CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-115

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 22,115

Drug Name: Lamictal XR

Indication(s): Partial Seizures Adjunctive Therapy Age 13 and up

Applicant: GlaxoSmithKline

Date(s): November 22, 2006

Review Priority: Standard

Biometrics Division: Division of Biometrics I

Statistical Reviewer: Tristan Massie, Ph.D.

Concurring Reviewers: Kun Jin, Ph.D., Team Leader

Jim Hung, Ph.D. Director DB1

Medical Division: Neurology

Clinical Team: Leonard Kapcala, M.D.

John Feeney, M.D., Team Leader and Acting Deputy Director

Russ Katz, M.D., Director

Project Manager: Teresa Wheelous

Keywords:

Unexplained Sample size increase; U.S. vs. non-U.S. treatment effect difference

Table of Contents

LIST OF TABLES **3**

LIST OF FIGURES **3**

1 EXECUTIVE SUMMARY **4**

1.1 CONCLUSIONS AND RECOMMENDATIONS 4
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES 4
1.3 STATISTICAL ISSUES AND FINDINGS 5

2 INTRODUCTION **6**

2.1 OVERVIEW 6
2.2 DATA SOURCES 7

3 STATISTICAL EVALUATION **8**

3.1 EVALUATION OF EFFICACY 8
3.1.1 Study LAM100034 ..... *8*
3.1.1.1 Patient Disposition 13
3.1.1.2 Sponsor's Analysis Results 21
3.1.1.3 Reviewer's Results 24
3.1.1.3.1 Primary Analysis 24
3.1.1.3.2 Assessment of the Impact of Dropouts on the Primary Analysis Result 24
3.1.1.3.3 Secondary Endpoints 25
3.1.1.3.4 Impact of Individual Centers and Countries 26
3.2 EVALUATION OF SAFETY 30

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS **31**

4.1 GENDER, RACE AND AGE 31
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS 32

5 SUMMARY AND CONCLUSIONS **33**

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE 33
5.2 CONCLUSIONS AND RECOMMENDATIONS 33

LIST OF TABLES

Table 1 Study Phase Duration 9
Table 2 Sponsor's Sample Size Calculations....11
Table 3 Subject Accountability (All Randomized Subjects: Study LAM100034) 14
Table 4 Subject Populations Analyzed (Study LAM100034) 15
Table 5 Demographic Characteristics (ITT Population: Study LAM100034)....16
Table 6 Baseline Seizure Data (ITT Population: Study LAM100034)....17
Table 7 Most Common (Incidence of Greater Than or Equal to 5% of Subjects in Either Treatment Group) Previous AED Therapy (ITT Population: Study LAM100034)....18
Table 8 Most Common (Incidence of Greater Than or Equal to 5% ofSubjects in Either Treatment Group) Concurrent AED Therapy (ITT Population: Study LAM100034)....18
Table 9 Number of AED Concomitant Medications and AED Group (ITT Population: Study LAM100034) 19
Table 10 Most Common (Incidence of Greater Than or Equal to 5% of Subjects in Either Treatment Group) Concomitant Medications (Safety Population: Study LAM100034)....20
Table 11 Sponsor's Primary Analysis of Percent Change in Seizure Rate....21
Table 12 Analysis of the Percent Reduction in Partial Seizure Frequency During Escalation, Maintenance, and the Last 8 Weeks of Maintenance (ITT Population: Study LAM100034) 22
Table 13 Percent Change from Baseline in Seizure Rate in Observed Cases (defined as > 16 weeks of seizure data) 24
Table 14 Absolute Change from Baseline in Seizure Rate for all Partial Seizures....26
Table 15 Treatment Effects by Country 28
Table 16 Percent Change in Seizure Rate at End of DB Phase by Gender....31
Table 17 Percent Change in Seizure Rate at End of DB Phase by Race....31
Table 18 Percent Change in Seizure Rate at End of DB Phase by Age Group....32

LIST OF FIGURES

Figure 1 Time to 50% Reduction in Seizure Frequency (ITT Population: Study....23
Figure 2 Pct. Change from Baseline over the course of the Study 25
Figure 3 Treatment Group Differences in Percent Change in Seizure Rate by Site 26
Figure 4 Baseline Entry Times by Country 29
Figure 5 Treatment Group Differences in Percent Change in Seizure Rate by Country 30

1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The data from study LAM100034 support the efficacy of Lamictal XR for adjunctive therapy in patients suffering from partial seizures. Lamictal XR was superior to placebo in terms of the primary endpoint, percent change from baseline in the seizure rate at the end of the 19 week double blind phase of the study ($p<0.001$). The Lamictal XR group also showed a significantly shorter time to 50% reduction, one of the key secondary endpoints, than the placebo group ($p<0.001$). The group difference in time to 50% reduction in seizure rate was nominally significant in favor of Lamictal XR by Week 3 of the double blind phase, in terms of patient follow up time. There was some evidence that the treatment effect was smaller in the U.S. than in the other countries represented in the study but it did at least numerically favor Lamictal XR in the U.S.

1.2 Brief Overview of Clinical Studies

LAM100034 was an international, multicenter, double-blind, randomized, parallel-group study evaluating the efficacy, safety, pharmacokinetics and health outcomes of once daily lamotrigine XR, as adjunctive therapy, compared to placebo for the treatment of partial seizures. The study included male or female subjects who were ≥13 years of age with a confident diagnosis of epilepsy. Subjects must have had partial seizures inadequately controlled by a stable regimen of one or two antiepileptic drugs (AEDs). This was a flexible dose study. Target Lamictal XR doses ranged from 200 to 500 mg/day once daily depending on the preexisting stable AEDs. This study consisted of a Screen visit and four phases: Baseline (8 weeks Prospective Baseline or 4 Prospective Baseline and 4 Historical Baseline), Double-Blind Treatment Phase (Escalation [7 weeks] and Maintenance [12 weeks]=19 weeks), Continuation (Blinded Transition [7 weeks] and Open-label [45 weeks]=52 weeks), and Taper/Follow-up Phase (3-6 weeks). The primary endpoint was the median percent change from Baseline in partial seizure frequency during the entire Double-Blind Treatment Phase.

LEP103944 was an open-label, multicenter study conducted in the US designed to characterize the pharmacokinetic (PK) profile of lamotrigine when administered as extended-release once daily compared to the current formulation (lamotrigine IR) administered twice daily.

LAM100036 is an ongoing international multicenter, double-blind, randomized, placebo controlled, parallel-group study evaluating the efficacy, safety, pharmacokinetics and health outcomes of once daily lamotrigine XR, as adjunctive therapy, compared to placebo for the treatment of PGTC seizures. LAM100036 (adjunctive treatment of PGTC seizures in subjects ≥13 years of age) was ongoing at the time of the NDA submission; available data from the study was limited to blinded safety information (deaths, serious adverse events [SAEs], and discontinuations due to adverse events [AEs]) and unblinded data from the Open-label Continuation Phase as of the cut-off date of 28 June 2006.

Only LAM100034 will be reviewed because it is the only controlled study for which data is available at the present time.

1.3 Statistical Issues and Findings

The protocol stated that 204 patients would be enrolled in order to obtain 132 randomized patients total based on an assumed baseline dropout rate of 35%. However, a much larger number was randomized (243 patients). We can order the randomized patients by the time they started the baseline from earliest to latest and see if the Wilcoxon rank sum test for the first 132 patients is still significant. This approach suggests that the Wilcoxon test reached nominal significance after 132 total patients (p=0.023). Although this p-value is closer to 0.05 than that based on all the patients ultimately randomized (p<0.001) and the p-value shows some higher fluctuations for sample sizes in the vicinity of 132 it does give some indication that the primary analysis result would likely have still been significant if the number randomized had been closer to the sample size planned. Considering this, the over-randomization may not be a serious issue but there are other complications to be considered below.

U.S. sites accounted for 87 (36%) of the randomized patients, which was more randomized patients than any other country in study LAM100034. Eight other countries randomized patients. The country with the second to most patients randomized was Russia with 48 (20%) patients randomized. The treatment effect in the subgroup of patients randomized in the United States did favor Lamictal XR numerically, but it did not reach nominal significance (p=0.68). Of course, the study was not powered to detect a difference in the U.S. subgroup. However, when the non-U.S. countries represented in the LAM100034 study were pooled together there was some evidence that the treatment effect was smaller in the United States than in the other countries (test for treatment by U.S. vs. non-U.S. interaction: p=0.03). The estimated treatment difference was 3.5 in the U.S. (N=84) as compared to 26.2 for non-U.S. countries pooled (N=152). Note that 7 randomized patients (including 3 from the U.S.) had no post-baseline efficacy data.

