, randomized, placebo-controlled, parallel group study to investigate the potential interaction between lamotrigine and olanzapine in healthy, nonsmoking male volunteers

SCA10910 Single center, randomized, partially blinded, parallel group study to investigate the potential interaction between lamotrigine and oxcarbazepine in healthy, non-smoking male volunteers

*Open-label Continuation Phase of Clinical Study*

SCA40910 6-month open-label continuation phase of an 8-week double-blind, placebo-controlled study in acute bipolar depression

*Foreign Local Operating Company Studies*

SCA30905 Multicenter, double-blind, randomized, placebo-controlled, add-on, fixed-dose study to evaluate the efficacy of lamotrigine compared with placebo, as add-on treatment to lithium in the acute and prophylactic treatment of patients with bipolar disorder who suffer from depressive episodes

LAM30046 Open-label, randomized, parallel-group multicenter study comparing the prophylactic efficacy of lamotrigine versus lithium in subjects diagnosed with bipolar disorder who have recently had a manic, depressive or mixed index episode requiring hospitalization (2 - 4 year study)

SCA30923 Open-label, prospective, multicenter study of the efficacy of lamotrigine in the prevention of recurrence of bipolar disorder (9 month study)

Subject disposition as of 2/28/03 for these 6 ongoing studies is provided in Table 3. Since submission of the NDA, the double-blind phase of study SCA40910 has been completed. The Sponsor has updated proposed labeling adverse event sections to incorporate data from this completed trial (see labeling section).

Table 3. Subject Disposition in Ongoing Studies as of February 28, 2003

	SCA10908	SCA10910	SCA40910 OL Phase	SCA30905	LAM30046	SCA30923
# Planned	46	39	NA	220	120	600
# Enrolled	52	47	161	21	73	409
# Randomized	52	47	NA	21	73	379
# Completed	40	29	105	0	24	0
# Prematurely Withdrawn	7	8	56	5	10	73

NA = not available

The final safety update included deaths, SAE and pregnancy information from the six ongoing studies as well as postmarketing data and an updated summary of published literature. The final safety update did not include comments regarding study SCA40912, a study that was ongoing at the time of the second safety update but no longer funded by the Sponsor. The Sponsor was contacted to provide SAEs for this study. The Sponsor replied (via email) on 6/5/03 that

SCA40912 is ongoing and that, as of June 4, 2003, there have been no SAE reports from this study.

#### Deaths

No deaths were reported for any of the six ongoing studies for the time period covered by the final safety report.

#### Serious Adverse Events

No SAEs were reported for studies SCA10908, SCA10910 and the open-label continuation phase of SCA40910. Sixteen SAEs were reported for 12 subject in studies SCA30905 (double-blind), LAM30046 (open-label) and SCA30923 (open-label).

Study	SAE	Treatment	Age	Gender	Time to Onset	Comments
SCA30905	Suicide attempt	Lamotrigine	21	Male	8 weeks	Overdose (~2700 mg lamotrigine)
LAM30046	Mood disorder Schizophrenia	Lithium	46	Female	0 days	
LAM30046	Mania	Lithium	22	Female	Not reported	
LAM30046	Psychotic disorder	Lithium	48	Female	4 months	
SCA30923	Gastroenteritis NOS	Lamotrigine	65	Female	51 days	Concurrent prednisolone
SCA30923	Cellulitis	Lamotrigine	59	Male	28 days	
SCA30923	Limb injury NOS	Lamotrigine	55	Female	60 days	Knee injury following traffic accident
SCA30923	Headache NOS aggravated	Lamotrigine	66	Male	6 days	
SCA30923	Anxiety Agitation Psychosis aggravated	Lamotrigine	27	Female	6 weeks	
SCA30923	Psychosis aggravated Mania aggravated	Lamotrigine	36	Female	14 days 25 days	
SCA30923	Depression	Lamotrigine	68	Female	7 weeks	
SCA30923	Suicide attempt	Lamotrigine	21	Female	18 days	Overdose (tilidine [opioid], maprotiline, diphenhydramine)

Most of the SAEs reported were consistent with the underlying disorder being studied in these clinical trials.

#### Withdrawals Due to Adverse Events

Data for withdrawals due to adverse events was provided only for the open-label continuation phase of SCA40910. The Sponsor was contacted to provide this information for the other ongoing studies.

Per a 5/16/03 correspondence, the Sponsor stated that, as agreed to at the 2/1/02 pre-sNDA meeting with the Division, "discontinuations due to adverse events in ongoing studies were not to be reported in the ISS and accordingly have also not been included in the three safety update reports that have been submitted to the sNDAs". The Sponsor did, however, submit this

information for the two ongoing clinical pharmacology studies (see below). Due to difficulties in obtaining this information in a timely fashion for the three ongoing foreign local operating company studies, this data will not be submitted to the Division.

SCA10908: one subject was withdrawn due to elevated AST and ALT

SCA10910: 7 subjects were withdrawn due to the following adverse events: dizziness (1), nausea and vomiting (2), rash (4) – none of the rashes were suspected to be SJS and subjects were withdrawn per protocol.

#### Pregnancies

No pregnancies occurred in any of the ongoing studies during this reporting period.

#### Postmarketing Information

Five spontaneous reports of death were reported and included in the Final Safety Update for this reporting period and are summarized in Table 4.

Table 4. Postmarketing Reports of Death

Deaths	Age	Gender	Comments
Suicide	19	Female	Overdose (lamotrigine, citalopram, bupropion)
SJS	8	Not reported	Receiving VPA, lamotrigine initiated at twice the adult starting dose
Suicide	50	Male	No information available regarding method of suicide, taking concomitant meds
Acute hepatic failure	72	Male	~5 weeks after initiating lamotrigine, developed increase in AST/ALT, pleural effusion and left lung atelectasis (lung CA suspected not confirmed).
Fulminant hepatitis	33	Female	~6 weeks after initiating lamotrigine, developed purpura and thrombocytopenia. Medications stopped, but symptoms progressed (high fever, icterus). Concurrent meds: lithium, VPA.

A review of the serious adverse events did not reveal any adverse events not already included in labeling or in prior safety updates. The most common system for SAE reports was skin and subcutaneous tissue disorders. Of the 17 cases reported for this system, 13 were specified by the reporter as Stevens-Johnson syndrome. Of note, one case of "convulsions NOS" was described in a 74 year-old female patient without a prior history of seizure disorder who was receiving lamotrigine for bipolar disorder. Six days after abrupt discontinuation of lamotrigine, the patient experienced a seizure which was treated with phenytoin. At the time of the seizure, the patient was receiving clarithromycin, clindamycin, and levofloxacin; levofloxacin has been reported to cause seizures. The outcome of this case is unknown.

No reports of pregnancy were received during the reporting period.

#### Worldwide Literature Update

A case report describing fatal progressive hepatic necrosis was published during this reporting period (Overstreet K, Costanza C, Behling C, Hassanin T, Masliah E. Fatal progressive hepatic necrosis associated with lamotrigine treatment: a case report and literature review. Digestive Diseases and Sciences 2002;47:1921-1925). This 35 year-old female was taking other

concomitant medications (acetaminophen, chloral hydrate, olanzapine, topiramate, trazodone and risperidone). Approximately one month after initiating lamotrigine, the patient developed fever, chills, nausea, vomiting and chronic pelvic pain and was hospitalized. On hospital day 1 she developed a diffuse macular and papular rash and increases in ALT and AST. Her course worsened with development of coagulopathies and grade 4 hepatic encephalopathy. Liver biopsy showed hepatocyte necrosis, bile duct proliferation, focal cholestasis, and lymphocytic infiltration throughout the parenchyma.

This case appears similar to hypersensitivity reactions that have been described for lamotrigine (and other antiepileptic drugs). Current labeling includes information about these reactions in the Warnings section.

No pregnancies were reported from literature sources for the reporting period.

### 3. Regulatory Status Update

As of 3/21/03, lamotrigine was approved for use in the treatment of bipolar disorder in 12 countries worldwide with actions pending in an additional ~~\_\_\_\_\_~~ countries. The approved indication wording for most of the countries for which lamotrigine was approved for bipolar disorder is "indicated for the prevention of mood episodes in patients with bipolar disorder, predominantly by preventing depressive episodes". Approved labeling for these countries was submitted to the Division on 3/21/03, 3/27/03 and 5/16/03.

The Sponsor was asked whether lamotrigine has been withdrawn from any foreign market for any safety reasons. The Sponsor replied that the \_\_\_\_\_

### 4. Proposed Labeling

The following summarizes the modified proposed labeling submitted on April 21, 2003 in the complete response to the action letter.

#### Serious Rash Rates

Per a recommendation from the Division, the Sponsor has provided rates of serious rash in the mood disorders program with lamotrigine monotherapy and with lamotrigine as adjunctive therapy. These data appear in the following sections of labeling: black box warning, warnings, and adverse reactions. In the black box warning, proposed labeling states "In clinical trials of bipolar and other mood disorders, the rate of serious rash was 0.08% (0.8 per 1,000) in patients receiving Lamictal as initial monotherapy and 0.13% (1.3 per 1,000) in patients receiving Lamictal as adjunctive therapy". Upon further query, the Sponsor provided a clarification of the denominators used in these rate calculations (the denominator had changed since the initial proposed labeling due to completion of study SCA40910):

	Numerator (# serious rash)	Denominator	Rash Rate
All Bipolar Disorder Studies	3	—	0.12%
All Mood Disorder Studies	3	—	0.11%
Initial Monotherapy	1	—	0.08%
Adjunctive Therapy	2	—	0.13%

Recommend acceptance of proposed labeling for serious rash rates.

#### Indications and Usage - Bipolar Disorder

The Division had modified labeling to qualify the types of subjects for whom lamotrigine therapy would be indicated. Specifically, "Lamictal is indicated for the maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients \_\_\_\_\_"

\_\_\_\_\_ The Sponsor proposed to strike the qualifying term \_\_\_\_\_ and move the following sentence from the end of this labeling section to follow the indication "The effectiveness of Lamictal in the acute treatment of mood episodes has not been established". The Sponsor's argument regarding striking the qualifying terminology is that this language "may be misinterpreted by clinicians to mean that Lamictal should only be initiated in patients who are already stable".

The pivotal trials did include a preliminary phase in which lamotrigine was initiated in subjects who were symptomatic, only those subjects reaching certain criteria (one of which was a CGI definition of stability) were continued in the randomized phase. It was the intent of the Division to include language that would discourage clinicians from initiating lamotrigine to treat an acute episode since the effectiveness of lamotrigine in acute treatment has not been established.

Recommend changing to "Lamictal is indicated for the maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients \_\_\_\_\_ *treated for acute mood episodes with standard therapy.*" It is important to emphasize that lamotrigine should not be initiated for the acute treatment of a mood episode.

This language also appears in the Dosage and Administration section.

#### Warnings

##### Serious Rash – Adult Population

The Division had suggested changing from 1 case \_\_\_\_\_ of SJS-like rash. However, since these cases reflect cases that did not lead to hospitalization : \_\_\_\_\_ the original labeling language of 1 case can remain.

Recommend: Accept Sponsor's change.

#### Withdrawal Seizures

Proposed labeling: "As with other AEDs, Lamictal should not be abruptly discontinued. In patients with epilepsy there is a possibility of increasing seizure frequency. In clinical trials in patients with bipolar disorder, 2 patients experienced seizures shortly after abrupt \_\_\_\_\_ of Lamictal. However, there were confounding factors that \_\_\_\_\_ have contributed to the occurrence of seizures in these bipolar patients."

Recommend: Accept Sponsor's change. Since these cases did involve patients taking other concomitant medications and who had other comorbidities (serious rash in one), confounding factors were present.

Adverse Reactions

Bipolar Disorder

The Sponsor had originally included data on adverse events occurring during the open-label preliminary phase of the pivotal trials, a phase in which subjects are either already on other concomitant medications or in which concomitant medications could be initiated. The Division originally suggested deleting this information due to the difficulty in interpretation given the study design. However, the Sponsor has requested that this information remain in labeling largely because some adverse events (esp. rash) have higher incidences when lamotrigine is initiated and that if rashes are reported for only the randomized phase of the trials, this may underestimate the true risk of rash. "All rash" occurred in 11% of subjects in the preliminary phases compared to 7% (corrected in 6/5/03 correspondence) of subjects in the randomized phases. In the 6/5/03 correspondence, the Sponsor indicated problems in their statistical program which misattributed some adverse events to the wrong phases of the trials. The Sponsor made additional modifications to the adverse event data in this section based on this reanalysis.

Recommend: Accept Sponsor's change. Although difficult to interpret, it is important to include the incidence of rash that may occur with initiation of lamotrigine, as captured in the preliminary phases. This also provides some estimate of incidence of rash for the dose titration that was followed in the preliminary phase - esp. since some of these dose titration recommendations are not already included in labeling for epilepsy (e.g. dosing of lamotrigine in subjects not taking valproate or enzyme-inducing agents).

Incidence in Controlled Clinical Studies of Lamictal for the Maintenance Treatment of Bipolar I Disorder

No Header - Section under "Urogenital"



In the original proposed labeling, the Sponsor proposed reporting \_\_\_\_\_

In the complete response to the action letter, the Sponsor has proposed the following language under this section in labeling: \_\_\_\_\_

Per the Sponsor, this statement is based on a reanalysis of the data to evaluate the numbers of subjects with clinically important changes ( \_\_\_\_\_ (see Table below).

#### Other Adverse Events

This section was modified to include adverse event data from the completed trial SCA40910. Additionally, it appears that incidence of adverse events pertaining to females and males were calculated using the denominator for the entire demographic group rather than for each gender – this was corrected.

During review of the proposed labeling, the Sponsor had proposed to remove several adverse events appearing in this section that were not addressed in the Final Safety Update with inclusion of data from SCA40910. The Sponsor clarified that these adverse events were incorporated into the epilepsy adverse event tables. The Sponsor had wanted to modify the tables to include adverse events with ~~—~~ incidence, the Division suggested that the tables include adverse events with  $\geq 2\%$  incidence.

Some additional changes were submitted in the 6/5/03 correspondence (see adverse events for preliminary phase discussion).

Recommend: Accept Sponsor's proposed changes.

**Conclusions and Recommendations**

The Sponsor has addressed all clinical issues outlined in the action letter issued on 4/4/03. The Division has made modifications to the proposed labeling submitted by the Sponsor. Once agreement is made with the Sponsor regarding these changes, an approval action could be taken.

Cara Alfaro, Pharm.D.  
Interdisciplinary Scientist/Pharmacist  
Division of Neuropharmacological Drug Products

6/6/03

cc: Laughren/Andreason/Ware/Alfaro

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

/s/

-----  
Cara Alfaro  
6/9/03 08:17:17 AM  
PHARMACIST

Thomas Laughren  
6/17/03 10:08:19 AM  
MEDICAL OFFICER

As of 6-17-03, we have reached agreement with the  
sponsor on final labeling, and I agree that  
these supplements can now be approved; see memo  
to file for more detailed comments.--TPL

CLINICAL REVIEW

NDA 20-241/S-017  
Cross reference NDA 20-764/S-011

Sponsor: GlaxoSmithKline

Drug Name: Lamictal (lamotrigine)

Proposed Indication: Long-term management of Bipolar I Disorder to delay the  
relapse/recurrence of depressive episodes

Date Submitted: 06/05/2002

User Fee Due Date: 04/05/2002

Draft Review Submitted: 01/31/2003

Final Review Completed: 03/06/2003

Reviewer: Cara Alfaro, Pharm.D.

# CLINICAL REVIEW

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## CLINICAL REVIEW

### Executive Summary Section

# Clinical Review for NDA 20-241/S017 (Cross reference NDA 20-764/S-011)

## Executive Summary

### I. Recommendations

I recommend that the Division take an approvable action on supplemental NDA 20-241/S-017 and NDA 20-764/S-011. This recommendation for an approvable action is not based on the analyses performed by the Sponsor, but rather additional analyses performed by the Division using a modified primary endpoint for pivotal trial SCAB2003 (see summary below).

With regard to this submission and the proposed labeling, the Sponsor should provide additional data (as outlined in Section VIII) to support the safety of the abrupt discontinuation of lamotrigine as well as data to support the doubling of the lamotrigine dose upon discontinuation of valproate.

### II. Summary of Clinical Findings

#### A. Brief Overview of Clinical Program

The efficacy and safety of lamotrigine in affective disorders has been evaluated in 15 completed clinical trials: 4 long-term trials in bipolar disorder (two in rapid cyclers); three acute trials in bipolar disorder, depressed phase; two acute trials in bipolar disorder, manic phase; three acute trials in major depressive disorder and three open-label continuation studies. Three additional studies were ongoing at the time of this submission. The Sponsor submitted two pivotal trials (SCAB2003 and SCAB2006) to support a claim indicating that lamotrigine was effective in the long-term management of bipolar I disorder to delay the relapse/recurrence of depressive episodes. Only one relapse trial would have been required if data were available to support the acute efficacy of lamotrigine in bipolar disorder.

#### B. Efficacy

The originally defined primary endpoint for both pivotal studies (SCAB2003 and SCAB2006) was TIME [a.k.a. TIME(Only)]. TIME was defined as 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. After review of SCAB2003 and a statistical reanalysis which excluded site #55466 (site was closed by Sponsor due to significant GCP issues), TIME(Only) was no longer statistically different from placebo.

## CLINICAL REVIEW

### Executive Summary Section

After both pivotal trials were completed, but prior to unblinding of the data, the Sponsor submitted amendments that significantly changed the primary endpoint to TIME(ABE) which included TIME(Only) and all premature discontinuations (except for adverse events not related to bipolar disorder). Using TIME(ABE) as the primary endpoint, both pivotal studies are positive. This reviewer did not accept TIME(ABE) as the primary endpoint since all premature discontinuations (which included categories such as "other", protocol violations, lost to follow-up, consent withdrawn) were considered bipolar events and were not separately evaluated with regard to their relatedness to bipolar disorder. Secondary analyses included TIDep and TIMan which were defined as TIME to a depressive or manic/hypomanic/mixed episode. In the reanalysis of SCAB2003 with exclusion of site #55466, lamotrigine no longer separates from placebo for TIDep.

The Division analyzed the data with a modified endpoint, termed TIME(BipEvent), which included TIME(Only), premature discontinuation due to adverse events related to bipolar disorder, and premature discontinuations due to "other" = inadequate efficacy and excluding site #55466. Based on this modified TIME endpoint, which this reviewer feels is acceptable and correctly identifies events that are likely due to bipolar disorder, lamotrigine is statistically significant from placebo. However, for these additional "other" events, no data is available to determine the polarity of the episode. Therefore TIDep and TIMan were not determined for TIME(BipEvent).

If the Division chooses to accept TIME(BipEvent) as the primary endpoint, it should be noted that the reanalysis excluding site #55466 did not show significant differences between lamotrigine and placebo for TIDep. Therefore the claim of efficacy in the long-term management of bipolar I disorder to delay the relapse/recurrence of depressive episodes is not supported. TIME(BipEvent) could support a delay in the relapse/recurrence of mood episodes.

The acute efficacy of lamotrigine in mood disorders has been evaluated in 8 trials. Three trials were conducted in bipolar disorder, depressed phase; all three were failed trials. Two trials were conducted in bipolar disorder, manic phase; one trial failed and one was negative. Three trials were conducted in major depressive disorder, all three were failed trials. Granting an indication of long-term management of bipolar I disorder to delay the relapse/recurrence of mood episodes without evidence for acute efficacy is an unusual circumstance in psychiatry. Proposed labeling, and the study design of the pivotal trials, would suggest

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Though this reviewer cannot think of similar situations in psychiatry, this general approach has been used with valproate, a medication that is not indicated for the acute treatment of migraines but is indicated for the prophylaxis of migraine headaches.

## CLINICAL REVIEW

### Executive Summary Section

#### C. Safety

The integrated summary of safety included all safety data from the 15 completed clinical trials and the 3 ongoing trials comprising 2642 lamotrigine-exposed subjects (2272 subjects in bipolar trials). Lamotrigine was approved in the United States in December 1994 as adjunctive therapy in adults with partial seizures. The clinical trials did not reveal uncommon, unexpected or unreported adverse events likely to be drug-related. Of the 2272 lamotrigine exposures in the bipolar studies, 3 cases of serious rash were reported that occurred during open-label treatment. Ten deaths occurred in the clinical trials (9 – lamotrigine, 1 – placebo). Most deaths were due to suicide, a recognized risk factor in patients with bipolar disorder. When evaluating rates of suicide and suicide attempts per year of exposure, the rates between lamotrigine and placebo were similar.

#### D. Dosing

The Sponsor indicates a target dose of 200 mg/day for bipolar disorder, with a range from 100 – 400 mg/day (maximum of 200 mg/day with concomitant valproate). This maximum dose, 400 mg/day, is the maximum approved dose for epilepsy indications [maximum dose with valproate = 200 mg/day, with carbamazepine or other enzyme-inducing antiepileptics (EIAEDs) = 500 mg/day]. Similar to dosing information for epilepsy indications, the Sponsor includes a table for the dosing of lamotrigine in the presence of valproate and other enzyme-inducing drugs. The Sponsor also includes a table for adjusting the dose of lamotrigine upon discontinuation of valproate or enzyme-inducing drugs. Current labeling includes lamotrigine dosing information for conversion from a single EIAED to monotherapy with lamotrigine and states that the concomitant EIAED was withdrawn by 20% decrements each week over a 4-week clinical trial in epilepsy patients. For bipolar disorder, proposed dosing guidelines are included for patients not taking valproate or enzyme-inducing drugs. Current labeling does not provide dosing information for initiating lamotrigine in the absence of either valproate or EIAEDs.

Proposed labeling states that the lamotrigine dose should be doubled during the first week that valproate is discontinued (see Section VIII). The Sponsor should provide additional data to support the safety of this proposed dosing strategy with regard to the drug interaction between lamotrigine and valproate and the potential increased risk of rash. Though a similar dosing strategy was incorporated into the two pivotal trials, it is unclear how many patients this involved and whether this dosing guideline was followed.

**Clinical Review****I. Introduction and Background****A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups**

Lamictal® (lamotrigine) is an antiepileptic drug of the phenyltriazine class. As of labeling approved 1/17/03, lamotrigine tablets and chewable dispersible tablets are indicated for adjunctive therapy in partial seizures in adults and pediatric patients ( $\geq 2$  years of age), adjunctive therapy for the generalized seizures of Lennox-Gastaut syndrome in adults and pediatric patients ( $\geq 2$  years of age), and for conversion to monotherapy in adults with partial seizures who are receiving treatment with a single enzyme-inducing antiepileptic drug.

The Sponsor indicates a target dose of 200 mg/day for bipolar disorder, with a range from 100 – 400 mg/day (maximum of 200 mg/day with concomitant valproate). This maximum dose, 400 mg/day, is the maximum approved dose for epilepsy indications [maximum dose with valproate = 200 mg/day, with carbamazepine or other enzyme-inducing antiepileptics (EIAEDs)= 500 mg/day]. Similar to dosing information for epilepsy indications, the Sponsor includes a table for the dosing of lamotrigine in the presence of valproate and other enzyme-inducing drugs. The Sponsor also includes a table for adjusting the dose of lamotrigine upon discontinuation of valproate or enzyme-inducing drugs. Current labeling includes lamotrigine dosing information for conversion from a single EIAED to monotherapy with lamotrigine and states that the concomitant EIAED was withdrawn by 20% decrements each week over a 4-week clinical trial in epilepsy patients. For bipolar disorder, proposed dosing guidelines are included for patients not taking valproate or enzyme-inducing drugs. Current labeling does not provide dosing information for initiating lamotrigine in the absence of either valproate or EIAEDs.

Proposed labeling states that the lamotrigine dose should be doubled during the first week that valproate is discontinued (see Section VIII). The Sponsor should provide additional data to support the safety of this proposed dosing strategy with regard to the drug interaction between lamotrigine and valproate and the potential increased risk of rash (this has been requested from the Sponsor). Though a similar dosing strategy was incorporated into the two pivotal trials, it is unclear how many patients this involved and whether this dosing guideline was followed.

Lamotrigine is not currently approved for use in either the acute or long-term management of mood disorders in the U.S. The Sponsor proposes new labeling that describes lamotrigine as being effective in the long-term management of bipolar I disorder to delay the relapse/recurrence of depressive episodes for up to 18 months.

## CLINICAL REVIEW

### B. State of Armamentarium for Indication(s)

Lithium is the only agent currently indicated for maintenance treatment in bipolar disorder. No drugs are currently approved for long-term management of bipolar disorder to delay the relapse/recurrence of depressive episodes.

Lithium, divalproex sodium and olanzapine are indicated for the short-term treatment of the manic episodes associated with bipolar disorder. No drugs are currently approved for the acute treatment of bipolar depression.

### C. Important Milestones in Product Development

Lamotrigine was approved in the United States in December 1994 as adjunctive therapy in adults with partial seizures. Additional indications include adjunctive therapy in generalized seizures of the Lennox-Gastault syndrome in children and adults (August 1998) and conversion to monotherapy in adults with partial seizures receiving therapy with a single enzyme-inducing antiepileptic drug (December 1998). An indication for use as adjunctive treatment in pediatric patients ( $\geq 2$  years of age) with partial seizures was approved in January 2003.

The development program for lamotrigine in bipolar disorder was designed in 1996 to obtain indications for both acute and long-term treatment of mania and depression. The Sponsor had several meetings with the Division in regard to this development program (September 1996, April 1998 [end of Phase II], February 2002 [pre-sNDA]) in addition to teleconferences and general correspondences. During the September 1996 and April 1998 meetings, the Division expressed concern regarding the pseudospecificity of an indication for bipolar depression and encouraged the Sponsor to add studies evaluating lamotrigine in patients with unipolar depression. A March 2001 correspondence shared with the Sponsor changes in Division policy such that broad claims for "depression" are no longer being granted and that claims will focus on the specific subtypes of depression studied. The Division communicated that issues regarding pseudospecificity are no longer a concern since the Division considers bipolar depression and major depressive disorder to be clinically distinct entities. In the September 1996 meeting, the Division expressed concern about the proportion of patients that would reach endpoint with the proposed 12 month duration of the study. The Division suggested an interim look at the placebo patients, if the proportion reaching endpoint was low, patients could be followed longer than 12 months.

In a November 2001 teleconference, the Sponsor discussed their intention to submit a supplemental NDA for the long-term treatment of bipolar disorder without data to establish efficacy in the acute treatment of the disorder. The Division stated that they have consistently requested acute data for this type of indication in the past but that this sNDA would be considered fileable. At that time, it was the opinion of the Division that it would seek advice from the Psychopharmacological Drugs Advisory Committee (PDAC) before a final action could be taken.

In the February 2002 meeting the Sponsor discussed their intention to submit the sNDA for the claim "to delay depressive episodes in patients with bipolar I disorder". The

## CLINICAL REVIEW

Division commented that since the protocol specified primary endpoints were time to mood episode (either depression or mania), the claim to delay depressive episodes will have to be addressed in the review. At the time the sNDA was submitted, the Sponsor requested a priority review for this application. After preliminary review of the application, the Division denied priority review status since lithium is currently available for maintenance treatment of bipolar disorder. In November 2002, the Division communicated to the Sponsor that the Division will not seek advice from PDAC regarding the proposed indication.

### II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

There are no chemistry or animal pharmacology/toxicology issues in this submission. Some *in vitro* and *in vivo* drug interaction studies were included in this submission and are being reviewed by the biopharmaceutics reviewer.

### III. Human Pharmacokinetics and Pharmacodynamics

A number of drug interactions have been identified such that dosing in current labeling is outlined for scenarios where lamotrigine is added to enzyme-inducing antiepileptic drugs (phenytoin, carbamazepine, phenobarbital, etc.) or to regimens containing valproate (an inhibitor of lamotrigine metabolism).

Included in this sNDA are two clinical pharmacokinetic studies evaluating drug interactions between lamotrigine and bupropion (SCAA1001) and lamotrigine and lithium (SCAB1001) and two new *in vitro* drug interaction studies. Biopharmaceutics will review these studies in detail.

#### SCAA1001

A randomized, crossover study to evaluate the pharmacokinetic effect of multiple doses of bupropion hydrochloride (Wellbutrin SR) [150 mg BID x 14 days] on a single 100 mg oral dose of lamotrigine.

Bupropion did not affect the pharmacokinetics of lamotrigine or its metabolite, lamotrigine glucuronide. Bupropion samples were obtained but only to assess compliance.

#### SCAB1001

A study to investigate the effect of multiple oral doses of lamotrigine (100 mg x 6 days) affect the pharmacokinetics of multiple oral doses of lithium in a cross-over study in healthy volunteers. Lithium was administered as lithium gluconate 2 grams BID (approximately 300 mg BID lithium carbonate) x 6 days with and without lamotrigine.

Lamotrigine did not affect the pharmacokinetics of lithium gluconate.

*In vitro* inhibition experiments evaluating the effects of several psychotropic drugs (clozapine, phenelzine, risperidone, sertraline, trazodone, amitriptyline, bupropion, clonazepam, fluoxetine, haloperidol, and lorazepam) on formation of the primary metabolite of lamotrigine, 2-N glucuronide, were performed. Per a statement in the Summary document, "the production of the N2-glucuronide of lamotrigine was significantly reduced in the presence of amitriptyline,

## CLINICAL REVIEW

bupropion, clonazepam, haloperidol or lorazepam (at therapeutic concentrations). None of these compounds inhibited glucuronidation to a greater extent than sodium valproate”.

*In vitro* experiments also evaluated the inhibitory effect of lamotrigine on CYP2D6 (bufuralol metabolism). No significant inhibition was seen at \_\_\_\_\_ and weak inhibition at \_\_\_\_\_

### Lamotrigine dose/concentration versus response

Pharmacokinetic samples were collected in studies 105-601, SCAB2005, SCAA2008, SCAB2009, SCAA2011, SCAA2012, and SCA30901. Samples from the two pivotal trials, SCAB2003 and SCAB2006, were collected but not analyzed since half of the samples were 3 to 4 years old and stability data were not available on samples > 2 years old and “there is a good possibility that many of the samples would have lyophilized resulting in bioanalytically highly suspect results”. The decision not to analyze these samples was also made with the knowledge that studies SCAB2005 and SCAA2012 did not demonstrate any correlation between dose and/or concentration and response. SCAB2005 and SCAA2012 are flexible-dose studies in the long-term treatment of rapid cycling bipolar disorder. Very little is included in the study reports regarding dose/concentration versus response analyses for these two studies. Both of these trials failed to separate from placebo on their primary efficacy measure.

Very few of the clinical trials included in this sNDA incorporated a fixed-dose design to investigate dose/response relationships. SCAB2001 included two fixed doses, lamotrigine 50 mg and 200 mg, in the acute treatment of bipolar disorder, depressed phase. Neither lamotrigine group separated from placebo on the primary endpoint, both doses separated from placebo on some of the secondary endpoints. Lamotrigine doses (50 mg vs. 200 mg) were not significantly different on any of the efficacy measures. SCAB2003, one of the pivotal trials, incorporated three fixed doses (50, 200, and 400 mg) in the long-term treatment of bipolar disorder. Unfortunately the 50 and 400 mg groups were discontinued (Amendment 12) during the trial and only half the intended enrollment had been achieved in these two groups. Since Amendment 12 also significantly changed the inclusion criteria, the Sponsor evaluated the data for subjects enrolled prior to this amendment. Two hundred seventy-nine subjects were enrolled prior to this amendment: placebo (n = 60), lithium (n = 63), lamotrigine 50 mg (n = 50), lamotrigine 200 mg (n = 61), and lamotrigine 400 mg (n = 45). While the Sponsor did not perform a dose-response analysis, the Sponsor did note that “the data do not appear to indicate a linear dose-response relationship for lamotrigine...the 50 mg and 400 mg lamotrigine doses were less efficacious than the 200 mg dose of lamotrigine on most efficacy measures analyzed”.

Correlations between concentration and primary endpoint were included in study reports for three trials:

SCAB2008, SCAB2009— no clear relationship observed between the change from baseline in MRS-11 and serum lamotrigine concentration. See Figures 1-A and 2-A in Appendix A.

SCAA2011 — no clear relationship between HAM-D<sub>17</sub> mean score change from baseline and lamotrigine concentration. See Figure 3-A in the Appendix A.

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### IV. Description of Clinical Data and Sources

#### A. Overall Data

The efficacy and safety of lamotrigine in affective disorders has been evaluated in 15 completed clinical trials: 4 long-term trials in bipolar disorder (two in rapid cyclers); three acute trials in bipolar disorder, depressed phase; two acute trials in bipolar disorder, manic phase; three acute trials in major depressive disorder and three open-label continuation studies. Three additional studies were ongoing at the time of this submission. A brief summary of the results from the acute studies is in Appendix B.

