U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

COMBINED STATISTICAL & CLINICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	sNDA 22115 / SN 0024
Drug Name:	Lamictal® XR™ (lamotrigine) Extended-Release Table
Indication(s):	Monotherapy of partial seizures in patients 13 years of age and older
Applicant:	SmithKline Beecham Corporation d/b/a GlaxoSmithKline
Date(s):	Submission date: March 31, 2010 PDUFA date: Jan. 31, 2011 (Extension date: April 30, 2011)
Review Priority:	Standard
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Keywords: historical control, binomial proportion, Kaplan-Meier estimate of proportion, meta analysis, regional comparison, bias

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1. EXECUTIVE SUMMARY

Statistical Reviewer Summary

This supplemental New Drug Application (sNDA) consisted of a single pivotal clinical study (Study LAM30055) evaluating conversion to monotherapy with LTG XR in subjects 13 years of age and older with partial seizures using an historical control from the White Paper (see French et al, Epilepsia 2010[1] for the published version of the White Paper). The use of historical control for monotherapy was mainly due to ethical and clinical consideration. However, due to lack of internal control, Study LAM30055 suffered from the common problems that usually arose in historical controlled trials, such as potential bias, non-comparability of treatment groups to the historical control, and difficulty in interpreting efficacy results.

Specifically, in this study, there was potential bias due to under-reporting of escapes. The investigator-reported escape rate was about 6%, compared to about 30% calculated escapes rate based on seizure data, and 42% reported rate for LTG IR in Study US30/31. In addition, none met escape criterion #4 in this study compared to up to 45% in the historical controls; and post-hoc evaluation of criterion #4 events could not be performed due to the subjective nature of this criterion. Another source of bias came from the handling of dropouts. The sponsor counted dropouts as completers which biased for treatment success.

The study population in Study LAM30055 was not comparable to those in the historical control studies. Study LAM30055 had approximately 75% of subjects enrolled outside US while all of the subjects in the historical control database were enrolled in US. A higher proportion of subjects at US sites met Escape Criteria compared to non-US sites. In addition, Study LAM30055 allowed one background AED while most White Paper studies allowed two background AEDs. The White Paper data suggested that patients with one background AED had fewer escapes than patients with two AEDs.

To make an attempt to adjust for biases, the reviewer conducted analyses which

(1) calculated escapes according to more stringent Escape Criteria used in some of the White Paper studies
(2) included dropouts as treatment failures in the analyses of the White Paper Per Protocol population and the ITT population,
(3) compared to a subgroup of historical control subjects who were on one background AED (consequently the 95% prediction limit changed to 58.6%, from the original 65.3%).

[1] J. French, S. Wang, B. Warnock and N. Temkin: Historical control monotherapy design in the treatment of epilepsy. Epilepsia 1-8, 2010

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With above adjustments, LTG XR monotherapy remained superior to the historical controls for both dose groups. For the subgroup of US subjects pooled from the two dose groups, with adjustments (1) and (2), LTG XR monotherapy remained superior to the historical controls except in the ITT worst case analysis. With additional adjustment (3), LTG XR failed to show superiority in the White Paper PP sensitivity analysis or the ITT worst case analysis.

The potential bias due to under-reporting of criterion #4 events was not accounted for in above analyses. It was uncertain how to adequately assess this potential bias.

In summary, the data seemed to suggest some evidence of efficacy of LTG XR as monotherapy treatment of partial seizures. However, interpretability of these analysis results was undermined by the limitations of the historical control design and the problems described above; thus, it was uncertain that the efficacy of LTG XR as monotherapy treatment of partial seizures was conclusive based on this study.

Clinical Reviewer Summary

This submission represents a novel pathway for approval by using an historical control method to demonstrate efficacy of Lamictal XR for use in conversion to monotherapy. Prior approval for monotherapy has been gained through a clinical trial design known as the "pseudo-placebo withdrawal to monotherapy study" which assigns treatment resistant patients to receive study drug or a suboptimal maintenance dose of a safe and effective active drug. Development of the historical control methodology has been motivated by the danger of the "pseudo-placebo" which allows patients to participate in a study arm which is intrinsically sub-therapeutic.

To use an historical control method a study is required to have design features which allow comparability between a current study and the historical control studies. Key criteria are similarity of study design, population, evaluation criteria and analysis plan. Study LAM30055 met this requirement in the elements of conversion to monotherapy, study endpoint and analysis plan; however there was notable divergence in the study population. The first point of divergence was in the composition of the historical control population which was approximately 100% of US patients while LAM30055 was only 25% US. The second divergence was in the allowed number of background AEDs prior to monotherapy conversion. Six of the 8 historical control studies allowed 2 baseline AEDs whereas LAM30055 allowed only one AED for eligibility. In addition to these disparities a difference in study endpoint profile emerged. In the calculation of the White Paper prediction interval and the Lamictal XR monotherapy endpoint confidence interval both were based on percent of patients meeting any of 4 escape criteria; however the Lamictal Study had no criteria # 4 escapes where the historical control studies had escapes due to criteria # 4 ranging from 4% to 45%. In addition the Lamictal XR monotherapy study had lower rates of escape reporting across all criteria.

The statistical reviewer identifies the sources of bias which include different methods of calculating escapes between the Lamictal XR study and the White Paper studies, treatment of dropouts, medical (1 or 2 background AEDs) and regional differences in the study population and under reporting of escapes, especially problematic in Criteria 4. The statistical approach to compensate for the bias was to perform a recalculation of escapes using more stringent criteria

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which included dropouts as treatment failures and reanalyzed the historical control (White Paper) dataset using only those patients on a single background AED. There was no clear approach to compensate for the divergence in escape criteria # 4 between the Lamictal XR study and the White Paper studies.

A recalculation of the White Paper prediction interval lower bound based on the population taking only 1 AED yielded a value of 58.6%. Both the 300mg/day and 250mg/day dose groups of the Lamictal XR monotherapy study retain superiority to this threshold in all adjustments to the White Paper escapes (table 8). The US subset of the Lamictal XR monotherapy study retains superiority only in the least conservative White Paper per protocol analysis (table 9).

If the White Paper is accepted as a valid platform for historical control comparison and the population restricted to 1 background AED, the resultant lower bound of the pseudoplacebo group prediction interval is 58.6%. All analysis for overall LAM30055 populations in both dose groups remain superior to this White Paper lower bound. The US subset remains superior only in the White Paper per protocol analysis. The US subset is small and not powered to independently test for significance, therefore this finding in isolation does not supersede the overall study results.

Clinical Reviewer Conclusion

There is adequate support for approval of Lamictal XR for use in conversion to monotherapy for patients ≥13 years of age who are receiving treatment with a single AED. The recommended target dose is 300mg daily, although the 250mg/day dose remained superior to the pseudoplacebo, this dose was not the protocol directed primary efficacy endpoint.

2. INTRODUCTION

Overview

Lamotrigine extended–release (LTG XR) formulation is currently approved as adjunctive treatment of partial seizures and primary generalized tonic clonic seizures in subjects ≥13 years of age. LTG Immediate-release (IR) was initially approved for adjunctive use and was later demonstrated to also be effective as monotherapy following conversion from add-on therapy with a single enzyme-inducing antiepileptic drug (EIAED).

This supplemental New Drug Application (sNDA) consisted of a single pivotal clinical study evaluating conversion to monotherapy with LTG XR in subjects 13 years of age and older with partial seizures using an historical control (referred to as Study LAM30055 subsequently in this document). The study used a conversion to monotherapy design in which eligible subjects with refractory partial seizures had LTG XR added to their current background antiepileptic drug (AED) (valproate or a non-enzyme inducing AED) followed by gradual withdrawal of the background AED and 12 weeks of monotherapy.

Approximately 230 male or female ≥13 years of age with seizures uncontrolled (≥2 per 28 days) by AED monotherapy were enrolled to randomize 164 subjects to the two dosing groups in a 1:1 ratio. The primary treatment comparison evaluated the proportion of subjects who discontinue LTG at 300 mg/d (pre-specified) / meet Escape Criteria (post-hoc) during the last 16 weeks of treatment with LTG compared to an historical pseudo-placebo control rate.

The historical control dataset was the aggregated data from eight monotherapy studies. All of these studies utilized a "pseudoplacebo", either a sub-therapeutic dose of an active drug or a low dose of study drug, and efficacy was based on the proportion of patients who exited the studies as a result of predefined Escape Criteria related to worsening of seizures. In the White Paper, French et al proposed that using the lower bound of the 95% prediction interval (PI) based on the combined percent escape rate (65.3%) for a single study or the lower bound of the 80% PI based on the combined escape rate (72.2%) for 2 studies. Specifically, the upper 95% confidence limit of the test group was compared to the lower prediction limit of the aggregated historical data. Non-overlap indicated a determination that the treatment was efficacious. FDA agreed in principle to accept their use as control during a meeting with GSK on September 08, 2005.

The previous study US 30/31 of LTG IR (immediate-release) was provided as a supportive study. It had a similar design to Study LAM30055 but used a low dose as internal pseudoplacebo. Study US 30/31 supported approval of LTG IR for conversion to monotherapy and was one of the eight studies from which the historical control endpoint was derived.

Clinical Reviewer Comment

History Of Lamictal And Lamictal XR Pertaining To The Current Application

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LTG Immediate-release (IR) was initially approved for adjunctive use in December 1994 and was later demonstrated to also be effective as monotherapy following conversion from add-on therapy with a single enzyme-inducing antiepileptic drug (EIAED) and approved for this use in December 1998. Lamictal XR was approved in May of 2009 for adjunctive therapy of partial seizures and in January 2010 as adjunctive therapy for primary generalized tonic-clonic. This background has provided extensive experience in the use and effectiveness of lamotrigine.