Another noticeable issue is that the first 37 patients were randomized in the U.S. and no other countries enrolled patients during the 9 months that it took to enroll these 37 U.S. patients. If one looks at the primary endpoint in this first half of the U.S. patients the estimated treatment difference in percent change is 1.0. The estimated treatment difference in the second half of the U.S. patients is not much larger (8.1). This can be compared with the observed treatment difference overall of 18.2 and the difference of 40 assumed for the original sample size calculation. If one had access to the unblinded data from the first 37 patients, although it would not necessarily be a large enough sample to rely on, it could have suggested increasing the sample size and possibly enrolling from non-U.S. countries. If such sample size re-estimation was done it would require a p-value adjustment to protect the type I error. However, the addition of other countries and the sample size increase could also possibly be explained by the slow enrollment (37 patients in 9 months) early in the study. This was the explanation the sponsor gave for the dramatic sample size increase and they stated that there were no interim analyses or sample size re-estimation.

2 INTRODUCTION

2.1 Overview

LAMICTAL® (lamotrigine, LTG), a phenyltriazine anticonvulsant, was first approved in the US in December 1994 (NDA 20-241) for adjunctive treatment of partial seizures in adults. Subsequent to this approval, LAMICTAL was approved in August 1998 for adjunctive treatment of the generalized seizures of Lennox-Gastaut syndrome in pediatric (2-16 years of age) and adult subjects (along with a chewable dispersible tablet formulation; NDA 20-764), in December 1998 for conversion to monotherapy in adults receiving therapy with a single enzyme-inducing antiepileptic drug (EIAED), and in January 2003 as adjunctive treatment for partial seizures in pediatric subjects (2-16 years of age). LAMICTAL was approved in June 2003 for long-term management of mood episodes in subjects with Bipolar I disorder and in January 2004 for conversion to monotherapy from valproate (VPA) in adult subjects with partial seizures. Most recently, LAMICTAL was approved for primary generalized tonic-clonic (PGTC) seizures in September 2006 in adults and pediatric subjects (2-16 years of age).
Lamotrigine is currently marketed as immediate-release compressed or chewable dispersible tablets (lamotrigine IR). The current dosing recommendations in the US for lamotrigine IR are twice daily for concurrent administration with EIAEDs or as monotherapy and once or twice daily administration with valproic acid (VPA).
Lamotrigine extended-release (lamotrigine XR) is a new, enteric coated, formulation that may allow subjects with seizures to be on a once daily dosing regimen. Lamotrigine XR slows the dissolution rate of lamotrigine by releasing 80% of drug over a period of 12-15 hours, compared to a 15 minute time period for lamotrigine IR. This results in a slower rate of absorption, a reduction in the peak to trough fluctuations and fewer fluctuations in lamotrigine concentrations over a 24-hour interval for lamotrigine XR, compared to lamotrigine IR.

The application for lamotrigine XR tablets consists of two completed clinical studies in subjects with epilepsy: LAM100034 (adjunctive treatment of partial seizures in subjects ≥13 years of age), and LEP103944 (open-label study evaluating the conversion from immediate-release to extended-release lamotrigine). LAM100034 is the pivotal clinical study supporting this application, while LEP103944 provides supporting information for conversion from immediate-release to extended-release lamotrigine. LAM100036 (adjunctive treatment of PGTC seizures in subjects ≥13 years of age) was ongoing at the time of the NDA submission; available data from the study was limited to blinded safety information (deaths, serious adverse events [SAEs], and discontinuations due to adverse events [AEs]) and unblinded data from the Open-label Continuation Phase as of the cut-off date of 28 June 2006.

Excerpt from Sponsor's Meeting Minutes for a 6/25/2006 meeting
Sponsor Question: Does the Agency agree that a single clinical study, plus bioavailability studies to characterize the pharmacokinetics of the extended release formulation, are sufficient to support approval of lamotrigine extended release tablets for adjunctive treatment of partial seizures in patients 13 years of age and older?

Agency Response:
Yes, study LAM10034, plus bioavailability studies to characterize the pharmacokinetics of the extended release formulation, are sufficient to support approval of lamotrigine extended release tablets for adjunctive treatment of partial seizures in patients 13 years of age and older.

2.2 Data Sources

The data files are located in the following directory:
\\cdsesub1\n22115\N_000\2006-11-22\crt\datasets\lam100034.

The study report for pivotal study LAM100034 is in the directory
\\cdsesub1\n22115\N_000\2006-11-22\clinstat\lam100034.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study LAM100034

LAM100034 was a Multicenter, Double-Blind, Randomized, Parallel-group Evaluation of LAMICTAL® Extended-release Adjunctive Therapy in Subjects with Partial Seizures.

The study was conducted between 15 Oct 2004 and 26 Jun 2006. Nine countries participated in this study.

Objectives

The primary objective of the study was to assess the efficacy of once-daily adjunctive therapy with LTG XR in subjects with partial seizures.

The secondary objectives were:
• To evaluate the safety and tolerability of LTG XR adjunctive therapy in subjects with partial seizures.
• To evaluate the effect of adjunctive therapy with LTG XR on mood and quality of life in this population.
• To characterize the population PK of lamotrigine in subjects with partial seizures and to assess the presence of PK/pharmacodynamic (PD) relationship between systemic lamotrigine exposure and clinical outcome.

Study Design

This was to be an international, multicenter, double-blind, randomized, placebo (PBO)-controlled, parallel-group study. This trial was to consist of a Screen visit, and four Phases: Baseline, Double-Blind Treatment, Continuation, and Taper/Follow-up, as outlined in Table 1 below.

Table 1 Study Phase Duration

Phase		Duration
Screen		≤2 weeks
Baseline		8 weeks
Double-Blind Treatment	Escalation	7 weeks
	Maintenance	12 weeks
Continuation	Blinded Transition	7 weeks
	Open-label	45 weeks
Taper/Follow-up		3-6 weeks
TOTAL (maximum)		87 weeks

The study was to enroll male or female subjects ≥13 years of age with inadequately controlled partial seizures receiving 1-2 antiepileptic drugs (AEDs). After completion of all screening procedures, subjects who met the enrollment criteria were to enter an 8-week (i.e., 56 days) Baseline Phase for determining baseline seizure frequency. With authorization from GlaxoSmithKline (GSK), a maximum of four weeks (i.e., 28 days) of historical seizure data could be used to replace up to four weeks (i.e., 28 days) of the prospective Baseline Phase for subjects providing reliable documentation of seizure and background AED data.
At the end of the Baseline Phase, subjects who met or exceeded the minimum seizure frequency criteria were to be randomized (1:1 ratio) to receive either escalating doses of LTG extended-release or matching placebo (PBO). The minimum seizure frequency criteria were having at least 8 partial seizures (i.e., simple or complex partial seizures with or without secondary generalization) during the 8-week (i.e., 56 days) prospective Baseline Phase with at least one partial seizure occurring during each 4-week (i.e., 28-day) Baseline period.

Subjects were to be assigned to one of three dosing schedules depending on their concurrent AED(s):
1. A dosing schedule for subjects taking concurrent VPA with or without another AED.
2. A dosing schedule for subjects taking a concurrent EIAED, with or without another AED other than VPA.
3. A dosing schedule for subjects taking concurrent AED(s) other than VPA and EIAEDs (e.g, levetiracetam, oxcarbazepine, gabapentin, topiramate).

Visits 2 and 3 were to be at weeks 4 and 8, respectively, of the baseline period. Visits 4, 5, 6, 7 and 8 were to occur at weeks 3, 7, 11, 15, 19, of the treatment period, respectively.
All subjects were to have a Follow-up Visit (Taper/Follow-up Phase) three weeks after the last dose of study drug. Randomized subjects who did not enter the Continuation Phase were to be tapered off of study drug in a blinded fashion. Subjects completing or withdrawing from the Continuation Phase who did not switch to commercially available LAMICTAL IR after study completion were also to have their dose of study drug tapered. The Taper/Follow-up Phase was to last a maximum of 6 weeks for subjects tapering off of study drug and a minimum of 3 weeks for subjects completing or withdrawing from the Continuation Phase who would take

commercially available LAMICTAL IR upon discontinuing study drug. The maximum duration of the study was to be approximately 87 weeks.

Daily Seizure Record
Subjects were to record the number of seizures, by seizure type, as well as duration of episodes of innumerable seizure activity in their daily diaries during all phases of this study. The site personnel were to transcribe the diary information into the CRF, with the diary pages serving as source documentation.

Innumerable Seizure Activity and Status Epilepticus
Any continuous seizure activity that occurred for less than 30 minutes, with individual seizures occurring so frequently that a caregiver could not distinguish the commencement and completion of each seizure, was to be recorded as innumerable seizure activity. The date and duration of each episode of innumerable seizure activity was to be recorded in the CRF. Medications were to be instituted as medically required.