#### B. Tables Listing the Clinical Trials Trials included in the ISS

##### *Long-term studies in Bipolar Disorder*

Trial	Design	Treatment, Dose, and Number of Subjects	Duration
SCAB2003 (pivotal) Long-term prevention relapse/recurrence of mood episodes Monotherapy	Preliminary Phase: Open-label	Lamotrigine 100 – 200 mg/day: 958	8 to 16 weeks
	Randomized Phase: DB, PC, fixed dose	Lamotrigine 50 mg: 50 Lamotrigine 200 mg: 122 Lamotrigine 400 mg: 47 Lithium 0.8 – 1.1 mEq/L: 120 Placebo: 121	76 weeks
SCAB2006 (pivotal) Long-term prevention relapse/recurrence of mood episodes Monotherapy	Preliminary Phase: Open-label	Lamotrigine 100 – 200 mg/day: 347	8 to 16 weeks
	Randomized Phase: DB, PC, flexible dose	Lamotrigine 100 – 400 mg/day: 58 Lithium 0.8 – 1.1 mEq/L: 46 Placebo: 69	76 weeks
SCAA2012 Long-term prevention of mood episodes in rapid-cyclers Monotherapy	Preliminary Phase: Open-label	Lamotrigine 100 – 300 mg/day: 324	12 weeks
	Randomized Phase: DB, PC, flexible dose	Lamotrigine 100 – 500 mg/day: 92 Placebo: 88	26 weeks
SCAB2005 Long-term prevention of mood episodes in rapid cyclers Adjunctive therapy	Randomized, DB, PC, add-on, flexible dose	Lamotrigine up to 500 mg/day: 68 Placebo: 69	32 weeks

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### *Acute Studies in Bipolar Disorder, Depressed Episode*

Trial	Design	Treatment, Dose, and Number of Subjects	Duration
SCAB2001 Acute study Monotherapy	Randomized, DB, PC, fixed dose	Lamotrigine 50 mg/day: 66 Lamotrigine 200 mg/day: 63 Placebo: 66	7 weeks
SCAA2010 Acute study Monotherapy	Randomized, DB, PC, flexible dose	Lamotrigine 100 – 400 mg/day: 103 Placebo: 103	10 weeks
SCA40910 Acute study Monotherapy	Randomized, DB, PC, fixed dose	Lamotrigine 200 mg/day: 133 Placebo: 124	8 weeks

### *Acute Studies in Major Depressive Disorder (Unipolar Depression)*

Trial	Design	Treatment, Dose, and Number of Subjects	Duration
SCAA2011 Acute study Monotherapy	Randomized, DB, PC, fixed dose	Lamotrigine 200 mg/day: 152 Desipramine 200 mg/day: 151 Placebo: 150	8 weeks
SCA20022 Acute study Monotherapy	Randomized, DB, PC, fixed dose	Lamotrigine 200 mg/day: 75 Placebo: 77	7 weeks
SCA20025 Acute study Monotherapy	Randomized, DB, PC, fixed dose	Lamotrigine 200 mg/day: 151 Placebo: 150	7 weeks

### *Acute Studies in Bipolar Disorder, Manic Episode*

Trial	Design	Treatment, Dose, and Number of Subjects	Duration
SCAA2008 Acute study Monotherapy	Randomized, DB, PC, fixed dose	Lamotrigine 50 mg/day: 85 Lithium 0.8 – 1.3 mEq/L: 36 Placebo: 95	3 weeks
SCAB2009 Acute study Adjunctive therapy	Randomized, DB, PC, fixed dose	Lamotrigine 200 mg/day: 74 Lithium 0.7 – 1.3 mEq/L: 78 Placebo: 77	6 weeks

### *Open-Label Extension Studies – Bipolar Disorder*

Trial	Design	Treatment, Dose, and Number of Subjects	Duration
SCAA2014 Open-label extension of SCAA2010 Adjunctive therapy	Open-label, flexible dose	Lamotrigine up to 500 mg/day: 127	52 weeks
SCAB2002 Open-label extension of SCAA2001 Adjunctive therapy	Open-label, flexible dose	Lamotrigine up to 500 mg/day: 124	52 weeks
105-601 Adjunctive therapy	Open-label, flexible dose	Lamotrigine 50 – 700 mg/day: 75	48 weeks

## CLINICAL REVIEW

Included in the submission are spontaneous post-marketing serious adverse events from The GlaxoSmithKline Worldwide Safety Database received between January 1, 2000 and on or before October 31, 2001 where the indication for the use of lamotrigine was affective disorder. The 120-day safety update submitted on October 4, 2002 included spontaneous post-marketing serious adverse events received from November 1, 2001 through March 31, 2002

### D. Literature Review

The Sponsor provided a literature review covering the period up to October 31, 2001 that summarizes the clinical data on the efficacy and safety of lamotrigine in bipolar disorder. Approximately 32 articles were identified to support the efficacy of lamotrigine in bipolar disorder, at least 8 of these articles were publications of data from the clinical trials included in this submission (105-601, SCAB2001, SCAB2002, SCAA2012 and SCAA2014). The majority of the other articles were open-label studies, case reports and case series publications. Two double-blind, active-control (lithium, olanzapine) studies evaluated lamotrigine in acute mania (n = 30 lamotrigine subjects) with similar results between treatments. One placebo-controlled crossover trial was conducted in refractory bipolar and unipolar subjects (n = 31) - one case of toxic epidermal necrolysis was reported in this trial.

### F. Foreign Regulatory Action

Per a safety update submitted February 26, 2003, the Sponsor has submitted applications for lamotrigine in the treatment of bipolar disorder in —foreign countries (see Table 4-A in Appendix A). These applications were submitted between August 21, 2002 and October 29, 2002. Lamotrigine is currently approved for bipolar disorder in 5 of these countries: Czech Republic, Latvia, New Zealand, Panama, and Romania (see Table 4-A in Appendix A). The table provided by the Sponsor indicates which countries have approved lamotrigine for bipolar disorder, but does not state what the specific indications are — acute efficacy, relapse/prevention, bipolar depression, bipolar mania, etc. The Sponsor has been contacted to provide this information to the Division.

## V. Clinical Review Methods

### A. How the Review was Conducted

This submission contained study reports for 18 efficacy studies (15 completed and 3 ongoing) including the two pivotal efficacy trials. An integrated efficacy summary and integrated safety summary were available for review. The efficacy review focused on the two pivotal trials, SCAB2003 and SCAB2006. Clinical studies evaluating the acute efficacy of lamotrigine in bipolar mania, bipolar depression and unipolar depression were also reviewed as the indication for long-term prevention of relapse/recurrence of mood episodes in bipolar disorder in the absence of acute efficacy is a novel claim for currently approved medications used to treat bipolar disorder. Since there is no data to support acute efficacy of lamotrigine in bipolar disorder, the Division required two positive clinical trials to support an indication for long-term prevention of relapse/recurrence of mood episodes in bipolar disorder. .

## CLINICAL REVIEW

### **B. Overview of Materials Consulted in Review**

Supplement 017 to NDA 20-241 and Supplement 011 to NDA 20-764 were electronic submissions. Correspondences and meeting minutes for teleconferences and face-to-face meetings filed under IND 49,916 were consulted to review regulatory issues and decisions made with respect to this supplement.

### **C. Overview of Methods Used to Evaluate Data Quality and Integrity**

Raw data were submitted to the Division of Biometrics via SAS transport files and analyzed according to the methods described in the Sponsor's protocol. The submission was also examined for internal consistency. DSI was consulted to inspect three domestic sites that recruited subjects for SCAB2003 and/or SCAB2006.

### **D. Were Trials Conducted in Accordance with Accepted Ethical Standards**

The trials were performed in accordance with the declaration of Helsinki and its subsequent revisions and the FDA Guideline 21 CFR Parts 50, 56, and 312.

### **E. Evaluation of Financial Disclosure**

A financial disclosure and certification statement was included. This certified that GlaxoSmithKline had not entered into any financial agreement with the clinical investigators whereby the value of the compensation would be effected by the outcome of the study. As outlined and agreed to during the February 2002 pre-sNDA meeting, the following studies met the definition of covered studies for the purposes of financial disclosure as outlined in 21 CFR Part 54: SCAB2003, SCAB2006, SCAA2012, SCAB2005, SCAB2001 and SCAA2010.

## **VI. Integrated Review of Efficacy**

### **A. Brief Statement of Conclusions**

In filing this supplemental NDA, the Sponsor sought a claim indicating that lamotrigine was effective in the long-term management of bipolar I disorder to delay the relapse/recurrence of depressive episodes. Efficacy data from two pivotal trials was included in this submission to support this indication.

The originally defined primary endpoint for both pivotal studies (SCAB2003 and SCAB2006) was TIME [a.k.a. TIME(Only)]. TIME was defined as 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. After

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review of SCAB2003 and a statistical reanalysis which excluded site #55466 (site was closed by Sponsor due to significant GCP issues), TIME(Only) was no longer statistically different from placebo.

After both pivotal trials were completed, but prior to unblinding of the data, the Sponsor submitted amendments that significantly changed the primary endpoint to TIME(ABE) which included TIME(Only) and all premature discontinuations (except for adverse events not related to bipolar disorder). Using TIME(ABE) as the primary endpoint, both pivotal studies are positive. This reviewer did not accept TIME(ABE) as the primary endpoint since all premature discontinuations (which included categories such as "other", protocol violations, lost to follow-up, consent withdrawn) were considered bipolar events and were not separately evaluated with regard to their relatedness to bipolar disorder. Secondary analyses included TIDep and TIMan which were defined as TIME to a depressive or manic/hypomanic/mixed episode. In the reanalysis of SCAB2003 with exclusion of site #55466, lamotrigine no longer separates from placebo for TIDep.

The Division analyzed the data with a modified endpoint, termed TIME(BipEvent), which included TIME(Only), premature discontinuation due to adverse events related to bipolar disorder, and premature discontinuations due to "other" = inadequate efficacy and excluding site #55466. Based on this modified TIME endpoint, which this reviewer feels is acceptable and correctly identifies events that are likely due to bipolar disorder, lamotrigine is statistically significant from placebo. However, for these additional "other" events, no data is available to determine the polarity of the episode. Therefore TIDep and TIMan were not determined for TIME(BipEvent).

If the Division chooses to accept TIME(BipEvent) as the primary endpoint, it should be noted that the reanalysis excluding site #55466 did not show significant differences between lamotrigine and placebo for TIDep. Therefore the claim of efficacy in the long-term management of bipolar I disorder to delay the relapse/recurrence of depressive episodes is not supported. TIME(BipEvent) could support a delay in the relapse/recurrence of mood episodes.

### **B. General Approach to Review of the Efficacy of the Drug**

This submission contained study reports for 18 efficacy studies (15 completed and 3 ongoing) including the two pivotal efficacy trials. An integrated efficacy summary was available for review. The efficacy review focused on the two pivotal trials, SCAB2003 and SCAB2006. Since the acute efficacy of lamotrigine has not been established in bipolar disorder, the Division required two pivotal trials for the proposed claim.

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### C. Detailed Review of Trials by Indication

Two pivotal trials (SCAB2003 and SCAB2006) were submitted to support the proposed indication "long-term management of Bipolar I Disorder to delay the relapse/recurrence of depressive episodes". Each trial is reviewed separately. These two pivotal trials differed primarily in the current bipolar episode (SCAB2003 = depressed phase, SCAB2006 = manic phase) and dosing of lamotrigine (SCAB2003 = fixed doses, SCAB2006 = flexible dosing).

**SCAB2003: A multicenter, double-blind, placebo-controlled, randomized, fixed-dose evaluation of 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.**

SCAB2003 was initiated on July 12, 1997 and completed on August 8, 2001 with the final study report completed on March 20, 2002. The original protocol was submitted to the Division on April 25, 1997, this protocol contained amendments 1 – 7. Six additional amendments to the protocol were submitted between May 1997 and August 2001, the last amendment was submitted after the study completion date. The last amendment, which changed the definition of the primary efficacy measure, has an "authorization date" of 8/28/01 but was submitted to the Division per correspondence dated 9/27/01. The database was authorized for release on October 26, 2001.

#### C-1 Investigators and Sites

A list of investigators and sites may be found in Table C-1-A in Appendix A. A total of 38 U.S and 41 non U.S. centers recruited subjects in this multicenter study.

#### C-2 Objectives

Per original protocol:

The primary objective was to compare the safety and efficacy of lamotrigine with therapeutic levels of lithium and placebo in preventing the relapse and recurrence of depressive or manic episodes over a long period in subjects with bipolar I disorder who have experienced a recent major depressive episode which has responded to lamotrigine treatment as monotherapy or in combination with other psychotropic medication. A "long period" was defined as 52 weeks in the original protocol and was later lengthened to 76 weeks by amendment. See Table C-2-A in Appendix A for significant protocol amendments.

#### C-3 Study Population

As originally submitted, this protocol included outpatient men and women  $\geq 18$  years of age with bipolar I disorder, with their most recent episode depressed as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).

Subjects had to be currently experiencing a major depressive episode and have had at least one additional major depressive episode and one manic or mixed episode within 3 years of enrollment. The protocol was amended in February 1998 (Amendment #10) to permit enrollment of subjects with  $\leq 6$  bipolar disorder episodes within 12 months of enrollment, thereby including rapid cyclers (definition per DSM-IV =  $\geq 4$  episodes of a

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mood disturbance in the previous 12 months). The protocol was amended in January 1999 (Amendment #12) to allow enrollment of patients who were not currently depressed but had a well-documented major depressive episode within 60 days of enrollment and some current depressive symptoms *or* were being treated for depressive symptoms with a recognized, effective regimen. Severity criteria (HAM-D<sub>17</sub>  $\geq$  18) was necessary for subjects with current depressive symptoms but not for subjects who were currently being treated for a depressive episode.

### C-4 Design

This was an enriched study design with a "preliminary phase" and a randomized phase. The preliminary phase included weekly visits for 8 to 16 weeks and consisted of open-label lamotrigine in addition to any other psychotropic agent considered to be necessary for the treatment of the depressive episode. The January 1999 amendment (Amendment #12) allowed treatment of mania, hypomania or mixed states occurring during this phase. Medications that were not allowed included fluoxetine, initiation of lithium, depot psychotropics, and drugs with a  $t_{1/2} > 14$  days. The target dose for lamotrigine was 200 mg/day (100 mg/day if receiving valproate, 400 mg/day if receiving inducing agents such as carbamazepine). The lamotrigine dosing schedule (see Table C-4.1-A in Appendix A.1) is consistent with product labeling though the titration schedule with concomitant valproate is slower than current labeling. The target dose for lamotrigine could be reached as early as week 6 or 7.

Patients meeting the following criteria could be enrolled in the randomized phase of the protocol (see Table C-2-A in Appendix A for inclusion/exclusion criteria):

1. Met criteria for response defined as CGI-S  $\leq$  3 for 4 consecutive weeks prior to randomization.
2. Withdrawn from all concomitant psychotropic medications for 1 to 2 weeks (depending on medication) prior to randomization  
Antipsychotics, antidepressants (except MAOIs), lithium, benzodiazepines (except those allowable) = 1 week washout; anticonvulsants and MAOIs = 2 week washout. Dose of lamotrigine was adjusted after discontinuation of valproate or carbamazepine (see Table C-4.2-A in Appendix A.1)
3. Receiving a minimum of 100 mg/day of lamotrigine during the last two weeks of the preliminary phase
4. No change in lamotrigine dose during the last week of the preliminary phase

During the 1 to 2 week concomitant psychotropic medication washout and during the randomized phase of the protocol, the "short-term" use of chloral hydrate ( $\leq$  2 g/day), lorazepam ( $\leq$  4 mg/day), temazepam ( $\leq$  30 mg/day) or oxazepam ( $\leq$  90 mg/day) was permitted as needed for control of agitation, irritability, restlessness, insomnia and hostile behavior.

Subjects were randomized to placebo, lithium (0.8 – 1.1 mEq/L), lamotrigine 50 mg, lamotrigine 200 mg or lamotrigine 400 mg. Dose escalation for the lamotrigine groups is in Table C-4.3-A in Appendix A.1. Randomization was stratified based on adequate

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lithium treatment ( $\geq 0.4$  mEq/L or 600 mg/day for one month) within 5 months. Study visits were weekly x 4 weeks, every 2 weeks for two visits then monthly thereafter.

The randomized phase was 52 weeks with the option to extend to 76 weeks if insufficient primary outcome events had occurred, this option was exercised in Amendment 12 (January 1999).

Amendment 12 (January 1999), in addition to changing the study population who could be enrolled in the study, also changed the study design. This amendment discontinued enrollment in the 50 and 400 mg lamotrigine groups ostensibly to allow for full enrollment into the remaining treatment arms. Subjects who were already randomized to the 50 and 400 mg groups continued to protocol completion.

When a subject reached the study endpoint (by definition = prescribing psychotropic medication for a mood event), the subject was permitted to remain in the study. Subjects treated with ECT or marketed lamotrigine were not permitted to remain in the study.

### C-5 Statistical Analysis Plan

The topic of statistical analysis was discussed at many of the meetings held between the Sponsor and the Division. The focus of this summary is the analysis of the primary efficacy measure.

Original protocol document (8/12/96) – The original protocol specified that the primary analysis would be TIME [e.g. TIME(Only)], 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, manic, hypomanic or mixed episode, whichever occurs first” for the combined data from SCAB2003 (only the lamotrigine 200 and 400 mg groups) and SCAB2006.

Amendment #4 (11/15/96) – Still retained comments of a combined analysis with a primary analyses of the combined data lamotrigine 200 mg + lamotrigine 400 mg (from SCAB2003) + lamotrigine-flex dose (from SCAB2006) vs. placebo with respect to TIDep and TIMan

The primary analysis in SCAB2003 will be a pairwise comparison of TIME testing lamotrigine 200 mg + lamotrigine 400 mg vs. placebo ( $\alpha = 0.05$ ) using the Log Rank Test.

Also included option to extend follow-up an additional 6 months (total = 76 weeks) if not enough events had occurred in the placebo group per review at regular intervals by an independent statistician from outside the Sponsor organization.

Amendment #12 (1/6/99) – Eliminated the lamotrigine 50 mg and 400 mg treatment arms of the study. Data remained blinded and no interim analyses were performed. This amendment also significantly changed inclusion criteria.

An issue raised by the Division was that the subjects enrolled after Amendment 12 may be a less severely ill cohort and therefore continued enrollment could potentially “enrich” the lamotrigine 200 mg. However, since Amendment 12 applied to the lamotrigine 200

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mg, lithium and placebo groups, the primary comparison between lamotrigine 200 mg + 400 mg versus placebo would include similar populations.

Amendment #13 (8/28/01) – Submitted after completion of protocol and, per Sponsor, finalized prior to unblinding of the database. Eliminated the analysis of the combined SCAB2003 and SCAB2006 data as the primary analysis. Changed the definition of the primary efficacy measure (TIME) to capture premature discontinuations (see section C-6). The primary analysis endpoint was modified to TIME(ABE), supportive analyses include TIME(SIS) and TIME(Only) [the original TIME] (see section C-6).

### C-6 Assessments

The primary efficacy measure TIME was defined as the “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.” After TIME was reached, subjects were permitted to continue on their blinded medications plus any other psychotropics for up to 76 weeks.

A data analysis appendix included in the sNDA submission clarified how the TIME endpoint was derived. Since “the date of reaching the endpoint was not specifically recorded in the CRF...the endpoint was derived based on an algorithm defined prior to the unblinding and subsequent analysis of the database”. Usually this resulted in the TIME event defined as the date of the first dose of a concomitant medication prescribed for a primary treatment intervention for a mood episode. In addition to searching the concomitant medication dataset, the database was also searched for the presence of a relapse visit. The General Assessment of Mood States dataset was also searched to determine a TIME event.

Amendment 13 (August 2001) was submitted after completion of the protocol and, per Sponsor, prior to unblinding the data. This amendment significantly changed the primary endpoint of the study. The Sponsor wished to capture premature discontinuations in addition to TIME events as these “may provide a more sensitive measure of efficacy than TIME alone”. The revised primary analysis was defined as TIME(Any Bipolar Event) [TIME(ABE)] “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”. Therefore, TIME(ABE) included subjects who reached TIME as well as those who prematurely discontinued due to protocol violation, “other”, lost to follow-up, consent withdrawn and adverse events related to bipolar disorder. As explained in a supplement to the briefing packet for the February 2002 meeting, adverse event listings for all patients withdrawing due to an adverse event were reviewed by a blinded Sponsor physician. If the adverse event was consistent with a bipolar event (e.g. mania, hypomania, depression) the patient was deemed to have withdrawn due to a bipolar adverse event. If adverse events such as insomnia or agitation were listed, HAM-D and MRS scores were reviewed to determine whether the adverse event was related to a bipolar event. Evidence of elevation in psychiatric rating scores at time of withdrawal also led to a designation of a bipolar adverse event.

In this amendment, the Sponsor also included a supportive analysis termed TIME(Survival in Study) [TIME(SIS)]. TIME(SIS) = “the premature discontinuation of

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a subject prior to reaching TIME, for any reason, was treated as an event related to bipolar disorder”.

The Sponsor also included another supportive analysis termed TIME(Only).

TIME(Only) = “all subjects who prematurely discontinued from the study for any reason before the TIME event were censored”.

Secondary efficacy variables included:

TIDep = “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”

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 manic, hypomanic, or mixed episode”

Mean change from baseline (randomized day 1) scores on the HAM-D<sub>17</sub>, HAM-D<sub>31</sub>, MRS from SADS-C, CGI-I, CGI-S, GAS  
General Assessment of Mood State (GAMS)

Additional efficacy variables included the domains of quality of life and side effect impact (Medical Outcomes Trust SF-36, Medical Outcomes Trust Cognitive Scale, AB Neurotoxicity Scale) and resource utilization (medical care/consult, number of days missing work or school, how often leisure activities missed/cancelled due to bipolar disorder).

Safety assessments are summarized in Table C-6-A in Appendix A.1. Per recommendations from the Division, a DSMB for monitoring suicide and suicide attempts was constituted for this protocol.

### C-7 Subject Disposition

A total of 966 subjects were enrolled into the preliminary phase of which 480 (50%) completed the preliminary phase of the protocol and were randomized to placebo, lithium, lamotrigine 50 mg, lamotrigine 200 mg or lamotrigine 400 mg. The disposition of subjects is listed in Tables C-7.1 and C-7.2. In the subject disposition provided by the Sponsor (see Table C-7.1-A in Appendix A.1), the subject discontinuation category of “other” comprised 20-30% of subjects. Additionally, the discontinuation category “failure to meet randomization criteria” was not a useful category since it could include a range of failures from a positive urine toxicology screen to nonresponse. The Sponsor was asked to provide a more detailed reason for these subject discontinuations which have been incorporated into Table C-7.1.

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Table C-7.1. Subject Disposition in Preliminary Phase

	Preliminary Phase
	Open-Label Lamotrigine
# Subjects Enrolled	966
# Subjects Discontinued Prematurely	484 (50%)
Lack of efficacy <sup>1</sup>	97 (10%)
Fail to meet randomization criteria <sup>2</sup>	18 (2%)
Adverse event	128 (13%)
Consent withdrawn	125 (13%)
Lost to follow-up	60 (6%)
Protocol violation	20 (2%)
Other	36 (4%)

<sup>1</sup>Category created by reviewer with additional data from Sponsor regarding subjects who discontinued for failure to meet randomization criteria and "other" categories that indicated lack of efficacy. "Other" descriptors included: lack of efficacy, worsening depression, hypomania, manic episode, mood event, mental deterioration or nonresponder. Also included was failure to meet randomization criteria that was consistent with lack of efficacy, e.g. not meeting response criteria.

<sup>2</sup>Not including reasons suggestive of lack of efficacy (see above footnote).

Table C-7.2. Subject Disposition in Randomized Phase

	Randomized Phase				
	Placebo	Lithium	Lamotrigine		
			50 mg	200 mg	400 mg
# Subjects Enrolled	121	121	50	124	47
# Subjects Withdrawn w/o TIME	43 (35%)	45 (37%)	9 (18%)	42 (34%)	15 (32%)
Lack of efficacy <sup>1</sup>	4 (3%)	0	0	2 (2%)	0
Adverse event	12 (10%)	19 (16%)	4 (8%)	11 (9%)	5 (11%)
Consent withdrawn	13 (11%)	13 (11%)	4 (8%)	12 (10%)	3 (6%)
Lost to follow-up	7 (6%)	5 (4%)	0	9 (7%)	4 (9%)
Protocol violation	2 (2%)	3 (2%)	0	2 (2%)	3 (6%)
Other	5 (4%)	4 (3%)	1 (2%)	6 (5%)	0
Sponsor discontinued <sup>2</sup>	0	1 (1%)	0	0	0

<sup>1</sup>Separated from "other" discontinuation category; included descriptors lack of efficacy and inadequate efficacy

<sup>2</sup>Study closed at one site due to a number of GCP issues.

Ten percent of the subjects enrolled in the preliminary phase discontinued due to lack of efficacy. Lack of efficacy as a reason for discontinuation was not disproportionate among other reasons for patient discontinuation (e.g. adverse events, consent withdrawn). Reasons for discontinuation were fairly uniform among the treatment groups in the randomized phase of the study, discontinuations due to lack of efficacy were slightly higher in the placebo group.

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The numbers of subjects included in the ITT, safety, and efficacy analyses are included in Table C-7.3.

Table C-7.3. SCAB2003 Study Populations

	Preliminary Phase	Randomized Phase					
	Open-Label Lamotrigine	Placebo	Lithium	Lamotrigine 200 + 400 mg	LTG 50 mg	LTG 200 mg	LTG 400 mg
ITT Population	966	121	121	171	50	124	47
Safety Population	958	121	120	169	50	122	47
Efficacy Population	943	119	120	165	50	120	45

ITT population: all subjects who were randomized

Safety population: all subjects in the ITT population who received at least one dose of study drug.

Efficacy population: all subjects in the ITT population who received at least one dose of study drug and had at least one post-screen (preliminary phase) or post-randomization (randomized phase) efficacy assessment.

### C-8 Baseline Demographics/Severity of Illness

Table C-8.1 Patient Demographics at Screening and Randomization (mean ± SD)

	Preliminary Phase	Randomized Phase		
	Open-label Lamotrigine (n = 958)	Placebo (n = 121)	Lithium (n = 120)	Lamotrigine 200 + 400 mg (n = 169)
Sex				
Female	588 (61%)	60 (50%)	72 (60%)	99 (59%)
Male	370 (39%)	61 (50%)	48 (40%)	70 (41%)
Race				
White	857 (89%)	109 (90%)	113 (94%)	153 (91%)
Black	55 (6%)	5 (4%)	5 (4%)	8 (5%)
Asian	14 (1%)	2 (2%)	2 (2%)	3 (2%)
Hispanic	24 (3%)	3 (2%)	0	3 (2%)
Other	8 (0.8%)	2 (2%)	0	2 (1%)
Age (years)	42 ± 12	42 ± 13	44 ± 12	44 ± 12
Weight (kg)	79 ± 18	82 ± 19	80 ± 18	79 ± 17
Height (cm)	170 ± 11	172 ± 10	170 ± 11	170 ± 10

Modified from Sponsor tables 6.3, 6.4, 6.5, 6.6

Demographic traits were fairly similar between groups. A very high percentage (>90%) of subjects were Caucasian with little representation among other racial groups.

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Table C-8.2. Severity of Illness Indicators

	Preliminary Phase	Randomized Phase		
	Open-label lamotrigine (n = 958)	Placebo (n = 121)	Lithium (n = 120)	Lamotrigine 200 + 400 mg (n = 169)
DSM-IV Diagnosis severity <sup>1</sup>				
Mild	18 (2%)	2 (2%)	5 (4%)	4 (2%)
Moderate	600 (63%)	79 (65%)	78 (65%)	111 (66%)
Severe (without psychotic features)	284 (30%)	36 (30%)	33 (28%)	44 (26%)
Severe (with psychotic features)	56 (6%)	4 (3%)	4 (3%)	10 (6%)
HAM-D <sub>17</sub>				
at screening		23 ± 4	23 ± 4	23 ± 4
at randomization		5 ± 4	6 ± 5	6 ± 4
MRS-11				
at screening		2.3 ± 4	2.0 ± 3	1.8 ± 3
at randomization		1.6 ± 3	1.7 ± 3	1.5 ± 3
CGI-S				
at screening		4 ± 0.7	4 ± 0.7	4 ± 0.6
at randomization		2 ± 0.7	2 ± 0.8	2 ± 0.7
Duration of current mood episode <sup>1</sup>				
2 to ≤ 4 weeks	186 (19%)	25 (21%)	20 (17%)	26 (15%)
4 to ≤ 8 weeks	267 (28%)	33 (27%)	40 (33%)	48 (28%)
8 to ≤ 24 weeks	373 (39%)	49 (40%)	47 (39%)	63 (37%)
> 24 weeks	131 (14%)	14 (12%)	13 (11%)	31 (18%)
Duration of bipolar illness (years)	20 ± 12	20 ± 12	21 ± 12	22 ± 13
Age of onset				
Depressive episode	23 ± 12	22 ± 12	23 ± 12	23 ± 12
Manic/Mixed episode	27 ± 12	26 ± 13	28 ± 15	28 ± 12
Hospitalized in past (% of subjects)	66	64	63	57
# Hospitalizations	4 ± 6	4 ± 5	5 ± 5	4 ± 6
# Mood episodes in last year				
Mania	0.9 ± 0.7	1.0 ± 0.8	0.9 ± 0.7	0.7 ± 0.7
Hypomania	0.3 ± 0.7	0.3 ± 0.5	0.3 ± 0.8	0.3 ± 0.6
Depression	1.7 ± 0.7	1.8 ± 0.7	1.7 ± 0.7	1.6 ± 0.7
Mixed	0.1 ± 0.4	0.1 ± 0.6	0.2 ± 0.5	0.1 ± 0.3
# Mood episodes in lifetime				
Mania	8 ± 11	9 ± 13	7 ± 7	8 ± 16
Hypomania	4 ± 10	4 ± 11	5 ± 13	5 ± 12
Depression	14 ± 16	17 ± 19	14 ± 16	14 ± 22
Mixed	1 ± 6	2 ± 8	1 ± 2	1 ± 3
Rapid cyclers (% of subjects)	28	34	32	26
Suicide attempt in past (% of subjects)	37	36	35	35
Psychotic episodes with bipolar disorder (% of subjects)	31	30	29	29

Modified from Sponsor's table 6.5, <sup>1</sup>At screening

The severity, duration and history of bipolar illness were consistent between the treatment groups. Most subjects were moderately ill with a duration of current mood episode between 8 and 24 weeks. The mean duration of current mood episode could not be reported since the data in the case report forms were collected into specified categories of duration.

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### C-9 Concomitant Medications

#### Preliminary Phase

Psychotropic medications, with some exceptions, could be used in the preliminary phase with the exception of one to two weeks prior to randomization. The protocol did not specify tapering strategies other than the 1 or 2 week washout period prior to randomization. Eighty percent (180/410) of subjects used at least one concomitant psychiatric medication during the preliminary phase. The most common concomitant psychotropics are listed in Table C-9.1.

Table C-9.1. Most Common Concomitant Psychotropics in the Preliminary Phase for Subjects Progressing to the Randomized Phase

	Number (%) of Subjects		
	Placebo (n = 121)	Lithium (n = 120)	Lamotrigine (n = 169)
Antidepressants	51 (42%)	60 (50%)	69 (41%)
Citalopram	8 (7%)	7 (6%)	12 (7%)
Venlafaxine	7 (6%)	11 (9%)	11 (7%)
Bupropion	6 (5%)	6 (5%)	10 (6%)
Benzodiazepines	47 (39%)	54 (45%)	73 (43%)
Lorazepam	25 (21%)	26 (22%)	34 (20%)
Clonazepam	8 (7%)	12 (10%)	19 (11%)
Oxazepam	9 (7%)	11 (9%)	16 (9%)
Temazepam	11 (9%)	18 (15%)	13 (8%)
Anticonvulsants/Mood Stabilizers	41 (34%)	45 (38%)	62 (37%)
Lithium	28 (23%)	21 (17%)	33 (19%)
Carbamazepine	3 (2%)	7 (6%)	9 (5%)
Valproate/valproic acid	14 (11%)	19 (16%)	24 (14%)
Antipsychotics	29 (24%)	17 (14%)	28 (17%)
Olanzapine	6 (5%)	3 (3%)	12 (7%)

From Sponsor's table 6.16

#### Randomized Phase

Per protocol, subjects could receive "short-term use" of certain pre-specified benzodiazepines during the study for control of agitation, irritability, restlessness, insomnia and hostile behavior. A review of the most commonly used concomitant benzodiazepines are included in Table C-9.2.

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Table C-9.2 Most Commonly Used Benzodiazepines During Randomized Phase up to TIME

	Randomized Phase		
	Placebo (n = 121)	Lithium (n = 120)	Lamotrigine (n = 169)
<b>Lorazepam</b>			
# (%) of Subjects	24 (20%)	24 (20%)	33 (20%)
Mean (SD) Daily Dose (mg)	1.4 (1)	1.1 (0.7)	1.3 (0.7)
Mean (SD) Duration (Days)	114 (126)	38.7 (50.7)	70.6 (97.1)
<b>Oxazepam</b>			
# (%) of Subjects	8 (7%)	10 (8%)	10 (6%)
Mean (SD) Daily Dose (mg)	44.5 (12.7)	19.1 (7.4)	24.3 (10)
Mean (SD) Duration (Days)	66 (117)	325 (325)	32 (28)
<b>Diazepam</b>			
# (%) of Subjects	2 (2%)	1 (< 1%)	7 (4%)
Mean (SD) Daily Dose (mg)	0	15 (0)	13.8 (8)
Mean (SD) Duration (Days)	0	15 (0)	27 (34)
<b>Temazepam</b>			
# (%) of Subjects	10 (8%)	12 (10%)	6 (4%)
Mean (SD) Daily Dose (mg)	27.3 (5.6)	20 (3)	17.2 (4.4)
Mean (SD) Duration (Days)	97 (208)	150 (138)	82 (116)

While the proportions of patients receiving benzodiazepines per treatment group were submitted in the sNDA, the daily dose and duration of use were not. The Sponsor was contacted to submit the mean and SD for these parameters. The number of subjects receiving benzodiazepines includes PRN use, however the mean daily dose and mean duration of use listed in the table include only scheduled use. Lorazepam was the most frequently used benzodiazepine with equal proportions of subjects in each treatment group receiving it as a scheduled or PRN medication. The mean daily dose for lorazepam was similar between groups while the mean duration was longer for the placebo and lamotrigine groups compared to lithium. In addition the variability of duration of use was quite large in each group (SD > mean). While the mean duration of lorazepam use appears longer than the "short-term" use of benzodiazepines specified in the protocol, this duration does not reflect days of continuous use but rather mean duration of use over the 76 weeks of the protocol. The duration is similar between the lamotrigine and placebo groups which would make comparisons between these groups equitable with regard to this potential confounding concomitant medication.