A clinical pharmacology review was performed for the submission of Lamictal XR for adjunctive therapy of partial seizures[2]. In the evaluation of proposed conversion dose from lamotrigine IR to Lamictal XR the reviewed examined the lamotrigine steady state relative bioavailability in 3 groups of patients receiving different concomitant AEDs (enzyme inducers, inhibitors and neutrals). The reviewer found the following:

- The steady-state mean trough concentrations for Lamotrigine XR were equivalent to or higher than those of lamotrigine IR depending on concomitant AED.

- A mean reduction in the lamotrigine Cmax by 11-29% was observed for lamotrigine XR compared to lamotrigine IR resulting in a decrease in the peak to trough fluctuation in serum lamotrigine concentrations.

- The fluctuation index was reduced by 17% in patients taking enzyme-inducing AED, 34% in patients taking VPA and 37% in patients taking neutral AEDs.

- Lamotrigine XR and lamotrigine IR regimens were almost similar (6% decrease) with respect to mean AUC(0-24ss), apart from patients receiving EIAEDs, where the relative bioavailability of lamotrigine XR was approximately 21% lower than for lamotrigine IR.

PK parameter	AED Group	Ratio XR:IR	90% CI
AUC(0-24)/Total Daily Dose	Overall	0.90	0.84 – 0.98
	Induced	0.79	0.69 – 0.90
	Neutral	1.00	0.88 – 1.14
	Inhibited	0.94	0.81 – 1.08
Cmax/Total Daily Dose	Overall	0.82	0.76 – 0.90
	Induced	0.71	0.61 – 0.82
	Neutral	0.89	0.78 – 1.03
	Inhibited	0.88	0.75 – 1.03
Cτ/Total Daily Dose	Overall	1.04	0.98 – 1.10
	Induced	0.99	0.89 – 1.09
	Neutral	1.14	1.03 – 1.25
	Inhibited	0.99	0.88 – 1.10

[2] Tandon V. Clinical Pharmacology/Biopharmaceutics Review, NDA22115, Product: Lamictal XR, Indication: Adjunctive therapy for partial onset seizures with or without generalization in patients ≥ 13 years. 9/6/2007

There were however some outlier subjects taking enzyme inducing AEDs with a more marked reduction in AUC and Cmax. In the case of AUC there were two subjects, one with a 57% reduction, the second with a 70% reduction. In the case of Cmax there were three subjects with a range in reduction from 45% to 77%.

These observations offer some support for an expected similarity in performance between Lamictal IR (immediate release), already approved for conversion to monotherapy based on study 30/31, and Lamictal XR. Although those on inducers fell outside of the bioequivalence boundary, this is not relevant to use in monotherapy except in the transition phase where in proposed labeling Lamictal XR is maintained at a higher dose (500mg/day) until two weeks after the completion of background AED withdrawal and is then reduced to a target dose of 250mg to 300mg / day.

There is a robust history of Lamictal XR use, as shown in the table below representing the interval from May 29, 2009 to July 24, 2010. There were 1,423,935,000 mg (the equivalent of 7,119,675 200mg tablets) of Lamictal XR sold in the US in this interval, not including start up kits, freely provided drug or samples[3].

DISTRIBUTION DATA
NDA 022-115; LAMICTAL XR EXTENDED-RELEASE TABLETS
May 29, 2009 to July 24, 2010

Description	NDC Code	Domestic Sales	Domestic Free Issues	Domestic Samples
LAMICTAL XR TABLETS 25MG 30s	0173075400	17,064	298	0
LAMICTAL XR TABLETS 50MG 30s	0173075500	42,044	836	0
LAMICTAL XR TABLETS 100MG 30s	0173075600	144,237	4,896	0
LAMICTAL XR TABLETS 200MG 30s	0173075700	152,560	5,073	0
LAMICTAL XR TABLETS 25MG/50MG STARTER KT	0173075800	1,148	5	0
LAMICTAL XR TAB BLUE DE KIT 25MG/50MGSPL	0173075860	0	0	37,218
LAMICTAL XR TABLETS 50MG/100MG/200MG KIT	0173075900	1,182	5	0
LAMICTAL XR TAB GREEN DE KIT 50/100/200	0173075960	0	0	82,900
LAMICTAL XR TABLETS 25MG/50MG/100MG KIT	0173076000	1,892	5	0
LAMICTAL XR TAB ORANGE DE KIT 25/50/100	0173076060	0	0	81,216

Data Sources

The data files are located in the following directory:
\\Cdsesub1\evsprod\NDA022115\0024\m5\datasets\lam30055-double-blind\analysis
\\Cdsesub1\evsprod\NDA022115\0050\m5\datasets\lam30055-double-blind\analysis\datasets
\\Cdsesub1\evsprod\NDA022115\0052\m5\datasets

The study reports are located in the following directory:
\\Cdsesub1\evsprod\NDA022115\0024\m5\53-clin-stud-rep\535-rep-effic-safety-stud\monotherapy\5351-stud-rep-contr\lam30055-double-blind

[3] Lamictal Annual Report covering 7/25/09 through 7/24/10

3. STATISTICAL EVALUATION

Evaluation of Efficacy

Study LAM30055

The study was initiated on 16 May 2006, and completed of double-blind phase on 06 May 2008. The original protocol (dated 19 December 2005) was amended twice (19 January 2006, 30 August 2006) with both amendments applying to all study sites. There were no changes to study conduct implemented with either amendment. SAP was dated 19 December 2007.

Study Design (see 5.3)

This was an international, multicenter, double-blind, randomized study of 2 doses (300 and 250 mg/day) of lamotrigine extended-release (LTG XR) tablets comparing the premature discontinuation rate for each dose to an historical escape rate (65.3%) determined from aggregated pseudo-placebo data. The purpose of the study was to demonstrate the effectiveness of a lower monotherapy dose of LTG XR than the currently approved 500 mg/day of LTG IR.

The study used a conversion to monotherapy design in which eligible subjects with refractory partial seizures had LTG XR added to their current background antiepileptic drug (AED) (valproate or a non-enzyme inducing AED) followed by gradual withdrawal of the background AED and 12 weeks of monotherapy. Subjects who completed the Treatment phase or met Escape Criteria were allowed to enter the Continuation phase. Study phase and duration was shown in Table 1. Approximately 230 male or female ≥13 years of age with partial epilepsy with seizures uncontrolled (>=2 per 28 days) by AED monotherapy were enrolled to randomize 164 subjects to the two dosing groups in a 1:1 ratio.

Table 1. Study Design

Phase	Duration
Screen	<2 weeks
Baseline	8 weeks[1]
LTG XR escalation	6-7 weeks [2]
Background AED withdrew and continuation of LTG XR escalation	4 weeks
Monotherapy	12 weeks
Optional Continuation Phase	24 weeks
Taper-Follow-up or Conversion to immediate release	~2 weeks ~3 days
Total (maximum)	59 weeks

1. With approval from GSK, up to the first 4 weeks of Baseline may be retrospective
2. Differs based on background AED and escalation schedule for LTG-XR

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Efficacy Measures

Efficacy measures were variables derived from seizure information that were monitored through subject diary and evaluated at each study visit. Subjects recorded the number of seizures, by seizure type, as well as duration of episodes of innumerable seizure activity in their daily diaries. Site personnel transcribed the daily seizure information from the diary into the electronic Case Report Form (eCRF).

The planned primary endpoint was the proportion of subjects in the 300 mg/day treatment group who prematurely discontinued at any time after starting withdrawal of background AED.

A "completer" was defined as a subject who completed the Baseline, Conversion and Maintenance Phases of the study. In all other cases, the subject was considered to have prematurely discontinued.

Post-hoc primary endpoint was the proportion of subjects meeting pre-defined efficacy Escape Criteria. These criteria were the occurrence of any of the following compared to Baseline:

1. doubling of average monthly seizure frequency calculated as the sum of countable, partial seizures starting the day prior to the study visit and extending back 28 days
2. doubling of the highest consecutive 2-day seizure frequency
3. emergence of a new, more severe seizure type
4. clinically-significant prolongation of generalized tonic-clonic seizures

This post-hoc primary endpoint was one of the original secondary endpoint but transitioned to primary endpoint as discussed in Efficacy Analysis. Other secondary endpoints were:

- Proportion of subjects in the 250 mg/day treatment group who prematurely discontinue
- Time to discontinuation
- Percent change from Baseline in seizure frequency
- Percent seizure-free at last visit

Statistical Analysis Methods

Analysis Population

Per Protocol (PP)
All subjects randomized to treatment who took at least one dose of study medication and began withdrawal of the background AED, excluding those with major protocol violations. The planned primary efficacy analysis was based on the PP population.

Intent-to-Treat (ITT)
All subjects randomized to treatment who took at least one dose of study medication.

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White Paper Per Protocol
All subjects randomized to treatment that took at least one dose of study drug and began withdrawal of the background AED. This population was defined post-hoc in order to make a direct comparison with the White Paper. This was the primary population for this review.

Efficacy Analyses

The planned primary treatment comparison in study LAM30055 evaluated the proportion of subjects who discontinued LTG at 300 mg/d during the last 16 weeks of treatment with LTG XR compared to an historical pseudo-placebo control rate. This pre-specified primary endpoint of 'all-cause' discontinuation was based on the way Study US 30/31 data was analyzed as part of the aggregation of 8 studies included in the historical database. After completion of the double-blind phase of LAM30055, it was learned that the analysis of US 30/31 in the 2005 version of the White Paper was incorrect. US 30/31 data were subsequently re-analyzed utilizing only escape data. In response to this, data from LAM30055 were analyzed post-hoc focusing only on subjects who met Escape Criteria. Since this was the endpoint used in the White Paper, the Escape Criteria analyses was referred as post-hoc primary analysis.

