CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-509

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #/Serial #:	22-509
DRUG NAME:	LAMICTAL XR (Lamotrigine)
INDICATION:	Adjunctive therapy of primary generalized tonic-clonic seizures in patients 13 years and older
APPLICANT:	SmithKline Beecham Corp.
DATE OF RECEIPT:	03/31/2009
REVIEW PRIORITY:	Standard
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KEY WORDS: PGTC-Primary generalized tonic-clonic

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The data from study LAM100036 supported the efficacy of Lamictal XR for adjunctive therapy in patients older than 13 years of age with PGTC seizures. Lamictal XR was superior to placebo in terms of the primary endpoint, median percent change from baseline in the PGTC seizures during the entire Treatment Phase ($p<0.001$). The group difference in time (in weeks) to 50% reduction in seizure frequency for the entire Treatment Phase was shorter for the Lamictal XR group compared with the Placebo group ($p<0.0001$) for the ITT population. 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

LAM100036 was an international, multicenter, double-blind, randomized, placebo controlled, parallel-group study was to assess the efficacy, safety, pharmacokinetics, and health outcomes of once daily adjunctive therapy with lamotrigine extended-release (LTG XR) in subjects with primary generalized tonic-clonic (PGTC) seizures. A total of 153 subjects were randomized and 146 received study drug, including 72 in the LTG XR group and 74 in the placebo group. The total duration of the study was approximately 87 weeks. The study was divided into a Screen visit (≤2 weeks) and four Phases: 1. Baseline Phase (8 weeks), 2. Double-Blind Treatment Phase consisting of an Escalation period (7 weeks), and Maintenance period (12 weeks). 3. Continuation Phase consisting of a blinded Transition period (7 weeks) and Open label period (45 weeks). 4. Taper/Follow-up Phase (3-6 weeks). The trial was conducted in nine countries. The primary efficacy endpoint was percent change from Baseline in weekly PGTC seizure frequency during the double-blind Treatment Phase.

1.3 Statistical Issues and Findings

U.S. sites accounted for 21 (15%) of the randomized patients, which was the third largest country in study LAM100036. Eight other countries randomized patients. The largest two countries are Indian and Russian Federation, which combine enrolled 88 (62%) of the randomized patients. These two countries also had the most favorable treatment for Lamictal XR. 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 ($p=0.099$). 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 LAM100036 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: $p=0.7814$). The estimated treatment difference was 22.15 in the U.S. as compared to 34.55 for non-U.S. countries pooled.

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 (b) (4) of drug over a period of 12-15 hours, compared to a 15 minute time period for lamotrigine IR. This result 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 current application seeks approval of LTG XR as an adjunctive treatment of PGTC seizures in subjects ≥13 years of age. Study LAM100036 constitutes the pivotal clinical trial in this application for the adjunctive treatment of PGTC seizures in subjects ≥13 years of age.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room: \\Cdsesub1\evsprod\NDA022509\0000\m5\datasets

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The following description is based on the sponsor's clinical study report. Any discrepancy between the study report and study protocol will be discussed in the section of statistical reviewer's comments.

3.1.1 STUDY LAM100036

LAM100036 was an international, multicenter, double-blind, randomized, parallel-group evaluation of LTG XR adjunctive therapy in subjects with PGTC seizures. The study was conducted between 07 Dec 2004 and 03 July 2007. This international study was conducted in 9 countries.

Objectives

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

The secondary objectives of this study were:

- To evaluate the safety and tolerability of adjunctive therapy with LTG XR in subjects with PGTC seizures.
- To evaluate the effect of adjunctive therapy with LTG XR on mood and quality of life in this population.
- To characterize the population pharmacokinetics of lamotrigine in subjects with PGTC seizures and to assess the presence of pharmacokinetic/pharmacodynamic relationship between systemic lamotrigine exposure and clinical outcome.

Study Design

This was an international, multicenter, double-blind, randomized, parallel-group evaluation of LTG XR adjunctive therapy in subjects with PGTC seizures. The study was to consist a Screen visit, and four phases: Baseline, Double-blind treatment, Continuation, and Follow-up, as provided in Table 1.