A review of concomitant medications identified subjects who were taking concomitant psychotropic medications during the randomized phase but who were not noted as reaching TIME.

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Table C-9.3. Concomitant Psychiatric Medications Taken During the Randomized Phase Prior to TIME.

	Placebo (n = 121)	Lithium (n = 120)	Lamotrigine (n = 169)
Antipsychotics	4 (3%)	1 (< 1%)	5 (3%)
Antidepressants	7 (6%)	6 (5%)	6 (3%)
Anticonvulsants/Mood stabilizers	2 (2%)	1 (< 1%)	3 (2%)

Concomitant antipsychotics included various phenothiazines, olanzapine, risperidone and haloperidol. Concomitant antidepressants included citalopram, venlafaxine, reboxetine, mirtazapine, sertraline, trazodone, desipramine and amitriptyline. Concomitant anticonvulsants/mood stabilizers included lamotrigine, valproate and lithium. The Sponsor provided brief summaries for the subjects using marketed lamotrigine prior to TIME during the randomized phase. One subject began taking marketed lamotrigine on the same day as the final dose of study medication (placebo). Another subject taking marketed lamotrigine (dose/duration not specified) withdrew from the randomized phase after one week and was only included in Preliminary Phase efficacy population (lamotrigine 400 mg/day group); there was no record of the subject having taken the randomized study medication. The third subject used marketed lamotrigine 25 mg BID prior to and continuing throughout the protocol in violation of the protocol (lamotrigine 400 mg/day group).

The Sponsor was asked to provide more information regarding the use of concomitant psychotropic medications during the randomized phase of the protocol. The Sponsor submitted a listing that include the start and stop dates of concomitant medications as well as the reason for the concomitant medication. Most of the concomitant medications were started prior to randomization and continued into the randomized phase in violation of the protocol, though the duration of use cannot be determined for half of these subjects since no stop date for the concomitant medication is available (see Table C-9.3A in Appendix A.1). In reviewing these concomitant medications, this reviewer noted that 6 subjects received concomitant antipsychotics, antidepressants, and/or mood stabilizers that were initiated after randomization for depression, "bipolar", or hypomania (see Table C-10.2.1). A separate analysis was performed changing the TIME date for these 6 subjects to the start date of the concomitant medication (see section C-10.2, Division's Analysis).

Twenty-four subjects received concomitant psychotropic medications either started prior to the randomized phase and continued into the randomized phase or initiated in the randomized phase for non-mood event conditions (e.g. insomnia). Use of concomitant medications were fairly uniform between the treatment groups: 7% placebo, 6% lithium and 4% lamotrigine 200 mg + 400 mg group. TIME was not redefined for subjects for whom the concomitant medication was initiated in the randomized phase for the treatment of insomnia, anxiety or restlessness.

Though patients could have positive urine toxicology results for marijuana and/or cocaine and continue in the trial, few randomized patients had these positive findings (see Table C-9.4-A in Appendix A.1)

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### C-10 Efficacy Results

#### C-10.1 Sponsor's Analyses

##### SCAB2003

As mentioned in sections C-5 and C-6, the Sponsor submitted an amendment (Amendment #13) which changed the primary efficacy endpoint after the protocol had been completed. The Sponsor wished to capture premature discontinuations in addition to TIME events as these "may provide a more sensitive measure of efficacy than TIME alone". The revised primary analysis was defined as TIME(Any Bipolar Event) [TIME(ABE)] defined as "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". The methodology as to how TIME(ABE) was retrospectively assessed is discussed in section C-6. Of note, the TIME(ABE) and TIME(SIS) added significantly more subjects with events compared to the TIME(Only) analyses and added a few more events to the placebo group compared to the lamotrigine 200 mg + 400 mg group (see Table C-10.1.1). Important to the survival analyses are not only the numbers of subjects having the event but the time to the event itself.

Table C-10.1.1 Number (%) of subjects in each TIME analysis

	Placebo (n = 119)	Lithium (n = 120)	Lamotrigine 200 + 400 mg (n = 165)
Number of subjects with event, n (%)			
TIME(ABE)	98 (82%)	83 (69%)	123 (75%)
TIME(SIS)	107 (90%)	99 (83%)	134 (81%)
TIME(Only)	66 (55%)	56 (47%)	83 (50%)

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Table C-10.1.2. Sample size (%) included in TIME analyses

	Efficacy Population (n = 404)	Placebo (n = 119)	Lithium (n = 120)	Lamotrigine (n = 165)
Time(Only) ↓ TIME(ABE) ↓ TIME(SIS) ↓	Subjects reaching TIME	205 (51%)	66 (55%)	83 (50%)
	Discontinuation without reaching TIME			
	Protocol violation	10 (2%)	2 (2%)	3 (3%)
	"Other"	21 (5%)	9 (8%)	4 (3%)
	Lost to follow-up	23 (6%)	6 (5%)	5 (4%)
	Consent withdrawn	38 (9%)	13 (11%)	12 (7%)
	AE related to bipolar disorder	7 (2%)	2 (2%)	3 (3%)
	AE not related to bipolar disorder	36 (9%)	9 (8%)	16 (13%)
	Sponsor discontinued	3 (< 1%)	0	1 (< 1%)
	Completed study on monotherapy	61 (15%)	12 (10%)	20 (17%)
			20 (17%)	29 (18%)

Data from Sponsor correspondence 11/15/02

TIME(ABE) included subjects with adverse events related to bipolar disorder (n = 7). The Sponsor was contacted to provide the adverse events that were deemed related to bipolar disorder. These adverse events included mania (2), psychotic disorder (1), depression (1), agitation/restlessness and tremor (1), dizziness/lightheaded and somnolence/lethargic (1), emotional lability/irritability insomnia and weight gain (1). When questioned about the adverse events dizziness/lightheaded, somnolence/lethargic, and weight gain, the physician who performed the blinded review stated that other sources (HAM-D etc.) were used to determine whether an adverse event was related to bipolar disorder. For bipolar-related adverse events such as mania and psychotic disorder, the subject withdrew from the study prior to receiving a psychotropic medication that would have qualified as TIME.

Table C-10.1.3. Sponsor's Table: Summary of Analysis of TIME(ABE)

### Summary of Analysis of TIME(ABE), Efficacy Population, SCAB2003

Statistical Parameter	PBO N=119	LI N=120	LTG Comb.* N=165	By LTG Treatment Group		
				LTG 50 N=50	LTG 200 N=120	LTG 400 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 <sup>b</sup>	-	0.006 <sup>c</sup>	0.004 <sup>c</sup>	ns	0.003 <sup>c</sup>	ns

a. Lamotrigine 200 mg and 400 mg treatment groups combined

b. Difference in survival distribution between treatments tested using Log-Rank test

c. Significantly different from placebo

## CLINICAL REVIEW

Figure C-10.1.1. Sponsor's Figure: Survival Estimates for TIME(ABE)

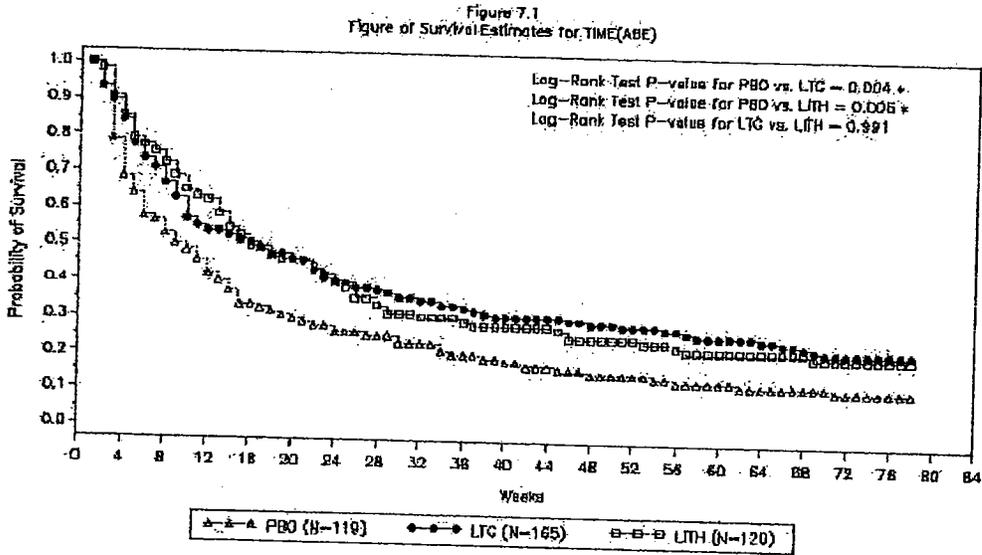


Table C-10.1.4. Sponsor's Table: Summary of Analysis of TIME(SIS)

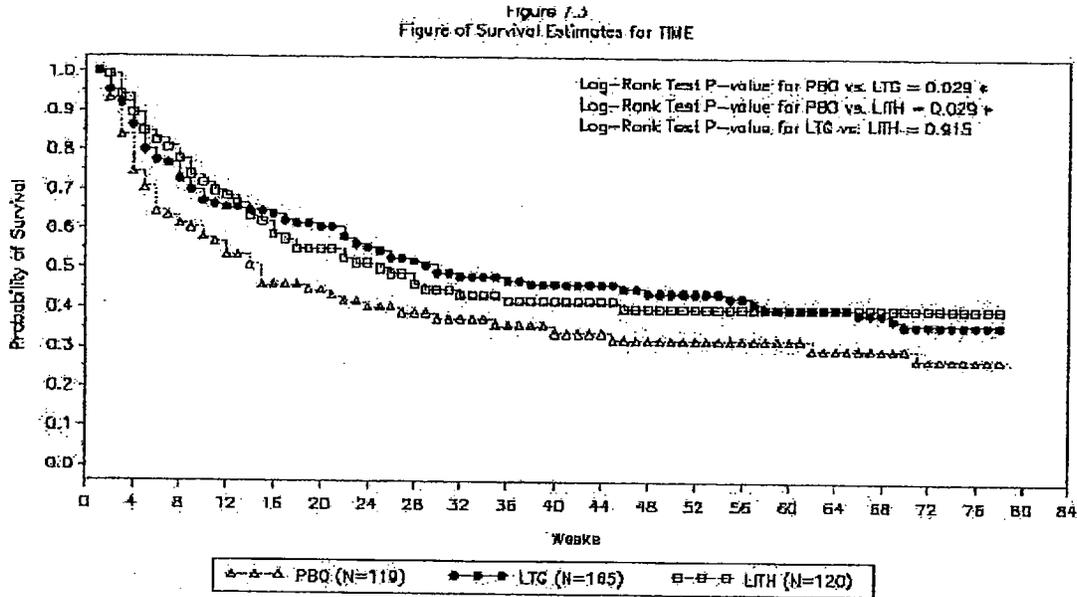
**Summary of Analysis of TIME(Survival in Study),  
Efficacy Population, SCAB2003**

Statistical Parameter	PBO N=119	Li N=120	LTG Comb. <sup>a</sup> N=165	By LTG Treatment Group		
				LTG 50 N=50	LTG 200 N=120	LTG 400 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 at Week 76	0.100	0.169	0.193	0.178	0.201	0.171
p-value <sup>b</sup>	-	0.022 <sup>c</sup>	0.003 <sup>c</sup>	ns	0.001 <sup>c</sup>	ns

- a. Lamotrigine 200 mg and 400 mg treatment groups combined  
 b. Difference in survival distribution between treatments tested using Log-Rank test  
 c. Significantly different from placebo

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Figure C-10.1.3. Sponsor's Figure: Survival Estimates for TIME(Only)



Secondary efficacy measures included time to recurrence or relapse of a manic episode (TIMan) and time to recurrence or relapse of a depressive episode (TIDep). The primary analyses for TIMan and TIDep did not include premature discontinuations. For the TIMan analysis, the median time to event was not calculated for any groups since the probability of survival remained above 50%.

Table C-10.1.6. Summary of Analysis of TIMan

	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 (%)	19 (16%)	10 (8%)	26 (16%)	12 (24%)	18 (15%)	8 (18%)
Median Time to Event (days)	n/c	n/c	n/c	504	n/c	n/c
Confidence Interval	-	-	-	(241, n/c)	-	-
Survival Estimate, Week 76	0.665	0.862	0.700	0.499	0.699	0.713
p-value*		0.026	0.339	0.725	0.237	0.937

n/c = not calculable due to insufficient number of events  
\*significantly different from placebo

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Figure C-10.1.4. Sponsor's Figure: Survival Estimates for TIMan

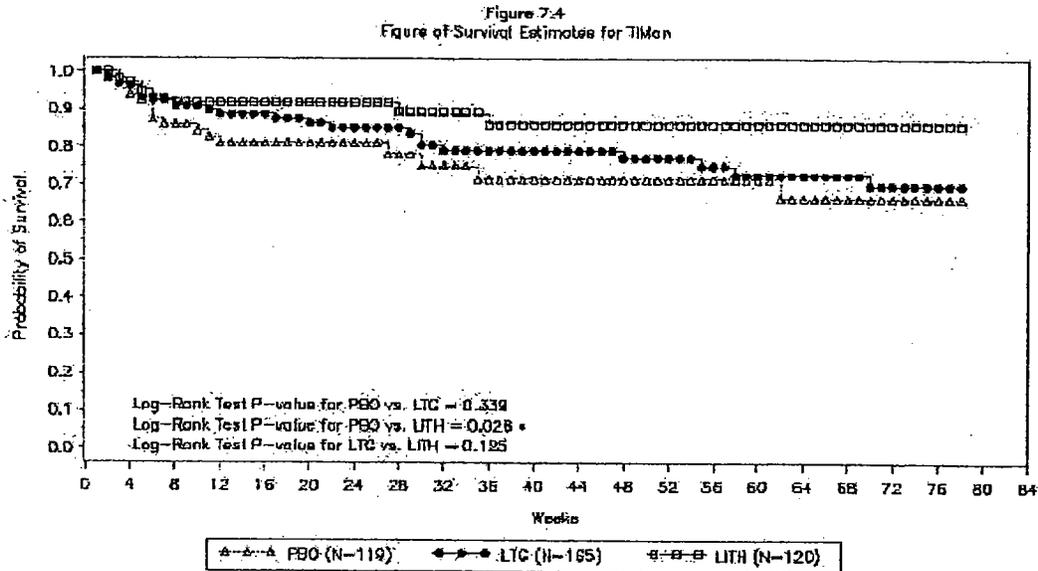


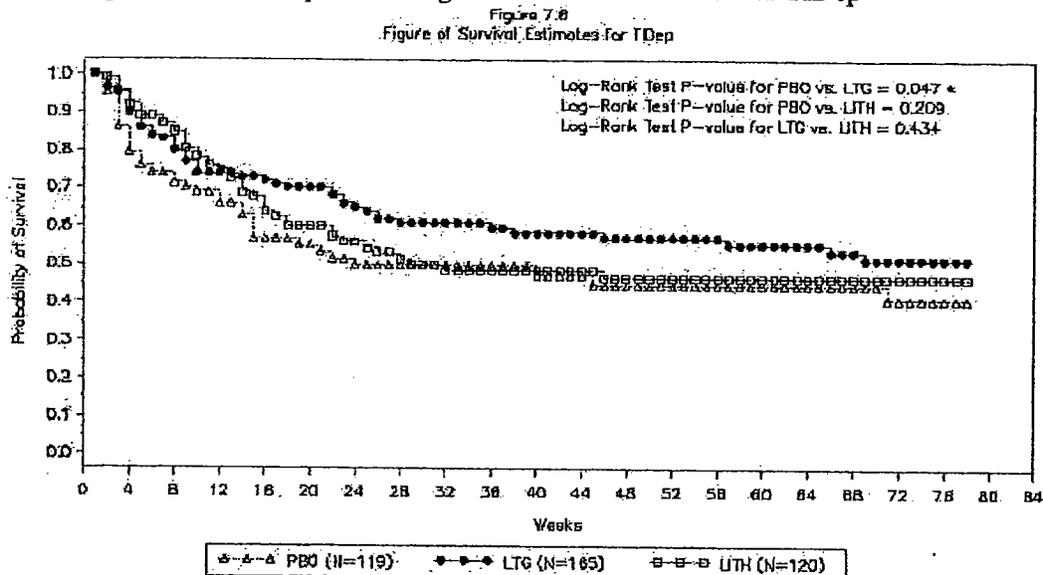
Table C-10.1.7. Summary of Analysis of TIDep

	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 (%)	47 (39%)	46 (38%)	57 (35%)	20 (40%)	40 (33%)	17 (38%)
Median Time to Event (days)	162	197	n/c	162	n/c	453
Confidence Interval	(93, n/c)	(119, n/c)	-	(115, n/c)	-	(120, n/c)
Survival Estimate, Week 76	0.409	0.464	0.514	0.492	0.535	0.458
p-value*		0.209	0.047	0.413	0.028	0.533

n/c = not calculable due to insufficient number of events  
 \*significantly different from placebo

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Figure C-10.1.5. Sponsor's Figure: Survival Estimates for TIDep



A number of subgroup analyses were performed by the Sponsor. One subgroup analysis evaluated TIME in the patients enrolled prior to Amendment 12 versus patients enrolled after Amendment 12 (see Section C-3). Prior to Amendment 12, only patients with a current major depressive episode of defined severity and duration could be enrolled in the study. Amendment 12 changed enrollment criteria to also include patients who were not currently depressed but had a well-documented major depressive episode within 60 days of enrollment and some current depressive symptoms or were being treated for depressive symptoms with a recognized, effective regimen. Severity criteria ( $HAM-D_{17} \geq 18$ ) was necessary for subjects with current depressive symptoms but not for subjects who were currently being treated for a depressive episode.

In addition, Amendment 12 discontinued the 50 mg and 400 mg lamotrigine treatment groups while continuing to enroll in the 200 mg lamotrigine group. The Sponsor has stated that no interim analyses were performed prior to the decision to implement Amendment 12. Table C-10.1.8-A in Appendix A.1 is a summary of the different TIME analyses statistical results included in the final study report for the population enrolled prior to Amendment 12. These data indicate that only the TIME(ABE) and TIME(SIS) analyses showed any indication of efficacy for lamotrigine compared to placebo and only at the 200 mg dose.

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Table C-10.1.8. TIME Analyses for Subjects Enrolled Prior to and After Amendment 12

		Placebo (n = 119)	Lithium (n = 120)	Lamotrigine 200 + 400 mg (n = 165)
Subjects enrolled before Amendment 12	N	60	63	106
	TIME(ABE)			
	# subjects with event	47 (78%)	43 (68%)	79 (75%)
	Median time to event (days)	56	142	108
	p-value <sup>a</sup>		NS	NS
	TIME(SIS)			
	# subjects with event	52 (87%)	53 (84%)	86 (81%)
	Median time to event (days)	42	100	93
	p-value <sup>a</sup>		NS	NS
Subjects enrolled after Amendment 12	N	59	57	59
	TIME(ABE)			
	# subjects with event	51 (86%)	40 (70%)	44 (75%)
	Median time to event (days)	58	86	128
	p-value <sup>a</sup>		0.03 <sup>b</sup>	0.01 <sup>b</sup>
	TIME(SIS)			
	# subjects with event	55 (93%)	46 (81%)	48 (81%)
	Median time to event (days)	50	72	86
	p-value <sup>a</sup>		0.05 <sup>b</sup>	0.01 <sup>b</sup>
TIME(Only)	# subjects with event	35 (59%)	26 (46%)	30 (51%)
	Median time to event (days)	87	170	200
	p-value <sup>a</sup>		NS	0.04 <sup>b</sup>

From Sponsor tables on pages 156-158 of study report

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

b. Significantly different from placebo

The lamotrigine 200 mg + 400 mg group was significantly different from placebo for all TIME analyses only for subjects enrolled after Amendment 12. Since Amendment 12 included subjects who were currently being treated for depressive symptoms and therefore did not have to meet HAM-D severity criteria for enrollment, the Sponsor was asked to provide HAM-D<sub>17</sub> scores for the subjects enrolled prior to and after Amendment 12 (Table C-10.1.9). Though the subjects enrolled after Amendment 12 could include subjects without significant current depressive symptomatology, it does not appear that the HAM-D<sub>17</sub> scores differed significantly between these two cohorts.

Table C-10.1.9. HAM-D<sub>17</sub> Scores at Screening Prior to and After Amendment 12  
[Mean, SD and Range]

	Pre Amendment 12	Post Amendment 12
Placebo	23.5 ± 3.4	23.0 ± 4.6
Lithium	23.1 ± 4.1	23.2 ± 5
Lamotrigine	23.2 ± 3.6	22.4 ± 5

\*Probable violation of protocol since minimum score required was 18

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The Sponsor also analyzed the subgroup of subjects who had an adequate course of lithium treatment within 5 months prior to enrollment. Approximately 75% of subjects in each treatment group were categorized as not having an adequate course of lithium. For the TIME(Only) analysis, the survival distributions for both the lamotrigine 200mg + 400 mg group ( $p = 0.010$ ) and the lithium group ( $p = 0.002$ ) were statistically significant from placebo for the subjects with a previous adequate course of lithium only. Similar findings were reported for the TIME(ABE) and TIME(SIS) analyses as well as TIMan, but no statistically significant differences were found for either group of subjects for TIDep. Though there were differences in some demographics between treatment groups in each cohort, the subjects who had an adequate course of lithium were more likely to have a psychotic episode with bipolar disorder and to be hospitalized for a mood episode. Other demographic variables such as family history, duration of illness, attempted suicide and total number of hospitalizations were similar between the cohorts.

Another subgroup analysis evaluated rapid cyclers enrolled in the trial. Approximately 30% of subjects in each treatment group were rapid cyclers ( $\geq 4$  episodes in the previous year). Per protocol, rapid cyclers could have no more than 6 cycles in the previous year to qualify for enrollment. For the TIME(Only) analysis, the survival distributions for both the lamotrigine 200 mg + 400 mg group ( $p = 0.03$ ) and the lithium group ( $p = 0.04$ ) were statistically significant from placebo for non-rapid cyclers only; no significant findings were reported for rapid cyclers. Similar findings were reported for the TIME(ABE) and TIME(SIS) analyses. The lamotrigine 200 mg + 400 mg group was significantly different from placebo ( $p = 0.014$ ) for TIDep for non-rapid cyclers only.

Table C-10.1.10-A in Appendix A.1 summarizes the results of several psychiatric rating scales as secondary efficacy measures.

### C-10.2 Division's Analyses

Though several reanalyses were performed and are reported below for all three TIME endpoints, this reviewer is focusing on the results from TIME(Only) as the primary endpoint. There are several reasons for this. First, the amendment which significantly altered the definition of the primary endpoint from TIME [e.g. TIME(Only)] to TIME(ABE) was submitted after the protocol was completed. The Sponsor had continued communication with the Division prior to submitting the sNDA which included teleconferences and meetings with specific outlined questions to the Division. However, during these meetings, the issue of significantly changing the definition of the primary endpoint was never one of these outlined issues that was discussed at any significant length with the Division nor was concurrence specifically sought from the Division. Meeting minutes from the November 2002 teleconference mention the change in endpoint stated by the Sponsor, but there was no significant discussion of this issue nor any significant comments that this change had been reviewed and agreed upon by the statisticians in the Division. Rather, much of the discussion on this meeting focused on the elimination of the 50 and 400 mg lamotrigine arms and the impact of this change. While unofficial, the minutes from the internal pre-meeting to this teleconference

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indicated that the statistician was not comfortable with this change in primary efficacy measure. Changing a primary endpoint after completion of a protocol is inherently problematic, though the Sponsor has stated that the data were still blinded at the time this decision was made. However, it is plausible that the Sponsor did know the number of events in TIME(Only) prior to making this decision. Second, since TIME(ABE) includes subject discontinuation categories such as "other", consent withdrawn, protocol violation, and lost to follow-up; it does not seem reasonable to consider all of these as bipolar events since the reason for many of these discontinuations may not be related to the mood disorder. The Sponsor only sought to determine bipolar-relatedness for the discontinuation category "adverse events" [if related to bipolar = TIME(ABE), if not it was included in TIME(SIS)] and not any of the other discontinuation categories. Though it may be nearly impossible to determine causality for some of these categories, the categories "other" and protocol violation could have been reasonably evaluated. During the review process, several concerns arose which prompted the Division to perform several different analyses excluding or including additional subjects. These analyses are described below.

### 1. Recoding of TIME events

Upon review of the concomitant medication data provided by the Sponsor upon query, the reviewer noted that antidepressants, antipsychotics, and/or antimanic concomitant medications were initiated in several subjects after randomization for conditions noted as "depression, bipolar, or hypomania" though these subjects were not identified as having reached TIME. The submission with this additional information stated that in these cases "this was not determined to be TIME by the investigator". The Sponsor could not provide a sound rationale as to why TIME was not identified as the date of concomitant drug initiation for these subjects. Since the definition of TIME is "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" it would appear that these subjects did reach TIME. Additionally, the case report forms for several subjects were reviewed and it appeared that some investigators may have been confused regarding the designation of a concomitant medication as a primary intervention for a mood episode (TIME). Some investigators checked "no" on the concomitant medication page indicating that the medication was not prescribed as a primary intervention, yet these responses were then changed to "yes" by what appears to have been a site monitor for the trial. Therefore, a reanalysis of the TIME endpoints was performed with these adjusted TIME events (see Table C-10.2.1). This reanalysis did not include subjects who were prescribed these concomitant medications for reasons not identified as a mood event (e.g. insomnia, anxiety, etc.).

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Table C-10.2.1. Redefined TIME Events According to Concomitant Psychotropic Medication Use for a Mood Event During the Randomized Phase

Subject	Treatment	Old TIME	New TIME	Medication and Condition treated
4103	Lamotrigine 400 mg	None	7/9/98	Citalopram - Depression
4104	Placebo	None	10/8/98	Sertraline - Depression
12790	Lamotrigine 400 mg	5/4/98	3/4/98	Olanzapine - Bipolar
4231	Lamotrigine 400 mg	None	12/1/98	Reboxetine - Depression
57035	Placebo	6/13/01	6/8/00	Mirtazapine - Depression
57038	Lamotrigine 200 mg	12/20/00	9/27/00	Haloperidol - Hypomania

Data from Listing 3

Table C-10.2.2. Log-Rank Test Results - Redefined TIME Endpoint Dates

	LTG 200 + 400 mg vs. Placebo
TIME(ABE)	0.0041
TIME(SIS)	0.0035
TIME(Only)	0.0297
TIMan	0.3938
TIDep	0.0416

Table C-10.2.3. Detailed Estimates from Survival Distribution for TIME(Only), TIMan, and TIDep - Redefined TIME Endpoint Dates

	PBO N=119	LTG 200 mg N = 120	LTG 400 mg N = 45
<b>TIME(Only)</b>			
Subjects with Event, n (%)	67 (56%)	58 (48%)	27 (60%)
Median Time to Event (days)	92	239	119
Confidence Interval	(57, 145)	(172, 481)	(44, 201)
Survival Estimate, Week 76	0.275	0.376	0.270
<b>TIMan</b>			
Subjects with Event, n (%)	19 (16%)	19 (16%)	8 (18%)
Median Time to Event (days)	n/c	373	201
Confidence Interval	(421, n/c)	(217, n/c)	(44, n/c)
Survival Estimate, Week 76	0.656	0.683	0.706
<b>TIDep</b>			
Subjects with Event, n (%)	48 (40%)	39 (33%)	19 (42%)
Median Time to Event (days)	145	n/c	153
Confidence Interval	(92, n/c)	(255, n/c)	(119, n/c)
Survival Estimate, Week 76	0.420	0.550	0.382

n/c = not calculable due to insufficient number of events

### 2. Deletion of Site #55466

While reviewing patient discontinuation data, a category termed "sponsor discontinued" comprising 7 randomized subjects (see Table C-7.1-A in Appendix A.1) was noted. The Sponsor was asked to clarify this term. In response, per correspondence 10/28/02, the Sponsor submitted the following:

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“The study was closed at this center at the initiative of GSK. There were a number of GCP issues raised with the investigator, some of which could have an impact on patient safety. These issues included:

1. Failure to notify subject's primary care physician of their participation in the study.
2. Failure to submit IND safety reports and revised CIB to the Ethics Committee in a timely manner.
3. Failure to obtain medical review of laboratory reports in a timely manner.
4. Inadequate procedures for storage of study medication at site.
5. Not using an appropriate taper of lithium for subjects who discontinue or complete the study.
6. Information related to primary treatment intervention was not collected in a timely manner for some subjects.

The investigator was unable to supply staffing resources to implement sufficient corrective measures in order to satisfy the GSK's concern and his participation was terminated. Extensive follow-up was conducted to ensure that all ongoing subjects were discontinued in a clinically safe and appropriate manner, and that the data for all enrolled patients was complete. None of the issues raised concerns about whether the subjects were appropriate for the study or the integrity of the data. Therefore, data for the seven subjects who were discontinued at sponsor request and the other four subjects who had previously completed participation were included in the efficacy and safety populations.”

This information regarding site #55466 was not included in the study report for this protocol. The Sponsor did not perform a separate analysis without this site. Further, the Sponsor kept these subjects in the safety and efficacy analyses since, in the Sponsor's opinion, there were no issues regarding the integrity of the data from this site. However, it is unclear to this reviewer how the integrity of these data could be guaranteed from a site with such significant GCP issues that the Sponsor, in effect, closed the site. Inappropriate lithium taper was listed as one of the reasons this site was closed. An inappropriate lithium taper certainly could have an effect on efficacy measures and it is unlikely that the inappropriate taper would be limited only to subjects completing or discontinuing the study. Due to these uncertainties, the integrity of these data is questionable in this reviewer's opinion. Therefore, a separate analysis was performed which excluded these 11 subjects [4 subjects receiving placebo or lamotrigine had reached TIME(Only)].

Table C-10.2.4. Log-Rank Test Results - Excluding Site #55466

	LTG 200 + 400 mg vs. Placebo
TIME(ABE)	0.0098
TIME(SIS)	0.0066
TIME(Only)	<b>0.0594</b>
TIMan	0.3650
TIDep	<b>0.0970</b>

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Table C-10.2.5 Detailed Estimates from Survival Distribution for TIME(Only), TIMan, and TIDep - Excluding Site #55466

	PBO N=116	LTG 200 mg N = 117	LTG 400 mg N = 45
<b>TIME(Only)</b>			
Subjects with Event, n (%)	63 (54%)	57 (49%)	25 (56%)
Median Time to Event (days)	92	255	144
Confidence Interval	(68, 197)	(162, 471)	(48, 452)
Survival Estimate, Week 76	0.280	0.372	0.325
<b>TIMan</b>			
Subjects with Event, n (%)	19 (16%)	18 (15%)	8 (18%)
Median Time to Event (days)	n/c	n/c	n/c
Confidence Interval	n/c	n/c	n/c
Survival Estimate, Week 76	0.667	0.697	0.712
<b>TIDep</b>			
Subjects with Event, n (%)	44 (38%)	39 (33%)	17 (38%)
Median Time to Event (days)	269	n/c	452
Confidence Interval	(96, n/c)	(255, n/c)	(119, n/c)
Survival Estimate, Week 76	0.421	0.533	0.456

n/c = not calculable due to insufficient number of events

### 3. Recoding of TIME events and deletion of Site #55466 (combination of #1 & #2 above)

Table C-10.2.6. Log-Rank Test Results - Redefined TIME Endpoint Dates and Excluding Site #55466

	Lamotrigine 200 mg + 400 mg versus placebo
TIME(ABE)	0.0098
TIME(SIS)	0.0084
TIME(Only)	0.0617
TIMan	0.4192
TIDep	0.0883

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Table C-10.2.7. Detailed Estimates from Survival Distribution for TIME(Only), TIMan, and TIDep – Redefined TIME Endpoint Dates and Excluding Site #55466

	PBO N=116	LTG 200 mg N = 117	LTG 400 mg N = 45
<b>TIME(Only)</b>			
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	0.282	0.372	0.269
<b>TIMan</b>			
Subjects with Event, n (%)	19 (16%)	19 (16%)	8 (18%)
Median Time to Event (days)	n/c	n/c	n/c
Confidence Interval	n/c	n/c	n/c
Survival Estimate, Week 76	0.656	0.679	0.706
<b>TIDep</b>			
Subjects with Event, n (%)	45 (39%)	38 (32%)	19 (42%)
Median Time to Event (days)	161	n/c	153
Confidence Interval	(92, n/c)	(255, n/c)	(119, n/c)
Survival Estimate, Week 76	0.431	0.548	0.382

n/c = not calculable due to insufficient number of events

#### 4. Modification of TIME(ABE)

One of the problematic issues with this reviewer's acceptance of TIME(ABE) was that it deemed all premature discontinuations, except for adverse events not considered due to bipolar disorder, to be related to bipolar disorder. The Sponsor was asked to provide more details regarding the premature discontinuation category "other" and provided the following reasons for these "other" discontinuations:

Table C-10.2.8. Reasons for Category "Other" for Premature Discontinuations

Premature Discontinuation Category	Reason
Other (n = 21)	Inadequate efficacy (n = 6) Patient "got retired" (n = 1) By request of monitor (n = 1) Patient moved (n = 3) Lab error (n = 1) Non compliance/bad compliance (n = 6) Gall bladder attack (n = 1) Patient terminated, on liquid diet supplement (n = 1) Subject discontinued at week 52 instead of week 76 (n = 1)

Upon review, it would appear that only the 6 subjects with inadequate efficacy in this category are likely related to bipolar disorder. Therefore, the Division performed another analysis which was a modification of TIME(ABE) – termed TIME(BipEvent). This modified endpoint included TIME(Only), premature discontinuations due to adverse events related to bipolar disorder (since this was assessed in a blinded fashion), and premature discontinuations due to "other" = inadequate efficacy. This analysis excluded Site #55466 as previously discussed.