Innumerable seizure activity was not to be counted towards the number of seizures required for randomization.

For the purposes of this study, status epilepticus was defined as any prolonged or repetitive seizure activity (convulsive, non-convulsive, partial, unilateral, or erratic) occurring without recovery for 30 minutes or longer. Status epilepticus was to be recorded as an adverse event or serious adverse event and not to be included in a subject's daily seizure count in the CRF.

Endpoints

Primary

Percent change from Baseline in partial seizure frequency during the entire Double-Blind Treatment Phase.

Secondary

• Percent change from Baseline in partial seizure frequency during the Escalation Phase, the Maintenance Phase, and during the last 8 weeks of the Maintenance Phase.
• Proportion of subjects with ≥25%, ≥50%, ≥75% or 100% reduction in partial seizure frequency during the entire Double-Blind Treatment Phase, the Escalation Phase, the Maintenance Phase, and the last 8 weeks of the Maintenance Phase.
• Time to ≥50% reduction in seizure frequency.
• Type and incidence of treatment-emergent adverse events.
• Change from Baseline in body weight.
• Proportion of subjects with improved clinical status on the Investigator assessment of subject's clinical status questionnaire and subject's satisfaction with seizure control.

Analysis Populations

The following populations were to be considered for analyzing the data:
• Intent-to-Treat (ITT) efficacy population: defined as all subjects who take at least

one dose of study drug and have at least one post-baseline efficacy assessment in the Double-blind Treatment Phase.
• Per Protocol efficacy population: defined as of all subjects who complete the double blind treatment phase, excluding those with major protocol violations.

Hypotheses

The primary endpoint is the percent change from baseline in weekly partial seizure frequency during the entire Double-Blind Treatment Phase. The hypothesis of interest is described as follows: Null Hypothesis (Ho): $\mu_{pbo} - \mu_{ltg} = 0$

Alternative Hypothesis (Ha): $\mu_{pbo} - \mu_{ltg} \neq 0$ where μ_{ltg} and μ_{pbo} represent the percent change from baseline for subjects on LTG and PBO, respectively. Since seizure data is not normally distributed, a median test will be used to assess statistical significance. Although the objective is to show superiority of LTG over PBO, the test of significance will remain a two-sided test with α=0.05.

Primary Comparisons of Interest

The primary statistical analysis compares LTG and PBO with respect to the percent change from baseline in weekly partial seizure frequency during the entire Double-Blind Treatment Phase. The primary comparison will be analyzed based upon the Intent-to-treat efficacy population. An additional analysis of the primary endpoint will be performed using the Per-Protocol efficacy population.

Sample Size Assumptions

The primary endpoint will be percent change in partial seizure frequency between the Baseline and Double-Blind Treatment Phase. Assuming an estimated pooled standard deviation of 3.5 seizures per week and a baseline rate of 4 seizures/week, 132 randomized subjects will provide 90% power to detect a 50% difference between treatment groups at a two-sided 5% alpha level based on a t-test (Data on file at GSK,US05, THRS/90/0041). Assuming a 35% drop-out rate during the Baseline Phase, approximately 204 subjects will be enrolled in order to randomize 132 subjects. Subjects will be centrally randomized in a 1:1 ratio to receive either lamotrigine or matching placebo.

Sample Size Sensitivity

The robustness and sensitivity of the above calculation are dependent upon the LTG/placebo response rate and standard deviation. Given a fixed standard deviation of 3.5 seizures per week and a fixed sample size, the power to detect the given difference between treatment arms will vary significantly, as shown below.

Table 2 Sponsor's Sample Size Calculations

Treatment Difference	Power	Number of patients needed for 90% power (per arm)
40%	74%	102
50%	90%	66
60%	97%	46

Missing Data

Seizures that are impossible to count, as noted on the innumerable seizure activity CRF page, will be imputed. The highest daily seizure count observed during a given phase (Baseline, Escalation, Maintenance) will be used as the seizure count on these days. For the change from baseline to end of study weight analysis only, LOCF will be used to impute missing weight data if at least one post baseline weight value is recorded. The last missing weight value recorded prior to the visit with the missing data will be assigned to the missing weight value. Screening values will not be carried forward.

Derived and Transformed Data

• Seizure frequency data recorded during the last 8 weeks of the Baseline Phase and during the first 19 weeks of the Double-Blind Treatment Phase will be determined for each subject. Average weekly seizure frequency, defined as the frequency of seizures divided by the number of study weeks in the Baseline or analyzed treatment time period contributing to the frequency counts, will be computed for each subject in order to derive the percent change from Baseline in seizure frequency value. Percent change from baseline will be computed as ((Baseline - Treatment)/Baseline)*100, where a positive value indicates a reduction from Baseline in seizure frequency.

• Time to ≥ 50% reduction in seizure frequency (in days) will be calculated from the first day of study medication to the day at which a ≥ 50% reduction from baseline in seizure frequency is observed. Only subjects who maintain the ≥ 50% reduction in seizure frequency for the remainder of the Treatment Phase will meet this endpoint. Percent change (relative to baseline) will be calculated at each day, after completion of 1 week on study drug. The cumulative experience during the treatment phase will be compared to baseline to determine success. Subjects who fail to meet this endpoint will be censored at the date of last dose.

Multiple Comparison Strategy

Since there are both primary and key secondary comparisons of interest, the overall Type I error will be controlled by employing sequential testing. The key secondary endpoints are shown below:

1. Time to ≥ 50% reduction (based upon change from baseline in seizure frequency)
2. Change from baseline in weight
3. Health Outcomes Questionnaires: Seizure Severity Questionnaire (SSQ, Total Score), Epworth Sleepiness Scale (ESS, Total Score), Quality of Life in Epilepsy (QOLIE-31, Total Score), Profile of Mood States (POMS, Total Score)

Adjustments will only be made for the key secondary endpoints listed above. Testing of the key secondary endpoint comparisons will be conducted only if the test of the primary endpoint, change from baseline in seizure frequency during the entire double-blind treatment phase, is statistically significant. If this test is not significant, then no further testing will be conducted and no claims of significance can be made for the primary or any key secondary endpoints.

Time to ≥ 50% reduction in Seizure Frequency

Time to ≥ 50% reduction in seizure frequency will be tested only if the primary endpoint is significant at the 0.05 level of significance.

Change from Baseline to Endpoint in Weight
The change from baseline to endpoint in weight will be tested only if the primary endpoint is significant at the 0.05 level of significance. A Confidence Interval (CI) approach will be used to evaluate the significance of the change from baseline in weight.

Health Outcomes Endpoints
If a significant difference is found for the primary comparison, then the step-up procedure derived by Hochberg [Hochberg, 1988] will be used to test the Health Outcomes endpoints to control Type I error. Significance probabilities (p-values) will be ranked for each of the tests from the most significant (lowest p-value) to the least significant (highest p-value). If the highest p-value (p_k) is <0.05, then all remaining secondary endpoints are statistically significant as well. If p_k >0.05, then the next test in the sequence (p_{k-1}) must be <0.05/2 (0.025) in order to reject the null hypothesis for the remaining tests. This process will continue sequentially (p_{k-2}, 0.05/3; etc.) until either significance is reached or no additional endpoints exist.

Center will not be included as a factor in any analysis because a central randomization scheme was to be used in this study.

Primary Analysis
The primary efficacy endpoint, percent change from Baseline in weekly partial seizure frequency during the Double-Blind Treatment Phase (DBTP), will be analyzed using the Wilcoxon Rank Sum test. A stratified version of the Wilcoxon Rank Sum test will be used if an examination of selected demographic and historical epilepsy information collected at screen/baseline reveals clinically significant differences between LTG and PBO. Analysis will be performed on the ITT and Per Protocol efficacy populations.

Seizure Frequency
The percent change from Baseline in weekly partial seizure frequency during the Escalation Phase, the Maintenance Phase, and during the last 8 weeks of the Maintenance Phase will be analyzed using the Wilcoxon Rank Sum test.
The proportion of subjects with ≥ 25%, ≥ 50%, ≥ 75% or 100% reduction in weekly partial seizure frequency during the entire Double-Blind Treatment Phase, the Escalation Phase, the Maintenance Phase, and the last 8 weeks of the Maintenance Phase will be analyzed using a Fisher's exact test.

Time to ≥ 50% reduction in seizure frequency
Time to ≥ 50% reduction in seizure frequency will be analyzed using a two-sided logrank statistic. Kaplan-Meier methodology will be used to estimate and graph the time to 50% reduction curve for each treatment group.

3.1.1.1 Patient Disposition
A total of 243 subjects (122 subjects in the placebo group and 121 subjects in the LTG XR group) were randomized from 9 countries. A greater percentage of subjects in the LTG XR group

(10%) compared with the placebo group (2%) were prematurely withdrawn due to adverse events.
Four patients (3 Lamictal XR and 1 placebo) neither took at least one dose of study medication nor had at least one post-baseline efficacy assessment. Patient disposition is summarized in Table 3.