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

[Source: Sponsor's Study Report]

The study was to enroll male or female subjects older than 13 years of age with inadequately controlled partial seizures receiving 1 or 2 antiepileptic drugs (AEDs). After completion of all screen procedures, subjects who met the enrollment criteria entered the Baseline Phase for determining baseline seizure frequency. At the end of Baseline Phase, subjects who met or exceeded the minimum seizure frequency criteria were randomized (1:1 ratio) to receive either escalating doses of LTG XR or matching placebo. The minimum seizure frequency criteria were having at least 3 PGTC seizures during the 8 weeks Baseline Phase. All randomized subjects

who completed the Maintenance Phase were offered the option to participate in the Continuation Phase for a long-term follow-up and received LTG XR for up to 52 weeks.

Efficacy Measures

The primary efficacy measure was percent change from baseline in weekly PGTC seizure frequency during the double-blind Treatment Phase.

The secondary efficacy endpoints were as follows:

- Percent change from Baseline in PGTC 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 PGTC 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.
- 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

Two populations were considered for analysis in this study:

- The Intent-to-Treat (ITT) efficacy population consisted of 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.
- The Per Protocol efficacy population consisted of all subjects who completed the double-blind treatment phase, excluding those with major protocol violations.

Statistical Hypotheses

The primary endpoint is the percent change from baseline in PGTC seizure frequency during the entire double-blind treatment phase. The hypothesis of interest is described as follows:

H_0: $\mu_{pbo}-\mu_{ltg}=0$

H_a: $\mu_{pbo}-\mu_{ltg}\neq 0$

Where μ_{pbo} and μ_{ltg} represent the percent change from baseline for subjects on Placebo and LTG, respectively. Since seizure data is not normally distributed, a median test will be used to assess statistical significance. The study is designed to show superiority of LTG over Placebo using a two-sided test with $\alpha=0.05$.

Sample Size Considerations

Assuming an estimated pooled standard deviation of 43%, 128 subjects will provide 90% power to detect a 25% difference in the PGTC seizure frequency at a two-sided 5% alpha level based on a ranked ANCOVA, controlling for ranked baseline weekly seizure frequency. Assuming 35% drop-out rate, approximately 197 subjects will be enrolled in order to obtain 128 randomized subjects. Subjects will be centrally randomized in a 1:1 ratio to receive either lamotrigine or matching placebo.

Missing Data

Seizures that are impossible to count, as noted on the innumerable seizure activity CRF page, will be imputed, using the highest daily seizure count observed during the given phase (Baseline, Escalation or Maintenance). Any continuous seizure activity that occurs for less than 30 minutes, with individual seizures occurring so frequently that a caregiver cannot distinguish the commencement and completion of each seizure, will be recorded as innumerable seizure activity. The date and duration of each episode of innumerable seizure activity will be recorded in the CRF. Medications should be instituted as medically required.

For the change from baseline to end of study body 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.

Multiple Comparisons and Multiplicity

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:

- Time to ≥ 50% reduction (based upon change from baseline in seizure frequency)
- Change from baseline in weight
- 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 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 will be tested only if the primary efficacy endpoint is significant at the 0.05 level of significance.

The change from Baseline to endpoint (last visit while still on study medication) in body weight will be tested only if the primary efficacy endpoint and time to ≥50% reduction in seizure frequency are significant at the 0.05 level of significance. A confidence interval (CI) approach will be used to evaluate the equivalence of the change from baseline in weight between the two treatment groups.

If a significant difference is found in the primary efficacy endpoint and time to ≥50% reduction in seizure frequency, and equivalence is found for change from baseline to endpoint in weight, then the step-up procedure for multiple comparisons derived by Hochberg will be used to test the Health Outcomes endpoints to control Type I error.

Efficacy Analysis

All statistical tests will be two-sided and performed at the 0.05 level of significance.

The primary analysis of the primary efficacy endpoint, percent change from Baseline in weekly PGTC seizure frequency during the DBTP, will be carried out using a ranked ANCOVA analysis, controlling for the ranked baseline weekly seizure frequency. The ranked percent change and baseline weekly seizure frequency will be modeled using an analysis of covariance. The residuals from this model will be used to calculate a Mantel-Haenszel mean score statistic to compare the two treatment groups. Analyses will be performed on the ITT and Per Protocol populations.