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The Sponsor was unable to provide details to determine whether the premature discontinuation categories lost to follow-up, consent withdrawn, and protocol violation were related to bipolar disorder since this data was not collected on the CRFs. Therefore, it was the opinion of the Division that these premature discontinuation categories could not be assumed to be related to bipolar disorder. All of these premature discontinuations were censored for this analysis.

Table C-10.2.9. Log-Rank Test Results and Detailed Estimates from Survival Distribution for TIME(BipEvent)

	PBO N=116	LTG 200 mg + LTG 400 mg	LTG 200 mg N = 117	LTG 400 mg N = 45
<b>TIME(BPD)</b>				
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	0.228	0.331	0.356	0.269
p-value*		0.034		

\*significantly different from placebo

The secondary endpoints, TIMan and TIDep, were not evaluated in the TIME(BipEvent) endpoint since this information was not available for the additional cases for “other” discontinuations = inadequate efficacy. The analysis closest to this analysis is the one in (3) which did not report significant results for either of these secondary endpoints. TIME(BipEvent) differs only slightly from TIME(Only) in analysis (3) in that it includes an additional 9 events (3 adverse events due to bipolar and 6 “other” premature discontinuations due to inadequate efficacy).

### 5. Questionable TIME endpoint

Per section C-6, the Sponsor derived the TIME endpoint in a number of ways. Per the original definition of TIME, however, only the prescription of a medication or administration of ECT for the treatment of a mood event is recognized as a valid TIME endpoint by the Division. A review of all subjects who reached TIME (Listing 7.3) found that 2 subjects had a derived TIME endpoint that was not consistent with the original definition of TIME. One placebo subject (#5293) had listed as the reason for the TIME event as “endpoint page” and the other was a lamotrigine 50 mg subject (#4414) with the reason “mood flagged” – all other reasons for TIME were defined as “psychotropic med flagged”.

In response to the query about this subject, the Sponsor stated (correspondence 01/03/03) that there were other indications that the subject had a mood event via CRF pages other than the concurrent medication page:

General assessment of mood states (GAMS) page Q: Was it necessary to administer drug or ECT as a primary treatment intervention?

Psychiatric evaluations page Q: Since the last assessment, has the patient had any mood events?

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Concurrent medication page Q: Was drug administered or ECT performed as a primary intervention?

Per the Sponsor, the investigator for subject #5293 stated that he wanted to treat the patient for a manic episode but the patient did not want treatment. Therefore, this reviewer thought it reasonable to accept this subject as having reached TIME.

6. Redefining adverse events related to bipolar disorder and not related to bipolar disorder. A review of the adverse event terms noted several descriptors that might lead to recategorization to either bipolar-related or non-related. As noted previously, one subject with adverse events "dizziness/light headed" and "somnolence/lethargic" was determined to have discontinued due to adverse events related to bipolar disorder. Similarly, two subjects with adverse events noted as "emotional lability/irritability" were not identified as bipolar-related adverse events. A reanalysis recoding these events was not done since this reviewer did not have access to other information that could have been helpful in assessing causality and the events in question were very few.

### 7. Concomitant Medications.

A separate analysis was performed excluding subjects taking concomitant medications that could have confounded the study results. This included subjects taking antidepressants, antipsychotics, and/or antimanic agents during the preliminary phase that continued into the randomized phase as well as those initiated during the randomized phase for non-mood events such as insomnia, anxiety, restlessness and smoking cessation (see Table C-9.3-A in Appendix A.1). The results from this analysis did not differ significantly from the Sponsor's analysis.

**SCAB2006: A multicenter, double-blind, placebo-controlled, randomized, flexible-dose evaluation of the safety and efficacy of lamotrigine in the long-term prevention of relapse and recurrence of mania and/or depression in patients with bipolar I disorder.**

SCAB2006 was initiated on August 14, 1997 and completed on December 31, 1999 with the final study report completed on April 3, 2002. The original protocol was submitted to the Division on April 25, 1997, this protocol contained amendments 1 – 3. Six additional amendments to the protocol were submitted between May 1997 and October 2000, the last amendment was submitted after the study completion date. The lithium arm of the study was eliminated in November 1998 (Amendment 8) and the protocol was terminated early, on December 10, 1999, because of difficulty achieving enrollment goals. When the study was terminated, all currently enrolled subjects were prematurely discontinued and not followed for the duration of the protocol. The database was authorized for release on October 31, 2000.

### C-1 Investigators and Sites

A list of investigators and sites may be found in Table C-1-A in Appendix A. A total of 40 U.S and 40 non U.S. centers recruited subjects in this multicenter study.

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### C-2 Objectives

Per original protocol:

The primary objective was to compare the safety and efficacy of lamotrigine with therapeutic levels of lithium and placebo in preventing the relapse and recurrence of manic, depressive, hypomanic or mixed episodes over a long period in subjects with bipolar I disorder who have experienced a recent manic episode which has responded to treatment (lamotrigine as monotherapy or in combination with other psychotropic medication). "Long period" was defined as 52 weeks in the original protocol and was later lengthened to 76 weeks by amendment. See Table C-2-A in Appendix A for significant protocol amendments.

### C-3 Study Population

As originally submitted, this protocol included outpatient men and women  $\geq 18$  years of age with bipolar I disorder, with their most recent episode depressed as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Subjects had to be currently experiencing a manic episode and have had at least one additional manic episode and one depressed or mixed episode within 3 years of enrollment. Similar to SCAB2003, this protocol was amended in February 1998 (Amendment #6) to permit enrollment of subjects who were not currently manic but who had a manic episode within 1 month of screening, permitted hypomania to be an indicator of bipolar disorder activity and permitted inclusion of rapid-cyclers ( $\leq 6$  bipolar disorder episodes within 12 months of enrollment). A subsequent amendment in November 1998 (Amendment #8) permitted enrollment of subjects who had a manic or hypomanic episode within 60 days (if hypomanic, needed evidence of prior manic episode). Severity criteria (MRS  $\geq 14$ ) was necessary for subjects with a current manic episode but was not necessary for subjects who were currently hypomanic or who were being treated for a manic or hypomanic episode. The duration criteria was  $\geq 1$  week for a manic episode or  $\geq 4$  days for a hypomanic episode, but not  $> 12$  months.

### C-4 Design

Similar to SCAB2003, this study was an enriched design with the same preliminary phase prior to the randomized phase of the protocol. The November 1998 amendment (Amendment #8) allowed treatment of depressive states occurring during the preliminary phase. Similar to SCAB2003, medications that were not allowed included fluoxetine, initiation of lithium, depot psychotropics, and drugs with a  $t_{1/2} > 14$  days.

Unlike SCAB2003, SCAB2006 utilized a flexible dose for the lamotrigine arm of the protocol. Subjects were randomized to placebo, lithium, and lamotrigine 100 – 400 mg/day (target dose = 200 mg/day). The criteria for enrolling in the randomized phase from the preliminary phase were the same as for SCAB2003.

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### C-5 Statistical Analysis Plan

Many of these changes are similar to the summary for SCAB2003.

Original protocol document (1/13/97) - Primary analyses of the combined data lamotrigine 200 mg + lamotrigine 400 mg (from SCAB2003) + lamotrigine-flex dose (from SCAB2006) vs. placebo with respect to TIDep and TIMan.

The primary analysis in SCAB2006 will be a pairwise comparison of TIME testing lamotrigine vs. placebo ( $\alpha = 0.05$ ) using the Log Rank Test.

Amendment #8 (11/25/98) - Eliminated the lithium treatment group. Also changed some inclusion criteria similar to SCAB2003.

Amendment #9 (10/24/00) - Submitted after completion of protocol. Eliminated the analysis of the combined SCAB2003 and SCAB2006 data as the primary analysis. Changed primary efficacy measure to TIME(ABE), same as SCAB2003.

SCAB2006 was terminated early, on December 10, 1999, because of difficulty achieving enrollment goals. When the study was terminated, all currently enrolled subjects were prematurely discontinued and not followed for the duration of the protocol. Upon query, the Sponsor explained that the decision to discontinue ongoing subjects "was made primarily because of internal budget constraints during that period". The decision was made on October 20 & 21, 1999 (correspondence 12/12/02).

### C-6 Assessments

The primary efficacy measure was TIME defined as in SCAB2003. Amendment 9 (October 2000) was submitted after completion of the protocol. Similar to SCAB2003, this amendment changed the primary efficacy measure to TIME(ABE) in order to capture premature discontinuations. TIME(SIS) and TIME(Only) were supportive analyses. As in SCAB2003, secondary efficacy variables such as TIMan and TIDep were included in SCAB2006.

### C-7 Patient Disposition

A total of 349 subjects were enrolled into the preliminary phase of which 184 (53%) completed the preliminary phase of the protocol and were randomized to placebo, lithium or lamotrigine 100 - 400 mg. The disposition of subjects is listed in Table C-7.1. Similar to SCAB2003, the Sponsor was asked to provide more details regarding subject discontinuations due to "other" and "failure to meet randomization criteria". This data was reviewed and subjects who appeared to discontinue due to lack of efficacy were separated into a different category of discontinuation.

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Table C-7.1 Subject Disposition in Preliminary Phase

	Preliminary Phase
	Open-Label Lamotrigine
# Subjects Enrolled	349
# Subjects Discontinued	164 (47%)
Lack of efficacy <sup>1</sup>	44 (13%)
Fail to meet randomization criteria <sup>2</sup>	4 (1%)
Adverse event	42 (12%)
Consent withdrawn	29 (8%)
Lost to follow-up	30 (9%)
Protocol violation	9 (3%)
Other	6

<sup>1</sup>Category created by reviewer with additional data from Sponsor regarding subjects who discontinued for failure to meet randomization criteria and "other" categories that indicated lack of efficacy. "Other" descriptors included: lack of efficacy, worsening depression, hypomania, manic episode, mood event, mental deterioration or nonresponder. Also included was failure to meet randomization criteria that was consistent with lack of efficacy, e.g. not meeting response criteria.

<sup>2</sup>Not including reasons suggestive of lack of efficacy (see above footnote).

Table C-7.2 Subject Disposition in Randomized Phase

	Randomized Phase		
	Placebo	Lithium	Lamotrigine
# Subjects Enrolled	70	46	59
# Subjects Withdrawn w/o TIME	21 (30%)	27 (59%)	28 (47%)
Lack of efficacy <sup>1</sup>	0	0	1 (2%)
Adverse event	3 (4%)	11 (24%)	3 (5%)
Consent withdrawn	3 (4%)	2 (4%)	4 (7%)
Lost to follow-up	1 (1%)	3 (7%)	1 (2%)
Protocol violation	1 (1%)	1 (2%)	2 (3%)
Other	2 (3%)	1 (2%)	2 (3%)
Sponsor discontinued <sup>2</sup>	11 (16%)	9 (20%)	15 (25%)

<sup>1</sup>Lack of efficacy separated from "other" discontinuations

<sup>2</sup>Sponsor discontinued = sponsor termination of study.

Thirteen percent of the subjects enrolled in the preliminary phase discontinued due to lack of efficacy. Lack of efficacy as a reason for discontinuation was similar to the percentage of subjects discontinuing due to adverse events. In the randomized phase of the study, the most common reason for discontinuation was "Sponsor discontinued" which was due to termination of the study and included 16-25% of subjects in each treatment group. The percent of subjects discontinuing were equivalent between groups. More subjects discontinued due to adverse events in the lithium group compared to the placebo and lamotrigine group. The numbers of subjects included in the ITT, safety, and efficacy analyses are included in Table C-7.3.

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**Table C-7.3. SCAB2006 Study Populations**

	Preliminary Phase	Randomized Phase		
	Open-Label Lamotrigine	Placebo	Lithium	Lamotrigine
# Subjects Enrolled	349	70	46	59
# Subjects in Safety Population	347	69	46	58
# Subjects in Efficacy Population	334	69	44	58

ITT population: all subjects who were randomized

Safety population: all subjects in the ITT population who received at least one dose of study drug.

Efficacy population: all subjects in the ITT population who received at least one dose of study drug and had at least one post-screen (preliminary phase) or post-randomization (randomized phase) efficacy assessment.

### C-8 Baseline Demographics/Severity of Illness

**Table C-8.1 Patient Demographics at Screening and Randomization (mean ± SD)**

	Preliminary Phase	Randomized Phase		
	Open-label lamotrigine (n = 347)	Placebo (n = 69)	Lithium (n = 46)	Lamotrigine (n = 58)
<b>Sex</b>				
Female	175 (50%)	35 (51%)	24 (52%)	32 (55%)
Male	172 (50%)	34 (49%)	22 (48%)	26 (45%)
<b>Race</b>				
White	311 (90%)	62 (90%)	45 (98%)	52 (90%)
Black	18 (5%)	4 (6%)	0	3 (5%)
Asian	3 (<1%)	2 (3%)	0	0
Hispanic	13 (4%)	0	1 (2%)	3 (5%)
Other	2 (<1%)	1 (1%)	0	0
<b>Age (years)</b>	41 ± 12	41 ± 11	42 ± 11	41 ± 13
<b>Weight (kg)</b>	78 ± 17	79 ± 18	79 ± 18	78 ± 18
<b>Height (cm)</b>	170 ± 11	170 ± 10	171 ± 10	171 ± 10

modified from Sponsor tables 6.3

Demographics were fairly similar between groups. A high percentage ( $\geq 90\%$ ) of subjects were Caucasian with little representation among other racial groups.

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Table 8.2. Severity of Illness Indicators

	Preliminary Phase	Randomized Phase		
	Open-label lamotrigine (n = 347)	Placebo (n = 69)	Lithium (n = 46)	Lamotrigine (n = 58)
DSM-IV Diagnosis severity <sup>1</sup>				
Mild	27 (8%)	9 (13%)	7 (15%)	5 (9%)
Moderate	167 (48%)	30 (43%)	21 (46%)	30 (52%)
Severe (without psychotic features)	89 (26%)	20 (29%)	12 (26%)	16 (28%)
Severe (with psychotic features)	64 (18%)	10 (14%)	6 (13%)	7 (12%)
MRS-11				
at screening		22 ± 8	22 ± 6	22 ± 7
at randomization		2 ± 3	3 ± 4	3 ± 4
HAM-D <sub>17</sub>				
at screening		7 ± 5	7 ± 4	8 ± 6
at randomization		3 ± 3	3 ± 3	3 ± 3
CGI-S				
at screening		4 ± 1	4 ± 0.7	4 ± 0.6
at randomization		2 ± 0.8	2 ± 0.7	2 ± 0.7
Duration of current mood episode <sup>1</sup>				
2 to ≤ 4 weeks	161 (46%)	31 (45%)	20 (43%)	24 (41%)
4 to ≤ 8 weeks	94 (27%)	18 (26%)	15 (33%)	14 (24%)
8 to ≤ 24 weeks	73 (21%)	15 (22%)	10 (22%)	14 (24%)
> 24 weeks	18 (5%)	4 (6%)	1 (2%)	6 (10%)
Duration of bipolar illness (years)	19 ± 12	20 ± 11	18 ± 12	17 ± 12
Age of onset				
Depressive episode	23 ± 12	22 ± 12	25 ± 12	25 ± 13
Manic/Mixed episode	26 ± 12	24 ± 10	30 ± 14	27 ± 11
Hospitalized in past (% of subjects)	66	61	67	60
# Hospitalizations	5 ± 6	5 ± 7	4 ± 3	5 ± 7
# Mood episodes in last year				
Mania	1.4 ± 0.8	1.6 ± 0.9	1.3 ± 0.7	1.3 ± 0.8
Hypomania	0.3 ± 0.6	0.3 ± 0.7	0.4 ± 0.6	0.2 ± 0.5
Depression	1.0 ± 0.8	1.0 ± 0.8	1.0 ± 0.9	0.9 ± 0.6
Mixed	0.2 ± 0.5	0.2 ± 0.7	0.2 ± 0.5	0.2 ± 0.5
# Mood episodes in lifetime				
Mania	10 ± 11	12 ± 13	8 ± 10	8 ± 7
Hypomania	4 ± 13	4 ± 10	3 ± 8	4 ± 14
Depression	9 ± 10	10 ± 10	8 ± 9	6 ± 5
Mixed	2 ± 7	3 ± 11	1 ± 3	1 ± 4
Rapid cyclers (% of subjects)	27	33	27	21
Suicide attempt in past (% of subjects)	29	19	41	28
Psychotic episodes with bipolar disorder (% subjects)	46	41	46	38

Modified from Sponsor's table 6.5, <sup>1</sup>At screening

The severity, duration and history of bipolar illness were consistent between the treatment groups. Most subjects were moderately ill with a duration of current mood episode between 2 and 4 weeks. The number of lifetime manic episodes and depressive episodes were slightly higher in the placebo group compared to the lithium and lamotrigine groups. The lithium group had a higher percentage of subjects with a history of suicide attempts.

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### C-9 Concomitant Medications

#### Preliminary Phase

Similar to SCAB2003, 75% (129/173) of subjects used at least one concomitant psychiatric medication during the preliminary phase. The most common concomitant psychotropics are listed in Table C-9.1.

Table C-9.1. Most Common Concomitant Psychotropics in the Preliminary Phase for Subjects Progressing to the Randomized Phase

	Number (%) of Subjects		
	Placebo (n = 69)	Lithium (n = 46)	Lamotrigine (n = 58)
Antidepressants	10 (14%)	6 (13%)	11 (19%)
Venlafaxine	4 (6%)	1 (2%)	3 (5%)
Benzodiazepines	19 (28%)	19 (41%)	23 (40%)
Lorazepam	7 (10%)	9 (20%)	12 (21%)
Diazepam	2 (3%)	0	5 (9%)
Clonazepam	6 (9%)	5 (11%)	4 (7%)
Anticonvulsants/Mood Stabilizers	27 (39%)	16 (35%)	27 (47%)
Lithium	13 (19%)	11 (24%)	16 (28%)
Valproate/valproic acid	12 (17%)	4 (9%)	10 (17%)
Carbamazepine	5 (7%)	2 (4%)	3 (5%)
Antipsychotics	25 (36%)	18 (39%)	19 (33%)
Haloperidol	6 (9%)	5 (11%)	5 (9%)
Risperidone	4 (6%)	4 (9%)	5 (9%)
Olanzapine	4 (6%)	1 (2%)	4 (7%)

From Sponsor's table 6.16

#### Randomized Phase

Similar to SCAB2003, subjects could receive "short-term use" of certain pre-specified benzodiazepines during the study for control of agitation, irritability, restlessness, insomnia and hostile behavior.

Table C-9.2. Most Commonly Used Benzodiazepines During Randomized Phase up to TIME

	Randomized Phase		
	Placebo (n = 69)	Lithium (n = 46)	Lamotrigine (n = 58)
Lorazepam			
# (%) of Subjects	9 (13%)	7 (15%)	12 (21%)
Mean (SD) Daily Dose (mg)	0.8 (0.3)	1.2 (0.4)	1.2 (0.3)
Mean (SD) Duration (Days)	2.3 (1.3)	15 (9)	37 (29)

As with SCAB2003, the Sponsor was contacted to provide the daily dose and duration of benzodiazepine use. In this study, lorazepam was used most frequently; other benzodiazepines were used in ~2-6% of subjects in each group. Lorazepam was used by more subjects in the lamotrigine group with a greater duration of use, though the mean daily dose and % of subjects receiving concomitant lorazepam was comparable to the other treatment groups.

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A review of concomitant medications identified subjects who were taking concomitant psychotropic medications during the randomized phase but who were not noted as reaching TIME.

Table C-9.3. Concomitant Psychiatric Medications Taken During the Randomized Phase Prior to TIME.

	Placebo (n = 69)	Lithium (n = 46)	Lamotrigine (n = 58)
Antipsychotics	1 (1%)	1 (2%)	1 (2%)
Antidepressants	2 (3%)	1 (2%)	1 (2%)
Anticonvulsants/Mood stabilizers	1 (1%)	3 (7%)	1 (2%)

Concomitant antipsychotics included thioridazine, zuclopenthixol depot and risperidone. Concomitant antidepressants included venlafaxine, bupropion, and paroxetine. Concomitant anticonvulsants/mood stabilizers included lamotrigine, valproate, lithium and carbamazepine. The Sponsor provided brief summaries for the two subjects using marketed lamotrigine prior to TIME during the randomized phase. One subject in the lithium group began using marketed lamotrigine on the last day of study participation, this subject was withdrawn from the study due to Sponsor discontinuation of the study. The other subject began using marketed lamotrigine one week after entering the randomized phase and continued throughout the entire study per the study database; when the CRF was reviewed the subject began using marketed lamotrigine at study completion (start date in database wrong). This subject completed the study without reaching TIME. A summary of the concomitant psychotropic medications is in Table C-9.3-A in Appendix A.2. As in SCAB2003, the results were reanalyzed with the TIME date defined as the start date of the concomitant medication. (see Table C-10.2.1 in Section 10.2, Division's Analysis)

Five subjects received concomitant psychotropic medications either started prior to the randomized phase and continued into the randomized phase or initiated in the randomized phase for non-mood event conditions. Use of concomitant medications were fairly uniform between the treatment groups: 3% placebo, 4% lithium and 2% in the lamotrigine group. TIME was not redefined for subjects for whom the concomitant medication was initiated in the randomized phase for the treatment of smoking cessation.

Though patients could have positive urine toxicology results for marijuana and/or cocaine and continue in the trial, few randomized patients had these positive findings (see Table C-9.4-A in Appendix A.2)

### C-10 Efficacy Results

#### C-10.1 Sponsor's Analysis

Similar to SCAB2003, the Sponsor submitted an amendment (Amendment #9) which changed the primary efficacy endpoint after the protocol had been completed. Please see this section of study SCAB2003 for further elaboration. The average total daily lamotrigine dose for all randomized subjects was  $177 \pm 54$  mg/day. The average modal total daily dose was  $207 \pm 73$  mg/day.

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Table C-10.1.1 Number (%) of Subjects in Each TIME Analysis

	Placebo (n = 69)	Lithium (n = 44)	Lamotrigine (n = 58)
Number of subjects with event, n (%)			
TIME(ABE)	55 (80%)	25 (57%)	37 (64%)
TIME(SIS)	58 (84%)	34 (77%)	40 (69%)
TIME(Only)	49 (71%)	18 (41%)	28 (48%)

Table C-10.1.2. Sample size (%) included in TIME analyses

	Efficacy Population (n = 171)	Placebo (n = 69)	Lithium (n = 44)	Lamotrigine (n = 58)
Subjects reaching TIME	95 (55%)	49 (71%)	18 (41%)	28 (48%)
Discontinuation without reaching TIME				
Protocol violation	4 (2%)	1 (1%)	1 (2%)	2 (3%)
"Other"	5 (3%)	2 (3%)	1 (2%)	2 (3%)
Lost to follow-up	4 (2%)	1 (1%)	2 (5%)	1 (2%)
Consent withdrawn	8 (5%)	2 (3%)	2 (5%)	4 (7%)
AE related to bipolar disorder	1 (< 1%)	0	1 (2%)	0
AE not related to bipolar disorder	15 (9%)	3 (4%)	9 (20%)	3 (5%)
Sponsor discontinued	35 (20%)	11 (16%)	9 (20%)	15 (26%)
Completed study on monotherapy	4 (2%)	0	1 (2%)	3 (5%)

From Sponsor correspondence 11/15/02

Table C-10.1.3. Sponsor's Table: Summary of Analysis TIME(ABE)  
 Summary of Analysis of TIME(ABE),  
 Efficacy Population, 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 <sup>a</sup>	-	0.006 <sup>b</sup>	0.023 <sup>b</sup>

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

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Figure C-10.1.1. Sponsor's Figure: Survival Estimates for TIME(ABE)

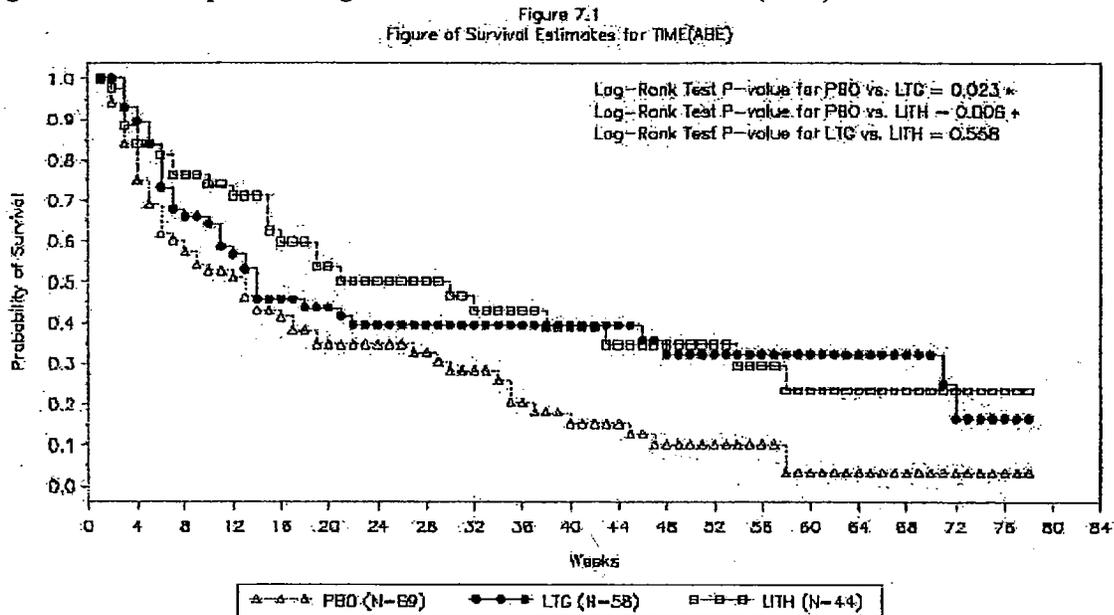


Table C-10.1.4. Sponsor's Table: Summary of Analysis of TIME(SIS)

**Summary of Analysis of TIME(Survival in Study),  
Efficacy Population, 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 <sup>a</sup>	-	ns	0.030 <sup>b</sup>

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

## CLINICAL REVIEW

Figure C-10.1.2. Sponsor's Figure: Survival Estimates for TIME(SIS)

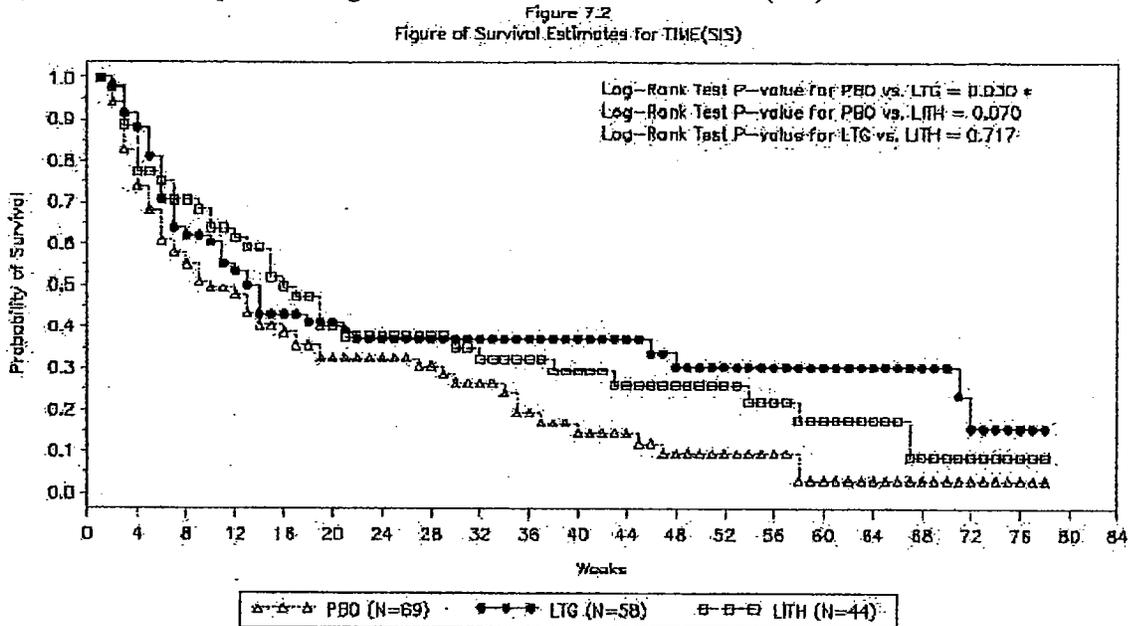


Table C-10.1.5. Sponsor's Table: Summary of Analysis of TIME(Only)

### Summary of Analysis of TIME(Only), Efficacy Population, 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 <sup>a</sup>	-	0.003 <sup>b</sup>	0.018 <sup>b</sup>

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

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Figure C-10.1.3. Sponsor's Figure: Survival Estimates for TIME(Only)

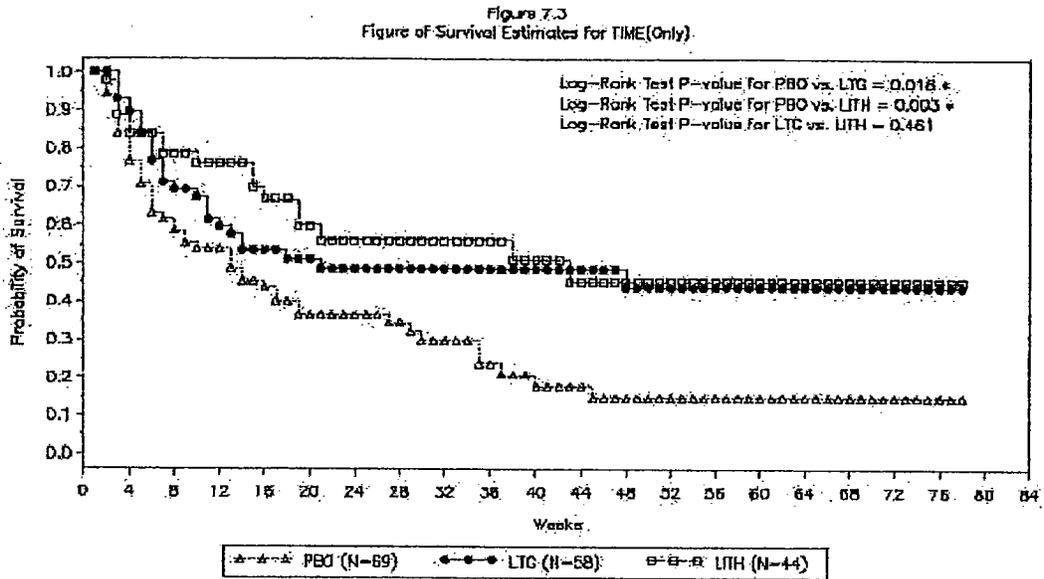
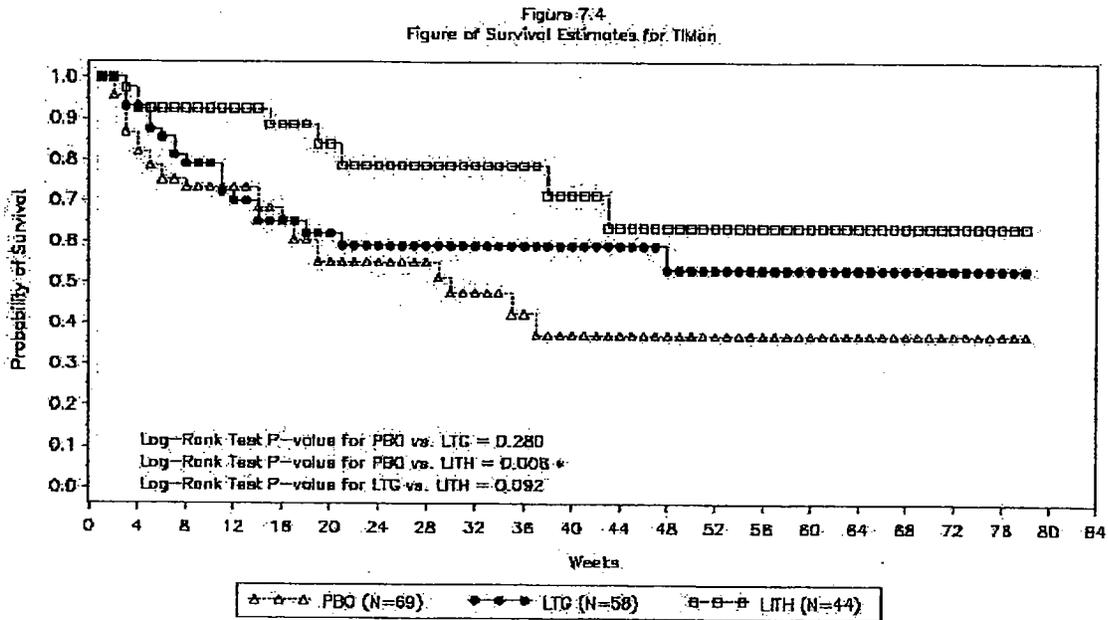


Figure C-10.1.4. Sponsor's Figure: Survival Estimates for TIMan



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Table C-10.1.6. Summary of Analysis of TIMan

	PBO N= 69	Li N= 44	LTG Flex Dose N = 58
Subjects with Event, n (%)	28 (40%)	8 (18%)	20 (34%)
Median Time to Event (days)	203	n/c	n/c
Confidence Interval	(108, n/c)	-	-
Survival Estimate, Week 76	0.371	0.635	0.532
p-value*		0.006	0.280

n/c = not calculable due to insufficient number of events

\*significantly different from placebo

Figure C-10.1.5. Sponsor's Figure: Survival Estimates for TIDep

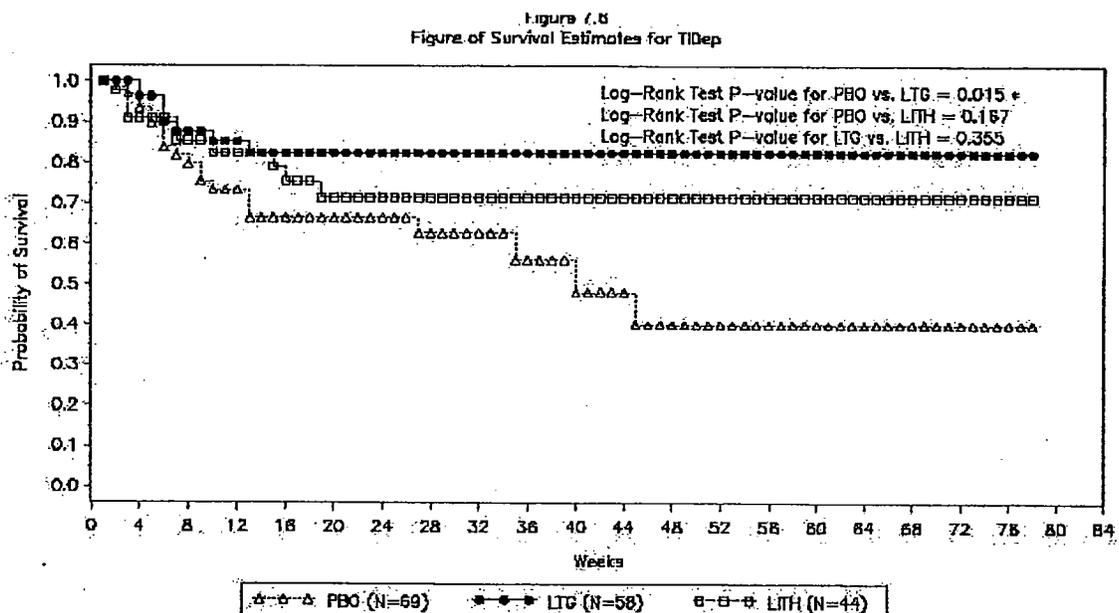


Table C-10.1.7. Summary of Analysis of TIMan

	PBO N= 69	Li N= 44	LTG Flex Dose N = 58
Subjects with Event, n (%)	21 (30%)	10 (23%)	8 (14%)
Median Time to Event (days)	269	n/c	n/c
Confidence Interval	(183, n/c)	-	-
Survival Estimate, Week 76	0.401	0.714	0.824
p-value*		0.167	0.015

n/c = not calculable due to insufficient number of events

\*significantly different from placebo

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lamotrigine] and TIME(Only) [ $p = < 0.001$  lithium,  $p = 0.05$  lamotrigine]. A similar pattern emerged for TIMan, only lithium differed from placebo for TIDep.