As the sponsor found that the Escape Criteria were not correctly applied at study sites (e.g., subjects who met an Escape Criterion were not discontinued), daily seizure data in the database were evaluated against the Escape Criteria (1, 2, and 3) to identify additional escapes following completion of the trial.

The estimated proportion and confidence interval were calculated using binomial distribution. Subjects who dropped out due to reasons other than meeting Escape Criteria were included in Sponsor's analyses as having successfully completed the treatment.

Patient Disposition, Demographic and Baseline Characteristics

A total of 226 subjects (113 per treatment group) were randomized from 7 countries. Three of the 226 randomized subjects did not receive study drug and were not included in ITT Populations (1 subject in each treatment group decided to withdraw, and 1 subject [250 mg/day] had a protocol violation). The PP Population included 93 subjects in the LTG XR 300 mg/day group and 81 subjects in the LTG XR 250 mg/day group. The White Paper PP Population, which did not exclude subjects with major protocol violations, included 108 subjects in the LTG XR 300 mg/day group and 97 subjects in the LTG XR 250 mg/day group. The most common reason for withdrawal from the LTG XR 300 mg/day group was "subject decided to withdraw from the study" (8%). For the LTG XR 250 mg/day group, AE was the most frequent cause for withdrawal (9%) (Table 2).

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Table 2. Subject Disposition

	Number (%) of Subjects	
	LTG XR 300 mg/day	**LTG XR 250 mg/day**
Population		
Randomized	113	113
Safety	112 (>99)	111 (98)
Intent-to-Treat (ITT)	112 (>99)	111 (98)
Per Protocol (PP)	93 (82)	81 (72)
White Paper PP	108 (96)	97 (86)
Subject Disposition (Randomized Subjects)		
Completed study	94 (83)	79 (70)
Prematurely withdrawn	19 (17)	34 (30)
Met Escape Criteria[1]	28/112 (25)	25/111 (23)
Reason for premature withdrawal		
Adverse event	4 (4)	10 (9)
Lost to follow-up	0	4 (4)
Protocol violation	0	4 (4)
Subject decided to withdraw from the study	9 (8)	8 (7)
Insufficient therapeutic response[2]	6 (5)	7 (6)
Other, specify[3]	0	1 (<1)

1. Includes post-hoc escape determination.
2. Escapes based on the CRF, does not include the post-hoc escape determination.
3. Other, specify = Subject 130 withdrew due to pregnancy.

Source: Sponsor ISE page 23.

The majority of subjects in both treatment groups were 16 to 65 years and of White – White/Caucasian/European heritage (Table 3).

Table 3. Demographics (ITT Population)

Demographic Characteristic	LTG XR 300 mg/day N=112	LTG XR 250 mg/day N=111
Age (years)		
Mean (SD)	33.8 (14.33)	32.9 (12.60)
Range	13-80	13-59
Age Group (years), n (%)		
<16	10 (9)	7 (6)
16-65	100 (89)	104 (94)
>65	2 (2)	0
Gender, n (%)		
Female	56 (50)	66 (59)
Male	56 (50)	45 (41)
Ethnicity, n (%)		
Hispanic/Latino	33 (29)	30 (27)
Not Hispanic/Latino	79 (71)	81 (73)
Race, n (%)		
African American/African Heritage	5 (4)	4 (4)
Asian - East Asian Heritage	11 (10)	11 (10)
White - Arabic/North African Heritage	0	2 (2)
White - White/Caucasian/European Heritage	96 (86)	94 (85)

Source: Sponsor ISE page 26.

Most subjects in both treatment groups had only partial seizures at Baseline. The median Baseline seizure frequency (number of partial seizures/week) over the entire Baseline was 1.4 for the LTG XR 300 mg/day group and 1.5 for LTG XR 250 mg/day group. Seizure history at Baseline was similar for the two treatment groups with a mean age of 20.5 and 18.7 years, respectively at first seizure, and a mean of 14.3 and 15.2 years, respectively for duration of epilepsy (Table 4.)

Table 4. Baseline Disease Characteristics (ITT Population)

Baseline Characteristic	LTG XR 300 mg/day N=112	LTG XR 250 mg/day N=111
Baseline Seizure Type[1], n (%)		
A (simple partial seizures)	49 (44)	53 (48)
B (complex partial seizures)	71 (63)	67 (60)
C (partial seizures evolving to secondarily generalized seizures)	60 (54)	59 (53)
D5 (primary generalized)[2]	1 (<1)	1 (<1)
Partial seizures only (A, B, or C)	111 (>99)	108 (97)
Both partial and generalized seizures	1 (<1)	1 (<1)
Baseline Seizure Frequency per Week - All Partial Seizures Entire Baseline		
Mean (SD)	3.3 (8.21)	4.3 (10.59)
Median (Range)	1.4 (0.5-69.9)	1.5 (0.5-67.0)
Age at First Seizure (years)		
Mean (SD)	20.5 (13.81)	18.7 (12.72)
Median (Range)	16.5 (1-76)	16.0 (1-49)
Duration of Epilepsy (years)		
Mean (SD)	14.3 (11.61)	15.2 (11.25)
Median (Range)	12.0 (2-67)	13.0 (1-55)

Data Source: CSR LAM30055 DB, Table 6.9, Table 6.10, Table 6.11

1. Subjects may have reported more than one seizure type.
2. One subject in each group (Subject 271 and Subject 1111) reported a history of D5 seizures prior to the Screen Visit. Neither subject experienced a primary generalized seizure in the 8 weeks prior to screen. Subject 271 experienced D5 seizures during the study; Subject 1111 did not.

Source: Sponsor ISE page 27.

Sponsor's Efficacy Results

Planned Analyses Results

Primary efficacy endpoint

The proportion of subjects who discontinued at any time after starting withdrawal (not including calculated escapes) of the background AED in Study LAM30055 was 12% for the LTG XR 300 mg/day group in the PP Population, with a 95% upper limit of 18.4%. However, this analysis was not considered primary analysis for regulatory evaluation as this was not the way the White Paper analyzed the pseudo-placebo data.

Secondary efficacy endpoints

The proportion of subjects who discontinued at any time after starting withdrawal (not including calculated escapes) of the background AED was 16% for the LTG XR 250 mg/day group in the PP Population.

The proportion of subjects in the PP Population who met Escape Criteria (not including calculated escapes) was 4% for the LTG XR 300 mg/day group and 6% for the LTG XR 250 mg/day group.

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Response to treatment, as measured by seizure frequency, showed a greater than 50% reduction in both treatment groups for the entire treatment period. Reduction in seizure frequency was evident in the Conversion phase and increased during the Monotherapy phase. During LTG XR monotherapy, the majority of subjects showed a ≥50% reduction in all partial seizure frequency at both 300 mg/day (64.0%; 57/89) and 250 mg/day (56.6%; 43/76) in the PP Population. Additionally, 24.7% (22/89) of subjects in the 300 mg/day group and 10.5% (8/76) of subjects in the 250 mg/day group became seizure-free.

Table 5. Summary of Planned Analyses (PP population)

	LTG XR 300 mg/day N=93	**LTG XR 250 mg/day N=81**
Percent of subjects who discontinued		
n/N (%)	11/93 (12)	13/81 (16)
[95% CI]	[5.3, 18.4]	[8.1, 24.0]
Percent of subjects meeting Escape Criteria		
n/N (%)	4/93 (4)	5/81 (6)
Percent change from Baseline in weekly seizure frequency[1]		
Conversion Phase, n	93	81
Median (range)	45.5 (-124.5-100.0)	50.2 (-168.6-100.0)
p-value[2]	<0.0001	<0.0001
Monotherapy Phase, n	89	76
Median (range)	67.4 (-100.0-100.0)	59.4 (-635.0-100.0)
p-value[2]	<0.0001	0.0150
Entire Treatment Period, n	93	81
Median (range)	54.8 (-124.5-100.0)	52.2 (-221.3-100.0)
p-value[2]	<0.0001	<0.0001
Categorical change in seizure frequency		
Conversion Phase, n	93	81
≥50% reduction, n (%)	43 (46.2)	41 (50.6)
Seizure-free (100% reduction), n (%)	5 (5.4)	6 (7.4)
Monotherapy Phase, n	89	76
≥50% reduction, n (%)	57 (64.0)	43 (56.6)
Seizure-free (100% reduction), n (%)	22 (24.7)	8 (10.5)
Entire Treatment Period, n	93	81
≥50% reduction, n (%)	54 (58.1)	42 (51.9)
Seizure-free (100% reduction), n (%)	3 (3.2)	4 (4.9)

1. Positive number means a decrease in seizure frequency
2. Paired t-test
Source: Sponsor ISE Table 5 & 6.

Post-hoc Analyses Results

The post-hoc primary analysis was the percent of subject meeting Escape Criteria in the White Paper population. While the trial was ongoing, the sponsor evaluated a random sample of subjects for correct application of the Escape Criteria and identified a number of errors (e.g.,

some patients met an Escape Criterion but were not discontinued). As a result, remedial training of study site personnel and monitors was undertaken. Following completion of the study, the analysis of escapes showed that the number of subjects who met pre-defined Escape Criteria was surprisingly small: only 6 to 7 subjects in each group were discontinued due to meeting Escape Criteria (Table 6).