The percent change from Baseline in weekly PGTC seizure frequency during the Escalation Phase, the Maintenance Phase, and during the last 8 weeks of the Maintenance Phase was analyzed in the same manner as the primary endpoint.

The proportion of subjects with ≥25%, ≥50%, ≥75%, and 100% reduction in weekly PGTC seizure frequency during the entire double-blind Treatment Phase, the Escalation Phase, the Maintenance Phase, and the last 8 weeks of the Maintenance Phase were analyzed using a Fisher's exact test.

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

The method of two one-sided t-tests [Schuirmann, 1987] will be used to evaluate the hypothesis that the mean change from baseline in weight is equivalent (to within Δ) for the LTG and PBO treatment groups. This statistical method consists of constructing two one-sided null hypotheses: a) the change in weight between treatment arms is < -Δ and b) the change in weight between treatment arms is > +Δ. These two hypotheses are each tested at α=0.05 level of significance, with rejection of both null hypotheses leading to the conclusion that the change in weight between treatment arms is simultaneously >-Δ and <+Δ, i.e. the treatments are equivalent to within Δ. The two one-sided t-tests procedure described above is operationally identical to the procedure of declaring equivalence only if the 90% confidence interval for the change in weight between treatment arms is completely contained within the equivalence interval of –Δ to +Δ. The margin of equivalence Δ will be 10% of the pooled baseline weight.

The proportion of subjects with improved clinical status on the investigator assessment of subject's clinical status questionnaire and subject's satisfaction questionnaire will be analyzed using a Chi-Square test assessing improvement (mild, moderate or marked), deterioration (mild, moderate or marked) and no change.

3.1.1.1 Patient Disposition, Demographic and Baseline Characteristics

A total of 153 subjects (77 subjects in the placebo and 76 subjects in the LTG XR) were randomized form 9 countries. A similar percentage of subjects in the both groups were prematurely withdrawn due to AEs. Patient disposition is summarized in Table 2.

Table 2 Subject Accountability

	Number (%) of Subjects	
	PBO N=74	LTG XR N=72
Completion Status		
Completed Study	69 (93)	66 (92)
Prematurely Withdrawn	5 (7)	6 (8)
Reason for Premature Withdrawal		
AE	2 (3)	1 (1)
Lost to Follow-Up	0	1 (1)
Protocol Violation	0	1 (1)
Subject Decided to Withdraw from the Study	2 (3)	3 (4)
Non-compliance	0	0
Other[1], Specify	1 (1)	0

[Source: Sponsor's Table 5 of CSR]

Demographic characteristics are presented in
Table 3. The age, sex, and ethnicity distributions were similar between treatment groups.

Table 3 Demographic Characteristics

Demographic Characteristic	PBO N=73	LTG XR N=70
Age, y		
Mean (SD)	28.4 (11.48)	29.4 (12.78)
Range	13-74	14-69
Age Group, y, n (%)		
<16	6 (8)	4 (6)
16-65	66 (90)	65 (93)
>65	1 (1)	1 (1)
Sex, n (%)		
Female	38 (52)	32 (46)
Male	35 (48)	38 (54)
Ethnicity, n (%)		
Hispanic/Latino	14 (19)	8 (11)
Not Hispanic/Latino	59 (81)	62 (89)
Race, n (%)		
African American/African Heritage	1 (1)	2 (3)
American Indian or Alaskan Native	2 (3)	0
Asian - Central/South Asian Heritage	31 (42)	28 (40)
Asian - East Asian Heritage	0	1 (1)
Asian - Japanese Heritage	1 (1)	0
Asian - South East Asian Heritage	0	2 (3)
Native Hawaiian or Other Pacific Islander	0	0
White - Arabic/North African Heritage	0	0
White - White/Caucasian/European Heritage	41 (56)	37 (53)

[Source: Sponsor's Table 7 of CSR]

Baseline seizure data are summarized in Table 4. The distribution of screening seizure types and baseline medians were similar between treatment groups.