Another subgroup analysis evaluated rapid cyclers enrolled in the trial. Approximately 20 - 30% of subjects in each treatment group were rapid cyclers ( $\geq 4$  episodes in the previous year). Per protocol, rapid cyclers could have no more than 6 cycles in the previous year to qualify for enrollment. Only lithium was statistically different from placebo for TIME(ABE) [ $p = 0.02$ ] and TIME(Only) [ $p = 0.02$ ] and only for non-rapid cyclers.

A summary of the results of several psychiatric rating scales as secondary efficacy measures can be found in Table C-10.1.9-A in Appendix A.2.

### C-10.2 Division's Analyses

As with SCAB2003, the focus of the Division's analysis was on the original primary endpoint, TIME(Only).

During the review process, several concerns arose which prompted the Division to perform several different analyses excluding or including additional subjects. These analyses are described below.

#### 1. Recoding of TIME events (see SCAB2003)

Table C-10.2.1. Concomitant Psychotropic Medication Use, Redefined TIME Events

Subject	Treatment	Old TIME	New TIME	Medication and Condition treated
20765	Placebo	None	4/15/99	Paroxetine - Depression
20768	Lamotrigine	None	10/8/98	Thioridazine - Hypomania
6075	Placebo	None	12/11/97	Lithium - Mania
6565	Lithium	None	11/24/99	Valproate - Bipolar disorder
6575	Lithium	None	11/25/99	Carbamazepine - Bipolar disorder

Table C-10.2.1 Reanalysis with Redefined TIME Events

	Lamotrigine mg versus placebo
TIME(ABE)	0.0221
TIME(SIS)	0.0286
TIME(Only)	0.0138
TIMan	Not done
TIDep	Not done

A reanalysis of TIDep and TIMan were not performed since the Sponsor could not clarify which mood event was associated with the condition "bipolar" indicated in the case report forms.

**2. Questionable TIME endpoint**

Four subjects were categorized as having met TIME, but were never prescribed a psychotropic medication (or ECT) for treatment of a mood event (#23405, #6738, #20743, #5915). See discussion in SCAB2003.

The Sponsor submitted summaries for these four subjects and this reviewer thought it reasonable to accept these subjects as having reached TIME.

**3. Concomitant Medications.**

A separate analysis was also performed excluding subjects taking concomitant medications that could have confounded the study results. This included subjects taking antidepressants, antipsychotics, and/or antimanic agents during the preliminary phase that continued into the randomized phase as well as those initiated during the randomized phase for non-mood events such as insomnia, anxiety, restlessness and smoking cessation (see Table C-9.3-A in Appendix A.2). The results from this analysis did not differ significantly from the Sponsor's analysis.

**C.10.3 Combined Analysis**

Originally, the combined analysis of data from SCAB2003 and SCAB2006 was the primary efficacy analysis. Amendments to SCAB2003 and SCAB2006, submitted after the studies were completed but prior to unblinding of the data, eliminated this analysis as the primary analysis (see section C-5 for each protocol). The Sponsor did, however, provide this combined analysis in a separate report submitted in this NDA. Table 10.3 depicts these results, Sponsor figures for these analyses are in Appendix A.3. The combined analysis is robustly positive, however, this analysis may be overpowered.

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Table C-10.3. Summary of TIME Analyses for SCAB2003 + SCAB2006 (combined)

	PBO N= 188	Li N= 164	LTG N = 223
<b>TIME(ABE)</b>			
Subjects with Event, n (%)	153 (81%)	108 (66%)	160 (72%)
Median Time to Event (days)	58	123	97
Confidence Interval (95%)	(44, 85)	(94, 166)	(70, 146)
Survival Estimate, Week 76	NA	NA	NA
p-value*		< 0.001	< 0.001
<b>TIME(SIS)</b>			
Subjects with Event, n (%)	165 (88%)	133 (81%)	174 (78%)
Median Time to Event (days)	52	89	86
Confidence Interval (95%)	(34, 75)	(72, 114)	(62, 128)
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.006	< 0.001
<b>TIME(Only)</b>			
Subjects with Event, n (%)	115 (61%)	74 (45%)	111 (50%)
Median Time to Event (days)	86	184	197
Confidence Interval (95%)	(58, 121)	(119, n/c)	(144, 388)
Survival Estimate, Week 76	NA	NA	NA
p-value*		< 0.001	< 0.001
<b>TIMan</b>			
Subjects with Event, n (%)	47 (25%)	18 (11%)	46 (21%)
Median Time to Event (days)	n/c	n/c	n/c
Confidence Interval (95%)	-	-	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		< 0.001	0.034
<b>TIDep</b>			
Subjects with Event, n (%)	68 (36%)	56 (34%)	65 (29%)
Median Time to Event (days)	270	n/c	n/c
Confidence Interval (95%)	(138, n/c)	-	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.120	0.009

n/c = not calculable due to insufficient number of events, NA = not available  
 \*significantly different from placebo

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term management of bipolar I disorder to delay the relapse/recurrence of depressive episodes is not supported. TIME(BipEvent) could support a delay in the relapse/recurrence of mood episodes.

**VII. Integrated Review of Safety****A. Brief Statement of Conclusions**

The ISS includes a number of short-term acute trials and long-term trials. The long-term trials (26 to 76 weeks) were not designed to establish long-term safety. The acute and long-term controlled trials included a placebo treatment arm so that comparisons between lamotrigine and placebo regarding safety assessments could be made.

There were 10 deaths reported in the controlled trials, 9 deaths in subjects receiving lamotrigine and 1 death in a subject receiving placebo. Six of the 10 deaths were by suicide and one additional death was deemed a probable suicide. None of the lamotrigine-treated subjects' deaths was likely to be related to drug treatment. There were no serious adverse events that were unexpected. Most of the SAEs, with the exception of serious rash, were not considered likely to be drug-related. Separate safety evaluations focusing on rash, suicide and mania were conducted. Serious rash occurred in 3/2272 (0.1%) of lamotrigine-treated bipolar subjects, a rate lower than the rate of serious rash occurring in epilepsy patients in current labeling (0.3%). The occurrence of suicide and mania were not significantly different from placebo and are similar to rates reported in the literature; both suicide and mania are events that can occur in the course of bipolar illness.

**B. Description of Patient Exposure**

The cut-off dates for the collection of safety information for this submission was October 31, 2001 for all completed studies except SCAB2003, all ongoing studies, and spontaneous reports of deaths and serious adverse events. The cut-off date for collection of safety information for SCAB2003 was November 26, 2001. A 120-day safety update was submitted on 10/4/02 that provided safety data from 11/1/01 – 3/31/02, including three ongoing studies.

A total of 2272 subjects with bipolar disorder were treated with lamotrigine for a mean duration of 134 days for a total of 832 patient-years of exposure (average dose was not able to be calculated for some subjects). The mean dose of lamotrigine was  $122 \pm 79$  mg/day. Subjects  $\geq 65$  years of age had a total of 26 patient-years of exposure.

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Table B-1. Sponsor's Table: Cumulative Average Daily Lamotrigine Dose by Dose Range  
All Bipolar Disorder Studies  
(not all intervals included in table, data available out to 118 weeks)

Exposure to at Least	Total Number of Subjects	Number of Subjects Who Received Dose (mg/day)				
		0-≤25	>25-≤50	>50-<200	≥200-≤400	>400
1-7 Days	2272	2138	110	12	1	1
8-14 Days	2185	1836	315	25	1	1
15-21 Days	2108	390	1617	94	1	1
22-28 Days	1979	288	1563	122	1	1
29-35 Days	1908	160	1272	471	2	0
36-42 Days	1856	47	445	1360	2	0
7-10 Weeks	1702	6	84	1581	29	0
11-14 Weeks	1341	5	8	1220	106	0
15-18 Weeks	857	2	6	710	137	0
23-26 Weeks	545	3	4	360	177	0
27-30 Weeks	502	1	4	316	179	1
47-50 Weeks	309	0	2	181	121	5
51-54 weeks	264	0	1	158	102	3
75-78 Weeks	49	0	0	41	8	0
79-82 Weeks	46	0	0	38	8	0
Combined	2272	219	274	1510	259	7

From Sponsor's table on page 102 of ISS and table 7.4

In the bipolar disorder studies, 1510 (66%) of subjects received a cumulative average daily dose of lamotrigine in the range of 50-200 mg/day. The modal duration of exposure for the > 50- < 200 mg/day range was 7 to 10 weeks. Twenty-two percent (502/2272) of subjects received lamotrigine for at least 27 – 30 weeks (~7 months), 63% of these subjects received a cumulative average dose in the > 50- < 200 mg/day range and 36% in the ≥ 200 - ≤ 400 mg/day range. Twelve percent (264/2272) of subjects received lamotrigine for at least 51 to 54 weeks (~ 1 year), 60% of these subjects received a cumulative average dose in the > 50- < 200 mg/day range and 39% in the ≥ 200 - ≤ 400 mg/day range.

In the controlled bipolar disorder studies, a total of 827 subjects were treated with lamotrigine for a mean duration of 124 days for a total of 280 patient-years of exposure (average dose was not able to be calculated for some subjects). The mean dose of lamotrigine was 146 ± 114 mg/day.

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### C. Methods and Specific Findings of Safety Review

Medical, Conditions, Indications, Diseases, Adverse Events, Signs and Symptoms (MIDAS) coding dictionary was used in the original sNDA submission. In January 2002, the Global Clinical Safety and Pharmacovigilance (GCSP) event coding dictionary was changed from MIDAS to the Medical Dictionary for Regulatory Affairs (MedDRA). The 120-day safety update submitted on October 4, 2002 uses the MedDRA coding conventions.

### D. Adequacy of Safety Testing

The ISS includes a number of short-term acute trials and long-term trials. The long-term trials (26 to 76 weeks) were not designed to establish long-term safety. The acute and long-term controlled trials included a placebo treatment arm so that comparisons between lamotrigine and placebo regarding safety assessments could be made. Generally, the methods used to monitor safety were adequate. Other than adverse event queries, the long-term trials did not perform other safety assessments (vital signs, clinical laboratory assessments) at most study visits.

### E. Summary of Critical Safety Findings and Limitations of Data

#### E-1 Deaths in Controlled Trials

There were 10 deaths reported in the controlled trials, 9 deaths in subjects receiving lamotrigine and 1 death in a subject receiving placebo. Four of the 9 deaths in subjects receiving lamotrigine occurred during the preliminary phase of SCAB2003 that allowed concomitant psychotropic administration. Six of the 10 deaths were by suicide and one additional death was deemed a probable suicide. None of the lamotrigine-treated subjects' deaths was likely to be related to drug treatment. See summary table E-1-A in Appendix C.

#### E-2 Serious Adverse Events

There were no serious adverse events that were unexpected. Most of the SAEs, with the exception of serious rash, were not considered likely to be drug-related. Table E-2.1 provides a summary of SAEs occurring in > 2 subjects treated with lamotrigine in all bipolar studies. Table E-2.2-A in Appendix C provides a summary of SAEs occurring in > 1 subject treated with placebo, lithium, or lamotrigine in all controlled bipolar studies. The MIDAS term "suicide attempts" included attempted suicide, suicide gesture, possible suicide attempt, and "suicidal" included suicidal, suicidality, suicidal ideation, suicidal ideation with plan, suicidal thoughts, fleeting thoughts of suicide, suicidal urges, hospitalization for either suicidal thoughts or suicidal ideation. See Section E-7 (Special Searches) for a further discussion of suicide.

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Table E-2.1. Serious Adverse Events Occurring in > 2 Subjects Treated with Lamotrigine  
All Bipolar Studies

Serious Adverse Event	Number (%) of Subjects Total N = 2272
Any Serious Event	238 (10%)
All Mania	84 (4%)
Mania	72 (3%)
Mixed	7 (< 1%)
Hypomania	7 (< 1%)
Emotional Lability	5 (< 1%)
Psychiatric Depression	41 (2%)
Psychotic Disorder	9 (< 1%)
All Suicidal Behavior	45 (2%)
Suicide	5 (< 1%)
Suicide Attempt	18 (< 1%)
Suicidal	22 (< 1%)
Accidental Injury	14 (< 1%)
Convulsions	4 (< 1%)
Infection	5 (< 1%)
Headache	3 (< 1%)
Cholelithiasis	3 (< 1%)
Syncope	3 (< 1%)
Confusion	3 (< 1%)
Reaction Unevaluable*	4 (< 1%)

from Sponsor Table 10.1 in ISS

\*Per Sponsor, included alcohol abuse, appendix mass, sphincter muscle release surgery/hemorrhoid removal, inflamed appendix

The SAE “convulsions” are discussed in section E-9 (other safety issues) with narratives provided in Table E-9-A in Appendix C.

Serious rash occurred in 3 subjects treated with lamotrigine in all bipolar trials and one subject receiving placebo. Narrative summaries for the lamotrigine serious rash cases is in Table E-2.3-A of Appendix C. One of these three cases was classified as a mild case of Stevens-Johnson syndrome. The rash in the subject receiving placebo was classified as erythema multiforme. No cases of toxic epidermal necrolysis occurred. No SAEs for serious rash were reported for subjects treated with lamotrigine in the controlled trials. See Section E-7 (Special Searches) for a further discussion of rash.

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### E-3 Discontinuations Due to Adverse Events

#### All Bipolar Studies

Table E-3.1 Adverse Events Leading to Discontinuation of  $\geq 1\%$  of Subjects  
All Bipolar Studies

	Number (%) of Subjects
All Rash	126 (6%)
Rash	118 (5%)
Maculopapular Rash	4 (< 1%)
Urticaria	3 (< 1%)
Bullous Eruption	1 (< 1%)
Erythema Multiforme	1 (< 1%)
Stevens Johnson Syndrome	1 (< 1%)
Pruritis	13 (< 1%)
Contact Dermatitis	1 (< 1%)
All Mania	56 (2%)
Mania	49 (2%)
Mixed	3 (< 1%)
Hypomania	5 (< 1%)
Psychiatric Depression	31 (1%)

From Sponsor Table 11.1

For all bipolar studies, approximately one-third to one-half of rashes led to withdrawal from the study. The Sponsor stated that this high rate of discontinuation due to rash was due to the study guidelines instituted for the bipolar program. Investigators were instructed to withdraw subjects from the study if they developed a rash unless the rash was clearly unrelated to the study medication.

Thirty subjects (1%) were withdrawn from all bipolar studies due to suicide/suicidal behavior: suicidal (n = 15), attempted suicide (n = 5), suicide (n = 5) and overdose (n = 1). "Convulsions" led to withdrawal of 3 subjects (see Table E-9-A in Appendix C for narrative summaries).

#### Controlled Bipolar Studies

In the controlled bipolar studies, 10 – 18% of subjects withdrew due to adverse events (Table E-3.2-A in Appendix C). The adverse events causing subject withdrawal were fairly similar between treatment groups with some exceptions. For the lamotrigine group, 3% of subjects withdrew due to "all rash" compared to 1% of subjects in the placebo and lithium groups. A more detailed breakdown of withdrawals due to "all rash" and related adverse events is in Table E-3.2.

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Table E-3.2. Subject Discontinuation Due to Rash

	Number (%) of Subjects		
	Placebo (n = 685)	Lithium (n = 280)	Lamotrigine (n = 827)
All Rash	10 (1%)	4 (1%)	25 (3%)
Rash	9 (1%)	3 (1%)	21 (3%)
Maculopapular Rash	0	0	1 (< 1%)
Urticaria	2 (< 1%)	1 (< 1%)	2 (< 1%)
Bullous Eruption	0	0	1 (< 1%)
Erythema Multiforme	0	0	0
Stevens Johnson Syndrome	0	0	0
Pruritis	2 (< 1%)	1 (< 1%)	4 (< 1%)
Contact Dermatitis	0	0	1 (< 1%)

### E-4 Adverse Events

#### All Controlled Bipolar Studies

Table E-4.1. Sponsor's Table: Adverse Events Reported in > 5% of Subjects in Any Group

**Adverse Events Occurring in ≥5% of Subjects in Any Group  
Safety Population, All Controlled Bipolar Disorder Studies**

Adverse Event	Number (%) of Subjects		
	PBO N=685	LI N=280	LTG N=827
Any Adverse Event	513 (75)	194 (69)	628 (76)
Headache	147 (21)	38 (14)	204 (25)
Nausea	102 (15)	45 (16)	118 (14)
Infection	73 (11)	22 (8)	87 (11)
Dizziness	52 (8)	20 (7)	77 (9)
All Rash <sup>a</sup>	53 (8)	12 (4)	73 (9)
Rash	43 (6)	9 (3)	62 (7)
Somnolence	43 (6)	27 (10)	72 (9)
Pain	51 (7)	11 (4)	71 (9)
Back Pain	30 (4)	7 (3)	56 (7)
Insomnia	47 (7)	20 (7)	61 (7)
Accidental injury	42 (6)	16 (6)	55 (7)
Influenza	52 (8)	16 (6)	49 (6)
Diarrhea	63 (9)	39 (14)	47 (6)
Dyspepsia	31 (5)	12 (4)	46 (6)
All Mania <sup>b</sup>	27 (4)	9 (3)	45 (5)
Xerostomia (Dry Mouth)	27 (4)	7 (3)	44 (5)
Fatigue	29 (4)	13 (5)	42 (5)
Vomiting	25 (4)	24 (9)	40 (5)
Tremor(s)	36 (5)	32 (11)	41 (5)
Rhinitis	31 (5)	12 (4)	36 (4)
Abnormal Thoughts	11 (2)	13 (5)	11 (1)

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The adverse events occurred in a similar percentage of subjects when comparing lamotrigine to placebo. Adverse events termed "rash" occurred in 6% of placebo subjects and 7% of lamotrigine-treated subjects. "All mania" occurred in 4% of placebo subjects and 5% of lamotrigine-treated subjects. More detailed information regarding adverse events of rash, mania, and suicide are in Section E-7. A review of all adverse events noted few that appeared to be more frequent in the lamotrigine group compared to the placebo group: menstrual disorder (2% vs. < 1%), arthralgia (4% vs. 2%), agitation (4% vs. 2%), sinusitis (3% vs. 1%) and contact dermatitis (2% vs. < 1%). Arthralgia, agitation and sinusitis are listed in the proposed labeling for adverse events but menstrual disorder and contact dermatitis are not (though contact dermatitis is listed in the section on epilepsy trials).

### E-5 Laboratory

Clinical chemistry and hematology data were collected for the protocols in the mood disorders program. Thyroid function data was collected for all controlled studies with the exception of SCA20022 and SCA20025. Clinical chemistry analytes included creatinine, alkaline phosphatase, ALT, T4, T3 uptake, FTI, TSH; hematology analytes included hemoglobin, platelets and total WBC.

The laboratory data were included in the ISS but summarized separately into the categories pivotal long-term, supportive long-term 26 weeks, supportive long-term 32 weeks, acute controlled bipolar depression monotherapy studies, acute controlled mania monotherapy study, acute controlled mania adjunctive study and uncontrolled studies. This review focused on the two pivotal trials and the acute controlled trials. Threshold limits (expanded normal range) were defined for several analytes in the clinical studies (Table E-5.1). An expanded normal range was not defined for thyroid function tests.

Table E-5.1. Sponsor's Table: Expanded Normal Range for Clinical Studies

Sample	Test	Units	Expanded Normal Range
Hematology	Hemoglobin	g/dL	11.5 - 20.0 (male) 9.5 - 18.5 (female)
	WBC	thou/cu.mm	2.5 - 16.0
	Platelets	thou/cu.mm	75 - 700
Clinical Chemistry	Creatinine	Umol/L	30 - 180
	Alkaline Phosphatase	U/L	≤ 350
	ALT	U/L	≤ 180

Sponsor's table on page 213 ISS

The number of subjects with clinical chemistry and hematology changes from randomization day 1 are listed in Table E-5.1-A in Appendix C. Table E-5.2 lists subjects with laboratory values outside of the expanded normal range.

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Table E-5.2. Number of Subjects with Laboratory Values Outside of Expanded Normal Range  
SCAB2003 + SCAB2006

	Placebo (n = 190)	Lithium (n = 166)	Lamotrigine (n = 227)
Creatinine Low/High	0/0	1/0	0/2 (RD1), 1 (Week 52)
ALT High	1 (Week 52)	0	1 (RD1), 1 (Week 28)
Hemoglobin Low	0	1 (RD1)	2 (Week 52)
Total WBC High	1 (RD1)	1 (Week 52)	0

RD1 = Randomized Day 1

A review of the data from the acute controlled monotherapy trials did not indicate significant laboratory changes in the lamotrigine groups compared to the placebo groups that is not already included in labeling.

### E-6 Vital Signs

#### Blood pressure and pulse

For the two pivotal studies, vital signs were obtained at very few visits (randomized day 1, week 52 and week 76). No significant differences were noted between placebo and lamotrigine-treated subjects. A review of the mean changes in vital signs obtained in the acute controlled monotherapy trials did not reveal any significant differences between placebo and lamotrigine-treated subjects.

#### Weight

Weight was obtained at multiple visits throughout the study (12 visits in 76 weeks). Subjects in the placebo and lithium-treated groups tended to gain weight over the course of the study while subjects in the lamotrigine-treated group tended to lose weight – though attrition was substantial over the course of these long-term trials. The acute controlled trials had similar weight changes between lamotrigine and placebo groups.

Table E-6. Mean Change in Weight (kg) from Randomized Day 1

	Placebo (n = 190)	Lithium (n = 166)	Lamotrigine (n = 227)
Week 8	+ 0.2 (n = 127)	+ 0.3 (n = 117)	+ 0.5 (n = 172)
Week 20	+ 0.2 (n = 101)	+ 0.6 (n = 89)	0.0 (n = 138)
Week 28	+ 0.2 (n = 81)	+ 0.7 (n = 74)	-0.5 (n = 116)
Week 52	+ 2.2 (n = 39)	+2.5 (n = 53)	-0.4 (n = 82)
Week 76	+ 1.2 (n = 11)	+4.2 (n = 15)	-2.2 (n = 27)

Sponsor's table 56, combined analysis report

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**Table E-7.1. Severity of Rashes in Lamotrigine-Treated Subjects for Categories Adverse Event, Serious Adverse Event, and Discontinuation due to Adverse Event  
All Bipolar Studies**

	Number (%) of Subjects (N = 2272)	Mild	Moderate	Severe
<b>AE rash</b>				
All rash	323 (14%)	192	112	14
Rash	294 (13%)	174	102	13
Maculopapular rash	8 (< 1%)	6	2	0
Urticaria	22 (< 1%)	13	8	1
Bullous Eruption	2 (< 1)	1	1	0
Erythema Multiforme	6 (< 1%)	5	0	1
Stevens Johnson Syndrome	1 (< 1%)	1	0	0
Pruiritis	112 (5%)	82	24	6
Contact Dermatitis	28 (1%)	20	8	0
Exfoliative Dermatitis	2 (< 1%)	2	0	0
<b>SAE rash</b>				
All rash	3 (1%)	0	1	1
Rash	2 (< 1%)	0	1	1
Maculopapular rash	0	-	-	-
Urticaria	0	-	-	-
Bullous Eruption	0	-	-	-
Erythema Multiforme	0	-	-	-
Stevens Johnson Syndrome	1 (< 1%)*	1	-	-
Pruiritis	1 (< 1%)	0	1	0
<b>D/C due to rash</b>				
All rash	126 (6%)	45	67	11
Rash	118 (5%)	42	63	10
Maculopapular rash	4 (< 1%)	2	2	0
Urticaria	3 (< 1%)	0	2	1
Bullous Eruption	1 (< 1%)	1	0	0
Erythema Multiforme	1 (< 1%)	0	0	1
Stevens Johnson Syndrome	1 (< 1%)	1	0	0
Pruiritis	13 (< 1%)	4	6	3
Contact Dermatitis	1 (< 1%)	1	0	0

from Sponsor Tables 8.1, 10.1, 11.1

\*Rash was originally not thought to be a SAE, rash was subsequently diagnosed as mild SJS and considered to be serious

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ON ORIGINAL**

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### All Controlled Bipolar Studies

Table E-7.2 summarizes the reports of rash occurring in the controlled bipolar studies.

Table E-7.2. Reports of Rash for Categories Adverse Event, Serious Adverse Event, and Discontinuation due to Adverse Event - Controlled Studies

	Number (%) of Subjects		
	Placebo (n = 685)	Lithium (n = 280)	Lamotrigine (n = 827)
<b>AE rash</b>			
All rash	53 (8%)	12 (4%)	74 (9%)
Rash	43 (6%)	9 (3%)	62 (9%)
Maculopapular rash	2 (< 1%)	0	3 (< 1%)
Urticaria	5 (< 1%)	2 (< 1%)	6 (< 1%)
Bullous Eruption	1 (< 1%)	0	1 (< 1%)
Erythema Multiforme	2 (< 1%)	1 (< 1%)	2 (< 1%)
Stevens Johnson Syndrome	0	0	0
Pruritis	24 (4%)	8 (3%)	23 (3%)
Contact Dermatitis	2 (< 1%)	2 (< 1%)	14 (2%)
Exfoliative Dermatitis	2 (< 1%)	0	1 (< 1%)
<b>SAE rash</b>			
All rash	1	0	0
Rash	0	0	0
Maculopapular rash	0	0	0
Urticaria	0	0	0
Bullous Eruption	0	0	0
Erythema Multiforme	1	0	0
Stevens Johnson Syndrome	0	0	0
Pruritis	0	0	0
<b>D/C due to rash</b>			
All rash	10 (1%)	4 (1%)	25 (3%)
Rash	8 (1%)	3 (1%)	21 (3%)
Maculopapular rash	0	0	1 (< 1%)
Urticaria	2 (< 1%)	1 (< 1%)	2 (< 1%)
Bullous Eruption	0	0	1 (< 1%)
Erythema Multiforme	0	0	0
Stevens Johnson Syndrome	0	0	0
Pruritis	2 (< 1%)	1 (< 1%)	4 (< 1%)
Contact Dermatitis	0	0	1 (< 1%)

More "all rash" adverse events occurred in lamotrigine-treated subjects in all bipolar versus all controlled bipolar studies (14% versus 8%). A similar finding was observed with comparing discontinuations due to "all rash" (6% versus 3%). In the controlled trials, "rash" and contact dermatitis appeared to occur more frequently in the lamotrigine group compared to the placebo and lithium groups. When comparing the number of subjects in the categories "all rash", pruritis, contact dermatitis and exfoliative dermatitis combined, the findings were similar between lamotrigine (13%) and placebo (12%).

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### Suicide

Per a request from the Division, a DSMB was constituted to review all suicide and suicide attempt data as studies were ongoing. The DSMB was comprised of three experts (two academic psychiatrists and a statistician) independent of the Sponsor. When evaluating the rates of suicide and suicide attempts by exposure, the Sponsor concluded that “for all controlled bipolar disorder studies, the lamotrigine suicide and suicide attempt rates were 0.7% and 1.8% per year of exposure, respectively. The placebo suicide and suicide attempt rates were 0.6% and 1.1% per year of exposure, respectively”. These rates of suicidal behavior appear to be similar to that occurring in patients taking placebo or investigational antidepressants in major depressive disorder clinical trials. Suicidal behavior is an inherent risk in patients with bipolar disorder. Suicidal ideation is currently in labeling with a frequency of 4.6% (2/43) in patients receiving lamotrigine monotherapy for partial seizures.

Table E-7.3. Sponsor’s Table: Number of Subjects with Suicidal Behavior  
All Bipolar Studies

Study	N	Total Number of Subjects					
		Suicidal		Suicide Attempt		Suicide	
		PBO	LTG	PBO	LTG	PBO	LTG
All Bipolar Disorder Studies	2272 <sup>a</sup>	--	28	--	19	--	5
All Controlled Bipolar Disorder Studies	1512 <sup>b</sup>	2	7	2 <sup>c</sup>	5	1 <sup>c</sup>	2
Pivotal Long-term Studies, Preliminary Phase							
Combined Pivotal (8-16 wks)	1305	--	15	--	7	--	2
SCAB2003 (8-16 wks)	958	--	12	--	7	--	2
SCAB2006 (8-16 wks)	347	--	3	--	0	--	0
Pivotal Long-term Studies, Randomized Phase							
Combined Pivotal (76 wks)	583	1	3	1	1	0	1
SCAB2003 (76 wks)	410	1	2	1	0	0	1
SCAB2006 (76 wks)	175	0	1	0	1	0	0
Supportive Long-term Studies							
SCAA2012 (Prelim) (8-12 wks)	324	--	1	--	1	--	0
SCAA2012 (Rand) (26 wks)	180	0	1	0	0	0	0
SCAB2005 (32 wks)	137	0	1	0	1	0	0
Acute Controlled Bipolar Studies							
SCAB2001 (7 wks)	194	0	2	1 <sup>c</sup>	1	1 <sup>c</sup>	0
SCAA2010 (10 wks)	204	1	0	0	2	0	1
SCAA2008 (3 wks)	215	0	0	0	0	0	0
SCAB2009 (6 wks)	229	0	0	0	0	0	0
Uncontrolled Bipolar Studies							
SCAB2002 (52 wks)	124	--	2	--	2	--	0
SCAB2014 (52 wks)	127	--	0	--	0	--	1
105-601 (48 wks)	75	--	0	--	4	--	0
Unipolar Depression Studies							
SCA20022 (7 wks)	149	0	0	0	1	0	0
SCA20025 (7 wks)	301	1	1	0	0	0	0
SCAA2011 (8 wks)	437	0	0	0	0	0	0

a. Includes lamotrigine-exposed subjects only

b. Placebo, n = 685; lamotrigine, n = 827

c. For one placebo subject the outcome of the AE coded as suicide attempt was fatal and is summarized in this table as a suicide

Sponsor’s Table page 173 of ISS

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hypothyroidism and suicide attempt. No SAEs had been reported for SCA40912. No analysis of laboratory data were conducted as these studies were ongoing.

A total of 257 subjects were randomized in study SCA40910 (n = 247 in safety population). No deaths occurred in this study. Twelve SAEs were reported during this study. Seven SAEs occurred in subjects receiving placebo (n = 118): dystonic movements, psychiatric depression, suicidal (2), meningitis, attempted suicide and motor dysfunction. Five SAEs occurred in subjects receiving lamotrigine (n = 129): suicidal (2), mixed manic episode, attempted suicide and hypoglycemia.

The most common adverse events leading to discontinuation (> 1 subject) included suicidal (2% each group), mania (< 1% placebo, 2% lamotrigine) and rash (< 1% placebo, 4% lamotrigine). The rash discontinuations were classified as "rash" under all rash. There were no cases of serious rash or rash resulting in hospitalization during this study. Rash occurred in 7 (6%) of placebo subjects leading to discontinuation in 1 subject. Rash occurred in 12 (9%) of lamotrigine-treated subjects leading to discontinuation in 5 subjects.