Post-hoc evaluation of the seizure data led to reclassification of many subjects as escapes (i.e., having met Escape Criteria) (Table 6). The proportion of subjects who met calculated Escape Criteria was 24% for the LTG XR 300 mg/day group and 26% for the LTG XR 250 mg/day group. The upper 95% confidence limit did not overlap the lower 95% prediction limit (65.3%) from the historical pseudo-placebo control data for both groups.

Table 6. Proportion of Subjects Meeting Escape Criteria (Sponsor Results for White Paper PP Population)

	LTG XR 300 mg/day	**LTG XR 250 mg/day**
Investigator Determined Escapes (based on CRF)		
n/N (%)	6/108 (6)	7/97 (7)
[95% CI]	[1.2, 9.9]	[2.1, 12.4]
Calculated Escapes		
n/N (%)	26/108 (24)	25/97 (26)
[95% CI]	[16.0, 32.1]	[17.1, 34.5]

Source: Sponsor ISE Table 2, 8, 11.

Reviewer's Results

Use of an historical control requires that the study design, study population, efficacy evaluation and analyses are consistent with the historical pseudo-placebo studies, which is the focus of the review.

Evaluation of the Escape Criteria

Escape Criterion #1: doubling of average monthly seizure frequency

The White Paper mentioned that "it was unclear if this was done on a rolling basis in all cases. Discussion with the companies involved has determined that the statistical methodology may have varied from trial to trial".

In Study LAM30055, the sponsor calculated the average monthly seizure frequency as the sum of countable, partial seizures starting the day prior to the study visit and extending back 28 days. As calculating the highest seizure frequency for *any* consecutive 28 days was more stringent and was used for some of the White Paper studies, the reviewer used this method for Study LAM30055. Three additional subjects in each group were identified to have met this Escape Criterion, resulting in 3 more escapes for the LTG XR 300 mg/day group and 2 more escapes for

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the LTG XR 250 mg/day group (one subject in the 250 mg/day group met multiple Escape Criteria).

Escape Criterion #2: doubling of the highest consecutive 2-day seizure frequency.

In study LAM30055, the highest consecutive 2-day seizure frequency was calculated for the 28 days prior to each visit. The reviewer calculated the highest consecutive 2-day seizure frequency for the *whole treatment phase*. One more subject the LTG XR 300 mg/day group was identified to have met this Escape Criterion but resulting in no additional escapes as this subject met Escape Criterion #1 already.

Escape Criterion #3: emergence of a new, more severe seizure type

In the White Paper, this criterion varies among studies: occurrence of a single generalized seizure if none had occurred in the previous 6 months (Study 6), within two years of study entry (Study 1), during Baseline (Studies 3, 5, 7, 8), and "emergence of a more severe seizure type (which would include generalized seizure).

The criterion in the study LAM30055 Protocol was 'emergence of a new, more severe seizure type compared to the Baseline'. However, the sponsor calculated the escapes by comparing the seizure types during the Double-Blind Phase to the seizure types the subject had in their lifetime history. The reviewer requested that the sponsor re-calculate the escapes using Baseline period for comparison. Two more escapes were identified for LTG XR 300 mg/day group and three more escapes were identified for LTG XR 250 mg/day group.

Escape Criterion #4: clinically-significant prolongation of generalized tonic-clonic seizures

The data suggested that none of the subjects met this criterion (Table 7). The escapes based on this criterion were solely evaluated by the sites/investigators. The sponsor did not perform the re-calculation due to the subjective nature of this criterion. It was recognized the investigators tended to under-report escapes for criteria 1, 2 and 3. Therefore, there was concern that the escapes due to this criterion were also under-reported.

In addition, the criterion #4 in the study LAM30055 may be more restrictive than the White Paper criterion, which was "prolongation or worsening of seizure duration or frequency considered by the investigator to require intervention." Some events may be considered escapes according to the White Paper criteria, but not by the Study LAM30055 criteria. The medical reviewer examined the adverse event database and identified a patient who may have met Escape Criteria according to the White Paper criterion: subject 255 required intervention in the form of hospital admission.

Furthermore, Study US 30/31 was for LTG IR (with an internal control) and the Escape Criteria were defined the same as Study LAM30055. There were 10% subjects in the LTG IR group who met criterion #4 vs 4% for the pseudoplacebo. Other White Paper studies tended to have a large percentages of subjects meeting criterion #4 (19%, 17%, 11%, 7%, 45% and 29% for study 1, 3, 5, 6, 7, 8, respectively).

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Therefore, there was serious concern about the bias due to potential under-reporting of escapes for criterion #4.

Table 7. Percentage of Subjects Meeting Each Criterion

Criterion	**LTG XR 300 mg/day**	**LTG XR 250 mg/day**
Criterion #1	12/108 (11)	19/97 (20)
Criterion #2	20/108 (19)	18/97 (19)
Criterion #3	8/108 (7)	7/97 (7)
Criterion #4	0	0

* White Paper Per Protocol Population
* Numbers are n/N (%).
* Patients may meet more than one criterion.
Source: FDA reviewer.

Statistical Analysis of the Proportion of Subjects Meeting Escape Criteria

The post-hoc primary analysis by the sponsor estimated the binomial proportion of subjects meeting Escape Criteria. The analyses were conducted for White Paper PP Population in order to make a direct comparison with the White Paper. Subjects who dropped out due to reasons other than meeting Escape Criteria were treated as treatment successes. However, the White Paper used Kaplan-Meier estimate of the proportion, in which subjects who dropped out for other reasons were censored. The estimated binomial proportion will be smaller than the Kaplan-Meier estimate due to the different ways of handling dropouts.

The reviewer conducted a sensitivity analysis in which subjects who dropped out for other reasons were considered treatment failures/escapes. This way the estimated binomial proportion will be larger than the Kaplan-Meier estimate. This was also the planned primary analysis of 'all-cause' discontinuation.

To deal with potential bias due to conducting an essentially open-label study (all patients were on potentially effective test drug), a worst case analysis was conducted by the reviewer in which ITT subjects who dropped out before the background AED withdrawal were also considered escapes.

None of the upper 95% confidence limits generated by all of these analyses are greater than the White Paper 95% prediction limit for escapes (65.3%) from the historical pseudo-placebo control data (Table 8).

Table 8. Proportion of Subjects Meeting Escape Criteria

	LTG XR 300 mg/day	**LTG XR 250 mg/day**
White Paper PP		
n/N (%)	31/108 (29)	30/97 (31)
[95% CI]	[20.2, 37.2]	[21.7, 40.1]
White Paper PP Sensitivity Analysis		

	LTG XR 300 mg/day	LTG XR 250 mg/day
n/N (%)	37/108 (34)	37/97 (38)
[95% CI]	[25.3, 43.2]	[28.5, 47.8]
ITT Worst Case Analysis		
n/N (%)	41/112 (37)	51/111 (46)
[95% CI]	[27.7, 45.5]	[36.7, 55.2]
The 95% prediction limit is 65.3% for all escapes. The 95% prediction limit is 58.6% for escapes in the subgroup of patients with 1 background AED (the subgroup will be mentioned later in the review).		

*Includes calculated escapes (none met escape criterion #4)
Source: FDA reviewer.

Clinical Reviewer Comment

Study LAM30055 had no escapes due to category #4. This raises a concern of under reporting of escapes. One escape was identified in the adverse event dataset which fits the more general category 4 of the white paper. The observation of no criteria 4 escapes prompts a closer examination of the parity of escape criteria between study LAM30055 and the White Paper composite criteria. The individual criteria are captured for each study and shown in appendix 1. The White Paper creates a composite criteria 3 and 4 which acceptably captures criteria 3 and 4 of the 8 White Paper studies; however as can be seen in the "matching" column of the table (appendix 1), 5 of 7 studies where the data is available do not have strict 1:1 matching with the criteria of LAM30055. Criteria 1 and 2 best approximate a clear 1:1 mapping between the Lamictal XR monotherapy study and the White Paper studies but the distinction is blurred for criteria numbers 3 and 4 which confounds a clear statistical solution to this bias.

Evaluation of the Study Population

Background AED

Most White Paper studies allowed two background AEDs. The percent of subjects receiving two background AEDs ranged between 17% and 34%. Enzyme-inducing antiepileptic drugs (EIAEDs) such as carbamazepine (CBZ) were often the background AED from which subjects were converted. Study LAM30055 allowed one background AED and excluded subjects taking EIAEDs. The White Paper indicated that withdrawal from CBZ did not increase the likelihood of escape, which was confirmed by the reviewer.

The White Paper data suggested that patients on one background AED had fewer escapes than patients on two AEDs. For patients on one background AED, the estimated percent escape is 83.0% with a lower prediction limit of 58.6%. Comparing to this limit, both groups remained superior to the historical pseudo-placebo.

Clinical Reviewer Comment

The LAM30055 design allowed patients only on stable monotherapy to enter the trial. As noted above, this design is divergent from White Paper studies which allowed up to two background

AEDs. There is a potential for the population on stable monotherapy to be less refractory than those requiring polytherapy. Those on two AEDs may be more prone to escape events. The statistical reviewer has reanalyzed the White Paper dataset with modifications which restricted analysis to patients on one background AED. When compared to the revised 58.6% lower bound prediction interval the upper 95% CI of both the 300mg/day and 250mg/day dose groups of study LAM30055 remain superior to the pseudoplacebo group (table 8).