Table 4 Baseline Seizure Data

Baseline Data	PBO N=73	LTG XR N=70
Screening Seizure Type[1], n (%)		
Absence	10 (14)	10 (14)
Myoclonic	11 (15)	7 (10)
Clonic	1 (1)	0
Tonic	1 (1)	0
Tonic-Clonic	73 (100)	69 (99)[2]
Atonic	1 (1)	0
Baseline Seizure Frequency per Week – PGTC Seizures		
Entire Baseline, n	73	70
Median (Range)	0.6 (0.0, 7.4)	0.8 (0.0, 7.3)
Historical Baseline, n	17	19
Median (Range)	0.75 (0.3, 2.0)	0.75 (0.0, 7.3)
Mean (SD) Age at First Seizure, y	14.8 (9.83)	16.5 (11.29)
Mean (SD) Duration of Epilepsy, y	14.6 (8.77)	13.9 (9.88)

[Source: Sponsor's Table 8 of CSR]

3.1.1.2 Primary Efficacy Results

The primary endpoint was the median percent change from baseline in average weekly PGTC Seizure frequency during the entire double-blind treatment phase. The median percent reduction from Baseline in all PGTC seizure frequency during the entire Treatment Phase was greater in the LTG XR group (75.4%) than in the placebo group (32.1%; $p<0.0001$)

Table 5 Analysis of Median Percent Reduction in PGTC Seizure Frequency during the Entire Treatment Phase (ITT)

Statistics	Placebo	LTG XR
N	72	69
Median (Range)	32.1 (-427, 100)	75.4 (-100, 100)
Estimate Difference[a]	31.6	
95% CI for Difference	15.8, 47.9	
p-value	<.0001	

[Source: Reviewer's results]

a. Hodges Lehman estimates for the median treatment difference, 95% CI and p-value are based on a Cochran-Mantel-Haenszel Rank Sum test.

3.1.1.3 Secondary Efficacy Results

Seizure Frequency

The median percent reduction from baseline in average weekly PGTC 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 6. The median percent reduction from baseline in PGTC seizure frequency was numerically greater in the LTG XR group than placebo for all three phases for the ITT population.

Table 6 Analysis of the Percent Reduction in PGTC Seizure Frequency during Escalation, Maintenance, and the Last 8 Weeks of Maintenance (ITT)

PGTC Seizures	Placebo	LTG XR
Escalation Phase		
N	72	69
Estimate Difference[a]	25.7	
95% CI for Difference	7.6, 42.9	
p-value	0.0016	
Maintenance Phase		
N	72	68
Estimate Difference[a]	35.8	
95% CI for Difference	13.3, 47.6	
p-value	0.0001	
Last 8 week of Maintenance Phase		
N	72	68
Estimate Difference[a]	40.0	
95% CI for Difference	20.0, 53.3	
p-value	0.0001	

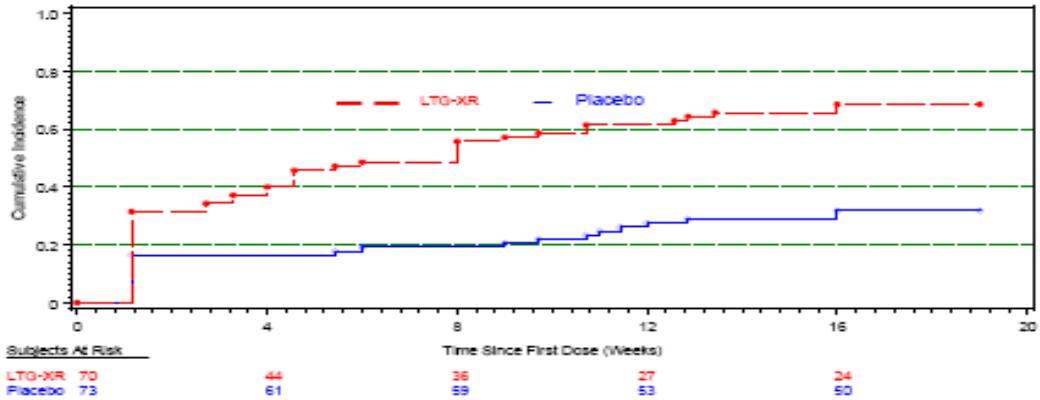
[Reviewer's Results]

a. Hodges Lehman estimates for the median treatment difference, 95% CI and p-value are based on a Cochran-Mantel-Haenszel Rank Sum test.