A review of the data contained in the 120-day safety report and the final study report for the double-blind phase of SCA40910, including laboratory data, does not identify any new adverse events not previously reported in the ISS or in current labeling for lamotrigine.

Of note, the Sponsor submitted another safety update on February 26, 2003. Due to the timing of this submission and the pending application deadline, this reviewer was not able to incorporate this material into the final review of the application. However, it does appear that much of the data in this update is from the final study report for SCA40910 which was reviewed and incorporated into this report.

### E-9 Other Safety Issues

#### Abrupt Discontinuation of Lamotrigine

The Sponsor has proposed the following language under Dosing and Administration:

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

This section is in contrast to the discontinuation statement for epilepsy which incorporates a step-wise reduction in the dose of lamotrigine. It is common practice in psychiatry to discontinue antiepileptic drugs in a step-wise fashion unless an adverse event (e.g. rash) dictates otherwise. Anecdotal cases of seizures occurring in patients with no prior history of epilepsy have occurred, though there is no good published data regarding this issue.

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Table E-9. Sponsor's Table: Evaluation of Potential Lamotrigine Discontinuation Effects

**Adverse Events Occurring in  $\geq 5\%$  of Subjects  
in the First 21 Days Following Randomization  
Pivotal Long-term (76 Weeks) Controlled Monotherapy Studies  
Safety Population, SCAB2003 and SCAB2006 Combined Analysis**

Adverse Event	Number (%) of Subjects	
	PBO N=190	LTG N=227
Any Adverse Event	91 (48)	109 (48)
Headache	26 (14)	20 (9)
Nausea	17 (9)	14 (6)
Dizziness	12 (6)	3 (1)
Insomnia	9 (5)	9 (4)
Diarrhea	9 (5)	11 (5)
Fatigue	8 (4)	11 (5)
Somnolence	7 (4)	14 (6)

From Sponsor's table on page 248 of ISS

Events that occurred more often in the subjects randomized to placebo may indicate a lamotrigine-discontinuation effect. The only adverse events that appeared to occur more frequently in the placebo group were headache, dizziness and possibly nausea. A review of all nervous system adverse events did not note any cases of convulsion or adverse events consistent with seizures.

The Sponsor also evaluated adverse events occurring in the post-treatment (follow-up) phases of all controlled bipolar studies (except study 105-601 that did not have a follow-up visit). A post-treatment adverse event was any event that occurred more than one day after the last dosing date. In general, across all treatment groups, a low incidence of adverse events was reported during this phase. One adverse event termed "convulsions" occurred in the lithium group (< 1%).

### Dosing of Lamotrigine After Discontinuation of Valproate

In the preliminary phase of the pivotal trials, the dosing directions for lamotrigine stated that if valproate was discontinued, the dose of lamotrigine should be doubled immediately. The proposed labeling for lamotrigine dosing states that the lamotrigine dose should be doubled during the first week of discontinuation of valproate. Due to the well documented drug interaction between lamotrigine and valproate, and the potential increased risk of rash, the safety of this proposed lamotrigine dosing should be further evaluated.

It is unknown how many subjects underwent this immediate lamotrigine dose doubling during the preliminary phase after valproate was discontinued. During the preliminary phase of the two pivotal trials, approximately 15% of subjects

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(201/1305) received valproate. The overall disposition of these subjects is not known. For subjects in the preliminary phase who progressed to the randomized phase, 83 were receiving concomitant valproate; these 83 would have likely had their lamotrigine dose doubled when valproate was discontinued for the washout period prior to randomization. However, no data is available to determine if this lamotrigine dose doubling was followed per protocol. The Sponsor has been asked to submit data to support the safety of doubling the lamotrigine dose upon discontinuation of valproate therapy.

Per request, the Sponsor submitted concomitant medication information for the 3 subjects who experienced "serious rash" for the two weeks prior to development of rash and at the time of rash (see Section E-7 Special Searches). These cases were reviewed and none of these subjects were taking valproate within 2 weeks of the diagnosis of serious rash.

### VIII. Dosing, Regimen, and Administration Issues

The target dose for lamotrigine in bipolar disorder in the proposed labeling is 200 mg/day with a range of 100 mg/day to 400 mg/day. This dosing is consistent with the dosing during the two pivotal trials. Since the fixed dose study (SCAB2003) terminated two of the lamotrigine dose arms prior to completion of the study, the dose-response relationship for lamotrigine in bipolar disorder is not well characterized.

In proposed labeling, the Sponsor has provided tables that depict the lamotrigine dose escalation for patients not taking valproate or enzyme-inducing drugs, patients taking valproate and patients taking enzyme-inducing drugs. Dosing for the latter two populations is consistent with current labeling for lamotrigine dosing in the presence of these drugs. The dosing information for initiating lamotrigine in the absence of these drugs is consistent with the dosing in the pivotal trials. Current labeling does not provide for lamotrigine dosing recommendations in patients not receiving either valproate or enzyme-inducing drugs. The Sponsor also provides information for lamotrigine dosing when either valproate or enzyme-inducing drugs are added to lamotrigine therapy. The proposed labeling for these three dosing scenarios are depicted in Tables 1, 2, and 3.

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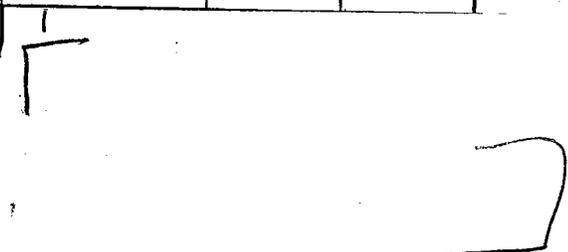
Table 1. Sponsor's Table. Lamotrigine Escalation Regimen

**Table 13. Escalation Regimen for LAMICTAL for Patients With Bipolar Disorder**

	For Patients Not Taking Carbamazepine (or Other Enzyme-Inducing Drugs) or Valproate	For Patients Taking Valproate	For Patients Taking Carbamazepine (or Other Enzyme-Inducing Drugs) and Not Taking Valproate
Weeks 1 and 2	25 mg daily	25 mg every other day	50 mg daily
Weeks 3 and 4	50 mg daily	25 mg daily	100 mg daily, in divided doses
Week 5	100 mg daily	50 mg daily	200 mg daily, in divided doses
Week 6	200 mg daily	100 mg daily	300 mg daily, in divided doses
Week 7	200 mg daily	100 mg daily	up to 400 mg daily, in divided doses

Table 2. Sponsor's Table. Lamotrigine Dose Adjustment Following Discontinuation of Psychotropic Medication

**Table 14. Adjustments to LAMICTAL Dosing for Patients With Bipolar Disorder Following Discontinuation of Psychotropic Medications**

	Discontinuation of Psychotropic Drugs excluding Valproate, Carbamazepine, or Other Enzyme-Inducing Drugs	Discontinuation of Valproate	Discontinuation of Carbamazepine or Other Enzyme-Inducing Drugs		
			Current LAMICTAL dose (mg/day)		
			—	—	—
Week 1	Maintain current LAMICTAL dose				
Week 2	Maintain current LAMICTAL dose				
Week 3 onward*	Maintain current LAMICTAL dose				

\*Dose may be increased to a maximum of 400 mg/day (200 mg/day in combination with valproate) as needed.

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### IX. Use in Special Populations

#### A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The Sponsor provided a gender efficacy analysis in an analysis of the combined results from SCAB2003 and SCAB2006. A gender efficacy analysis was not performed separately for each study.

#### Females

<u>Female</u>	PBO N=94	Li N=96	LTG Comb. N=128
<b>Statistical Parameter</b>			
<b>TIME(ABE)</b>			
Subjects with Event, n (%)	75 (80%)	62 (65%)	90 (70%)
Median Time to Event (days)	85	101	108
Confidence Interval (95%)	(56, 111)	(72, 156)	(69, 146)
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.109	0.041
<b>TIME(SIS)</b>			
Subjects with Event, n (%)	82 (87%)	82 (85%)	98 (77%)
Median Time to Event (days)	66	72	92
Confidence Interval (95%)	(44, 97)	(56, 98)	(63, 141)
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.597	0.034
<b>TIME(Only)</b>			
Subjects with Event, n (%)	54 (57%)	44 (46%)	64 (50%)
Median Time to Event (days)	97	150	156
Confidence Interval (95%)	(73, 198)	(96, 310)	(110, 482)
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.168	0.107
<b>TIMan</b>			
Subjects with Event, n (%)	21 (22%)	9 (9%)	25 (19%)
Median Time to Event (days)	n/c	n/c	n/c
Confidence Interval (95%)	-	-	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.018	0.314
<b>TIDep</b>			
Subjects with Event, n (%)	33 (35%)	35 (36%)	39 (30%)
Median Time to Event (days)	270	197	n/c
Confidence Interval (95%)	(138, n/c)	(114, n/c)	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.939	0.210

Data from Sponsor's tables 43, 47, 49 of Combined Analysis

n/c = not calculable due to insufficient number of events, NA = not available

\*significantly different from placebo

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### Males

<u>Males</u>	PBO N=94	Li N=68	LTG Comb. N=95
Statistical Parameter			
<b>TIME(ABE)</b>			
Subjects with Event, n (%)	78 (83%)	46 (68%)	70 (74%)
Median Time to Event (days)	44	146	86
Confidence Interval (95%)	(27, 80)	(94, 243)	(59, 190)
Survival Estimate, Week 76	NA	NA	NA
p-value*		< 0.001	0.005
<b>TIME(SIS)</b>			
Subjects with Event, n (%)	83 (88%)	51 (75%)	76 (80%)
Median Time to Event (days)	34	125	78
Confidence Interval (95%)	(24, 58)	(87, 193)	(55, 150)
Survival Estimate, Week 76	NA	NA	NA
p-value*		NA	0.006
<b>TIME(Only)</b>			
Subjects with Event, n (%)	61 (65%)	30 (44%)	47 (49%)
Median Time to Event (days)	77	259	256
Confidence Interval (95%)	(34, 162)	(139, n/c)	(141, 472)
Survival Estimate, Week 76	NA	NA	NA
p-value*		< 0.001	0.002
<b>TIMan</b>			
Subjects with Event, n (%)	26 (28%)	9 (13%)	21 (22%)
Median Time to Event (days)	422	n/c	n/c
Confidence Interval (95%)	(203, n/c)	-	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.002	0.048
<b>TIDep</b>			
Subjects with Event, n (%)	35 (37%)	21 (31%)	26 (27%)
Median Time to Event (days)	233	n/c	n/c
Confidence Interval (95%)	(86, n/c)	-	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.037	0.017

Data from Sponsor's tables 44, 48, 50 of Combined Analysis

n/c = not calculable due to insufficient number of events, NA = not available

\*significantly different from placebo

As mentioned in section C-10.2 (Division's Analysis), TIME(Only) is the most appropriate endpoint to evaluate with regard to these data provided by the Sponsor. Interestingly, for female subjects, lamotrigine did not separate from placebo for TIME(Only), TIMan, or TIDep. However, for male subjects, lamotrigine did separate from placebo for these three endpoints. These findings were consistent with the Division's analysis for SCAB2003 (SCAB2006 approaches significance, sample sizes are much smaller in this trial).

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### Division's Gender Efficacy Analysis in the Pivotal Trials – for Endpoint TIME(Only)

#### SCAB2003

Female Statistical Parameter	PBO N=59	Li N=72	LTG Comb. N=96	By LTG Treatment Group		
				LTG50 N=28	LTG200 N=72	LTG400 N=24
<b>TIME(Only)</b>						
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
<b>TIME(Only)</b>						
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

#### SCAB2006

Female Statistical Parameter	PBO N=35	Li N=24	LTG Flex N=32
<b>TIME(Only)</b>			
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
<b>TIME(Only)</b>			
Subjects with Event, n (%)	26 (76)	8 (40)	14 (54)
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

The Sponsor did investigate the adverse event profiles between males and females in all bipolar disorder studies. The frequency of adverse events was similar between males and females with the exception of headache (34% females/25% males) and nausea (21% females/10% males). Of note, though there were only 3 cases of serious rash occurring in lamotrigine-treated subjects in all bipolar disorder studies, all three occurred in female subjects.

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In the controlled bipolar disorder studies females generally reported more adverse events compared to males in all treatment groups. Compared to males, lamotrigine-treated females reported more nausea (19% versus 8%) and "all rash" (12% versus 5%).

### B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The Sponsor provided an efficacy analysis for age and race in an analysis of the combined results from SCAB2003 and SCAB2006. These efficacy analyses was not performed separately for each study.

#### Age Efficacy Analysis

##### Subjects < 65 Years of Age

<u>&lt; 65 Years</u>	PBO N=180	Li N=158	LTG Comb. N=216
Statistical Parameter			
<b>TIME(ABE)</b>			
Subjects with Event, n (%)	147 (82%)	104 (66%)	156 (72%)
Median Time to Event (days)	58	123	93
Confidence Interval (95%)	(44, 85)	(96, 174)	(69, 144)
Survival Estimate, Week 76	NA	NA	NA
p-value*		< 0.001	0.001
<b>TIME(SIS)</b>			
Subjects with Event, n (%)	157 (87%)	127 (80%)	169 (78%)
Median Time to Event (days)	55	94	86
Confidence Interval (95%)	(33, 75)	(66, 119)	(62, 128)
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.008	0.001
<b>TIME(Only)</b>			
Subjects with Event, n (%)	111 (62%)	71 (45%)	109 (50%)
Median Time to Event (days)	86	187	190
Confidence Interval (95%)	(56, 121)	(123, n/c)	(141, 388)
Survival Estimate, Week 76	NA	NA	NA
p-value*		< 0.001	0.002
<b>TIMan</b>			
Subjects with Event, n (%)	44 (24%)	18 (11%)	44 (20%)
Median Time to Event (days)	n/c	n/c	n/c
Confidence Interval (95%)	-	-	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		< 0.001	0.057
<b>TIDep**</b>			
Subjects with Event, n (%)	NA	NA	NA
Median Time to Event (days)	NA	NA	NA
Confidence Interval (95%)	NA	NA	NA
Survival Estimate, Week 76	NA	NA	NA
p-value*		NA	NA

Data from Sponsor's tables 51, 53, and 55 of Combined Analysis

n/c = not calculable due to insufficient number of events, NA = not available

\*significantly different from placebo

\*\*TIDep NA = Data in Sponsor's table TIDep is incorrect, data is for all TIME analyses for  $\geq 65$  years of age

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### Subjects $\geq$ 65 Years of Age

$\geq$ 65 Years	PBO N=8	Li N=6	LTG Comb. N=7
Statistical Parameter			
<b>TIME(ABE)</b>			
Subjects with Event, n (%)	6 (75%)	4 (67%)	4 (57%)
Median Time to Event (days)	87	86	147
Confidence Interval (95%)	(30, 90)	(57, n/c)	(71, n/c)
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.371	0.036
<b>TIME(SIS)</b>			
Subjects with Event, n (%)	8 (100%)	6 (100%)	5 (71%)
Median Time to Event (days)	35	86	147
Confidence Interval (95%)	(15, 90)	(57, 86)	(43, n/c)
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.491	0.033
<b>TIME(Only)</b>			
Subjects with Event, n (%)	4 (50%)	3 (50%)	2 (28%)
Median Time to Event (days)	90	86	n/c
Confidence Interval (95%)	(87, n/c)	(57, n/c)	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.806	0.037
<b>TIMan</b>			
Subjects with Event, n (%)	3 (37%)	0	2 (28%)
Median Time to Event (days)	90	n/c	n/c
Confidence Interval (95%)	(90, n/c)	-	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.129	0.080
<b>TIDep</b>			
Subjects with Event, n (%)	1 (12%)	3 (50%)	0
Median Time to Event (days)	n/c	86	n/c
Confidence Interval (95%)	-	(57, n/c)	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.281	0.248

Data from Sponsor's tables 52, 54, and 56 of Combined Analysis  
n/c = not calculable due to insufficient number of events, NA = not available  
\*significantly different from placebo

Since very few subjects  $\geq$  65 years of age were enrolled in these trials, it is not possible to adequately assess response in this population.

The Sponsor did investigate the adverse event profiles in subjects  $<$  65 years of age and  $\geq$  65 years of age in all bipolar disorder studies. Rates of adverse events tended to be lower in subjects  $\geq$  65 years of age with the exception of depression (10% versus 2%) and dizziness (20% versus 12%).

In lamotrigine-treated subjects in the controlled bipolar disorder studies, rates of adverse events tended to be lower in subjects  $\geq$  65 years of age with the exception of "all mania" (10% versus 5%).

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**Division's Age Efficacy Analysis in the Pivotal Trials – Cohorts were divided differently compared to Sponsor's analysis**

### SCAB2003

<u>Age&lt;40</u> 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
<u>Age&gt;40</u> 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

### SCAB2006

<u>Age&lt;40</u> 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
<u>Age&gt;40</u> 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

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### Race Efficacy Analysis

#### White

<u>White</u>	PBO N=171	Li N=156	LTG Comb. N= 201
Statistical Parameter			
<b>TIME(ABE)</b>			
Subjects with Event, n (%)	140 (82%)	102 (65%)	140 (70%)
Median Time to Event (days)	58	111	114
Confidence Interval (95%)	(42, 85)	(88, 156)	(71, 154)
Survival Estimate, Week 76	NA	NA	NA
p-value*		< 0.001	< 0.001
<b>TIME(SIS)</b>			
Subjects with Event, n (%)	152 (89%)	126 (81%)	154 (77%)
Median Time to Event (days)	50	87	86
Confidence Interval (95%)	(31, 73)	(65, 105)	(63, 144)
Survival Estimate, Week 76			
p-value*		0.006	< 0.001
<b>TIME(Only)</b>			
Subjects with Event, n (%)	107 (63%)	72 (46%)	100 (50%)
Median Time to Event (days)	85	166	197
Confidence Interval (95%)	(56, 121)	(111, 310)	(144, 388)
Survival Estimate, Week 76	NA	NA	NA
p-value*		< 0.001	< 0.001
<b>TIMan</b>			
Subjects with Event, n (%)	44 (26%)	16 (10%)	45 (22%)
Median Time to Event (days)	n/c	n/c	n/c
Confidence Interval (95%)	-	-	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		< 0.001	< 0.050
<b>TIDep</b>			
Subjects with Event, n (%)	63 (37%)	56 (36%)	55 (27%)
Median Time to Event (days)	269	310	n/c
Confidence Interval (95%)	(121, n/c)	(146, n/c)	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.176	0.002

Data from Sponsor's tables 59, 64, and 69 of Combined Analysis

n/c = not calculable due to insufficient number of events, NA = not available

\*significantly different from placebo

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### Black

<u>Black</u>	PBO N=8	Li N=5	LTG Comb. N= 11
Statistical Parameter			
<b>TIME(ABE)</b>			
Subjects with Event, n (%)	7 (87%)	3 (60%)	9 (82%)
Median Time to Event (days)	30	309	91
Confidence Interval (95%)	(19, 89)	(35, n/c)	(32, n/c)
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.022	0.132
<b>TIME(SIS)</b>			
Subjects with Event, n (%)	7 (87%)	4 (80%)	9 (82%)
Median Time to Event (days)	30	175	91
Confidence Interval (95%)	(19, 89)	(35, n/c)	(32, n/c)
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.070	0.132
<b>TIME(Only)</b>			
Subjects with Event, n (%)	6 (75%)	1 (20%)	5 (45%)
Median Time to Event (days)	30	n/c	453
Confidence Interval (95%)	(19, n/c)	-	(32, n/c)
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.047	0.065
<b>TIMan</b>			
Subjects with Event, n (%)	1 (12%)	1 (20%)	1 (9%)
Median Time to Event (days)	n/c	n/c	n/c
Confidence Interval (95%)	-	-	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.968	0.461
<b>TIDep</b>			
Subjects with Event, n (%)	5	0	4
Median Time to Event (days)	86	n/c	453
Confidence Interval (95%)	(24, n/c)	-	(32, n/c)
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.017	0.091

Data from Sponsor's tables 60, 65, 70 of Combined Analysis

n/c = not calculable due to insufficient number of events, NA = not available

\*significantly different from placebo

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### Asian

<u>Asian</u>	PBO N=4	Li N=2	LTG Comb. N=3
Statistical Parameter			
<b>TIME(ABE)</b>			
Subjects with Event, n (%)	2 (50%)	2 (100%)	3 (100%)
Median Time to Event (days)	121	174	141
Confidence Interval (95%)	(9, n/c)	(174, n/c)	(15, n/c)
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.918	0.646
<b>TIME(SIS)</b>			
Subjects with Event, n (%)	2 (50%)	2 (100%)	3 (100%)
Median Time to Event (days)	121	174	141
Confidence Interval (95%)	(9, n/c)	(174, n/c)	(15, n/c)
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.918	0.646
<b>TIME(Only)</b>			
Subjects with Event, n (%)	1 (25%)	1 (50%)	0
Median Time to Event (days)	n/c	n/c	n/c
Confidence Interval (95%)	-	-	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.886	0.414
<b>TIMan</b>			
Subjects with Event, n (%)	1 (25%)	1 (50%)	0
Median Time to Event (days)	n/c	n/c	n/c
Confidence Interval (95%)	-	-	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.886	0.414
<b>TIDep</b>			
Subjects with Event, n (%)	0	0	0
Median Time to Event (days)	n/c	n/c	n/c
Confidence Interval (95%)	-	-	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		NA	NA

Data from Sponsor's tables 61, 66, 71 of Combined Analysis

n/c = not calculable due to insufficient number of events, NA = not available

\*significantly different from placebo

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### American Hispanic

<u>American Hispanic</u>	PBO N=2	Li N=1	LTG Comb. N= 6
Statistical Parameter			
<b>TIME(ABE)</b>			
Subjects with Event, n (%)	2 (100%)	1 (100%)	6 (100%)
Median Time to Event (days)	56	n/c	30
Confidence Interval (95%)	(56, n/c)	-	(23, 86)
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.225	0.631
<b>TIME(SIS)</b>			
Subjects with Event, n (%)	2 (100%)	1 (100%)	6 (100%)
Median Time to Event (days)	56	n/c	30
Confidence Interval (95%)	(56, n/c)	-	(23, 86)
Survival Estimate, Week 76	NA	NA	NA
p-value*		0.225	0.631
<b>TIME(Only)</b>			
Subjects with Event, n (%)	0	0	4 (67%)
Median Time to Event (days)	n/c	n/c	38
Confidence Interval (95%)	-	-	(23, n/c)
Survival Estimate, Week 76	NA	NA	NA
p-value*		NA	0.239
<b>TIMan</b>			
Subjects with Event, n (%)	0	0	0
Median Time to Event (days)	n/c	n/c	n/c
Confidence Interval (95%)	-	-	-
Survival Estimate, Week 76	NA	NA	NA
p-value*		NA	NA
<b>TIDep</b>			
Subjects with Event, n (%)	0	0	4 (67%)
Median Time to Event (days)	n/c	n/c	38
Confidence Interval (95%)	-	-	(23, n/c)
Survival Estimate, Week 76	NA	NA	NA
p-value*		NA	0.239

Data from Sponsor's tables 62, 67, 72 of Combined Analysis

n/c = not calculable due to insufficient number of events, NA = not available

\*significantly different from placebo

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### Other

<u>Other</u>	PBO N=3	Li N=0	LTG Comb. N= 2
Statistical Parameter			
<b>TIME(ABE)</b>			
Subjects with Event, n (%)	2 (67%)	-	2 (100%)
Median Time to Event (days)	286	-	44
Confidence Interval (95%)	(34, n/c)	-	(44, n/c)
Survival Estimate, Week 76	NA	-	NA
p-value*		-	0.364
<b>TIME(SIS)</b>			
Subjects with Event, n (%)	2 (67%)	-	2 (100%)
Median Time to Event (days)	286	-	44
Confidence Interval (95%)	(34, n/c)	-	(44, n/c)
Survival Estimate, Week 76	NA	-	NA
p-value*		-	0.364
<b>TIME(Only)</b>			
Subjects with Event, n (%)	1 (33%)	-	2 (100%)
Median Time to Event (days)	n/c	-	44
Confidence Interval (95%)	-	-	(44, n/c)
Survival Estimate, Week 76	NA	-	NA
p-value*		-	0.364
<b>TIMan</b>			
Subjects with Event, n (%)	1 (33%)	-	0
Median Time to Event (days)	n/c	-	n/c
Confidence Interval (95%)	-	-	-
Survival Estimate, Week 76	NA	-	NA
p-value*		-	0.414
<b>TIDep</b>			
Subjects with Event, n (%)	0	-	2 (100%)
Median Time to Event (days)	n/c	-	44
Confidence Interval (95%)	-	-	(44, n/c)
Survival Estimate, Week 76	NA	-	NA
p-value*		-	0.090

Data from Sponsor's tables 63, 68, 73 of Combined Analysis

n/c = not calculable due to insufficient number of events, NA = not available

\*significantly different from placebo

Most of the subjects enrolled in the pivotal trials were Caucasian, therefore it is not possible to adequately assess response in other racial groups.

Adverse events were compared between racial groups, however, conclusions regarding these results are limited due to the lack of racial diversity in these trials. No differences were noted between Black versus White subjects or Asian versus White subjects for those treated with lamotrigine.

### C. Evaluation of Pediatric Program

As of labeling approved 1/17/03, lamotrigine is indicated for adjunctive therapy in partial seizures in adults and pediatric patients ( $\geq 2$  years of age) and for adjunctive therapy for the generalized seizures of Lennox-Gastaut syndrome in adults and pediatric patients ( $\geq 2$  years of age). Prior estimates indicated that serious rash occurred in approximately 1%

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of pediatric patients (< 16 years of age) compared to 0.3% of adults. The Sponsor recently submitted new data to the Division indicating that the risk of serious rash is 0.8% in pediatric patients (< 16 years of age), a rate similar to serious rash occurring with other commonly used antiepileptic drugs.

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. The Sponsor is encouraged to submit a pediatric plan that describes development of lamotrigine in the pediatric population where it may be used.

### X. Conclusions and Recommendations

#### A. Conclusions

In filing this supplemental NDA, the Sponsor sought a claim indicating that lamotrigine was effective in the long-term management of bipolar I disorder to delay the relapse/recurrence of depressive episodes. Efficacy data from two pivotal trials was included in this submission to support this indication.

The originally defined primary endpoint for both pivotal studies (SCAB2003 and SCAB2006) was TIME [a.k.a. TIME(Only)]. TIME was defined as 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. After review of SCAB2003 and a statistical reanalysis which excluded site #55466 (site was closed by Sponsor due to significant GCP issues), TIME(Only) was no longer statistically different from placebo. Of note, the Sponsor did not inform the Division about the problems with this site; the reviewer raised the question to clarify a category "Sponsor discontinued" in the patient disposition table. Secondary analyses included TIDep and TIMan which were defined as TIME to a depressive or manic/hypomanic/mixed episode. In the reanalysis of SCAB2003 with exclusion of site #55466, lamotrigine no longer separates from placebo for TIDep.

After both pivotal trials were completed, but prior to unblinding of the data, the Sponsor submitted amendments that significantly changed the primary endpoint to TIME(ABE) which included TIME(Only) and all premature discontinuations (except for adverse events not related to bipolar disorder). Though the data was still blinded, the number of events was likely known at the time this decision was made. Using TIME(ABE) as the primary endpoint, both pivotal studies are positive. Amendments changing the primary efficacy measure to TIME(ABE) were submitted on 10/24/00 (SCAB2006) and 8/28/01 (SCAB2003). It is unclear when decisions were made to change the primary efficacy measure to TIME(ABE), how these decisions were made, and why these amendments were not submitted simultaneously.

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**Appendix A**  
**Appendices from Efficacy Evaluation**

Figure 1-A. Sponsor's Figure 33 SCAB2008 Study Report.

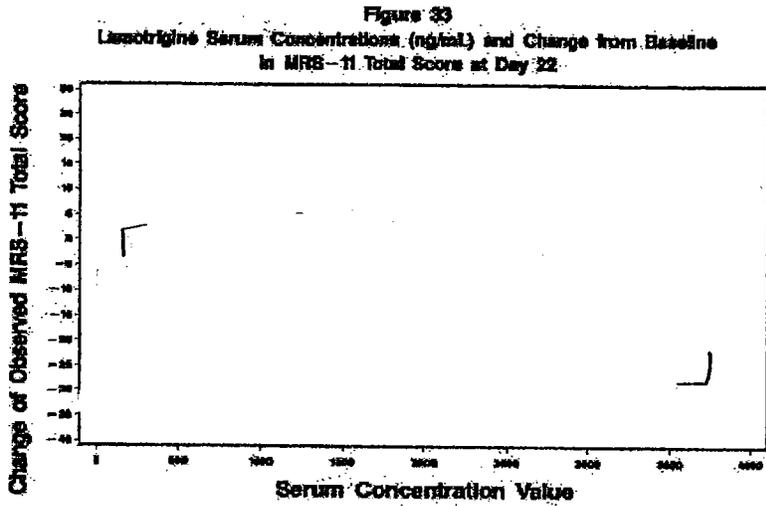
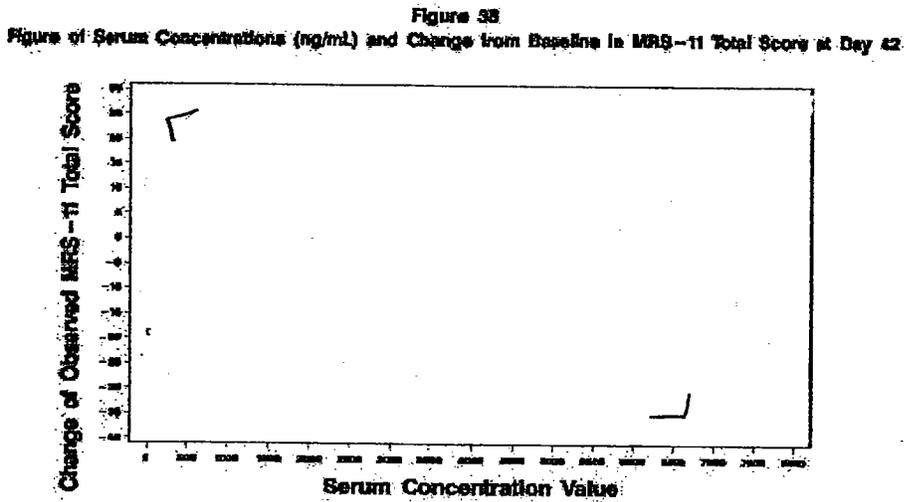
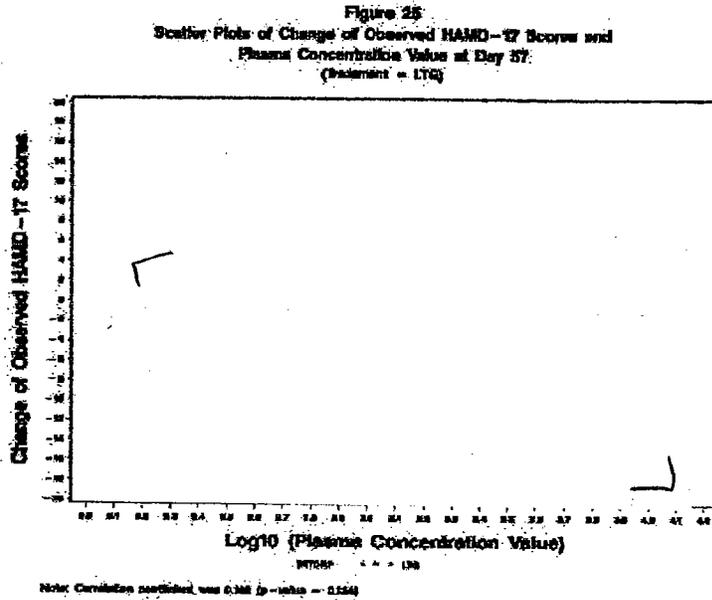


Figure 2-A. Sponsor's Figure 35 SCAB2009 Study Report.



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Figure 3-A. Sponsor's Figure 25 SCAA2011 Study Report.



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Table 4-A. Sponsor's Table: Lamotrigine in Bipolar Disorder, Foreign Status

**Table 12 Countries Where Applications Have Been Submitted for LAMICTAL for Use in the Treatment of Bipolar Disorder**

Country	Date of First Approval	Date of Submission for Bipolar	Date of Approval for Bipolar	Tablet Strength Approval (mg)	
				Compressed Tablets	Dispersible Tablets
Czech Republic	16 Dec 92	20 Sep 02	18 Dec 02	25, 50, 100	5, 25, 100

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Table 4-A. Sponsor's Table: Lamotrigine in Bipolar Disorder, Foreign Status (cont.)