Regional Comparisons

Study LAM30055 was conducted in 7 countries (Argentina, Chile, Costa Rica, Korea, Russian, Ukraine and US) with approximately 75% of subjects enrolled outside the US. In contrast, virtually all of the subjects in the historical control database were enrolled in the US. Table 9 showed the percent escape by region (US vs non-US). Due to the small size in the US, the two dose groups (300 mg/d and 250 mg/d) were pooled. A higher proportion of subjects at US sites met Escape Criteria compared to non-US sites. The proportion of US subjects meeting Escape Criteria remained superior to the historical control except for the ITT worst case analysis. When comparing to the prediction limit for subgroup of patients with one background AED, LTG XR did not show superiority over the historical pseudo-placebo for the US population in the White Paper PP sensitivity analysis or the ITT worst case analysis (Table 9).

Table 9. Proportion of Subjects Meeting Escape Criteria by Region

	US	Non-US
White Paper PP		
n/N (%)	19/50 (38)	42/155 (27)
[95% CI]	[24.5,51.5]	[20.1,34.1]
White Paper PP Sensitivity Analysis		
n/N (%)	25/50 (50)	49/155 (32)
[95% CI]	[36.1,63.9]	[24.3,38.9]
ITT Worst Case Analysis		
n/N (%)	31/56 (55)	61/167 (37)
[95% CI]	[42.3,68.4]	[29.2,43.8]
The 95% prediction limit is 65.3% for all escapes. The 95% prediction limit is 58.6% for escapes in the subgroup of patients with 1 background AED.		

* Includes calculated escapes (none met escape criterion #4)
Source: FDA reviewer.

The sponsor stated that the regionally unbalanced use of VPA was the most likely reason for the regional difference in escape percentage at US compared to non-US sites. Approximately 80% patients were receiving VPA as the background AED at non-US sites compared to about 20% at the US sites. The escape percentage was lower in subjects who transitioned from VPA vs neutral AEDs.

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The above argument was not convincing in the reviewer's opinion. As shown in Table 10, the escape rates were similar between VPA and neutral AEDs within each region. The escape rate was higher at US compared to non-US sites for each type of background AEDs.

Table 10. Region and Background AED Comparisons (White Paper PP)

	US		Non-US	
	Neutral AEDs	VPA	Neutral AEDs	VPA
n/N (%)	15/40 (38)	4/10 (40)	9/31 (29)	33/124 (27)
[95% CI]	[22.5,52.5]	[9.6,70.4]	[13.1,45.0]	[18.8,34.4]

* Includes calculated escapes (none met escape criterion #4)
Source: FDA reviewer.

The Agency requested the Sponsor to establish the comparability of placebo escape rate among the regions. The Sponsor provided US vs non-US placebo rates for recent LAMICTAL adjunctive studies, and conducted literature review of analysis of placebo response by region for various indications. While there may be regional differences in placebo response, the data was limited and the regional differences were inconsistent (sometimes higher in the US, sometimes non-US).

Clinical Reviewer Comment

As noted above in study LAM30055 25% of subjects were recruited from US sites while 75% were from non-US or Western European sites. This raises two concerns, first that study LAM30055 may not be generalizable to the US population. Second is the concern that the LAM30055 study population may not be comparable to the White Paper pseudoplacebo population which is 100% North American.

The concern of generalizability to the US population is addressed first. There is uncertainty about the comparability of US to foreign clinical trial sites, especially those that are non-North American, non-Western European sites. There may be differences between the US and foreign sites based on differences in practice of medicine, cultural framework of heath care, the level of investigator and staff training at non-US sites and pharmacogenomic differences in the studied population[4].

There is a suggestion of differences between US and Non-US populations in prior Lamictal XR trials. In study LAM0034 a placebo controlled trial of Lamictal XR for treatment of partial seizures, which was composed of approximately 40% US sites, the efficacy subset analysis of US sites did not reach a threshold of significance. This raised a concern that efficacy within the study as a whole was driven by the foreign data. In study LAM00036, a placebo controlled trial of Lamictal XR in primary generalized tonic-clonic seizures; the placebo response of the US sites was notably larger than in the non-US sites. In another placebo controlled study (LAM40097) of Lamictal XR in primarily generalized tonic-clonic seizures the findings were reversed with a placebo response in the non-US sites which was larger than the US placebo

[4] Glickman SW, McHutchinson JG, et.al. Ethical and Scientific Implications of the Globalization of Clinical Research. NEJM 2009;360(8):816-823.

response rate. The reversal in placebo response rate between studies LAM0036 and LAM40097 suggests non-systematic variation in the placebo response between studies, a favorable observation, which at face value poses less of a challenge to the generalizability of foreign data to the US. The situation may be more complex. In study LAM40097 the non-US placebo treatment patients were all from South America whereas in study LAM0036 only 16% of 62 non-US, placebo treated patients were from South America and the remainder were from Germany, Russia, Ukraine, Malaysia, and India. The majority were from India. Therefore it may be postulated that there is a higher placebo response in the South American cohort which was diluted, in this second case, by the larger numbers of European and Asian patients. In conclusion, regional differences in placebo response cannot be ruled out by the reversal of placebo response observations in studies LAM100036 and LAM40097.

In the current study, LAM0035, there is a divergence in the escape rate between the US and non-US patient groups. The upper 95% CI of the US subset was below the original White Paper lower CI of the prediction interval (65.3%) for the White Paper PP analysis and the White Paper sensitivity analysis (table 9), Subsequently following a reanalysis of the White Paper with only patients on one background AED included, the statistical reviewer has found the US subset breaches the resulting modified White Paper lower bound of 58.6% in both the ITT worst case analysis and the White Paper sensitivity analysis (table 9). This observation is again suggestive of a different population behavior in the US and non-US cohorts.

The sponsor analysis explained this difference as, quite plausibly, due to imbalance in treatment with valproic acid (VPA) as a background anticonvulsant agent. In order to further investigate this possibility the statistical reviewer has performed an analysis of the LAM30055 escape rate by background AED type, either VPA or enzyme induction neutral. The US and non-US escape rates were extracted. This analysis revealed that within region the background AED is not associated with a difference in escape rate (table 10). This observation undermines the proposition that difference in the proportion of patients entering the study with VPA as a background AED is responsible for the difference in US vs non-US escape rate. The cause of this difference remains unexplained but underscores the concern that non-US cohorts may not be generalized to the US population.

Is the LAM0035 treatment population appropriately paired with the historical control (pseudoplacebo group)? The first point of examination again is related to the US, non-US composition of the study population. The aggregate pseudoplacebo group derived in the White Paper is a very close approximation to a 100% US sample while study LAM30055 is 75% non-US. To be a valid placebo for LAM30055 it must be accepted that the non-US treatment component of the study (LAM30055) and the US pseudoplacebo will behave as homogenous groups in response to treatment. Based on the discussion of differences in placebo response and escape rate between US and non-US groups, adequate parity does not appear to be present for the composite pseudoplacebo cohort to act as a placebo comparator for study LAM30055.

Baseline Seizure Frequency

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In the White Paper studies, the minimum number of Baseline seizures required for randomization ranged from at least 2 seizures per 4 weeks (3 studies) to at least 4 seizures per 4 weeks (4 studies). The median Baseline seizure frequency ranged between 1.4 and 2.5 seizures per week. Study LAM30055 required at least 2 seizures per 4 weeks of Baseline. The median Baseline seizure frequency was 1.4 seizures per week for LTG 300 mg/d group and 1.5 for LTG 250 mg/d group, which is at the lower end of the range of the White Paper studies.

Table 11 showed that the escape rate was 42% for subjects with Baseline seizure frequency less than 4 per 4 weeks and 25% for subjects with Baseline seizure frequency of at least 4. The escape rate was higher for the subset of patients with 2-4 seizures per 4 weeks at Baseline. Therefore, there was no evidence that the relatively low Baseline seizure frequency in Study LAM30055 led to lower escape rate.

Table 11. Escape Rate by Baseline Seizure Frequency (White Paper PP)

	2- 4 Seizures per 4 weeks	**At Least 4 Seizures per 4 weeks**
n/N (%)	25/59 (42)	36/146 (25)
[95% CI]	[29.8,55.0]	[17.7,31.6]

* Includes calculated escapes (none met escape criterion #4)
Source: FDA reviewer.

Clinical Reviewer Comment

There is variability in the eligibility requirement for baseline seizure frequency among the White Paper studies. As noted by the statistical reviewer in the above section on baseline seizure frequency. Three White Paper studies had an eligibility of 2 seizures per four weeks and 4 studies had a requirement of 4 seizures per four weeks with a resulting range of 1.4 to 2.5 seizures per week at baseline, in the White Paper pseudoplacebo group. Study LAM30055 required 2 seizures per 4 weeks with a resulting median of 1.4 seizures / week. This places study LAM30055 at the lowest end of the White Paper pseudoplacebo baseline seizure frequency. This observation raises the possibility that the two populations are not matched. The lower baseline seizure frequency rate of the LAM30055 population may be represent a more stable population, physiologically inclined toward more stable epilepsy and lower escape rate. In order to test this hypothesis, the statistical reviewer examined the escape rate by baseline seizure frequency. The escape rate was found to be higher in those with a lower baseline seizure frequency. This finding, although counterintuitive, indicates the difference in baseline seizure rate between the White Paper pseudoplacebo group and the LAM30055 treatment group does not reduce the study validity.

Baseline Seizure Types

Data on the distribution of simple partial (SP), complex partial (CP) and secondarily generalized tonic-clonic (SGTC) seizure subtypes at Baseline were available from 4 of the 8 historical studies. There were 83 to 95 percent of the subjects in these 4 studies having CP seizures during Baseline compared to approximately 62% of subjects in Study LAM30055.