Table 3 Subject Accountability (All Randomized Subjects: Study LAM100034)

	Number (%) of Subjects	
	PBO N=122	LTG XR N=121
Completion Status		
Completed Study	106 (87)	97 (80)
Prematurely Withdrawn	16 (13)	24 (20)
Reason for Premature Withdrawal		
Adverse Event	2 (2)	12 (10)
Lost to Follow-Up	0	1 (<1)
Protocol Violation	1 (<1)	3 (2)
Subject Decided to Withdraw from the Study	7 (6)	6 (5)
Non-compliance	1 (<1)	2 (2)
Other, Specify	5 (4)	0

Data Source: Table 6.2, Table 6.3
Other=Research site closure (1 subject), parents of the subject were opposed (1 subject), mistake of IP group (1 subject), subject stopped taking study medication (1 subject), subject refused (1 subject)

Note: This table was copied from page 60 of the sponsor's study report

The number of subjects in each population is presented in Table 4.

Table 4 Subject Populations Analyzed (Study LAM100034)

Population	PBO	LTG XR
Number Randomized, N	122	121
Did Not Take at Least One Dose of Study Medication, n	1	3
Safety Population[1], n (%)	121 (99)	118 (98)
Did Not Have at Least One Post-baseline Efficacy Assessment, n	1	2
Intent-to-Treat[2], n (%)	120 (98)	116 (96)
<80% Compliant with AED or Study Meds, n	0	2
AED Dosing Changes During Study, n	0	3
Average Daily Dose was Less Than Protocol Allowed, n	2	1
Benzodiazepine Use For >2 Days During Any Treatment Phase, n	2	2
Blind Broken, n	1	2
Other Protocol Violation, n	1	0
Overall Baseline <6 Weeks (or <3 Weeks Prospective), n	1	0
Subject Received Wrong Treatment, n	1	0
Premature Discontinuation, n	16	24
Violated Inclusion Criteria 5[3], n	2	0
Per-Protocol Population[4], n (%)	101 (83)	94 (78)

Data Source: Table 6.6

1. Defined as all subjects who took at least one dose of study drug.
2. Defined as all subjects who took at least one dose of study drug and had at least one post-baseline efficacy assessment in the Double-blind Treatment Phase.
3. Inclusion criteria 5 = Was currently treated with a stable regimen of one or two AED(s) for at least 4 weeks prior to starting the Baseline Phase (historical or prospective).
4. Defined as all subjects who completed the Double-blind Treatment Phase, excluding those with major protocol violations. Subjects could have been in more than one exclusion category for the Per-Protocol Population.

Note: This table was copied from page 61 of the sponsor's study report

Demographic characteristics are presented in Table 5. The age, sex, and ethnicity distributions were similar between treatment groups.

Table 5 Demographic Characteristics (ITT Population: Study LAM100034)

Demographic Characteristic	PBO N=120	LTG XR N=116
Age (yrs)		
Mean (SD)	37.5 (14.40)	35.8 (12.68)
Range	14-73	13-70
Age Group (yrs), n (%)		
<16	4 (3)	5 (4)
16-65	112 (93)	108 (93)
>65	4 (3)	3 (3)
Sex, n (%)		
Female	57 (48)	62 (53)
Male	63 (53)	54 (47)
Ethnicity, n (%)		
Hispanic/Latino	17 (14)	18 (16)
Not Hispanic/Latino	103 (86)	98 (84)
Race, n (%)		
African American/African Heritage	10 (8)	3 (3)
American Indian or Alaskan Native	3 (3)	4 (3)
Asian - Central/South Asian Heritage	9 (8)	16 (14)
Asian - East Asian Heritage	14 (12)	15 (13)
Asian - Japanese Heritage	0	0
Asian - South East Asian Heritage	2 (2)	0
Native Hawaiian or Other Pacific Islander	0	0
White - Arabic/North African Heritage	0	0
White - White/Caucasian/European Heritage	83 (69)	77 (67)

Note: This table was copied from page 62 of the sponsor's study report

Baseline seizure data are summarized in Table 6. The distribution of seizure types and baseline means (all partials, historical, or prospective) were similar between the two treatment groups.

Table 6 Baseline Seizure Data (ITT Population: Study LAM100034)

Baseline Data	PBO N=120	LTG XR N=116
Baseline Seizure Type[1], n (%)		
A (Simple Partial Seizures)	58 (48)	54 (47)
B (Complex Partial Seizures)	91 (76)	83 (72)
C (Partial Seizures Evolving to Secondarily Generalized Seizures)	42 (35)	38 (33)
D1 (Generalized Seizures, Typical Absence)	1 (<1)	1 (<1)
E (Unclassified Seizures)	2 (2)	0
Both Partial and Generalized Seizures	1 (<1)	1 (<1)
Partial Seizures Only (A, B, or C)	119 (>99)	115 (>99)
Baseline Seizure Frequency per Week (last 8 weeks)- All Partial Seizures		
Entire Baseline, n	120	116
Median (Range)	2.1 (b) (4)	2.3 (b) (4)
Historical Baseline, n	41	31
Median (Range)	2.3 (b) (4)	2.6 (b) (4)
Mean (SD) Age at First Seizure (yrs)	16.4 (13.73)	14.9 (12.20)
Mean (SD) Duration of Epilepsy (yrs)	22.1 (16.08)	21.8 (13.20)

Data Source: Table 6.10, Table 6.11, Table 6.12

1. Subjects may have been counted more than once.

Note: This table was copied from page 63 of the sponsor's study report

A summary of the most common (incidence of ≥ 5% in either treatment group) previous AED therapy is presented in Table 7. Previous AED therapy was similar between the two treatment groups.

Table 7 Most Common (Incidence of Greater Than or Equal to 5% of Subjects in Either Treatment Group) Previous AED Therapy (ITT Population: Study LAM100034)

	Number (%) of Subjects	
Concurrent AED Therapy	PBO N=120	LTG XR N=116
Carbamazepine	45 (38)	41 (35)
Phenytoin	38 (32)	41 (35)
Valproic Acid	28 (23)	34 (29)
Phenobarbital	27 (23)	33 (28)
Topiramate	14 (12)	14 (12)
Levetiracetam	5 (4)	10 (9)
Clonazepam	12 (10)	9 (8)
Gabapentin	8 (7)	9 (8)
Primidone	7 (6)	9 (8)
Clobazam	9 (8)	7 (6)
Oxcarbazepine	7 (6)	5 (4)
Zonisamide	6 (5)	3 (3)

Note: This table was copied from page 64 of the sponsor's study report

A summary of the most common (incidence of ≥ 5% of subjects in either treatment group) concurrent AED therapy is presented in Table 8. Concurrent AED therapy was similar between the two treatment groups.

Table 8 Most Common (Incidence of Greater Than or Equal to 5% ofSubjects in Either Treatment Group) Concurrent AED Therapy (ITT Population: Study LAM100034)

	Number (%) of Subjects	
Concurrent AED Therapy	PBO N=120	LTG XR N=116
Any AED Medication	120 (100)	116 (100)
Carbamazepine	50 (42)	50 (43)
Valproic Acid	42 (35)	27 (23)
Topiramate	17 (14)	18 (16)
Phenytoin	16 (13)	16 (14)
Levetiracetam	13 (11)	15 (13)
Oxcarbazepine	22 (18)	11 (9)
Phenobarbital	5 (4)	9 (8)
Clobazam	7 (6)	3 (3)

Note: This table was copied from page 64 of the sponsor's study report

A summary of the number of AED concomitant medications and AED group is provided in Table 9. The incidence of subjects taking 1 AED was slightly higher in the LTG XR group (51%) compared with the placebo group (41%).

Table 9 Number of AED Concomitant Medications and AED Group (ITT Population: Study LAM100034)

	Number (%) of Subjects	
Concurrent AED Therapy	**PBO N=120**	**LTG XR N=116**
Number of AEDs		
1 AED	49 (41)	59 (51)
2 AEDs	70 (58)	57 (49)
3 AEDs	1 (<1)	0
AED Group		
VPA/DVS with EIAEDs	24 (20)	7 (6)
VPA/DVS Alone or With Non-EIAEDs	19 (16)	23 (20)
EIAEDs Alone or With Non-inducing/inhibiting AED	43 (36)	59 (51)
All Other Regimens	34 (28)	27 (23)

Note: This table was copied from page 65 of the sponsor's study report

A summary of the most common (incidence of ≥ 5% of subjects in either treatment group) concomitant medications is presented in Table 10.