Country	Date of First Approval	Date of Submission for Bipolar	Date of Approval for Bipolar	Tablet Strength Approval (mg)	
				Compressed Tablets	Dispersible Tablets

Latvia	03 Dec 97	10 Sep 02	Nov 02	25, 50, 100	5, 25, 50, 100, 200
New Zealand	17 Dec 92	02 Sept 02	12 Dec 02	25, 50, 100, 200	5, 25, 50, 100, 200

Panama	12 Dec 95	Sep 02	13 Nov 02	25, 50, 100	5, 25, 50, 100, 200
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Romania	30 Sep 93	30 Sep 02	16 Dec 02	25, 50, 100, 200	5, 25, 100
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Table C-1-A. List of Sites for Studies SCAB2003 and SCAB2006

	SCAB2003		SCAB2006	
	Prelim. Phase	Randomized Phase	Preliminary Phase	Randomized Phase
	# Pts Enrolled/Treated	# Pts Enrolled/Randomized	# Pts Enrolled/Treated	# Pts Enrolled/Randomized
<i>U.S. Sites</i>				
#2341 J. Small, IN	1/1	0/0	2/2	0/0
#2531 L. Cunningham, IL	4/4	1/1	2/2	1/1
#2539 R. Fieve, NY	42/42	16/16	19/19	9/9
#3905 J. Barbee, LA	5/5	0/0	-	-
#3941 G. Asnis, NY	10/9	4/4	1/1	0/0
#4071 A. Feiger, CO	6/6	4/4	2/2	2/2
#4371 J. Apter, NJ	23/23	8/8	-	-
#4701 S. West, FL	32/32	18/18	10/10	4/3
#4769 M. Bari, CA	20/20	9/9	10/10	3/3
#4818 B. Lydiard, SC	15/15	8/8	10/10	5/5
#4822 M. Rapaport, CA	15/15	9/9	9/9	5/5
#5058 F. Reimherr, UT	42/41	10/10	14/14	10/10
#6301 J. Simon, WI	12/12	6/6	8/8	6/6
#7557 C. Bowden, TX	25/25	10/9	9/9	4/4
#42992 A. Khan, WA	45/45	29/29	13/13	7/6
#44051 J. Calabrese, OH	32/32	15/15	11/11	4/4
#44052 J. Downs, TN	19/19	5/5	5/5	2/2
#44055 G. Sachs, MA	12/12	4/4	5/5	4/4
#44438 D. Mee-Lee, HI	19/19	6/6	3/3	2/2
#45758 J. Pahl, OK	16/16	7/7	3/3	1/1
#47454 I. Kolin, FL	6/6	2/2	1/1	1/1
#48003 L. Adler, NY	12/12	4/4	5/5	1/1
#48005 C. Casat, NC	17/17	7/7	5/5	2/2
#48009 S.N. Ghaemi Washington, DC	1/1	1/1	1/1	0/0
#48010 L. Gyulai, PA	16/16	10/10	-	-
#48024 D. Hellerstein, NY	2/2	0/0	1/1	0/0
#48025 L. Huey, NH, CT	11/11	6/6	3/3	1/1
#48027 R. Levine, NY	24/24	2/2	15/15	3/3
#48028 B. Maletzky, OR	2/2	0/0	1/1	0/0
#48029 A. Rosenbaum, MI	19/19	6/6	3/3	2/2
#48030 A. Rothschild, MA	6/6	2/2	1/1	1/1
#48031 M. Sajatovic, OH	1/1	0/0	1/1	1/1
#48032 A.C. Swann, TX	16/16	4/4	16/16	7/7
#48731 F. Petty, TX	-	-	8/8	5/5
#48793 J. Zajecka, IL	11/11	5/5	1/1	1/1
#50024 L. Adler, MD	23/23	10/10	10/10	5/5
#51542 L. Ginsberg, TX	24/24	11/10	5/5	3/3
#51965 K. Kaufman, NJ	-	-	1/1	0/0
#53023 A. Chakraborty, OK	9/9	6/6	6/6	5/5
#53963 B. Forester, NH	6/6	4/4	3/3	1/1

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	SCAB2003		SCAB2006	
	Preliminary Phase	Randomized Phase	Preliminary Phase	Randomized Phase
	# Pts Enrolled/Treated	# Pts Enrolled/Randomized	# Pts Enrolled/Treated	# Pts Enrolled/Randomized
<i>Non U.S. Sites</i>				
<i>Australia</i>				
#35487 T. George	4/4	3/3	3/3	1/1
#48121 F. Varghese	5/5	2/2	4/4	1/1
<i>Austria</i>				
#48109 S. Kasper	10/10	2/2	4/4	1/1
#48110 C. Stuppach	10/10	3/3	-	-
<i>Belgium</i>				
#47839 M. Dierick	-	-	1/1	1/1
#47840 H. D'Haenen	-	-	2/2	0/0
#47841 A. De Nayer	-	-	4/4	2/2
<i>Canada</i>				
#40423 L. Yatham	9/9	6/6	4/4	2/2
#46598 G. Chouinard	1/1	0/0	1/1	0/0
#46599 S. Kennedy	6/6	2/2	1/1	1/1
#46601 V. Kusumaker	5/5	2/2	3/3	1/1
#48519 T. Young	5/5	1/1	2/2	1/1
#55466 A. Dallal*	12/12	11/11	-	-
#55468 D. Rosales	2/2	1/1	-	-
<i>Denmark</i>				
#43932 K. Behnke	65/64	22/22	-	-
#43933 J. Soegaard	41/39	14/14	-	-
#47182 B. Bahr	6/6	3/3	-	-
#47183 S. Rasmussen	13/12	6/5	-	-
<i>Estonia</i>				
#54188 K. Konsap	6/6	5/5	-	-
<i>Finland</i>				
#48122 H. Naukkarinen	14/14	8/8	-	-
#48123 O. Mehtonen	15/15	9/9	-	-
#48124 S. Saarijarvi	10/10	6/6	-	-
#48125 T. Lamsa	4/4	3/3	-	-
#54346 R. Jokinen	2/2	1/1	-	-
<i>France</i>				
#34392 G. Clerc	3/3	0/0	-	-
#35509 F. Gheysen	1/1	1/1	-	-
#48117 G. Ruetsch	9/9	5/5	-	-
#48119 F. Rouillon	2/2	0/0	-	-
<i>Greece</i>				
#48368 A. Karastergiou	-	-	6/6	5/5
#48745 C. Ierodiakonou	-	-	1/1	0/0
<i>Hungary</i>				
#49483 Z. Janka	3/3	2/2	-	-
#49484 L. Tringler	2/2	1/1	-	-
#49653 Z. Rihmer	11/11	6/6	-	-

\*Sponsor withdrew site due to GCP issues

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	SCAB2003		SCAB2006	
	Prelim. Phase	Randomized Phase	Preliminary Phase	Randomized Phase
	# Pts Enrolled/ Treated	# Pts Enrolled/Randomized	# Pts Enrolled/Treated	# Pts Enrolled/Randomized
<i>Latvia</i>				
#54190 R. Andrezina	11/11	10/10	-	-
<i>New Zealand</i>				
#48360 W. Miles	-	-	1/1	1/1
#48361 A. Fraser	-	-	3/3	0/0
#48370 P. Joyce	-	-	2/2	1/1
#51338 R. Edwards	3/3	2/2	-	-
<i>Norway</i>				
#48126 O.J. Hoyberg	12/12	3/3	-	-
#48127 O. Knutsen-Baas	8/8	4/4	-	-
#48128 P. Sandvik	7/7	0/0	-	-
#48147 D. Norum	4/4	1/1	1/1	1/1
#48666 S. Akthar	6/6	2/2	11/11	9/9
#48667 J.M. Robasse	-	-	7/5	2/2
#49168 T. Faestoe	-	-	3/3	2/2
#53921 M. Hompland	-	-	13/13	8/8
<i>Poland</i>				
#51226 M. Olajossy	-	-	12/12	8/8
#51228 A. Kiejna	-	-	6/6	4/4
#51229 A. Zieba	-	-	18/18	8/8
#51230 J. Horodnicki	-	-	4/4	1/1
<i>South Africa</i>				
#40353 D. Wilson	2/2	1/1	-	-
#48120 S. Brook	5/5	0/0	-	-
<i>United Kingdom</i>				
#19320 R. Jacobson	5/5	1/1	4/4	2/2
#33481 D.E. Baldwin	2/2	0/0	-	-
#54481 R. Kermani	4/2	1/1	-	-
<i>Yugoslavia</i>				
#48528 I. Timotijevic	20/20	14/14	-	-
#48529 V. Paunovic	-	-	5/5	4/4

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Table C-2-A. Inclusion and Exclusion Criteria for SCAB2003 & SCAB2006, Including Significant Amendments

Preliminary Phase

	SCAB2003	SCAB2006	Major Amendments
<i>Inclusion Criteria</i>			
Written informed consent	X	X	
Male or female <sup>1</sup> > 18 years of age	X	X	
Generally good physical health	X	X	
DSM-IV diagnosis	Bipolar I Disorder, most recent episode depressed	Bipolar I Disorder, most recent episode manic	
Current symptoms	Currently experiencing a major depressive episode and has had ≥ 1 additional major depressive episode and 1 manic or mixed episode within 3 years of enrollment	Currently experiencing a manic episode and has had ≥ 1 additional manic episode and 1 depressed or mixed episode within 3 years of enrollment	SCAB2003 A #12 (1/6/99) SCAB2006 A#8 (11/25/98) Recent episode of major depression (SCAB2003), mania or hypomania (SCAB2006) either <i>current or within 60 days of screening</i>
Duration of current episode	≥ 2 weeks but < 12 months prior to enrollment	≥ 1 week but < 12 months prior to enrollment	
Severity of current episode	HAM-D <sub>17</sub> ≥ 18 at screening and baseline	≥ 14 on the first 11 items of the MRS from the SADS-C at screening and baseline	
Thyroid function tests	WNL	WNL	
Suitable candidate for lithium	X	X	
<i>Exclusion Criteria</i>			
DSM-IV criteria for rapid cycling or clinical course indicative of ultra-rapid cycling at any time during the 1 year prior to enrollment	X	X	SCAB2003 (A#10 2/23/98) SCAB2006 (A#6 2/23/98) Permitted enrollment of subjects with ≤ 6 manic, hypomanic, mixed or depressed episodes in the 12 month period prior to enrollment
Significant DSM-IV Axis II diagnosis which would suggest non-responsiveness to pharmacotherapy for bipolar disorder	X	X	
<i>Major Amendments</i>			
Received an investigational drug within 30 days of enrollment	X	X	
DSM-IV diagnosis of or has received treatment for panic disorder, obsessive-compulsive disorder, social phobia or bulimia nervosa within one year of enrollment	X	X	
Is actively suicidal and/or has a	X	X	

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score of $\geq 3$ on item 3 of the HAM-D			
Has a history of substance dependence (including alcohol) within 12 months or abuse within 1 month of enrollment or tests positive for an illicit drug during screening	Excluding cannabinoids	Excluding cannabinoids	SCAB2003 (A#12 1/6/99) SCAB2006 (A#8 11/25/98) Permitted + urine tox for cannabinoids and cocaine under specified conditions
Has a clinically significant acute or chronic cardiac, renal, hepatic, neoplastic or cerebrovascular illness	X	X	
Has an acute or chronic illness likely to impair drug pharmacokinetics or has any unstable medical condition or one likely to require hospitalization during the study	X	X	
Has a history or current diagnosis of epilepsy	X	X	
Has a history of treatment with lamotrigine	X	X	SCAB2003 (A#10 2/23/98) SCAB2006 (A#6 2/23/98) defined as within 6 months of enrollment, $\geq 6$ weeks in duration, resulted in intolerance or allergic/idiosyncratic reaction during a clinical study
Is pregnant, lactating or at risk of becoming pregnant	X	X	
Is morbidly obese (BMI > 40)	X	X	
Has received fluoxetine within 4 weeks prior to enrollment	X	-	

Females of non-childbearing and childbearing potential may be enrolled, the latter must agree to use medically acceptable form of birth control (detailed in protocol) or agree to be sexually inactive.

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### Randomized Phase

Each patient completing 8 to 16 weeks in the Preliminary Phase of the study must continue to meet inclusion/exclusion criteria as above along with the following criteria

	SCAB2003	SCAB2006	Amendments
<i>Inclusion Criteria</i>			
Has adequately tolerated lamotrigine at a minimum dosage of 100 mg/day during the final two weeks of the Preliminary Phase	X	X	
Has improved during the Preliminary Phase as indicated by CGI-I $\leq 2$ as early as the end of week 4 and as late as the end of week 12	X	X	SCAB2003 (A#10 2/23/98) SCAB2006 (A#6, 2/23/98) CGI-I changed to CGI-S $\leq 3$ as early as Day 36 and as late as Day 92
Improvement (CGI-I $\leq 2$ ) must be sustained for at least 4 continuous weeks of treatment immediately prior to randomization	X	X	
Has demonstrate adequate compliance with study requirements	X	X	
Is an outpatient	X	-	
<i>Exclusion criteria</i>			
Has signs or symptoms of psychosis	X	X	
Has become actively suicidal and/or has a score of $\geq 3$ on item 3 of the HAM-D	X	X	
Has tested positive for an illicit drug at the end of the 3 <sup>rd</sup> continuous week of response	Including cannabinoids	Including cannabinoids	SCAB2003 (A#12 1/6/99) SCAB2006 (A#8 11/25/98) Permitted + urine tox for cannabinoids and cocaine under specified conditions
Has had a change in lamotrigine dosage during the final week of the Preliminary Phase	X	X	
Has experienced a mood state (opposite of current episode) requiring additional treatment during the Preliminary Phase	mania, hypomania or mixed mood state	depressed mood state	SCAB2003 (A#12 1/6/99) SCAB2006 (A#8 11/25/98) Allows additional treatment of mood state (as indicated) and specified prohibited medications

### Other significant protocol amendments:

#### SCAB2003

(A#12 1/6/99) Eliminated the 50 and 400 mg lamotrigine treatment arms

(A#13 8/28/01) Changed the primary endpoint for the statistical analysis

Eliminated the analysis of the combined SCAB2003 and SCAB2006 data as the primary analysis

#### SCAB2006

(A#8 11/25/98) Eliminated the lithium treatment arm

(A#9 10/24/00) Changed the primary endpoint for the statistical analysis

Eliminated the analysis of the combined SCAB2003 and SCAB2006 data as the primary analysis

## CLINICAL REVIEW

### Appendix A.1 Appendices for SCAB2003

Table C-4.1-A Sponsor's Table: Lamotrigine Dose Escalation in Preliminary Phase  
Lamotrigine Dose Escalation Schedules  
Preliminary Phase

Week	LTG Monotherapy		LTG with VPA		LTG with CBZ <sup>a</sup>	
	Total Daily Dose	Number of Tablets <sup>b</sup>	Total Daily Dose	Number of Tablets <sup>b</sup>	Total Daily Dose	Number of Tablets <sup>b</sup>
1-2	25mg	1	12.5mg	1 QOD	50mg	2
3-4	50mg	2	25mg	1	100mg	4 (2+2)
5	100mg	4	50mg	2	200mg	8 (4+4)
6	up to 200mg	8	up to 100mg	4	300mg	12 (6+6)
≥7	up to 200mg	8	up to 100mg	4	up to 400mg	16 (8+8)

QOD = one tablet every other day

a. Or other hepatic enzyme-inducing drug

b. All lamotrigine tablets contained 25mg lamotrigine

From page 63 of Study Report

Table C-4.2-A Sponsor's Table: Lamotrigine Dose Adjustment  
When Discontinuing Carbamazepine:

Lamotrigine Dose Reduction<sup>a</sup> Schedule  
Preliminary Phase

Starting LTG Dose	LTG Dose (mg/day) Following CBZ Withdrawal		
	First Week	Second Week	Third Week
200mg/day	200mg/day	150mg/day	100mg/day
300mg/day	300mg/day	225mg/day	150mg/day
400mg/day	400mg/day	300mg/day	200mg/day

a. Only in the event of withdrawal of CBZ treatment (or other hepatic enzyme-inducing drug)

From page 64 of Study Report

When Discontinuing Valproate:

When valproate discontinued, the administered dose of lamotrigine was doubled immediately.

Table C-4.3-A. Sponsor's Table: Lamotrigine Dose Escalation in Randomized Phase

Dose Escalation Required Upon Entry into the Randomized Phase

Study Week	Lamotrigine Dose		
	50mg/day	200mg/day	400mg/day
1	50mg	100mg	100mg
2	50mg	200mg	200mg
3	50mg	200mg	300mg
4	50mg	200mg	400mg

## CLINICAL REVIEW

Table C-6-A. Safety Assessments

- Adverse events
- Clinical laboratory tests
  - Hematology: hemoglobin, platelet count, white blood cell count
  - Chemistry: creatinine, alkaline phosphatase, ALT
  - Thyroid function: T4, T3 uptake, FTI, TSH
  - Urinalysis: dipstick for proteinuria and hematuria
  - Urine drug screen
  - Pregnancy test: serum pregnancy test for females of childbearing potential
- Physical examination
- Patient history of skin rash
- Vital signs: blood pressure, pulse, weight
- ECG (screening only)
- AB Neurotoxicity scale

Table C-7.1-A Sponsor's Table: Subject Disposition

Summary of Subject Accountability,  
ITT Population, SCAB2003

Subject Status	Number (%) of Subjects *						
	Preliminary Phase	Randomized Phase			By LTG Treatment Group		
		PBO	LI	LTG Comb. †	LTG 50	LTG 200	LTG 400
Enrolled	966 ‡	121	121	171	50	124	47
Completed ††	480 (50)	23 (19)	36 (30)	58 (34)	21 (42)	43 (35)	15 (32)
Prematurely Discontinued	484 (50)	98 (81)	85 (70)	113 (66)	29 (58)	81 (65)	32 (68)
Failed to Meet Randomization Criteria	54 (6)	n/a	n/a	n/a	n/a	n/a	n/a
Adverse Event ‡	128 (13)	24 (20)	26 (21)	28 (16)	9 (18)	18 (15)	10 (21)
Consent Withdrawn	125 (13)	25 (21)	23 (19)	25 (15)	7 (14)	19 (15)	6 (13)
Lost to Follow-up	80 (8)	9 (7)	6 (5)	15 (9)	1 (2)	11 (9)	4 (9)
Protocol Violation	20 (2)	2 (2)	4 (3)	6 (4)	2 (4)	3 (2)	3 (6)
Other †	97 (10)	36 (30)	24 (20)	36 (21)	10 (20)	27 (22)	9 (19)
Sponsor Discontinued	-	2 (2)	2 (2)	3 (2)	-	3 (2)	-

Source Data: Table 6.2 and Table 6.2.1

n/a = not applicable

- a. Percentage of subjects calculated from ITT population
- b. LTG 200mg and LTG 400mg treatment groups combined
- c. Subjects 4082 and 4088 had missing termination records for the Preliminary Phase.
- d. Includes monotherapy completers as well as subjects who may have reached TIME and elected to continue in the study as allowed per protocol
- e. The End of Study Record for Subject 13166 indicates premature discontinuation for an AE; however, the AE that was ongoing at discontinuation was not indicated to have led to study withdrawal.
- f. The category "other" included subjects who experienced a worsening of mood and/or symptoms, failed to meet randomization criteria, had a mood event that required treatment, and/or violated protocol criteria. For two subjects (12710 and 4910) the End of Study Record indicates the reason for discontinuation as "other"; however, the associated text notes conditions that may be reflective of AEs (uncontrolled diabetes and an episode/severe axis II pathology, respectively). These conditions are not reflected in the number of subjects withdrawn due to an AE nor were they reported as AEs.

## CLINICAL REVIEW

Table C-9.3-A Concomitant Psychiatric Medications Taken During the Randomized Phase Prior to TIME

Subject #	Treatment Group	Medication	Condition Treated	Started Prior Randomized Phase (Y/N)	Estimated Days of Concomitant Medication use in Randomized Phase
13395	Placebo	Hypericum	Depression	Y	Unknown
13373	Placebo	Trazodone	Insomnia	N	~2 weeks
5300	Lamotrigine 200	Citalopram	Depression	Y	One year
15686	Lamotrigine 400	Venlafaxine	Depression	Y	Unknown
12550	Lamotrigine 400	Desipramine	Depression	Y	Unknown
4604	Lithium	Trazodone	Sleep	N	~3 weeks
3830	Lamotrigine 200	Methotrimeprazine <sup>1</sup>	Sleep disturbance	N	~3 weeks
3961	Placebo	Cyamemazine <sup>1</sup>	Anxiety	N	Unknown
3962	Lamotrigine 400	Cyamemazine <sup>1</sup>	Anxiety	N	3 days
4125	Lithium	Venlafaxine	Bipolar disorder	Y	8 months
4271	Lithium	Methotrimeprazine <sup>1</sup>	Insomnia	Y	Unknown
4273	Placebo	Venlafaxine	Depression	Y	Unknown
4281	Placebo	Methotrimeprazine <sup>1</sup> Olanzapine	Bipolar Bipolar	Y Y	Unknown
4283	Lithium	Venlafaxine	Depression	Y	Unknown
4241	Placebo	Chlorprothixene <sup>1</sup>	Restlessness	N	Unknown
57034	Placebo	Mirtazapine	Depression	Y	~1 month
12267	Placebo	Hypericum	Depression	Y	Unknown
13145	Lamotrigine 200	Venlafaxine	Depression	Y	~9 days
13099	Lithium	Mirtazapine Trazodone Amitriptyline	Insomnia Insomnia Insomnia	N Y N	8 months 7 months 6 months
15720	Lithium	Venlafaxine	Anxiety	N	6 days
12440	Lamotrigine 400	Lamotrigine	Bipolar	Unknown	Unknown
4556	Lamotrigine 400	Valproate	Bipolar	Y	~3 weeks
12842	Lamotrigine 400	Lamotrigine	Bipolar	Y	Unknown
4518	Placebo	Lithium	Bipolar	Y	Unknown

<sup>1</sup>phenothiazine antipsychotics: methotrimeprazine, cyamemazine; thioxanthenes antipsychotics: chlorprothixene modified from Sponsor's Listing 3

Table C-9.4-A Positive Urine Toxicology Results

	Placebo (n = 119)	Lithium (n = 120)	Lamotrigine (n = 165) <sup>1</sup>
<b>Screening</b>			
Marijuana	7 (6%)	2 (2%)	5 (3%)
Cocaine	0	0	1 (< 1%)
Other	0	0	0
<b>3<sup>rd</sup> week of response<sup>2</sup></b>			
Marijuana	2 (2%)	2 (2%)	7 (4%) <sup>3</sup>
Cocaine	1 (< 1%)	0	2 (1%) <sup>4</sup>
Other	0	0	1 (< 1%) <sup>4,5</sup>

<sup>1</sup>all in 200 mg/day group

<sup>2</sup>Preliminary Phase

<sup>3</sup>includes one unscheduled visit

<sup>4</sup>one patient retested one week later, negative for cocaine and methaqualone

<sup>5</sup>methaqualone

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Table C-10.1.8-A TIME Analyses For Subjects Enrolled Prior to Amendment 12

Subjects with event, n (%)	TIME(ABE)	TIME(SIS)	TIME(Only)
Placebo	47 (78%)	52 (87%)	31 (52%)
Lithium	43 (68%)	53 (84%)	30 (48%)
Lamotrigine 50 mg	38 (76%)	41 (82%)	32 (64%)
Lamotrigine 200 mg	45 (74%)	48 (79%)	28 (46%)
Lamotrigine 400 mg	34 (76%)	38 (84%)	25 (56%)
Lamotrigine 200 + 400 mg	79 (74%)	86 (81%)	53 (50%)
<i>P-values</i>			
Lithium vs. PC	0.08	0.20	0.19
Lamotrigine 50 mg vs. PC	0.24	0.19	0.99
Lamotrigine 200 mg vs. PC	0.06	0.03	0.11
Lamotrigine 400 mg vs. PC	0.53	0.56	0.91

From pages 133 – 135 of report and Table 7.65.1

Table C-10.1.10-A. Mean Change on Psychiatric Rating Scales (LOCF) at Week 76

	Placebo (n = 119)	Lithium (n = 120)	Lamotrigine 200 + 400 mg (n = 165)	P-value
HAM-D <sub>17</sub>				
Screening	23.3	23.2	22.9	
RD1	5.4	5.6	6.1	
Change from RD1	+7.5	+6.1	+5.9	NS
HAM-D <sub>31</sub>				
Screening	35.1	35.0	34.8	
RD1	7.5	7.8	8.5	
Change from RD1	+11.5	+9.2	+8.9	NS
MRS-11				
Screening	2.3	2.0	1.8	
RD1	1.6	1.7	1.5	
Change from RD1	+2.9	+1.0	+2.3	Li vs. P = 0.015
MRS-16				
Screening	4.4	3.6	4.0	
RD1	1.9	2.0	2.0	
Change from RD1	+4.3	+1.9	+3.3	Li vs. P = 0.017
CGI-S				
Screening	4.4	4.3	4.3	
RD1	2.0	2.0	2.0	
Change from RD1	+1.2	+0.8	+0.9	Li vs. P = 0.03
CGI-I*				
Week 1	3.5	3.5	3.6	
RD1	1.7	1.7	1.7	
Week 76	3.3	3.1	3.1	NS
GAS				
Screening	50.9	51.4	51.1	
RD1	76.4	76.0	75.3	
Change from RD1	-12.0	-8.7	-8.2	LTG vs. P = 0.03

RD1 = randomized day 1, \*Mean scores shown  
From Sponsor tables 7.27-7.30, 7.35-7.50

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Appendix A.2  
 Appendices for SCAB2006

Table C-9.3-A Concomitant Psychiatric Medications Taken During the Randomized Phase  
 Prior to TIME

Subject #	Treatment Group	Medication	Condition Treated	Started Prior Randomized Phase (Y/N)	Estimated Days of Concomitant Medication use in Randomized Phase
5847	Placebo	Venlafaxine	Depression	Y	10 months
20741	Lamotrigine	Bupropion	Smoking cessation	N	1 day
6538	Placebo	Zupenthixol depot	Mania	Y	4 months
21036	Lithium	Bupropion	Smoking cessation	N	Unknown
23409	Lithium	Risperidone	Mania	Y	Unknown

Table C-9.4-A Positive Urine Toxicology Results

	Placebo (n = 69)	Lithium (n = 46)	Lamotrigine (n = 58)
Screening			
Marijuana	5 (7%)	4 (9%)	2 (3%)
Cocaine	1 (1%)	0	0
Other	0	0	0
3 <sup>rd</sup> week of response			
Marijuana	1 (1%)	0	0
Cocaine	0	0	0
Other	0	0	0
Unscheduled <sup>1</sup>	0	0	1 (2%)

<sup>1</sup>Preliminary Phase

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Table C-10.1.9-A. Mean Change on Psychiatric Rating Scales (LOCF) at Week 76

	Placebo (n = 119)	Lithium (n = 120)	Lamotrigine 200 + 400 mg (n = 165)	P-value
<b>HAM-D<sub>17</sub></b>				
Screening	6.9	6.7	7.7	
RD1	3.0	2.7	2.8	
Change from RD1	+6.8	+5.6	+4.3	LTG vs. P = 0.04
<b>HAM-D<sub>31</sub></b>				
Screening	9.2	8.6	10.7	
RD1	4.2	3.6	4.2	
Change from RD1	+9.3	+8.4	+5.8	LTG vs. P = 0.05
<b>MRS-11</b>				
Screening	22.4	22.3	22.3	
RD1	2.3	2.7	2.9	
Change from RD1	+4.8	+2.0	+5.1	NS
<b>MRS-16</b>				
Screening	26.2	25.4	25.8	
RD1	2.8	3.0	3.4	
Change from RD1	+5.8	+2.7	+6.3	NS
<b>CGI-S</b>				
Screening	4.3	4.1	4.3	
RD1	1.8	1.6	1.8	
Change from RD1	+1.2	+1.1	+1.0	NS
<b>CGI-I*</b>				
Week 1	3.5	3.4	3.6	
RD1	1.6	1.3	1.6	
Week 76	3.2	3.0	3.2	NS
<b>GAS</b>				
Screening	48.4	49.3	47.6	
RD1	77.5	80.0	76.9	
Change from RD1	-11.0	-10.0	-11.0	NS

RD1 = randomized day 1, \*Mean scores shown  
From Sponsor tables 7.27-7.30, 7.35-7.50

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## Appendix A.3

### Appendices for Combination Analyses: SCAB2003 + SCAB2006

Figure C-10.3.1-A. Sponsor's Figure: Survival Estimates for TIME(ABE) for SCAB2003 + SCAB2006

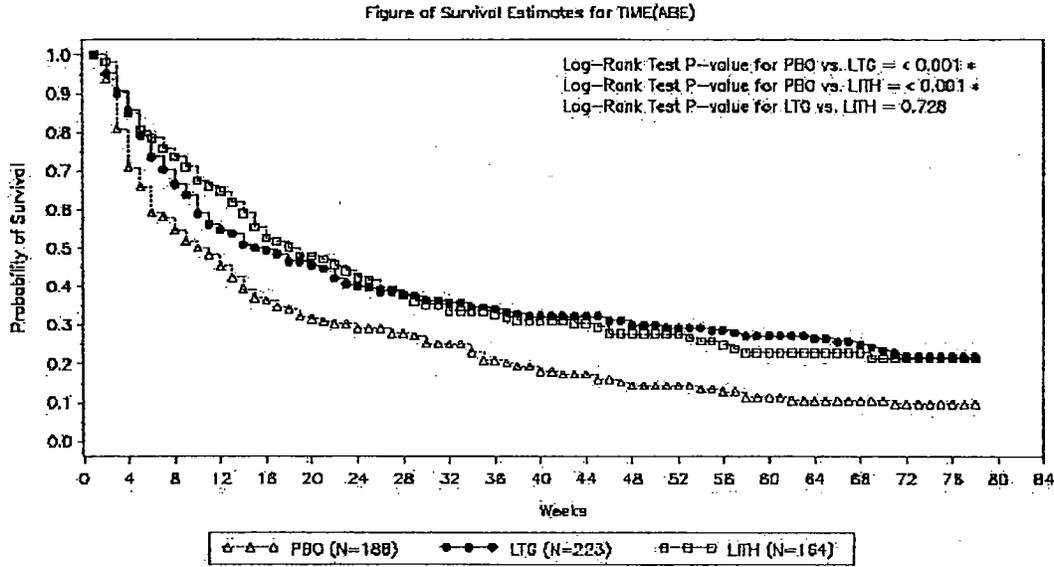
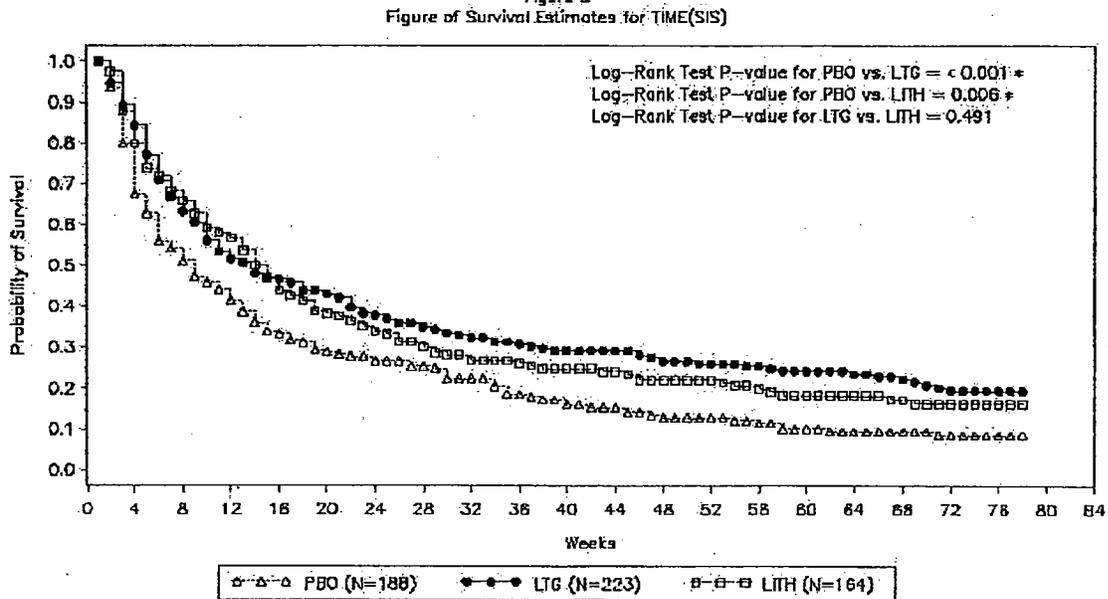


Figure C-10.3.2-A. Sponsor's Figure: Survival Estimates for TIME(SIS) for SCAB2003 + SCAB2006



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Figure C-10.3.3-A. Sponsor's Figure: Survival Estimates for TIME(Only) for SCAB2003 + SCAB2006