Table 12 showed that the escape rate was higher for the subset of patients without CP in Study LAM30055. Therefore, there was no evidence that the lower percentage of subjects with CP in Study LAM30055 contributed to the lower escape rate.

Table 12. Escape Rate by Baseline seizure Type (White Paper PP)

	Subjects without CP	Subjects with CP
n/N (%)	27/77(35)	34/128(27)
[95% CI]	[24.4,45.7]	[18.9,34.2]

* Includes calculated escapes (none met escape criterion #4)
Source: FDA reviewer.

Clinical Reviewer Comment

There is a notable difference in the baseline seizure type of study LAM30055 and in 4 studies of the White Paper pseudoplacebo group where this information is available. Those patients with complex partial seizures comprised 83 to 95 percent of the White Paper studies whereas 62% of patients in study LAM30055 had complex partial seizures. In order to determine if this difference of seizure type distribution would influence escape rate in a direction that would favor the success of study LAM30055, the statistical reviewer performed an analysis of the escape rate according to baseline seizure type. The sample from LAM30055 was analyzed. This revealed that patients with complex partial seizures had a lower escape rate. Study LAM30055 had a smaller proportion of CP seizures than the White Paper pseudoplacebo group, thus this difference in background seizure type does not bias toward success of study LAM30055.

Supportive Study (LTG IR) – US 30/31

The previous study US 30/31 which used the LTG IR formulation was the basis for the LTG IR monotherapy indication at a dose of 500 mg/day. Study US 30/31 was one of the eight studies from which the historical control endpoint was derived.

US 30/31 was combined from two studies US 30 and US 31 due to slow enrollment. The design of Study US 30/31 was similar to Study LAM30055 consisting of an 8-week Baseline phase followed by randomization to one of two treatment groups (LTG IR, 500 mg/day or pseudo-placebo valproic acid (VPA), 1000 mg/day). There was an 8-week Conversion phase from background AED monotherapy to either LTG IR or VPA comprised of 4 weeks of escalation of LTG IR or VPA followed by 4 weeks of withdrawal of the background AED. Twelve weeks of monotherapy followed and a Continuation phase was provided by roll-over to another study. Unlike Study LAM30055 which excluded subjects taking EIAEDs, Study US 30/31 included only subjects taking an EIAED as their background monotherapy.

Subject disposition was presented in Table 13. A total of 156 subjects were randomized. The ITT Population which consisted subjects randomized to treatment who received at least one dose of the assigned treatment included 76 subjects in the LTG IR group and 80 subjects in the VPA group. The PP Population of subjects who met Escape Criteria or completed 12 weeks of

monotherapy (i.e., completers; differently from Study LAM30055 PP) included 50 subjects in the LTG IR group and 64 subjects in the VPA group. More subjects in the LTG IR group than the VPA group prematurely discontinued the study (34% vs 20%, respectively) for reasons other than having met Escape Criteria, primarily due to a higher occurrence of AEs (20% vs 8%, respectively).

Table 13. Subject Disposition (All Randomized Subjects: Study US 30/31)

	Number (%) of Subjects	
	LTG IR	**VPA**
Population		
Randomized	76	80
Intent-to-Treat (ITT)	76	80
Per Protocol (PP)	50	64
Completion status		
Completed study	28 (37)	13 (16)
Met Escape Criteria	22 (29)	51 (64)
Prematurely withdrawn	26 (34)	16 (20)
Reason for premature withdrawal		
Adverse event (AE)	15 (20)	6 (8)
Protocol violation	2 (3)	4 (5)
Subject decided to withdraw from the study	4 (5)	2 (3)
Insufficient therapeutic response	5 (7)	3 (4)
Death	0	1 (1)

Source: Sponsor ISE Table 16.

The primary measure used to evaluate efficacy was the proportion of subjects meeting Escape Criteria (escapes) after the start of AED taper in the PP Population. A secondary measure used to evaluate efficacy was the proportion of escapes in the ITT Population. In this analysis, subjects who prematurely discontinued from the study and did not meet Escape Criteria were analyzed in two ways. In the first analysis, both LTG IR and VPA dropouts were also counted as escapes. This analysis was post-hoc and was labeled the ITT analysis. In the second ITT analysis, LTG IR dropouts were counted as escapes while VPA dropouts were counted as completers. This analysis was labeled the worst case analysis. An additional analysis was conducted on the ITT Population by the agency during the review of the LTG IR monotherapy sNDA that added subjects withdrawing due to inadequate response to those who met Escape Criteria (FDA Drug Approval Package; NDA 20-241/S003 and NDA 20-764/S001, approved 14 December 1998). The worst case analysis revealed no statistically significant difference between LTG and VPA. Other analyses showed that LTG was superior (Table 14).

Table 14. Proportion of Subjects Meeting Escape Criteria (Study US 30/31)

	Number n/N (%) of Subjects	
	LTG IR	**VPA**
US 30/31 PP Population[1]	22/50 (44)	51/64 (80)
ITT	48/76 (63)	67/80 (84)

	Number n/N (%) of Subjects	
	LTG IR	**VPA**
ITT worst case analysis	48/76 (63)	51/80 (64)
ITT Agency[2]	32/76 (42)	55/80 (69)

1. Different from the PP population is Study LAM30055.
2. Subjects who escaped were defined as meeting Escape Criteria or withdrawing due to an inadequate response. Subjects withdrawing due to AEs were not counted as escapes.
Source: Sponsor ISE Table 19-21.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Gender, Race and Age

Table 15 showed the subgroup analysis results for age, gender and race subgroups for Study LAM30055. Majority of the patients are 16 years old or older (92%), White (87%), female (53%). The escape rate was consistent across the race subgroups, but appeared higher in young (<16 years) and old (>=55 years) male patients. Logistic regressions indicated that there was no effect of age or gender on the escape rate.

Table 15. Escape Rate by Gender, Race and Age in Pooled Treatment Group (Study LAM30055 White Paper PP)

	Subgroups	**n/N (%)**	[95% CI]
Gender	Female	27/109 (25)	[16.7,32.9]
	Male	34/96 (35)	[25.8,45.0]
Race	White - White/Caucasian/European Heritage	53/178 (30)	[23.1,36.5]
	Asian - East Asian Heritage	6/19 (32)	[10.7,52.5]
	African American/African Heritage	2/6 (33)	[-4.4,71.1]
Age	Less than 16	8/17 (47)	[23.3,70.8]
	16 - 55	45/171 (26)	[19.7,32.9]
	55 or Greater	8/17 (47)	[23.3,70.8]

Source: FDA reviewer.

Reference ID: 2921075

5. SUMMARY AND CONCLUSIONS

Statistical Issues and Collective Evidence

The formulation and dosage of LTG were different in the pivotal study LAM30055 and the supportive study US 30/31. The main differences in study design between the two studies were (1) Study US 30/31 was placebo-controlled but Study LAM30055 was not; (2) Study US 30/31 was conducted in the US while Study LAM30055 was conducted in 7 countries with approximately 75% of subjects enrolled outside the US; (3) and Study US 30/31 included only subjects taking an EIAED as their background monotherapy but Study LAM30055 excluded subjects taking EIAEDs. The study results were presented in Table 16. The proportion of subjects meeting Escape Criteria was lower in Study LAM30055 than Study US 30/31. The identified issues were discussed below.

Table 16. Summary of Escape Rate by Study

	LAM30055[1]		US 30/31	
	LTG XR 300 mg/day	LTG XR 250 mg/day	LTG IR	VPA
White Paper PP	31/108 (29, 37.2)	30/97 (31, 40.1)		
White Paper PP Sensitivity Analysis[2]	37/108 (34, 43.2)	37/97 (38, 47.8)		
ITT Worst Case Analysis[2]	41/112 (37, 45.5)	51/111 (46, 55.2)	48/76 (63)	51/80 (64)
Study US 30/31 PP (Completer Analysis)	31/102 (30)	30/90 (33)	22/50 (44)	51/64 (80)
ITT[3]	33/112 (29)	30/111 (27)	32/76 (42)	55/80 (69)
The 95% prediction limit is 65.3% for all escapes. The 95% prediction limit is 58.6% for escapes in the subgroup of patients with 1 background AED.				

*Numbers are: n/N (%, confidence upper bound%) or n/N (%)
1.Includes calculated escapes (none met escape criterion #4)
3.LTG dropouts were counted as escapes while VPA dropouts were counted as completers.
2.Subjects who escaped were defined as meeting Escape Criteria or withdrawing due to an inadequate response. Subjects withdrawing due to other reasons were counted as treatment successes.

Post-hoc Analyses

The analyses of the pivotal trial Study LAM30055 were altered post-hoc in the following aspects.

The primary endpoint and analysis population were changed to reflect the analysis of the White Paper. This post-hoc change did not seem to be a concern since this analysis could be viewed as pre-specified in the White Paper.

While the trial was ongoing, the sponsor evaluated a random sample of subjects for correct application of the Escape Criteria and identified a number of errors (e.g., some patients met an Escape Criterion but were not discontinued). As a result, remedial training of study site personnel and monitors was undertaken. Following completion of the study, planned analysis of

escapes showed that the number of subjects who met pre-defined Escape Criteria was surprisingly small. Only about 6% of the subjects met Escape Criteria compared to 42% in Study US 30/31 (Table 17). Therefore, to correct errors by sites/investigators, seizure data were evaluated post-hoc leading to reclassification of many subjects as 'escapes' (Table 16).