Time to ≥ 50% Reduction in Seizure Frequency

The percentage of subjects who showed a ≥ 50% reduction in PGTC seizure frequency over the entire double-blind treatment phase was greater in the LTG XR group (69.6%) compared with the placebo group (31.9%). The time (in weeks) to ≥ 50% reduction in seizure frequency was statistically significant (p<0.0001), as shown in Figure 1.

Figure 1 Time to 50 % Reduction in Seizure Frequency



[Source: Sponsor's CSR Figure 1]

Weight

The mean difference in change from Baseline in weight between treatment groups was 0.94 kg for the ITT Population (90% CI: 0.095, 1.784). The pooled baseline weight was 62.5 kg for all subjects, so there was no difference (based on a 10% of the pooled Baseline weight) between placebo and LTG XR with respect to weight using two one-sided 95% CIs. Subjects in both treatment groups gained little weight.

Health Outcomes Results

None of the pre-specified questionnaires (SSQ, ESS, POMS and QOLIE-31P) reached statistical significance. Summary of the analysis of the change from Screen values in overall scores are presented in Table 7.

Table 7 Summary analysis of the change from Baseline in Overall Scores for Health Outcomes Results

Assessment Instrument	PBO N=73		LTG XR N=70		Diff [1]	p value
	n	LS Mean (SE)	n	LS Mean (SE)		
POMS Mood Disturbance Total Score						
End of Study	20	2.4 (6.97)	13	9.7 (8.65)	-7.34	0.5136
CES-D Total Score						
End of Study	9	2.9 (2.81)	11	2.4 (2.54)	0.49	0.8994
NDDI-E 6-Item Total Score						
End of Study	8	-0.1 (0.98)	5	-2.4 (1.24)	2.32	0.1729
QOLIE-31P Overall Score						
End of Study	18	-6.5 (3.97)	15	-8.5 (4.35)	2.01	0.7360
AEP Total Score						
End of Study	8	3.0 (2.16)	5	1.4 (2.77)	1.58	0.6730
SSQ Global Bother Score						
End of Study	5	0.9 (0.84)	3	1.2 (1.08)	-0.36	0.8015
ESS 8-Item Total Score						
End of Study	18	-0.6 (0.69)	19	1.0 (0.67)	-1.56	0.1154

[Source: Sponsor's CSR Table 32]

3.1.1.4 Reviewer's Results and Comments

This reviewer verified the sponsor's primary analysis result finding a statistically significant difference in the percent change from baseline in average weekly PGTC seizure frequency favoring Lamictal XR over placebo ($p<0.001$). However, this result did not follow the originally pre-specified nonparametric ANOVA. It used the Wilcoxon Rank Sum test instead, which was confirmed by the reviewer. Furthermore, the Wilcoxon Rank Sum test is the consistent method from the original Lamictal NDA submission. The reviewer does not have much issue with this procedure. On the other hand, if the sponsor truly wants to pursuit that pre-specified nonparametric ANOVA approach, it would have many problematic issues. Sponsor then need to justify the analysis method to be the valid one and then re-analyze the study with that approach.

The reviewer also verified that the Lamictal XR group had a significantly shorter time to reach 50% reduction in Seizure frequency ($p<0.001$).

Impact of Individual and Countries

The study was conducted in 9 different countries. The number of patients per country ranged from 1 to 61. Among treatment group differences within country, 5 favored Lamictal XR, 1 favored placebo, and 1 showed no difference and 3 countries had no patients in one group so no difference could be determined (see Figure 2). The Table 8 summarized the treatment effects by each individual country; the treatment difference is numerically favored Lamictal XR in the U.S., but the treatment effect of 22.15 is smaller than the whole population (31.6) and all Non U.S. countries (34.55). It did provide a reasonably significant p-value of 0.099.

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 much smaller in the U.S., but still in the right direction. The treatment by region interaction did not show a significant difference (p=0.7814). In this model, the treatment effect was still significant (p=0.003).

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=0.3626). 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 of Brazil and Argentina, the Asian countries of Malaysia, India and Korea, and to separately combine the Ukraine with the Russian Federation. If we then test whether the treatment difference varies across the standalone countries and these new groupings of countries the p-value is 0.3612. If the test is focused more on the U.S. versus the non-U.S. then there is no evidence of an interaction between treatment and country.