Table 10 Most Common (Incidence of Greater Than or Equal to 5% of Subjects in Either Treatment Group) Concomitant Medications (Safety Population: Study LAM100034)

Concomitant Medication	Number (%) of Subjects	
	PBO N=121	LTG XR N=118
Any Medications	84 (69)	70 (59)
Nervous System		
Paracetamol	38 (31)	23 (19)
Acetylsalicylic Acid[1]	18 (15)	17 (14)
Ibuprofen[1]	19 (16)	16 (14)
Caffeine	8 (7)	5 (4)
Alimentary Tract and Metabolism		
Vitamins Not Otherwise Specified	10 (8)	10 (8)
Minerals Not Otherwise Specified	6 (5)	3 (3)
Respiratory System		
Hydrocodone Bitartrate	8 (7)	3 (3)
Pseudoephedrine Hydrochloride	9 (7)	10 (8)
Musculoskeletal System		
Naproxen Sodium[1]	8 (7)	3 (3)
Naproxen[1]	7 (6)	2 (2)
Blood and Blood Forming Organs		
Folic Acid	9 (7)	7 (6)
Antiinfectives for System Use		
Amoxicillin	7 (6)	8 (7)
Systemic Hormonal Preparations, Excl. Sex Hormones		
Levothyroxine Sodium	4 (3)	7 (6)

Note: This table was copied from page 66 of the sponsor's study report

3.1.1.2 Sponsor's Analysis Results

The primary endpoint was the median percent change from Baseline in average weekly partial seizure frequency during the entire Double-Blind Treatment Phase. The median percent reduction from Baseline in all partial seizure frequency during the entire Treatment Phase was greater in the LTG XR group (46.1%) than in the placebo group (24.2%; p=0.0004).

Table 11 Sponsor's Primary Analysis of Percent Change in Seizure Rate

All Partial Seizures (A-C)	PBO N=120	LTG XR N=116
n	120	116
Median (Range)	24.2 (b) (4)	46.1 (b) (4)
Estimated Difference[1]	18.17	
95% CI for Difference[1]	8.301, 28.025	
p-value[1]	0.0004	

Data Source: Table 7.1, Table 7.2

1. Hodges Lehman estimates for the median treatment difference, 95% CI and p-value are based upon a Wilcoxon Rank Sum text. All positive values indicate a reduction in seizure frequency in favor of LTG XR

Note: This table was copied from page 67 of the sponsor's study report

Secondary Efficacy Results

Seizure Frequency

The median percent reduction from Baseline in average weekly partial seizure frequency during the Escalation Phase, the Maintenance Phase, and the last 8 weeks of Maintenance Phase for the ITT Population is summarized in Table 12.

The median percent reduction from Baseline in partial seizure frequency was greater in the LTG XR group than in the placebo group for the Escalation Phase (p=0.0277), the Maintenance Phase (p<0.0001) and the last 8 weeks of Maintenance Phase for the ITT Population (p<0.0001).

Table 12 Analysis of the Percent Reduction in Partial Seizure Frequency During Escalation, Maintenance, and the Last 8 Weeks of Maintenance (ITT Population: Study LAM100034)

All Partial Seizures (A-C)	PBO N=120	LTG XR N=116
Escalation Phase		
n	120	116
Median (Range)	16.3 ((b) (4))	28.0 ((b) (4))
Estimated Difference[1]	12.70	
95% CI for Difference[1]	1.299, 22.563	
p-value[1]	0.0277	
Maintenance Phase		
n	117	106
Median (Range)	26.7 ((b) (4))	58.0 ((b) (4))
Estimated Difference[1]	28.81	
95% CI for Difference[1]	16.667, 38.310	
p-value[1]	<0.0001	
Last 8 Weeks of Maintenance Phase		
n	117	106
Median (Range)	27.0 ((b) (4))	66.7 ((b) (4))
Estimated Difference[1]	30.00	
95% CI for Difference[1]	17.532, 42.157	
p-value[1]	<0.0001	

Data Source: Table 7.1, Table 7.2

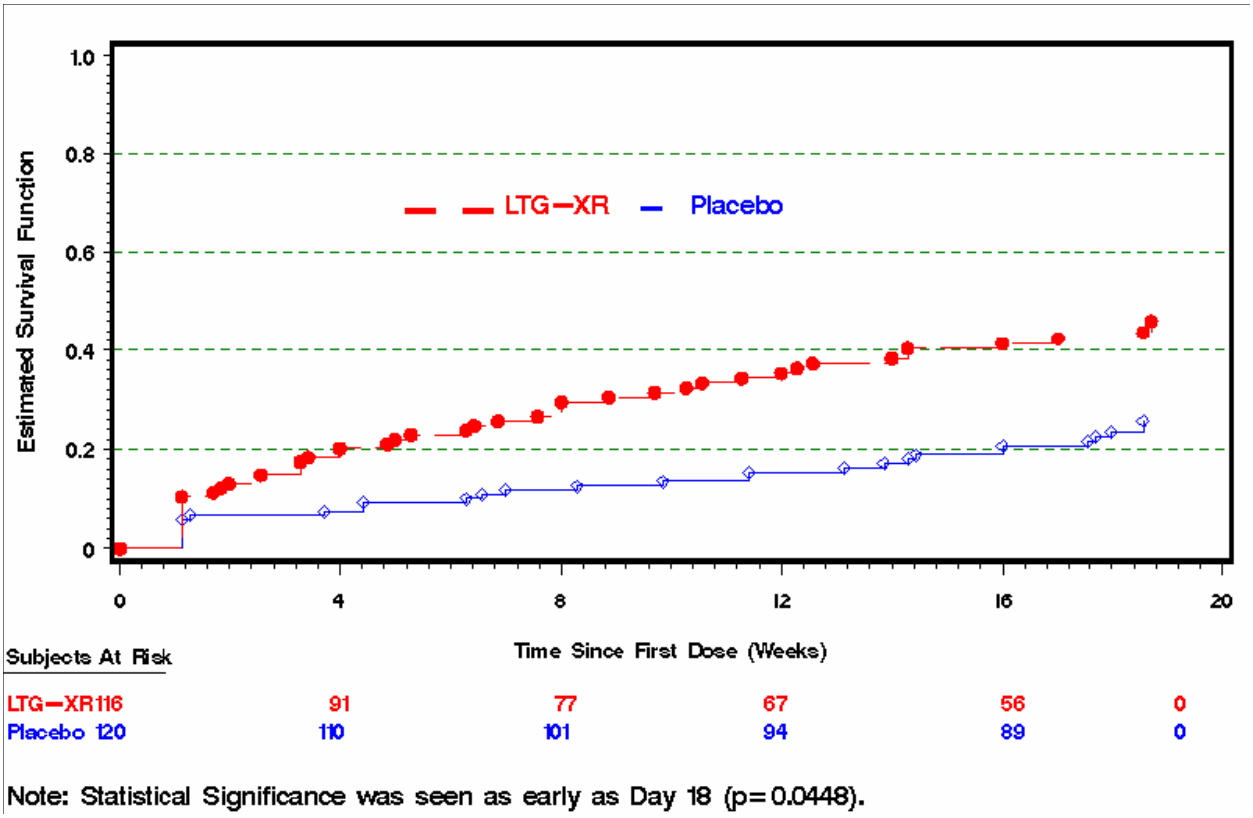
1. Hodges Lehman estimates for the median treatment difference, 95% CI and p-value are based upon a Wilcoxon Rank Sum text. All positive values indicate a reduction in seizure frequency in favor of LTG XR.

Note: This table was copied from page 67 of the sponsor's study report

The percentage of subjects who showed a ≥ 50% reduction in all partial seizure frequency over the entire Treatment Phase was greater in the LTG XR group (42.2%) compared with the placebo group (24.2%, p=0.0037). Likewise, the percentage of subjects who showed a 50% reduction in all partial seizure frequency during the Maintenance Phase and the last 8 weeks of Maintenance Phase was greater in the LTG XR group compared with the placebo group (p<0.001 for both Phases).

For the ITT Population, time (in weeks) to ≥ 50% reduction in seizure frequency for the entire Treatment Phase was statistically significant (p=0.0007). The treatment difference reached statistical significance as early as Day 18 of the Escalation Phase (p=0.0448), as shown in Figure 1.

Figure 1 Time to 50% Reduction in Seizure Frequency (ITT Population: Study LAM100034)



Note: This figure was copied from page 70 of the sponsor's study report.

If the primary endpoint and key secondary endpoints met statistical significance, specific health outcomes questionnaires would be tested using Hochberg's step-up procedure to control type I error. The key primary and secondary endpoints met statistical significance; however, none of the prespecified questionnaires (SSQ, ESS, POMS and QOLIE-31P) reached statistical significance.