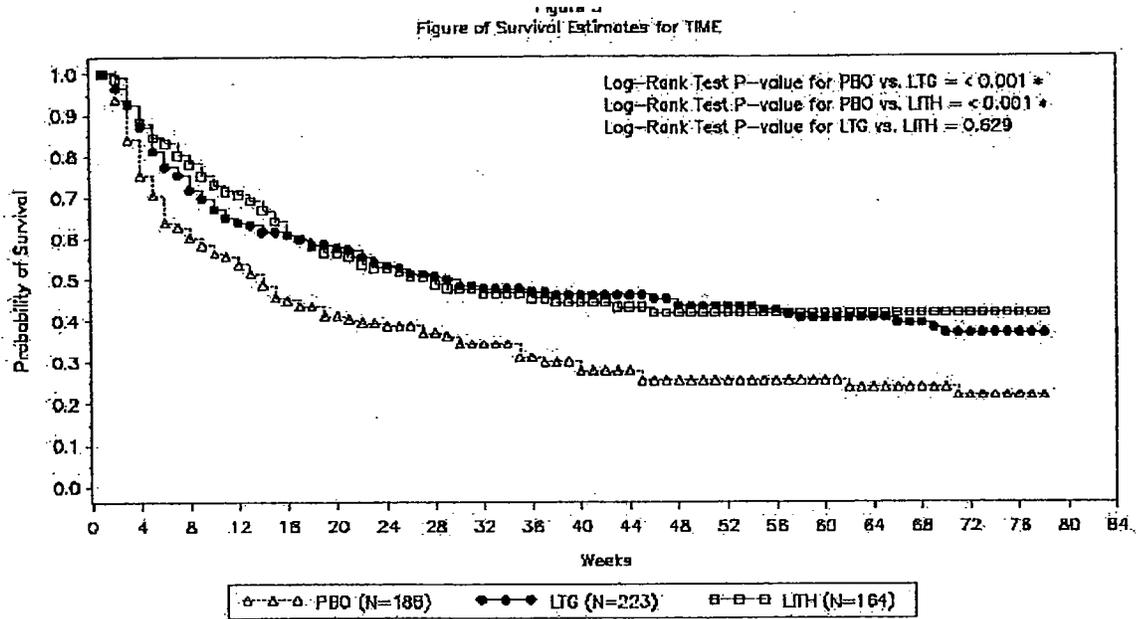
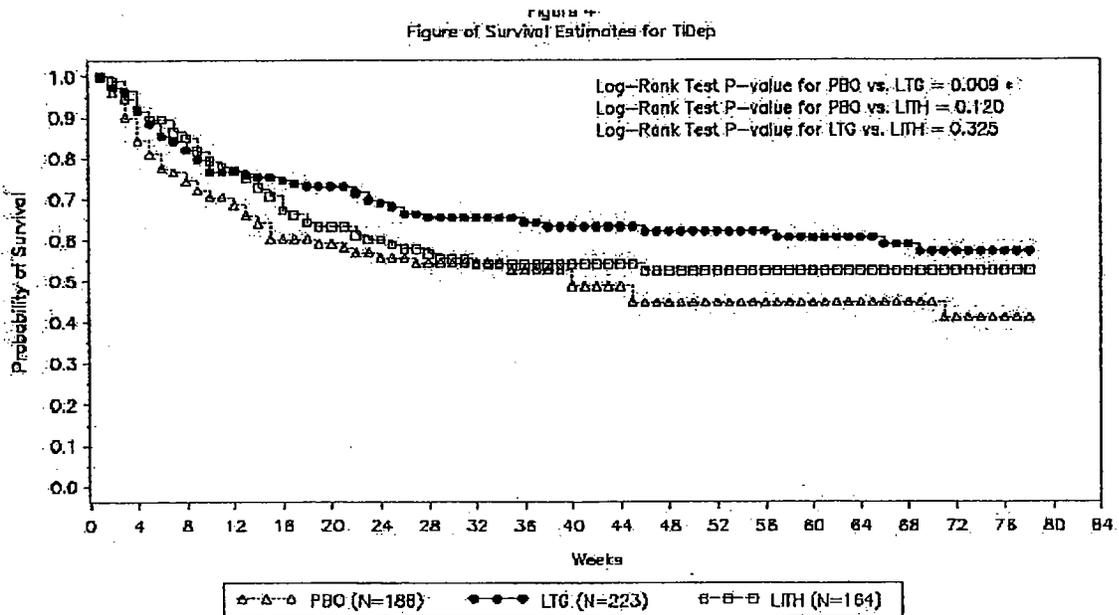
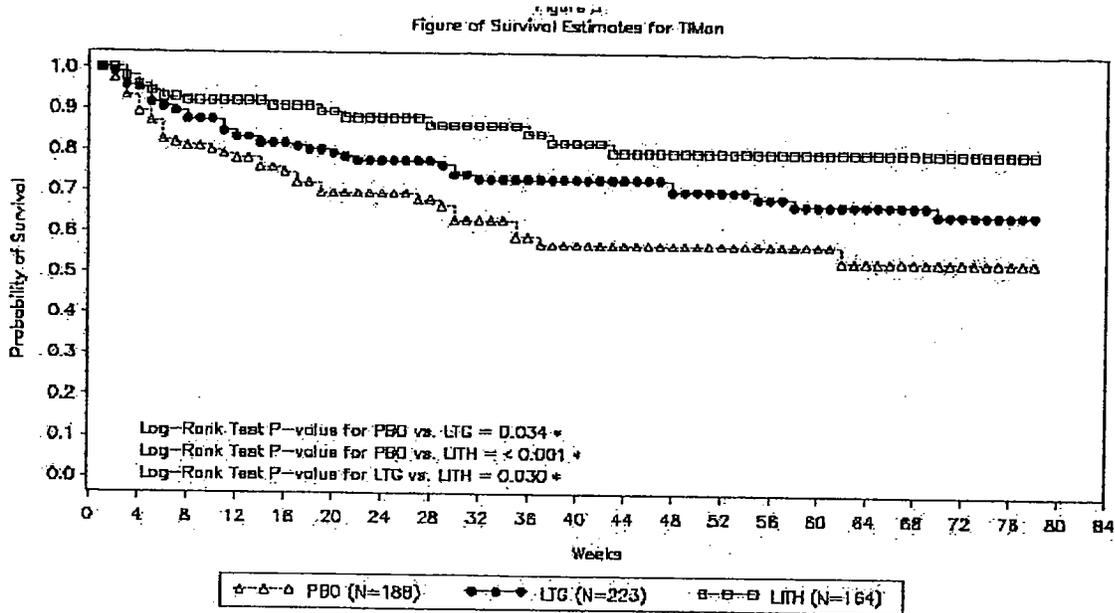


Figure C-10.3.4-A. Sponsor's Figure: Survival Estimates for TIDep for SCAB2003 + SCAB2006



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Figure C-10.3.5-A. Sponsor's Figure: Survival Estimates for TIMan for SCAB2003 + SCAB2006



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### Appendix B

#### Brief Summaries of Supportive and Acute Studies

Summaries are from study synopsis and reports, an in-depth analysis of these study reports was not done.

#### Brief Summary of Supportive Studies

SCAB2005 (5/31/97 – 6/1/00)

A multicenter, double-blind, placebo-controlled, flexible-dose evaluation of the safety and efficacy of lamotrigine in the long term treatment of subjects who have bipolar disorder with rapid cycling.

Bipolar I or II rapid-cycling subjects ( $CGI-S \leq 4$  x 2 weeks) were randomized to receive lamotrigine 50 - 400 mg/day (n = 68) or placebo (n = 69) as monotherapy or adjunctive therapy for 32 weeks. The primary efficacy measure was TIME as defined in the two pivotal trials [e.g. TIME(Only)]. Supportive primary efficacy analysis was TIME(ABE). Secondary efficacy measures included TIMan and TIDep (and others).

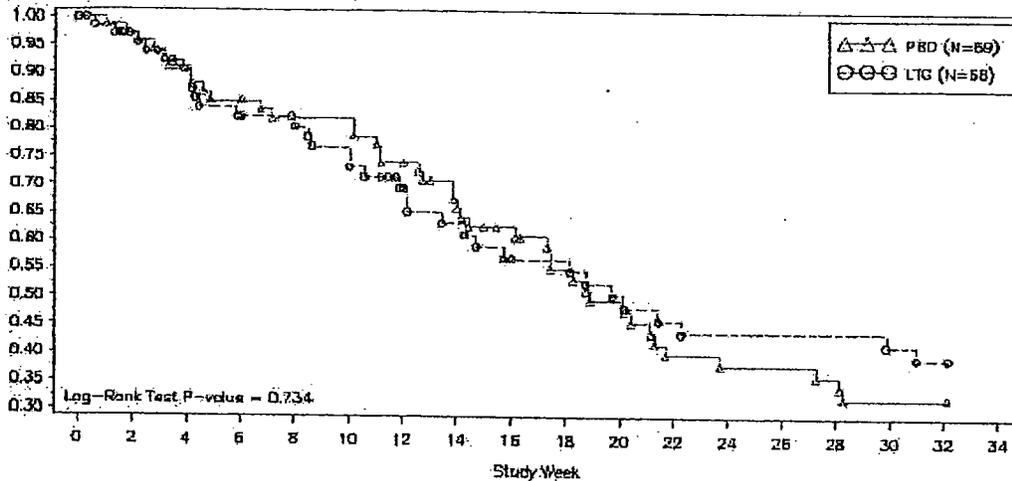
#### Median Survival Times (mean and CI)

	Placebo (n = 87)	Lamotrigine (n = 90)	Log-rank P-value
Primary endpoint			
TIME			
# Events	40	32	
Median Survival (days)	133 (114, 192)	142 (101, > 225)	0.73
Post-hoc supportive			
TIME(ABE)			
# Events	53	50	
Median Survival (days)	114 (98, 133)	85 (71, 113)	0.65
Secondary endpoints			
TIMan			
# Events	8	14	
Median Survival (days)	n/c	n/c	0.03
TIDep			
# Events	32	15	
Median Survival (days)	153 (123, > 225)	n/c	0.05

n/c = not calculable  
From Sponsor tables 48, 71, 85, 95

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Figure 1  
Kaplan-Meier Survival Functions for Time to First Alteration of Pharmacotherapy,  
or ECT, to Treat a Mood Episode or One that is Emerging



SCAA2012 (9/15/97 – 10/8/99)

A multicenter, double-blind, placebo-controlled, flexible-dose, parallel-group evaluation of the safety and efficacy of lamotrigine in the long-term prevention of mood episodes in patients with bipolar disorder with rapid cycling.

Preliminary phase as in the two pivotal trials (SCAB2003 and SCAB2006). Bipolar I or II rapid-cycling subjects could enter the study euthymic or currently experiencing any mood episode. Subjects were randomized to receive lamotrigine 100 – 500 mg/day (n = 93) or placebo (n = 89) for 26 weeks. The primary efficacy measure was TIME as defined in the two pivotal trials [e.g. TIME(Only)]. Post-hoc supportive analysis was TIME(ABE). Secondary efficacy measures included TIMan and TIDep (and others).

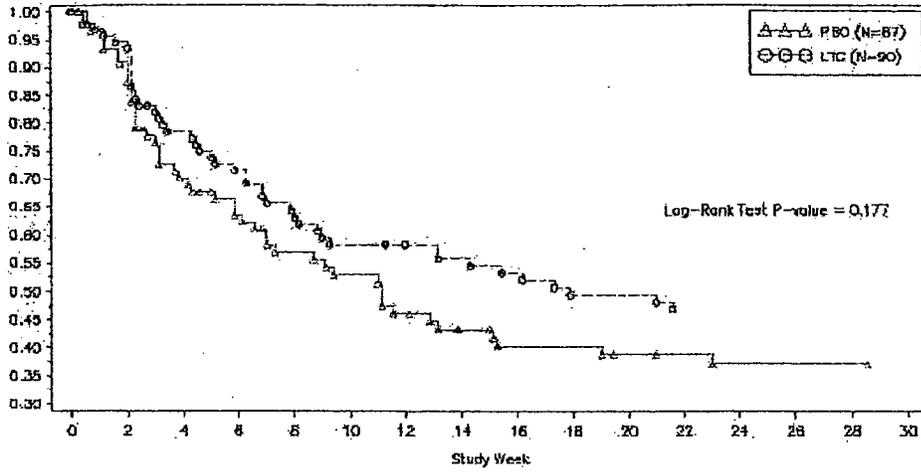
### Median Survival Times (mean and CI)

	Placebo (n = 87)	Lamotrigine (n = 90)	Log-rank P-value
<b>Primary endpoint</b>			
<b>TIME</b>			
# Events	49	45	
Median Survival (days)	79 (50, 134)	126 (64, > 547)	0.18
<b>Post-hoc supportive</b>			
<b>TIME(ABE)</b>			
# Events	64	53	
Median Survival (days)	50 (33, 82)	93 (56, > 547)	0.04
<b>Secondary endpoints</b>			
<b>TIMan</b>			
# Events	10	9	
Median Survival (days)	n/c	n/c	0.56
<b>TIDep</b>			
# Events	22	22	
Median Survival (days)	(62, > 547)	n/c	0.59

n/c = not calculable, From Sponsor tables 30, 42, 66, 78

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Figure 1  
Figure of Time to First Treatment of any Additional Pharmacotherapy or ECT for a Mood Episode (TIME)



## Brief Summary of Acute Studies

10 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

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Appendix C.  
Appendices from Safety Evaluation

Table E-1-A. Summary of Subject Deaths

Study	Patient Number	Treatment Group	Age	Sex	Time in Study	Highest Dose (mg/day)	Cause of Death
SCAB2003	3824	Preliminary Phase: OL Lamotrigine	64	F	41 days	50	Heart failure, pulmonary edema (multiple concomitant medications)
SCAB2003	3901	Preliminary Phase: OL Lamotrigine	48	M	17 days	50	Suicide by CO Asphyxiation
SCAB2003	12702	Preliminary Phase: OL Lamotrigine	41	M	14 days	50	Suicide by cutting carotid artery
SCAB2003	4046	Follow-up Phase: Lamotrigine	73	F	~4 months	200	Metastatic breast cancer
SCAB2003	4335	Preliminary Phase: OL Lamotrigine	49	F	13 weeks	200	Suicide by throwing self in front of train
SCAB2003	4556	Randomized Phase: Lamotrigine	33	M	5 months	400	Suicide by overdose (codeine)
SCAA2014	26015	OL Lamotrigine	52	M	9 months	500	Suicide by gunshot
SCAB2001	251	Placebo	63	F	~3 weeks	NA	Myocardial fibrosis Acute alcohol intoxication Probable suicide
SCAA2010	3166	Lamotrigine	38	M	17 days	Check CRF	Suicide by gunshot
SCA20022	54516	Lamotrigine	47	M	1 week	25	Cardiopulmonary arrest (no autopsy)

OL = open label, NA = not applicable

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Table E-2.2-A. Serious Adverse Events Occurring in > 1 Subject in Any Treatment Group  
All Controlled Bipolar Disorder Studies

Serious Adverse Event	Number (%) of Subjects						
	By Treatment Group			By Lamotrigine Dose			
	Placebo (n = 685)	Lithium (n = 280)	Lamotrigine (n = 827)	Lamotrigine 50 mg (n = 200)	Lamotrigine 200 mg (n = 259)	Lamotrigine 400 mg (n = 47)	LTG Flexible Dose (n = 321)
Any Serious Event	50 (7%)	22 (8%)	65 (8%)	17 (9%)	18 (7%)	6 (13%)	24 (7%)
All Mania	18 (3%)	7 (3%)	27 (3%)	7 (4%)	7 (3%)	2 (4%)	11 (3%)
Mania	15 (2%)	7 (3%)	21 (3%)	6 (3%)	6 (2%)	1 (2%)	8 (2%)
Mixed	3 (< 1%)	0	4 (< 1%)	1 (< 1%)	1 (< 1%)	1 (2%)	1 (< 1%)
Hypomania	1 (< 1%)	0	2 (< 1%)	0	0	0	2 (< 1%)
Psychiatric Depression	10 (1%)	5 (2%)	14 (2%)	4 (2%)	5 (2%)	3 (6%)	2 (< 1%)
Psychotic Disorder	1 (< 1%)	3 (1%)	5 (< 1%)	2 (1%)	2 (< 1%)	1 (2%)	0
All Suicidal Behavior	4 (< 1%)	1 (< 1%)	11 (1%)				
Suicide	0	0	2 (< 1%)	0	0	1 (2%)	1 (< 1%)
Suicide Attempt	3 (< 1%)	0	4 (< 1%)	1 (< 1%)	0	0	3 (< 1%)
Suicidal	1 (< 1%)	0	4 (< 1%)	1 (< 1%)	2 (< 1%)	0	1 (< 1%)
Overdose	0	1 (< 1%)	1 (< 1%)	0	0	0	1 (< 1%)
Accidental Injury	1 (< 1%)	1 (< 1%)	3 (< 1%)	1 (< 1%)	1 (< 1%)	0	1 (< 1%)
Diarrhea	1 (< 1%)	2 (< 1%)	0	-	-	-	-
Nausea	1 (< 1%)	2 (< 1%)	0	-	-	-	-
Syncope	1 (< 1%)	0	2 (< 1%)	0	1 (< 1%)	0	1 (< 1%)

From Sponsor Tables 10.2 and 10.3 in ISS

Table E-2.3-A. Sponsor Narrative Summaries of Serious Rash – Descriptions are Verbatim from Submission

1. In study 601, Subject 204, a 50-year old white female, was hospitalized for a pruritic rash beginning after 37 days of lamotrigine therapy during which the dose had been titrated to 100 mg total daily dose. Lamotrigine therapy was discontinued immediately. Three days later the subject developed fever, chills, tachypnea, and dyspnea in addition to the rash and was hospitalized. Skin biopsy was consistent with a purpuric drug eruption and treatment with high dose steroids was initiated. A complicated hospital course ensued including a diagnosis of status epilepticus. After nine days of hospitalization, the subject was discharged on phenobarbital, steroid taper, and erythromycin. The subject was readmitted four days later with rash, dyspnea, psychosis, and disorientation. The erythromycin, as a possible cause of the rash, was discontinued. Treatment with valproate was substituted for Phenobarbital, which was thought to be a possible cause of the psychosis. During a lengthy and complicated hospitalization, the subject's psychiatric difficulties were brought under control, and her rash was almost completely resolved at the time of discharge. The subject was discharged to follow-up outpatient care on the following medications: haloperidol, valproate, benzotropine mesylate, lorazepam, cyproheptadine, docusate sodium, trazodone (prn sleep) and chloral hydrate (prn sleep). The subject was lost to follow-up due to hospitalization for another psychotic decompensation. The investigator considered both event of rash possibly related to study drug treatment. Expert dermatological consultants to the Sponsor who reviewed subject records for this subject interpreted the rash as either a drug-induced exanthema, a hypersensitivity syndrome, or a drug-

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induced rash with underlying infection, but not Stevens-Johnson syndrome, and that it was likely to be due to lamotrigine.

2. In the preliminary phase of study SCAB2006, subject 5816, a 54 year-old female, exhibited signs of mania and was hospitalized primarily to treat mania and for observation of a rash. Both events were considered serious and possibly related to lamotrigine treatment by the investigator. After two months of treatment with lamotrigine, the subject developed maculopapular non-pruritic facial rashes associated with facial erythema. Lamotrigine was withdrawn and no treatment was given for the rash; the subject was followed for 6 weeks until the rash resolved. Expert dermatological consultants to GSK who reviewed subject records for this subject interpreted the rash as probably a morbilliform eruption related to lamotrigine exposure but otherwise benign, but could also be due to another etiology such as a viral or bacterial infection.

3. In the preliminary phase of study SCAB2003, an AE of Stevens-Johnson syndrome was reported for subject 12704. This 55 year-old female was on lamotrigine for 31 days and followed protocol-defined dose escalations. The subject developed a morbilliform rash on her trunk, shoulders, neck and face, exfoliation of the lips, facial swelling and lymphadenopathy three days after increasing the lamotrigine dose to 100 mg/day. The subject was also taking one concurrent psychotropic medication, nefazodone (100 mg/day), beginning two days prior to the onset of rash. In addition, the subject had a concurrent AE of upper respiratory infection (beginning 19 days prior to onset of rash) that was being treated with clarithromycin, prednisone and cefixime. Clarithromycin was started 16 days prior to the onset of rash, whereas prednisone and cefixime were started 2 days prior to the onset of rash. The final diagnosis of the rash was Stevens-Johnson syndrome, the severity of which was deemed mild but possibly attributable to study drug though a definite etiology could not be determined. The event led to study withdrawal. The subject was never hospitalized and recovered uneventfully. Expert dermatological consultants to the Sponsor who reviewed patient records for this subject determined that a diagnosis of mild Stevens-Johnson syndrome could not be made definitively. One expert interpreted the rash as either an erythema multiforme or an exanthema, possibly due to lamotrigine. A second expert interpreted the rash as exanthema and enanthem probably related to lamotrigine exposure, and noted that, because exfoliation appeared to have been limited to the oral mucosa, the rash did not meet criteria for diagnosis of Stevens-Johnson syndrome.

## CLINICAL REVIEW

Table E-3.2-A Sponsor's Table: Subject Withdrawal due to Adverse Events  
Controlled Bipolar Studies

**Adverse Events That Led to Withdrawal of More than One Subject in Any Treatment Group,  
Controlled Bipolar Disorder Studies**

Adverse Event That Resulted in Withdrawal	Number (%) of Subjects Withdrawn		
	PBO N=685	LI N=280	LTG N=827
Number of subjects withdrawn due to AEs	67 (10)	49 (18)	98 (12)
Headache	4 (<1)	2 (<1)	4 (<1)
Suicidal	1 (<1)	0	4 (<1)
Attempted suicide	2 (<1)	0	3 (<1)
Fatigue	1 (<1)	2 (<1)	2 (<1)
Accidental injury	2 (<1)	1 (<1)	0
Pain	2 (<1)	1 (<1)	0
All mania <sup>a</sup>	9 (1)	6 (2)	15 (2)
Mania	8 (1)	5 (2)	13 (2)
All depression	7 (1)	4 (1)	10 (1)
Psychiatric depression	7 (1)	4 (1)	10 (1)
Psychotic disorder	1 (<1)	3 (1)	7 (<1)
Emotional lability	1 (<1)	0	5 (<1)
Agitation	2 (<1)	1 (<1)	3 (<1)
Dizziness	4 (<1)	5 (2)	3 (<1)
Insomnia	3 (<1)	1 (<1)	3 (<1)
Dream abnormality	1 (<1)	0	2 (<1)
Hallucinations	0	0	2 (<1)
Somnolence	1 (<1)	6 (2)	2 (<1)
Tremor(s)	2 (<1)	8 (3)	2 (<1)
Abnormal thoughts	0	2 (<1)	0
Vertigo	0	2 (<1)	0
Nausea	3 (<1)	12 (4)	5 (<1)
Vomiting	1 (<1)	1 (<1)	2 (<1)
Diarrhea	4 (<1)	3 (1)	1 (<1)
Dyspepsia	2 (<1)	1 (<1)	1 (<1)
All rash <sup>b</sup>	10 (1)	4 (1)	25 (3)
Rash	8 (1)	3 (1)	21 (3)
Urticaria	2 (<1)	1 (<1)	2 (<1)
Pruritus	2 (<1)	1 (<1)	4 (<1)
Blurred vision	2 (<1)	0	0
Unintended pregnancy	2 (<1)	0	0
Weight gain	0	2 (<1)	2 (<1)
Edema	0	2 (<1)	1 (<1)
Edema of extremities	2 (<1)	0	0
Hypothyroidism	0	2 (<1)	0

## CLINICAL REVIEW

Table E-5.1-A Sponsor's Table. Subjects with Shifts in Clinical Chemistry and Hematology

Number (%) of Subjects With Clinical Chemistry Changes from Randomization Day 1,  
Safety Population SCAB2003, SCAB2006, and Combined Analysis

SCAB2003				
Shift	Lab Test	PBO N=121	LI N=120	LTG N=169
To Low	Alk. Phos	1/64 (2%)	1/75 (1%)	0
To High	Alk. Phos	1/64 (2%)	1/75 (1%)	4/101 (4%)
	ALT	2/63 (3%)	5/75 (7%)	3/102 (3%)
	Creatinine	1/64 (2%)	4/75 (5%)	1/102 (<1%)
SCAB2006				
Shift	Lab Test	PBO N=69	LI N=46	LTG N=58
To Low	ALT	0	0	1/41 (2%)
To High	Alk. Phos	1/50 (2%)	0	0
	ALT	3/50 (6%)	1/24 (4%)	2/58 (5%)
	Creatinine	0	1/27 (4%)	1/58 (2%)
Combined analysis				
Shift	Lab Test	PBO N=190	LI N=166	LTG N=227
To Low	Alk. Phos.	1/114 (<1%)	1/101 (<1%)	0
	ALT	0	0	1/143 (<1%)
To High	Alk. Phos.	2/114 (2%)	1/101 (<1%)	4/143 (3%)
	ALT	5/113 (4%)	6/99 (6%)	5/143 (3%)
	Creatinine	1/115 (<1%)	5/102 (5%)	2/144 (1%)

Number (%) of Subjects With Hematology Shifts from Randomization Day 1,  
Safety Population, SCAB2003, SCAB2006, and Combined Analysis

SCAB2003				
Shift	Lab Test	PBO N=121	LI N=120	LTG N=169
To Low	Hemoglobin	1/83 (2%)	1/71 (1%)	2/101 (2%)
To High	Hemoglobin	0	0	1/101 (<1%)
	Platelets	0	3/71 (4%)	2/99 (2%)
	Total WBC	4/63 (6%)	7/71 (10%)	1/101 (<1%)
SCAB2006				
Shift	Lab Test	PBO N=69	LI N=46	LTG N=58
To Low	Hemoglobin	2/50 (4%)	1/24 (4%)	1/40 (3%)
To High	Hemoglobin	1/50 (2%)	0	0
	Platelets	1/48 (2%)	2/24 (8%)	0
	Total WBC	1/50 (2%)	2/24 (8%)	0
Combined analysis				
Shift	Lab Test	PBO N=190	LI N=166	LTG N=227
To Low	Hemoglobin	3/113 (3%)	2/95 (2%)	3/141 (2%)
To High	Hemoglobin	1/113 (<1%)	0	1/141 (<1%)
	Platelets	1/111 (<1%)	5/95 (5%)	2/137 (1%)
	Total WBC	5/113 (4%)	9/95 (9%)	1/141 (<1%)

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Number (%) of Subjects With Thyroid Function Shifts from Screen,  
Safety Population, SCAB2003, SCAB2006, and Combined Analysis

<b>SCAB2003</b>				
<b>Shift</b>	<b>Lab Test</b>	<b>PBO N=121</b>	<b>LI N=120</b>	<b>LTG N=169</b>
To Low	T3 uptake	3/66 (5%)	3/74 (4%)	7/104 (7%)
	T4	1/66 (2%)	2/71 (3%)	0
	TSH	3/66 (5%)	0	2/104 (2%)
To High	T3 uptake	0	0	1/104 (<1%)
	T4	1/66 (2%)	0	4/103 (4%)
	TSH	0	3/72 (4%)	0
<b>SCAB2006</b>				
<b>Shift</b>	<b>Lab Test</b>	<b>PBO N=69</b>	<b>LI N=46</b>	<b>LTG N=58</b>
To Low	T3 uptake	7/50 (14%)	2/25 (8%)	3/40 (8%)
	TSH	5/50 (10%)	0	2/39 (5%)
To High	T3 uptake	7/50 (14%)	2/25 (8%)	3/40 (8%)
	T4	2/50 (4%)	0	1/40 (3%)
	TSH	1/50 (2%)	5/25 (20%)	0
<b>Combined Analysis</b>				
<b>Shift</b>	<b>Lab Test</b>	<b>PBO N=190</b>	<b>LI N=166</b>	<b>LTG N=227</b>
To Low	T3 uptake	10/116 (9%)	5/99 (5%)	10/144 (7%)
	T4	1/116 (<1%)	2/96 (2%)	0
	TSH	8/116 (7%)	0	4/143 (3%)
To High	T3 uptake	0	0	1/140 (<1%)
	T4	3/116 (3%)	0	5/143 (3%)
	TSH	1/116 (<1%)	8/97 (8%)	0

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## CLINICAL REVIEW

Table E-7.1-A. Sponsor's Table: Reports of Rash: All Bipolar Studies

Study		N	Percentage of Subjects Reporting					
			All Rash		All Rash Attributed to Study Drug		All Rash Leading to Withdrawal	
			PBO	LTG	PBO	LTG	PBO	LTG
All Mood Disorder and Epilepsy Studies		6565 <sup>a</sup>	-	-	-	8	-	-
All Bipolar Disorder Studies		2272 <sup>a</sup>	-	14	-	7	-	6
All Controlled Bipolar Disorder Studies		1512 <sup>b</sup>	8	9	3	4	1	3
Pivotal Long-term Studies, Preliminary Phase								
Combined Pivotal	(8-16 wks)	1305	-	11	-	6	-	5
SCAB2003	(8-16 wks)	958	-	11	-	5	-	4
SCAB2006	(8-16 wks)	347	-	11	-	6	-	5
Pivotal Long-term Studies, Randomized Phase								
Combined Pivotal	(76 wks)	583	5	6	2	4	2	3
SCAB2003	(76 wks)	410	2	7	<1	4	<1	4
SCAB2006	(76 wks)	175	9	3	3	2	3	0
Supportive Long-term Studies								
SCAA2012 (Prelim)	(8-12 wks)	324	-	14	-	8	-	5
SCAA2012 (Rand)	(26 wks)	180	3	5	0	2	0	1
SCAB2005	(32 wks)	137	12	12	3	6	3	3
Acute Controlled Bipolar Studies								
SCAB2001	(7 wks)	194	11	12	3	5	3	5
SCAA2010	(10 wks)	204	12	17	6	8	2	6
SCAA2008	(3 wks)	215	12	8	4	4	2	1
SCAB2009	(6 wks)	229	4	4	3	1	1	1
Uncontrolled Bipolar Studies								
SCAB2002	(52 wks)	124	-	17	-	9	-	5
SCAB2014	(52 wks)	127	-	20	-	8	-	9
105-601	(48 wks)	75	-	29	-	15	-	9
Unipolar Depression Studies								
SCA20022	(7 wks)	149	1	9	0	8	0	5
SCA20025	(7 wks)	301	4	6	2	3	<1	3
SCAA2011	(8 wks)	437	6	8	3	5	1	4

a. Includes lamotrigine-exposed subjects only

b. Placebo, n = 685; lamotrigine, n = 827

Sponsor's Table from page 152 of ISS

Table E-9-A. Narratives for Cases of "Convulsions" Occurring in All Bipolar Studies (Nearly verbatim from Sponsor submission)

Subject #04371, 59 year-old female in preliminary phase of SCAB2003. Concurrent medication included oxazepam and nitrazepam. After 53 days of treatment with lamotrigine, while receiving a dose of 125 mg daily, the patient was hospitalized due to

## CLINICAL REVIEW

increased anxiety and depression. Nortriptyline was commenced the same day, however, she subsequently complained of sweating. Four days after admission the nurses noted that the patient had become increasingly silent and had retired early. The following day she was evaluated as psychotic but refused to take any study medication and did not sleep that night. The next day she experienced convulsions, lasting 30 seconds, and was found next to her bed with a cut in the back of her head that required stitches. Fever was noted (38.3 C to 38.9 C) and paracetamol was commenced. Four and a half hours later she lost consciousness again and the convulsions recurred. These lasted 30 seconds and were associated with involuntary urination. She was examined by a neurologist and assessed as normal. The next day she was tired and drowsy but not psychotic; the fever had also resolved. Study medication was discontinued and the patient was withdrawn from the study. The investigator considered that there was not a reasonable possibility that the events were related to lamotrigine. However, the investigator reported that the events were probably caused by a combination of the change in the dose of benzodiazepine (from a higher dose before hospitalization to a lower dose as an inpatient) and the commencement of treatment with a tricyclic antidepressant. Laboratory data: An EEG on August 18, 1997 was normal and a CT scan of the brain, with and without contrast, was unremarkable.

Subject #12242, 41 year-old female in preliminary phase of SCAB2003.

The patient had been taking venlafaxine for approximately 2 years prior to entering the study. Approximately 3 weeks after beginning lamotrigine in the open label preliminary phase and while taking lamotrigine 50 mg/day, she experienced a seizure-like episode and was seen in the emergency room but not hospitalized. One week later, she had another seizure-like episode with tongue-biting and was hospitalized. CT scan of the head as well as EEG were normal. The physician felt the seizures were probably due to the high dose of venlafaxine, and dose was reduced to 150 mg twice daily. Lamotrigine was continued throughout, and the patient had no more seizures. In the investigator's opinion, the events were not likely to be related to lamotrigine.

Laboratory data: CAT scan negative, EEG normal, venlafaxine level = 800, desmethylvenlafaxine level = 840

Reviewer comment: Do not know when the blood was drawn relative to the ingestion of venlafaxine.

Subject #6151, 51 year-old male in preliminary phase of SCAB2006.

This patient had a history of ethanol withdrawal seizures. Concurrent with open-label lamotrigine, he received olanzapine, divalproex, venlafaxine, and buspirone. Approximately 8 weeks after initiating study treatment, the patient experienced a tonic clonic seizure and was hospitalized. He was intubated and treated with diazepam, lorazepam, and charcoal. Study drug was interrupted briefly. He remained intubated and 10 days later developed pneumonia as well as cholecystitis. This event resulted in an extended hospitalization. The events resolved and the patient was discharged after 18 days. In the investigator's opinion, the seizure was not reasonably attributable to the use of study medication, but was possibly caused by either ethanol withdrawal or concurrent medications. He also reported that the pneumonia was not reasonably attributable to study medication but was possibly due to his concurrent ventilator dependency.

Laboratory data: Brain CT scan negative. No ethanol detected in blood.

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Subject #204, 50 year-old female in Study 601.

The event "convulsion" also occurred at around the same time as the serious rash (see narrative Table E.2.3-A. While that narrative focused on the rash as the SAE, the narrative included here focused on the "convulsion".

This patient was hospitalized for a pruritic rash beginning after 37 days of lamotrigine therapy during which the dose had been titrated to 100 mg total daily dose. Lamotrigine therapy was discontinued immediately. Three days later the subject developed fever, chills, tachypnea, and dyspnea in addition to the rash and was hospitalized. Skin biopsy was consistent with a purpuric drug eruption and treatment with high dose steroids was initiated. Several days after admission, the subject developed unusual posturing and pulling movements which were thought to represent automatisms and stereotyped behaviors. Treatment with haloperidol was instituted. However, because the subject was able to remember having these movements and because she was able to stop them on command, the investigator felt that there was "substantial functional overlay" involved in these movements. An EEG at the time showed diffuse slowing with no epileptiform activity. Six days after admission and as her abnormal movements were resolving, the subject had an abrupt onset of movements considered by the consulting neurologist to be seizures. These involved loss of consciousness and posturing with head turned to the left and eyes deviated to the left followed by shaking of her right upper extremity progressing to involve her legs and trunk. The neurologist made the diagnosis of status epilepticus which was successfully treated with phenobarbital. None of the EEGs obtained during this time showed epileptiform activity but did reveal diffuse slowing consistent with diffuse encephalopathy.

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Cara Alfaro  
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PHARMACIST

Thomas Laughren  
3/14/03 02:10:45 PM  
MEDICAL OFFICER

I agree that these supplements are approvable; see memo  
to file for more detailed comments.--TPL