Impact of Equivalence Weight

The equivalence margin of 10% of the pooled Baseline weight was never agreed by the agency. Therefore, the equivalence in the change from baseline in weight between treatment groups can only be observed as an exploratory finding.

Figure 2 Treatment Group Differences in Percent Change in PGTC by Country

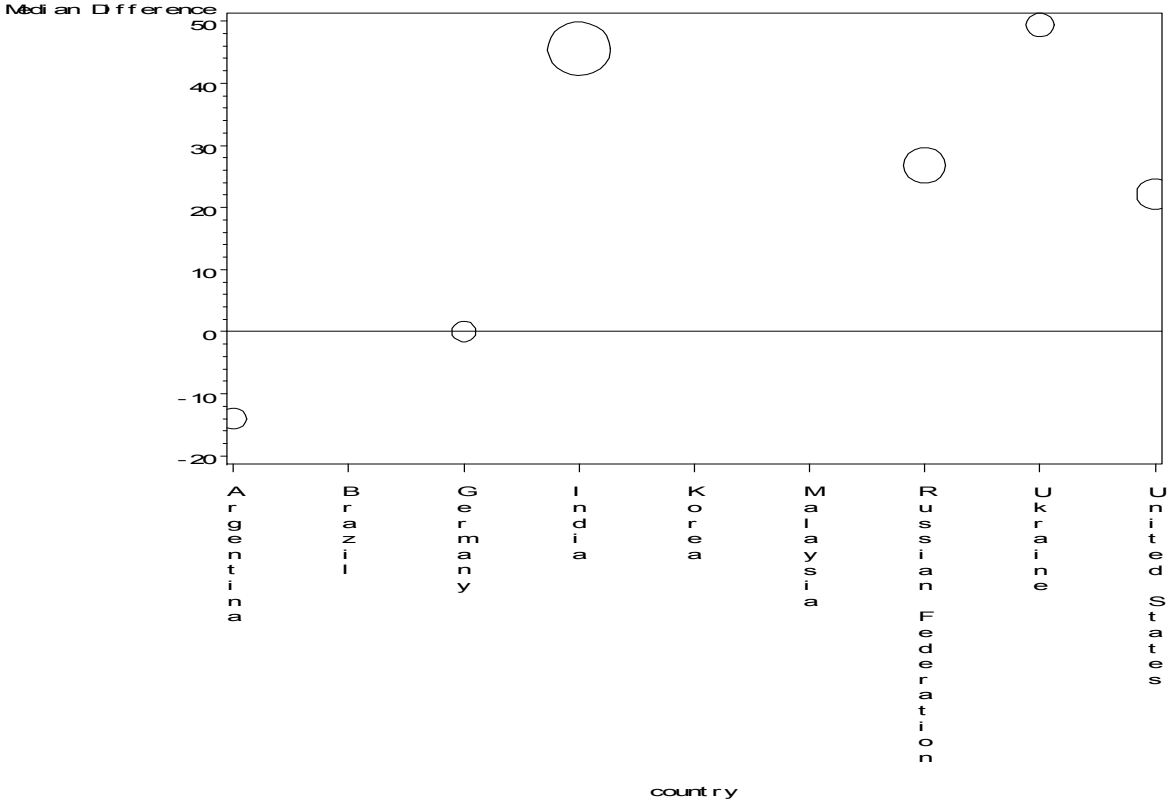


Table 8 Treatment Effects by Country

		Placebo				Lamictal XR			Median of Differences	Wilcoxon p-value
Country	**n**	**median**	**mean**	**std**	**n**	**median**	**mean**	**std**		
United States	**12**	**53.6**	**52.2**	**42.2**	**9**	**92.0**	**75.9**	**30.3**	**22.15**	**0.099**
All Non-U.S.	**61**	**29.8**	**16.3**	**80.8**	**62**	**75.1**	**56.1**	**51.1**	**34.55**	**<0.001**
Russian Federation	11	31.6	43.3	33.0	16	78.1	71.1	26.6	26.80	0.010
India	31	16.7	3.7	62.7	30	63.2	48.8	52.1	45.60	0.001
Germany	2	87.8	87.8	17.3	7	100.0	59.0	65.7	0.00	0.436
Brazil	2	47.5	47.5	1.8	0	--	--	--	--	--
Ukraine	7	43.9	24.5	56.0	5	84.2	85.6	11.9	49.40	0.011
Korea	0	--	--	--	1	88.0	88.0	--	--	--
Malaysia	0	--	--	--	1	-88.1	-88.1	--	--	--
Argentina	8	48.3	-4.7	175.1	2	18.0	18.0	96.2	-14.00	0.448

[Source: Reviewer's results]

3.2 Evaluation of Safety

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

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age and Race group

4.1.1 GENDER

There are 50% % of all patients were males and 50% were female. There was a suggestion of efficacy in both gender and there was no compelling evidence that the treatment effect was larger in one gender than the other.