3.1.1.3 Reviewer's Results

3.1.1.3.1 Primary Analysis

This reviewer verified the sponsor's primary analysis result finding a statistically significant difference in the percent change from baseline in seizure rates favoring Lamictal XR over placebo ($p<0.001$). Only 4 Lamictal XR patients and 4 placebo patients had seizure entries that were coded as innumerable, i.e., to frequent to count. This includes 1 patient in each group who had innumerable entries in both the baseline and the double blind phases, 2 Lamictal XR patients and 3 Placebo patients who had innumerable seizures only in the double blind period and 1 Lamictal XR and no placebo patients who had innumerable seizure entries only in the baseline period. These missing counts were imputed with the maximum count of the seizure of the same type from the same period as pre-specified in the protocol. The median percent changes were 24.2 for Placebo and 46.1 for Lamictal XR. The Hodges Lehmann estimate of the median of the differences was 18.2. There were no significant differences in the number of AEDs per patient between the U.S. (56% placebo and 49 % Lamictal XR had 2 concomitant AEDs) and non-U.S countries (58% placebo and 48% Lamictal XR had 2 concomitant AEDs).

3.1.1.3.2 Assessment of the Impact of Dropouts on the Primary Analysis Result

The primary analysis was based on all randomized patients that had some post-baseline data. Since there were more dropouts in the Lamictal XR group than in the placebo group (20% vs. 13 %) it is important to assess the sensitivity of the primary analysis result to the dropouts. One way to approach this is to carry out the analysis on the observed cases subgroup, i.e., those patients that completed the double blind treatment period. The similarity of the results for the observed cases, shown in Table 13, to the ITT results suggests that the dropouts had very little impact on the primary analysis results.

Table 13 Percent Change from Baseline in Seizure Rate in Observed Cases (defined as ≥ 16 weeks of seizure data)

All Partial Seizures	PLACEBO	LAMICTAL XR
N	109	97
Median (Range)	24.2 (b) (4)	48.5 (b) (4)
Estimated Difference	23.39	
95% CI for Difference	(12.96 , 33.40)	
Wilcoxon Rank Sum Test p-value	<.0001	

The graph in Figure 2 shows the percent change in seizure rates at various times in the double blind treatment period. The graph shows a curve for each group which connects the medians for the group at each time. From the gap between these two curves we can infer that the groups diverged in the escalation period and after that the difference remained fairly constant for the rest of the double blind period.

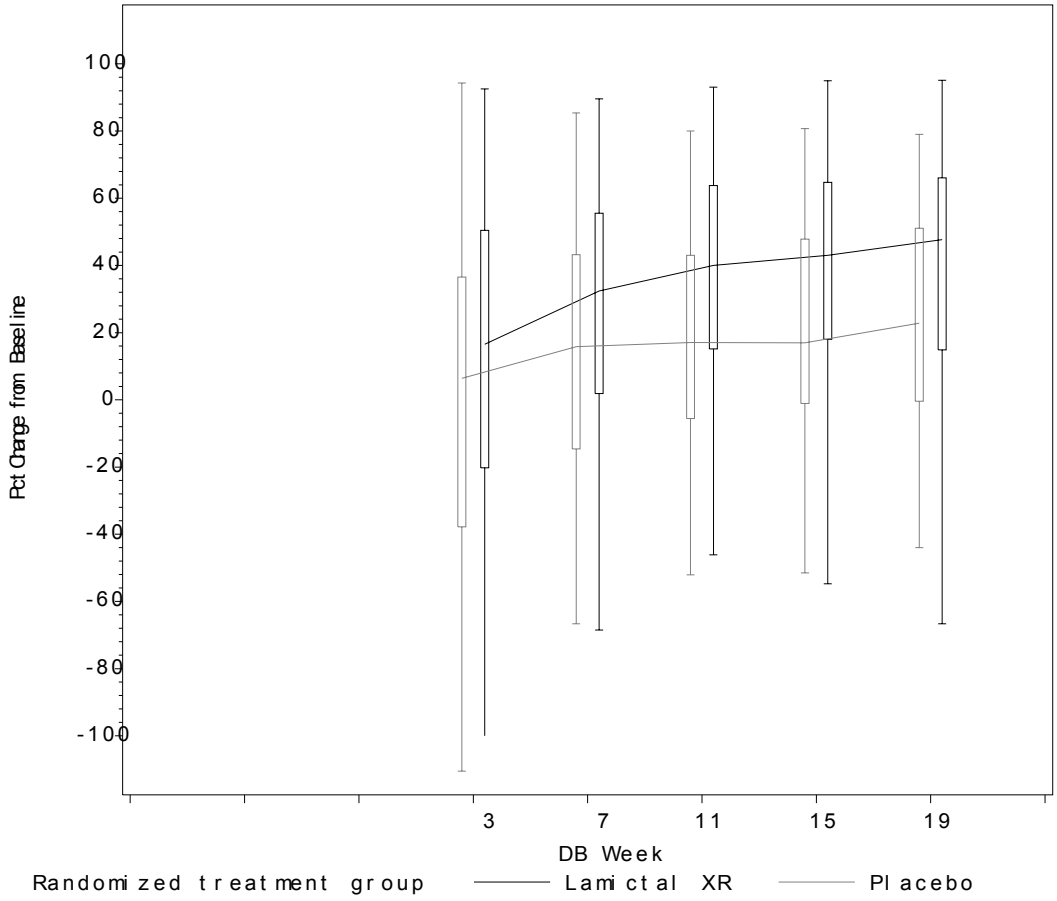
The analysis of the percent change was still significant in favor of Lamictal XR if dropouts observed percent changes were replaced with 0 (assuming no change from baseline) or the minimum of 0 and the observed percent change. This was even true if the replacement was only done for Lamictal XR dropouts. Therefore, it appears that the dropouts had an inconsequential effect on the primary analysis result.

3.1.1.3.3 Secondary Endpoints

This reviewer verified the sponsor's analyses of time to 50% reduction. This showed that the Lamictal XR group had a significantly shorter time to reach 50% reduction ($p<0.001$) and the group difference was first significant around day 18.

The sponsor's results, shown previously in Table 12, for the percent change in the escalation phase and percent change in the maintenance phase (not counting the escalation phase) were also verified. They lend further support to the primary analysis result. In particular, at the end of the esacalation phase the difference in percent changes was 12.7 ($p=0.028$) and at the end of the maintenance phase not counting seizures in the escalation phase it was 28.8 ($p<0.001$) (note: these p-values are not adjusted for multiple comparisons).

Figure 2 Pct. Change from Baseline over the course of the Study



The difference between the Lamictal XR group and the placebo group in the absolute change from baseline in all partial seizures at the end of the maintenance phase also favored Lamictal XR and reached the nominal significance level (see Table 14). The estimated median changes were 0.79 and 0.48 for Lamictal and placebo, respectively, and the means were 1.86 and 0.40, respectively.

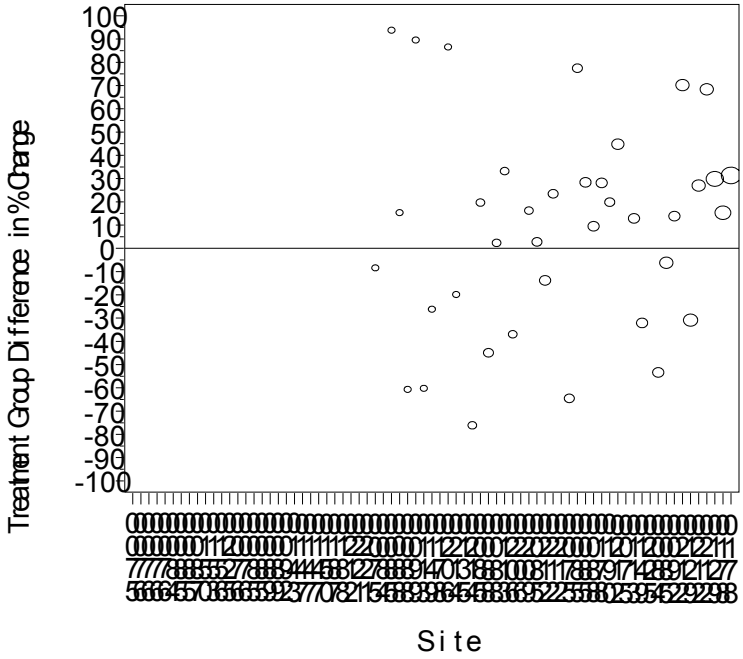
Table 14 Absolute Change from Baseline in Seizure Rate for all Partial Seizures

ALL PARTIAL SEIZURES	PBO	LTG XR
N	120	116
Median Baseline(Range)	2.08 (b) (4)	2.31 (b) (4)
Median Change (Range)	0.484 (b) (4)	0.787 (b) (4)
Estimated Difference	0.359	
95% CI for Difference	(0.0987 , 0.6411)	
Wilcoxon Rank Sum Test p-value	0.0094	

3.1.1.3.4 Impact of Individual Centers and Countries

There were 75 total centers. The number of patients per center ranged from 1 to 15. The median number of patients per center was 2 and the median number of patients per group was 1 for each group. Among treatment group differences within center, 28 favored Lamictal XR, 12 differences favored placebo, and 35 centers had no patients in one group so no difference could be determined (see Figure 3). The primary analysis result is robust to the exclusion of data from any single center.