Table 17. Escapes As Determined by Investigator (ITT Population)

LAM30055		US 30/31	
LTG XR 300 mg/day	**LTG XR 250 mg/day**	**LTG IR 500 mg/day**	**VPA**
6/112 (5)	7/111 (6)	32/76 (42)	55/80 (69)

* Numbers are n/N (%).
* Subjects who escaped were defined as meeting Escape Criteria or withdrawing due to an inadequate response, as determined by investigator.

Potential Biases

It is well known that trials with internal control provide greater assurance than afforded by comparison to historical controls. The absence of an internal control arm is of particular concern when the primary endpoint is adverse outcome and involves subjective evaluation. In epilepsy monotherapy trials, dropouts, under-reporting seizures/escapes, etc, could bias toward treatment success and undermine the validity of the trial.

In Study LAM30055 subjects who dropped out for reasons other than meeting Escape Criteria were treated as completers in the sponsor's analysis, which biased toward treatment success (analysis for White Paper PP population). The White Paper used Kaplan-Meier estimate of the proportion, in which subjects dropped out due to other reasons were censored. This gives a higher estimated escape rate. The reviewer conducted a sensitivity analysis which included dropouts as treatment failures. This was also the planned primary endpoint of 'all-cause' discontinuation. To deal with potential bias due to conducting an essentially open-label study (all patients were on potentially effective test drug), a worst case analysis was conducted by the reviewer in which ITT subjects who dropped out before the background AED withdrawal were also considered escapes. The results remained positive for those analyses (Table 16).

The bias from under-reporting escapes was present in Study LAM30055. This bias was corrected to some extend by performing the post-hoc calculation of escapes using seizure data. However, there was no criterion #4 events reported and it was difficult to identify such events post-hoc due to the subjective nature of this criterion. Of the White Paper studies, Study US 30/31 was designed most comparable with Study LAM30055. Study US 30/31 had 10% subjects in the LTG IR group who met criterion #4 and 4% in the pseudo-control group. Other White Paper studies tend to have a large percentage (19%, 17%, 11%, 7%, 45% and 29% for study 1, 3, 5, 6, 7, 8 pseudo-control group, respectively). The criterion #4 in the LTG studies may be more restrictive than the White Paper criterion. Some events may be considered escapes according to the White Paper criteria, but not by the Study LAM30055 criteria. Therefore, comparing the Study LAM30055 escape rate with the combined escape rate due to all 4 criteria from the White Paper studies may bias towards treatment success. However, it was uncertain how to adequately assess the potential bias due to under-reporting criterion #4 events.

Population Comparability

Study LAM30055 had approximately 75% of subjects enrolled outside the US while all of the subjects in the historical control database were enrolled in the US. A higher proportion of subjects at US sites met Escape Criteria compared to non-US sites. The comparability of the US and non-US subjects was not established. The result for the US subgroup was positive except for the ITT worst case analysis (Table 9).

The White Paper data suggested that patients on one background AED had fewer escapes than patients on two AEDs. For patients on one background AED, the estimated percent escape is 83.0% with a lower prediction limit of 58.6%. In comparison to this limit, both LTG dose groups remained superior to the historical pseudo-placebo. However, LTG XR failed to show superiority for the US subgroup in the White Paper PP sensitivity analysis or the ITT worst case analysis (Table 9).

Conclusions and Recommendations

In summary, the data seem to suggest some evidence of efficacy of LTG XR as monotherapy treatment of partial seizures. However, interpretability of these analysis results is undermined by the limitations of the historical control design; thus, it is uncertain that the efficacy of LTG XR as monotherapy treatment of partial seizures is conclusive based on this study.

Clinical Reviewer Comments

The sponsor analysis revealed an unexpectedly low escape rate prompting re-evaluation of seizure data to create "calculated escapes". The proportion of subjects meeting escape criteria based on this analysis was 26/108 (24%) with lower and upper bound of 95% confidence intervals of 16% and 32.1% respectively for the 300mg /day group. The statistical reviewer notes that the sponsor analysis conducted for the White Paper per protocol population is based on the binomial proportion of subjects meeting escape criteria. The reviewer indicates that the White Paper used Kaplan-Meier estimate of the proportion in which subjects who dropped out for other reasons were censored. This results in a larger estimate of escapes. The statistical reviewer also created two additional analysis of the proportion of subjects meeting escape criteria, these three analysis methods are defined for as follows:

- White Paper Per Protocol: White Paper per protocol population where Kaplan-Meier estimate of the proportion in which subjects who dropped out for other reasons were censored.

- White Paper Sensitivity Analysis: Subjects who dropped out for reasons other than meeting escape criteria were considered escapes.

- ITT Worst Case: ITT subjects who dropped out before the background AED withdrawal were also considered escapes.

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The results of study LAM30055 based on these analysis may be seen in table 8. Based on the White Paper 95% prediction limit of 65.3% all of the 300mg/day or 250mg/day upper 95% confidence intervals in addition to the US subset where the White Paper per protocol and sensitivity analysis remain superior to this threshold (table 9).

Comparability of the White Paper and LAM 30055 study populations reveals difference in two elements of composition; region and number of background anticonvulsant drugs allowed at study entry. The White Paper is derived from an almost 100% US population while study LAM30055 is 75% non-US.

In 6 the 8 White Paper studies where the data is available the participants were on 2 background AEDs at entry while study LAM30055 required background monotherapy for eligibility. The statistical reviewer has found that the White Paper data indicate that patients with one background AED had fewer escapes than patients with two AEDs. An analysis of the White Paper pseudoplacebo population on only 1 background AED is performed and reveals a Kaplan Meier escape rate of 83% with a lower bound prediction interval of 58.6%. The overall study LAM30055 results were not changed based on the statistical reviewer escape groups of table 8. The US subset results did lose superiority to the White Paper sensitivity analysis (table 9)

From within the White Paper studies there was only one non-US study site which was located in Canada. Study LAM30055 has only a 25% US composition. As discussed in the section on regional comparisons, the non-US results may not be generalizable to the US. The small US subset of LAM30055 was not designed to be a stand alone comparator to the White Paper pseudoplacebo composite.

The most valid modification for comparing study LAM30055 to the White Paper pseudoplacebo composite group appears to be restriction to those participants on 1 AED. It is not clear that those on 1 AED are a distinct population from those on 2 AED; however the statistical reviewer examined the White Paper data and found fewer escapes among those on 1 AED. Therefore those in the White Paper on 1 AED are most suited to compare to the study population of LAM30055.

The use of an historical control comparator is a novel methodology. There are multiple components of the White Paper pseudoplacebo aggregate which present a challenge to confidence in this approach as a valid comparator to study LAM30055. The populations are different across time and region. The span of the pseudoplacebo population ranges from approximately 1992 to 2001. In the oldest White Paper study the pseudoplacebo patients will be almost a generation older than the study population of LAM30055. The regional divergence is discussed above. The variation in mapping of escape criteria between the Lamictal XR monotherapy study and the White Paper studies are features which point to insufficient uniformity between studies to act as a pooled comparator. There are also features which support the validity of this aggregate pseudoplacebo group. First, in every study the pseudoplacebo escape rate was larger than the active therapy escape rate and in 6 of 7 studies where the data is available; the active therapy was statistically superior to the pseudoplacebo arm (see appendix 2).

The common core feature of all 8 White Paper trials was a study endpoint of patient exit (escape) rate.

Additional support for efficacy is provided by the bioequivalence data on Lamictal IR and XR presented in the Clinical Pharmacology review of Lamictal XR (adjunctive therapy in partial seizures)[5]. This data provides an expectation that this extended release form of Lamictal will perform similarly to Lamictal IR which is approved for conversion to monotherapy. Conceptual support for efficacy of Lamictal XR monotherapy is provided by the established effectiveness of Lamictal XR for treatment of partial and primary generalized tonic-clinic seizures.

Summary

If the White Paper is accepted as a valid platform for historical control comparison, modified by restricting the population to those on 1 background AED, then the resultant lower bound of the pseudoplacebo group prediction interval is 58.6%. All analysis subsets for study LAM30055 populations in both the 300mg/day and 250mg/day dose groups remain superior to this (58.6%) White Paper lower bound. The US subset remains superior only in the White Paper per protocol analysis derived by the statistical reviewer. The US subset is small and not powered to independently test for significance, therefore this finding in isolation does not supersede the overall study results.

Conclusion

There is adequate support for approval of Lamictal XR for use in conversion to monotherapy for patients ≥13 years of age who are receiving treatment with a single AED. The recommended target dose is 300mg daily, although the 250mg/day dose remained superior to the pseudoplacebo, this dose was not the protocol directed primary efficacy endpoint.