Table 9 Percent Change from Baseline in Weekly PGTC Seizure Frequency by Gender

Subgroup	Lamictal	Placebo
Male		
No. Subjects	37	35
Mean (SD)	61.6 (41.01)	32.7 (60.23)
Median	74.7	44.2
Female		
No. Subjects	32	37
Mean (SD)	52.6 (52.6)	10.2 (89.05)
Median	78.0	26.3

[Source: reviewer's result]

4.1.2 AGE

Age at entry was categorized to <16, 16 to 65 and > 65 years old. Treatment group differences were numerically in favor of Lamictal XR in all three subgroups and there was no compelling evidence that the treatment difference was larger in one age group than the other.

Table 10 Percent Change from Baseline in Weekly PGTC Seizure Frequency by Age

Subgroup	Lamictal	Placebo
Age group (< 16)		
No. Subjects	4	64
Mean (SD)	36.1 (58.38)	47.2 (30.52)
Median	57.8	38.3
Age group (16-65)		
No. Subjects	64	65
Mean (SD)	58.1 (49.2)	17.9 (79.6)
Median	76.0	30.2
Age group (>65)		
No. Subjects	1	1
Mean (SD)	100.0	75.5
Median	100.0	75.5

[Source: Reviewer's result]

4.1.3 RACE

Due to possible small sample sizes for certain ethnic groups, race was categorized into White, Asian (Central/South Asian) and Mixed Race (African, East and South East Asian, Other Race). Once again, treatment differences were numerically in favor of Lamictal XR in all three subgroups and there was no compelling evidence that the treatment difference was larger in one race group than the other.

Table 11 Percent Change from Baseline in Weekly PGTC Seizure Frequency by Race

Subgroup	Lamictal	Placebo
Race = White		
No. Subjects	37	38
Mean (SD)	67.7 (40.78)	35.4 (87.50)
Median	78.90	45.05
Race= Central South Asian		
No. Subjects	29	31
Mean (SD)	47.68 (52.6)	3.74 (62.69)
Median	62.30	16.70
Race = Mixed		
No. Subjects	5	4
Mean (SD)	54.9 (80.21)	40.38 (38.13)
Median	88.0	47.45

[Source: Reviewer's results]

4.2 Other Subgroup Populations

No other special populations were examined.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

U.S. sites accounted for 21 (15%) of the randomized patients, which was the third largest country in study LAM100036. Eight other countries randomized patients. The largest two countries are Indian and Russian Federation, which combine enrolled 88 (62%) of the randomized patients. These two countries also had the most favorable treatment for Lamictal XR. 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=0.099). Of course, the study was not powered to detect a difference in the U.S. subgroup. When the non-U.S. countries represented in the LAM100036 study were pooled together, the treatment effect was numerically larger in the non-U.S. countries than the United States. The estimated treatment difference was 22.15 in the U.S. as compared to 34.55 for the pooled non-U.S. countries. However, the treatment by U.S. vs. non-U.S. interaction was not statistically significant (p=0.7814).

5.2 Conclusions and Recommendations

The data from study LAM100036 supported the efficacy of Lamictal XR for adjunctive therapy in patients older than 13 years of age with PGTC seizures. Lamictal XR was superior to placebo

in terms of the primary endpoint, median percent change from baseline in the PGTC seizures during the entire Treatment Phase ($p<0.001$). The group difference in time (in weeks) to 50% reduction in seizure frequency for the entire Treatment Phase was shorter for the Lamictal XR group compared with the Placebo group ($p<0.0001$) for the ITT population. 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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22509	ORIG-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE	LAMICTAL XR(LAMOTRIGINE)ORAL TABLETS

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