Figure 3 Treatment Group Differences in Percent Change in Seizure Rate by Site



The percent changes can be ranked across all patients and then an ANOVA with effects for country, treatment group, and their interactions can be carried out on the ranked percent changes to test for an interaction between treatment group and country. If we compare the U.S. to all other countries pooled the Rank ANOVA model suggests that the treatment effect was significantly smaller in the U.S., but still in the right direction there (test for treatment by U.S. vs. non-U.S. interaction, p=0.03). If we allow for a different treatment effect on the mean for each country represented in the study and a different mean for each country given treatment then it is not clear that the treatment effects varied significantly with the country (p=0.50). However, many of the countries had only a few patients so this latter test is very likely underpowered. It seems reasonable to combine the South American countries, Brazil (N=5), Chile (N=10), and Argentina (N=4), and to separately combine the Ukraine (N=9) with the Russian Federation (N=46). If we then test whether the treatment difference varies across the standalone countries and these new groupings of countries the p-value is 0.21. Note that significance levels above 0.05 are frequently used for testing interactions because tests at the usual level may be seriously underpowered and increasing the significance level increases the power (at the expense of type I error). If the test is focused more on the U.S. versus the non-U.S. then there is even more evidence of an interaction between treatment and country.
We can test whether there is any non-U.S. country effect after adjusting for treatment effect, i.e., are the placebo means in each non U.S. country all equal and are the Lamictal XR means in each non U.S. country all equal. We do this by comparing a "full" model which assumes a different mean for each country (including the U.S.), given treatment, to a "reduced" model which assumes a different mean for the U.S. but the same mean for all other countries, given treatment. An F test comparing these two models suggests that we can not reject the hypothesis that all of the non-U.S. countries have the same mean, given treatment (p=0.74). Next, we can test that the treatment effect is different in the U.S. by fitting a model that assumes that the treatment effect is different in the U.S. but the same in all other countries. Comparing this model to the "reduced" model that assumes a common treatment effect across all countries and a common mean, given treatment, across all countries except the U.S yields a test for a treatment difference between the U.S. and non-U.S. countries. This test suggests that we can reject the hypothesis that the treatment effect in the U.S. is the same as the treatment effect common to all other countries, p=0.03.

In summary the significance of the treatment difference between the U.S. and non-U.S. depends on the model used to assess the difference. If the most general model for country is used which fits a separate mean for each combination of the treatment group and country factors then the evidence for differences in treatment effects among the countries is weak (p=0.50). However, the test based on this general model is likely seriously underpowered. The data suggests that the country variable in the model can be collapsed into two categories, U.S. and non-U.S., without a significant loss of model fit. After adding an effect for the interaction between treatment group and U.S. vs. non-U.S. to this model we find that the interaction effect is significant at the nominal level (p=0.03).

Table 15 Treatment Effects by Country

		Placebo				Lamictal XR			Median of Differences	95% C.I.	Wilcoxon Test p-value
Country	n	median	mean	std	n	median	mean	std			
United States	**42**	**32.8**	**24.3**	**51.0**	**42**	**37.1**	**27.0**	**49.8**	**3.4943**	**(-11.3360 , 19.1600)**	**0.6807**
All Non-U.S.	**78**	**22.8**	**17.3**	**43.5**	**74**	**49.6**	**39.3**	**50.8**	**26.1910**	**(13.9271 ; 38.3626)**	**<0.0001**
Russian Federation	23	15.8	8.7	59.5	23	49.7	49.8	58.9	44.6042	(17.7621 , 63.0631)	0.0007
India	9	29.8	20.2	39.4	16	54.7	31.2	59.4	18.8388	(-19.2520 , 51.9298)	0.2696
Germany	13	27.5	20.4	43.0	9	67.3	42.5	53.0	31.1339	(-22.2824 , 64.0936)	0.2853
Brazil	4	11.3	12.1	2.6	1	22.5	22.5	.	11.1846	(12.7756 , 12.7756)	0.2888
Ukraine	4	0.4	4.6	35.2	5	52.6	34.5	43.0	27.7124	(-62.1722 , 91.8660)	0.3913
Korea	16	32.2	29.2	38.3	15	48.5	36.7	37.8	9.4760	(-11.6396 , 32.7485)	0.3954
Chile	6	27.6	22.3	13.6	4	33.5	26.7	38.4	14.1963	(-51.0321 , 51.2759)	0.7491
Argentina	3	-0.8	10.4	26.6	1	26.3	26.3	.	27.0734	(35.1432 , 35.1432)	1.0000

Figure 4 shows the entry times for each country. There were 37 patients entered in the U.S. and the study ran for 9 months before patients were entered in any other countries.
When considering the ultimate overenrollment (80% more patients randomized) it is striking that the lowest treatment effect was observed in the U.S. and the U.S. was enrolled earliest because if one could have seen the early data one might have been inclined to increase the sample size and/or add sites outside the U.S. However, it is also true that entering just 40 patients in 9 months could be a reason to ramp up enrollment.

For the first 42 patients randomized in the U.S. the median percent changes were 32.0 for Lamictal XR (N=19) and 34.9 for Placebo (N=23). The Hodges Lehmann estimate of the treatment difference for the first 42 patients randomized in the U.S. was -0.5 with an associated 95% C.I. of (-25.5, 21.9).
For the last 42 patients randomized in the U.S. the median percent changes were 43.9 for Lamictal XR (N=23) and 32.3 for Placebo (N=19). The Hodges Lehmann estimate of the treatment difference for the last 42 patients randomized in the U.S. was 8.4 with an associated 95% C.I. of (-13.6, 29.4).

Figure 4 Baseline Entry Times by Country

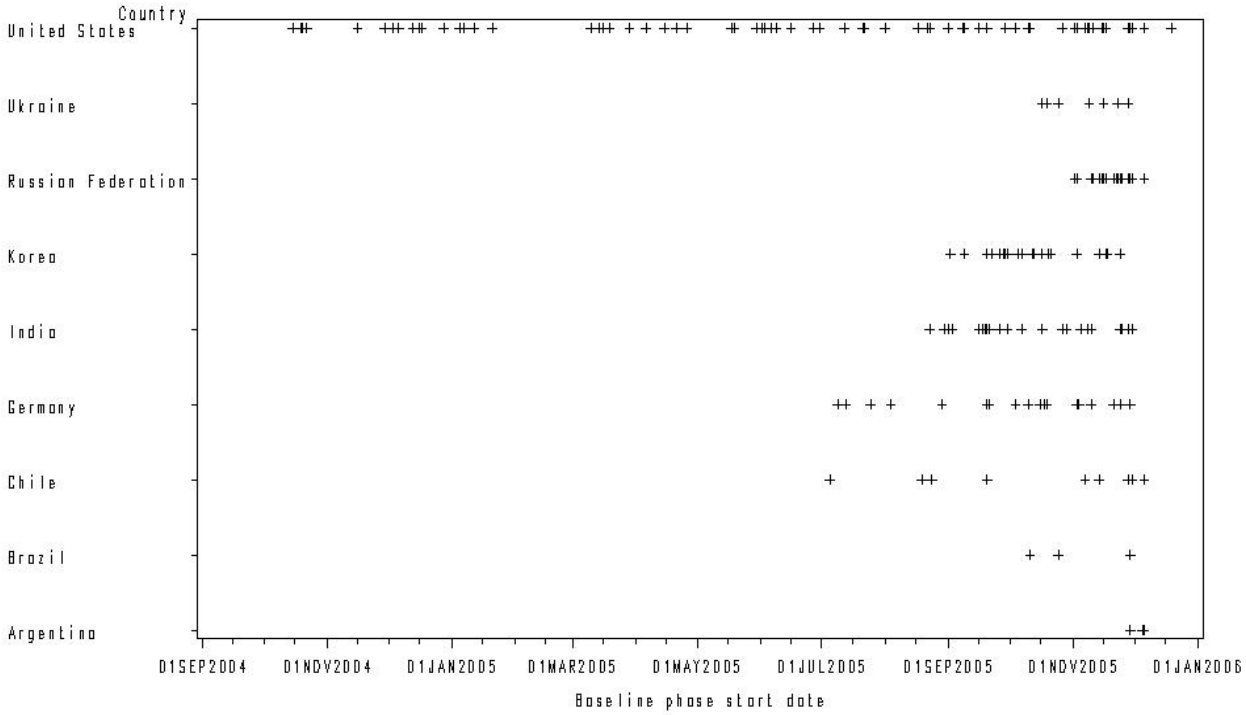
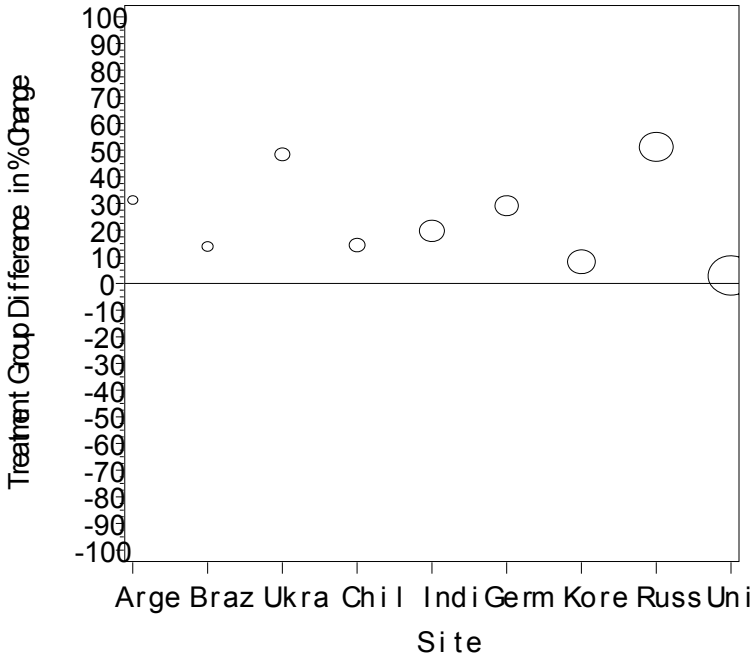