[5] Tandon V. Clinical Pharmacology/Biopharmaceutics Review, NDA22115, Product: Lamictal XR, Indication: Adjunctive therapy for partial onset seizures with or without generalization in patients ≥ 13 years. 9/6/2007

Appendix 1. Criteria Comparator

Study/ Pub date	Escape Criteria by Study	Matching Properties
1 (1992)	(1) **(3)**an episode of status epilepticus; (2) **(4)**a secondarily generalized tonic-clonic seizure if none had been experienced within 2 years of study entry; (3) (**1)** a 28-day study seizure rate greater than two times the maximum 28-day study seizure rate during baseline (a 28-day period is defined as any four consecutive study weeks); (4) **(2)**a 2-day study seizure rate greater than two times the maximum 2-day study seizure rate during baseline; or *(5)* **(3)** an unacceptable increase in the frequency or intensity of seizure activity that did not meet any of the exit criteria but that was, in the opinion of the treating physician, clinically significant	Does not have # 4 equivalent, removal of 4 leaves Parity **Inherent non-parity before removal of 4**
2 (1998)	1) doubling of average monthly seizure rate; 2) doubling of the highest consecutive 2-day seizure rate; 3) emergence of a new, more severe seizure type; or 4) clinically significant prolongation of generalized tonic-clonic seizures	Parity
3 (1997)	1. a doubling of the average monthly (28-day) baseline seizure frequency, 2. a doubling of the highest 2-day baseline seizure frequency, 3. a single GTCS if none occurred during baseline, 4. Prolongation of generalized seizure duration that was considered serious by the investigator, or serial seizures or status epilepticus of any seizure subtypes.	Criteria #3 could be placed in Criteria 4 in LAM30055 Criteria 4 = criteria 4 in LAM30055 but serial seizures or status epilepticus match "emergence of a new more severe seizure type" – criteria 3 No representation of criteria # 3, emergence of a new more severe seizure type (except for special case of " a single GTCS" The absence of clear 3 would leave contribution from 3 that is not matched here Non-parity with or without criteria 4- **Inherent Non-Parity**
4		
5 (2001)	1) a twofold increase in monthly seizure frequency in any 28-day period relative to the open-label baseline phase; 2) a twofold increase in the highest consecutive 2-day seizure frequency relative to the open-label baseline phase; 3) occurrence of a generalized seizure if none occurred during the open-label baseline phase; or 4) prolongation of generalized seizure duration that, in the opinion of the investigator, required intervention.	Criteria 3 in this study could represent a special case of criteria 3 in LAM30055. "emergence of a new more severe seizure type" is broader and should capture "occurrence of a generalized seizure if none occurred during open label or baseline". This could also satisfy LAM30055 category 4. It could be anticipated that criteria #3 of LAM30055 should capture more than this criteria 3
6 (2000)	1) a twofold increase in partial seizure frequency in any 28-day period compared to baseline; 2) a twofold increase in the highest consecutive 2-day seizure frequency that occurred during the baseline phase (patients with a single seizure as the highest 2-day baseline phase seizure frequency exited the trial if three or more seizures occurred during any 2-day period in the double-blind treatment phase); 3) occurrence of a single generalized seizure if none had occurred in the 6 months prior to randomization; or 4) a prolongation or worsening of seizure duration or frequency	Criteria 4 in this study is roughly equivalent to criteria 3 of LAM30055. Criteria 3 of this study could be captured by criteria 4 of LAM30055 Effect if criteria 4 is censored could be to remove balance to events which would asymmetrically remain in LAM30055 as criteria 3.

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	considered by the investigator to require intervention.	N**on-parity before and after #4 modification**
7 (1992)	(1) a two-fold increase in average monthly seizure frequency, (2) a two-fold increase in the highest 2-day seizure frequency, (3) a single generalized seizure if none occurred during the baseline period, and (4) a prolongation of generalized seizure duration (serial seizures or status epilepticus) deemed by the investigator to require intervention.	This study criteria #3 could represent a special case of LAM30055 criteria # 3 This criteria # 4 could capture LAM30055 criteria #3 if serial seizures or status epilepticus is considered emergence of new more severe seizure type **Inherent Non parity**
8 (1993)	(1) a doubling in monthly seizure number compared with the average monthly seizure number during the baseline period; (2) a doubling of 2-day seizure number over the worst 2-day period during the baseline (this frequency criterion applied only when two or more seizures had occurred during some 2- day period of the baseline); (3) **(4)** a single generalized tonic clonic tonic clonic seizure, if none had occurred during the baseline; and a significant prolongation of a generalized tonic clonic seizure considered serious by the investigator, **(3)** or serial seizures or status epilepticus of seizure types other than generalized tonic-clonic seizures.	**Parity**
LAM30055	1. Doubling of average monthly seizure frequency calculated as the sum of countable, partial seizures starting the day prior to the study visit and extending back 28 days. 2. doubling of the highest consecutive 2-day seizure frequency. 3. emergence of a new, more severe seizure type. 4. clinically-significant prolongation of generalized tonic-clonic seizures.	

Appendix 2. Comparison of White Paper Active and Pseudoplacebo Study Escapes

Study Escapes with total enrollment denominator (n^1)					
	Pseudoplacebo	**Active**	**Pseudoplacebo Escape / total enrollment (n/n^1) (%)**	**Active therapy Escape / total enrollment (n/n^1) (%)**	**Background AED**
1	Gabapentin 600mg	Gabapentin 2400mg	70/93 (75)	66/91 (73)	1 or 2
2	Valproic Acid 1000mg	Lamictal 500mg	55/80 (69)	32/76 (42)	1 (CBZ or PHT)
3	Topamax 100mg	Topamax 1000mg	21/24 (88)	12 /24 (50)	1
4	Not published				
5	Oxcarbazepine 300mg	Oxcarbazepine 2400mg	40/45 (89)	30/49 (61)	1 (CBZ)
6	Oxcarbazepine 300mg	Oxcarbazepine 2400mg	42/46 (91)	14/41 (34)	1 or 2
7	Valproic Acid 15mg/kg	Felbamate 3600mg	19/22 (86)	3/22 (14)	1 or 2
8	Valproic Acid 15mg/kg	Felbamate 3600mg	39/55 (71)	18/56 (32)	1 or 2

Study escapes as analyzed by study protocol, n^2 varies as directed by study handling of dropouts						
	Pseudoplacebo	**Active**	**Pseudoplacebo Escape / study directed denominator (n/n^2) (%)**	**Active therapy Escape / study directed denominator (n/n^2) (%)**	**Significance**	**1^0 efficacy endpoint**
1	Gabapentin 600mg	Gabapentin 2400mg	70/93 (75)	66/91 (73)	No, dropouts included NS	Primary efficacy = time to exit, secondary = completion rate
2	Valproic Acid 1000mg	Lamictal 500mg	51/64 (80)	22/50 (44)	P<.001, dropouts excluded	Primary efficacy = Per protocol % escape
3	Topamax 100mg	Topamax 1000mg			Not calculated for % escape Time to exit, p = 0.002	Primary efficacy= time to exit
4	Not published					
5	Oxcarbazepine 300mg	Oxcarbazepine 2400mg	40/40 (100)	30/46 (65)	P=0.0001, dropouts removed	1^0 efficacy = time to exit.
6	Oxcarbazepine 300mg	Oxcarbazepine 2400mg	42/45 (93)	14/34 (41)	P<0.0001 Dropouts excluded	1^0 efficacy = % meeting exit
7	Valproic Acid 15mg/kg	Felbamate 3600mg	19/22 (86)	3/22 (14)	P< 0.0001 Dropouts included	1^0 efficacy = % meeting exit
8	Valproic Acid 15mg/kg	Felbamate 3600mg	39/50 (78)	18/45 (40)	P<0.001 Dropouts excluded	1^0 efficacy = % meeting exit

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Addendum. Updated Results Including Additional Escapes Due To Meeting Escape Criterion #4

On February 16, 2011, the Sponsor submitted response to the Agency's January 6, 2011 request of identifying patients who qualify for escape based on the need for intervention by examining patient medication records and adverse event records. Additional 3 and 5 escapes were identified for 300mg/d group and 250 mg/d group, respectively, for the ITT population. Table 7-10 were updated to include those additional escapes.

Table 18. Percentage of Subjects Meeting Each Criterion (Updated)

Criterion	LTG XR 300 mg/day	LTG XR 250 mg/day
Criterion #1	12/108 (11)	19/97 (20)
Criterion #2	20/108 (19)	18/97 (19)
Criterion #3	8/108 (7)	7/97 (7)
Criterion #4	7/108 (6)	10/97 (10)

* White Paper Per Protocol Population
* Numbers are n/N (%).
* Patients may meet more than one criterion.
Source: FDA reviewer.

Table 19. Proportion of Subjects Meeting Escape Criteria (Updated)

	LTG XR 300 mg/day	LTG XR 250 mg/day
White Paper PP		
n/N (%)	34/108 (31)	34/97 (35)
[95% CI]	[22.7,40.2]	[25.6,44.5]
White Paper PP Sensitivity Analysis		
n/N (%)	40/108 (37)	40/97 (41)
[95% CI]	[27.9,46.1]	[31.4,51.0]
ITT Worst Case Analysis		
n/N (%)	44/112 (39)	54/111 (49)
[95% CI]	[30.2,48.3]	[39.4,57.9]
The 95% prediction limit is 65.3% for all escapes. The 95% prediction limit is 58.6% for escapes in the subgroup of patients with 1 background AED (the subgroup will be mentioned later in the review).		

*Includes calculated escapes
Source: FDA reviewer.

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Table 20. Proportion of Subjects Meeting Escape Criteria by Region (Updated)

	US	Non-US
White Paper PP		
n/N (%)	21/50 (42)	47/155 (30)
[95% CI]	[28.3, 55.7]	[23.1, 37.6]
White Paper PP Sensitivity Analysis		
n/N (%)	27/50 (54)	53/155 (34)
[95% CI]	[40.2, 67.8]	[26.7, 41.7]
ITT Worst Case Analysis		
n/N (%)	33/56 (59)	65/167 (39)
[95% CI]	[46.0, 71.8]	[31.5, 46.3]
The 95% prediction limit is 65.3% for all escapes. The 95% prediction limit is 58.6% for escapes in the subgroup of patients with 1 background AED.		

* Includes calculated escapes

Source: FDA reviewer.

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/s/

XIANG LING
03/21/2011

KUN JIN
03/21/2011
I concur with this review.

HSIEN MING J J HUNG
03/22/2011
concur with Stat Review

STEVEN T DINSMORE
03/24/2011

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04/05/2011