Figure 5 shows the treatment group differences by specific country. Treatment group differences numerically favored Lamictal XR in all 9 countries. The most patients were enrolled in the U.S. (indicated by "Uni" on the x-axis) but the smallest treatment group difference was observed there.

Figure 5 Treatment Group Differences in Percent Change in Seizure Rate by Country



3.2 Evaluation of Safety

Safety is not evaluated in this review. Please see the clinical review(s).

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Gender

About 50% of patients were male and 50% were female. There was a suggestion of efficacy in both genders (nominal significance level was reached) and there was no compelling evidence that the treatment effect was larger in one gender subgroup than the other.

Table 16 Percent Change in Seizure Rate at End of DB Phase by Gender

	MALE			FEMALE		
TREAT	N	MEDIAN (RANGE)	WILCOXON P VALUE VS. PLACEBO	N	MEDIAN (RANGE)	WILCOXON P VALUE VS. PLACEBO
Placebo	63	25.9 (-58.5, 100)	.	57	23.4 (-230.6, 97.4)	.
Lamictal XR	54	49.0 (-166.7, 9)	0.009	62	43.2 (-177, 100)	0.021

Interaction test p= 0.9104

Race

The proportions of patients of each race were as follows: 68% were recorded as White, 12% were recorded as East Asian, 11% were recorded as South or Central Asian, and 9% were others (including African Americans, Alaskan or Native Americans, South East Asians, and Mixed). The non-White subgroups were too small to permit reliable estimates of treatment differences between races.

Table 17 Percent Change in Seizure Rate at End of DB Phase by Race

	White			East Asian			South/Central Asian			Others		
TREAT	N	MEDIAN (RANGE)	WILCOXON P VALUE VS. PLACEBO	N	MEDIAN (RANGE)	WILCOXON P VALUE VS. PLACEBO	N	MEDIAN (RANGE)	WILCOXON P VALUE VS. PLACEBO	N	MEDIAN (RANGE)	WILCOXON P VALUE VS. PLACEBO
Placebo	82	19.2 (-231, 100)	.	14	32.2 (-66.1, 96.3)	.	9	29.8 (-42.6, 75.6)	.	15	47.4 (-36.8, 65.3)	.
Lamictal XR	77	44.4 (-177, 100)	0.003	15	48.5 (-80.3, 70.9)	0.383	16	54.7 (-140, 92.3)	0.258	7	44.4 (11.9, 66.1)	0.307

Interaction test p= 0.9471
The race was not recorded for one patient in the Lamictal group which explains why there are only 115 patients in the Lamictal row.

Age

Ages ranged from 13 to 73 and the mean and median ages were about 36. Less than 5% of patients were 65 or older. About 10% of patients were 18 or less. Treatment group differences were nominally significant in both subgroups in favor of Lamictal XR and there was no compelling evidence that the treatment difference was larger in one age group than the other.

Table 18 Percent Change in Seizure Rate at End of DB Phase by Age Group

	Age < 18			Age > 18		
TREAT	N	MEDIAN (RANGE)	WILCOXON P VALUE VS. PLACEBO	N	MEDIAN (RANGE)	WILCOXON P VALUE VS. PLACEBO
Placebo	10	33.3 (-58.5, 51.4)	.	110	22.8 (-230.6, 100)	.
Lamictal	13	85.9 (-140, 96)	0.017	103	44.4 (-177, 100)	0.003

Interaction test p= 0.2197

4.2 Other Special/Subgroup Populations

No other special populations were examined.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The protocol stated that 204 patients would be enrolled in order to obtain 132 randomized patients total based on an assumed baseline dropout rate of 35%. However, a much larger number was randomized (243 patients). We can order the randomized patients by the time they started the baseline from earliest to latest and see if the Wilcoxon rank sum test for the first 132 patients is still significant. This approach suggests that the Wilcoxon test reached nominal significance after 132 total patients (p=0.023). Although this p-value is closer to 0.05 than that based on all the patients ultimately randomized (p<0.001) and the p-value shows some higher fluctuations for sample sizes in the vicinity of 132 it does give some indication that the primary analysis result would likely have still been significant if the number randomized had been closer to the sample size planned. Considering this, the over-randomization may not be a serious issue but there are other complications to be considered below.

U.S. sites accounted for 87 (36%) of the randomized patients, which was more randomized patients than any other country in study LAM100034. Eight other countries randomized patients. The country with the second to most patients randomized was Russia with 48 (20%) patients randomized. The treatment effect in the subgroup of patients randomized in the United States did favor Lamictal XR numerically, but it did not reach nominal significance (p=0.68). Of course, the study was not powered to detect a difference in the U.S. subgroup. However, when the non-U.S. countries represented in the LAM100034 study were pooled together there was some evidence that the treatment effect was smaller in the United States than in the other countries (test for treatment by U.S. vs. non-U.S. interaction: p=0.03). The estimated treatment difference was 3.5 in the U.S. (N=84) as compared to 26.2 for non-U.S. countries pooled (N=152).

Another noticeable issue is that the first 37 patients were randomized in the U.S. and no other countries enrolled patients during the 9 months that it took to enroll these 37 U.S. patients. If one looks at the primary endpoint in this first half of the U.S. patients the estimated treatment difference is 1.0. The estimated treatment difference in the second half of the U.S. patients is not much larger (8.1). This can be compared with the observed treatment difference overall of 18.2 and the difference of 40 assumed for the original sample size calculation. If one had access to the unblinded data from the first 37 patients, although it would not necessarily be a large enough sample to rely on, it could have suggested increasing the sample size and possibly enrolling from non-U.S. countries. If such sample size re-estimation was done it would require a p-value adjustment to protect the type I error. However, the addition of other countries and the sample size increase could also be explained by the slow enrollment (37 patients in 9 months) early in the study. This was the explanation the sponsor gave for the dramatic sample size increase and they stated that there were no interim analyses or sample size re-estimation.

5.2 Conclusions and Recommendations

The data from study LAM100034 support the efficacy of Lamictal XR for adjunctive therapy in patients suffering from partial seizures. Lamictal XR was superior to placebo in terms of the

primary endpoint, percent change from baseline in the seizure rate at the end of the 19 week double blind phase of the study ($p<0.001$). The Lamictal XR group also showed a significantly shorter time to 50% reduction, one of the key secondary endpoints, than the placebo group ($p<0.001$). The group difference in time to 50% reduction in seizure rate was nominally significant in favor of Lamictal XR by Week 3 of the double blind phase, in terms of patient follow up time. There was some evidence that the treatment effect was smaller in the U.S. than in the other countries represented in the study but it did at least numerically favor Lamictal XR in the U.S.

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

/s/

Tristan Massie
8/22/2007 07:34:59 AM
BIOMETRICS

Kun Jin
8/23/2007 11:44:18 AM
BIOMETRICS

James Hung
8/23/2007 01:53:34 PM
BIOMETRICS